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THE RATIONAL USE OF ANTIBIOTICS IN CHILDREN

Systematic literature review: full report

Consensus conference
June 2nd 2016
Auditorium Lippens (Royal Library)
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2 Abbreviations

AB	Antibiotic
AE	Adverse events
AMPC	Amoxicillin
AOM	Acute otitis media
ARR	Absolute risk reduction
CAP	Community-acquired pneumonia
CCT	Controlled clinical trial
CI	Confidence interval
CKD	Chronic kidney disease
CO	Crossover RCT
CVA	Clavulanic acid
DB	Double blind
ESPGHAN	European Society for paediatric gastrointestinal hepatology and nutrition
ESPID	European society for paediatric infestious diseases
GABHS	Group A beta-haemolytic streptococci
GE	Gastro-enteritis
GGD	Gemeentelijke gezondheidsdienst (Communal health services)
GoR	Grade of Recommendation
HR	Hazard ratio
HUS	Hemolytic uremic syndrome
IM	Intramuscular
ITT	Intention-to-treat analysis
IV	Intravenous
LoE	Level of Evidence
MA	Meta-analysis
n	Number of patients
NR	Not reported
NS	Not statistically significant
NT	No statistical test
OL	Open label
PG	Parallel group
PO	Primary outcome
ROM	Recurrent otitis media
SB	Single blind
SO	Secondary outcome
SR	Systematic review
SWAB	Stichting Werkgroep antibioticabeleid
UTI	Urinary tract infection
VUR	Vesicoureteral reflux

Table 1: abbreviations used in this report

3 Methodology

3.1 Introduction and scope

This systematic literature review was conducted in preparation of the consensus conference on 'The rational use of antibiotics in children' which will take place on the 2nd of June 2016.

3.1.1 Questions to the jury

The questions to the jury, as they were phrased by the organising committee of the RIZIV/INAMI are

Chez un enfant (0 à 15 ans),

A. dans quelles situations cliniques précises est-il utile (efficacité (guérison clinique, prévention des complications)/sécurité/tolérance) de prescrire un antibiotique ?
B. quel est l'antibiotique de premier choix et quelles sont les alternatives ?
C. A quelle dose, quelle fréquence et pour quelle durée ?
D. L'approche doit-elle être différente en fonction
- de l'âge ?
- de la fréquence des récidives ?
- du contexte (crèche, traitement récent,…)

E. Dans quels cas faut-il référer ?

F. Une prévention de récidives d'infection est-elle nécessaire et dans quels cas ?

1. En cas de mal de gorge (y compris avis d'expert sur l'abcès latéro- et rétro- pharyngé)
2. En cas d'Otite Moyenne Aiguë
3. En cas de rhinosinusite
4. En cas de laryngite*, trachéite*, bronchite (+ avis d'expert sur l'épiglottite)
5. En cas de bronchiolite
6. En cas de pneumonie acquise en communauté
7. En cas de cystite
8. En cas de pyélonéphrite
9. En cas de gastro-entérite
10. En cas d'impétigo
11. En cas de cellulite ou d'érésipèle
12. En cas d'infection cutanée à MRSA
13. En cas de conjonctivite

In welke precieze klinische situaties is het bij een kind (0 tot 15 jaar)

E. nuttig om een antibioticum voor te schrijven (werkzaamheid, klinische genezing, preventie van complicaties, veiligheid, tolerantie)?
F. Welk antibioticum is het eerstekeuzemiddel en wat zijn de alternatieven?
G. Aan welke dosis, welke frequentie en hoe lang?
H. Moet de aanpak verschillen afhankelijk van
- de leeftijd?
- de frequentie van de recidieven?

- de context (crèche, recente behandeling,...)?

E. In welke gevallen moet er worden doorverwezen?

F. Is preventie van herhaaldelijke infecties nodig en in welke gevallen?

1. Bij keelpijn (+ expertadvies over para- en retrofaryngeaal abces
2. Bij acute otitis media
3. Bij rhinosinusitis
4. Bij laryngitis*, tracheïtis*, bronchitis (+ expertadvies over epiglottitis)
5. Bij bronchiolitis
6. Bij in de gemeenschap verworven pneumonie
7. Bij cystitis
8. Bij pyelonefritis
9. Bij gastro-enteritis
10. Bij impetigo
11. Bij cellulitis of erysipelas
12. Bij een huidinfectie met de MRSA-bacterie
13. Bij conjunctivitis

*Added on 19/01

3.1.2 Research task of the literature group

The organising committee has specified the research task for the literature review as follows:

- To discuss selected guidelines regarding jury questions numbers
  - *A, B, C, D, E, F;*
  - *1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13*
  - **We did not search for guidelines on laryngitis or tracheitis*

- To search for systematic reviews, meta-analyses, RCTs for the following populations, comparisons and endpoints:

3.1.2.1 Populations

The following population is to be evaluated:
Children up to 15 years of age with normal health status.
Studies in which both adults and children are included should not be considered for this review, except if a subgroup analysis of children is available.

On 19/02, due to lack of data in a purely pediatric population for some pathologies, the methodology was revised:
Meta-analyses that include both adults and children will also be reported if no subgroup analysis for the pediatric population alone is available. In these cases, the quality of evidence for indirectness will be downgraded (see 3.4: Assessing the quality of available evidence*)*

Excluded from the literature search are:

- children with immunodeficiency
- children with anatomical malformations that predispose to certain infections (an exception is made for the antibiotic prophylaxis in vesicoureteral reflux)

In this paediatric population, the following infections are to be evaluated.

- Ear, nose throat infections:
    - Acute sore throat
    - Acute otitis media
    - Acute rhinosinusitis
- Lower respiratory tract infections
    - Acute bronchitis
    - Bronchiolitis
    - Community acquired pneumonia
- Urinary tract infections
    - Cystitis
    - Pyelonephritis
- Gastro-intestinal infections
    - Acute gastro-enteritis
- Skin infections
    - Impetigo
    - Erysipelas
    - Cellulitis
- Infections of the eye
    - Acute infectious conjunctivitis

We will only consider infections that require ambulatory treatment. Trials of in-hospital treatment will also be considered if they study an intervention that can be administered at home (e.g. intramuscular treatment).

For potentially severe infections, such as pneumonia and pyelonephritis, in-hospital treatment of intravenous antibiotics will be considered in comparison to oral treatment, to better determine if and when these infections can be treated at home.

This literature review will not review post-operative infections, intensive care situations, severe infections like sepsis, osteomyelitis, infectious arthritis,….

Travel-related infections are also excuded.

The following infections are not part of the literature search but will be discussed by an expert on the day of the Consensus Conference:

- MRSA

3.1.2.2 Interventions

This literature review is focused antibiotic treatment. Only products with a registered indication in Belgium will be considered. These are listed here:

Systemic antibacterial agents
Penicillins
Benzylpenicillin (penicillin G)
Phenoxymethylpenicillin (penicillin V)
Flucloxacillin
Oxacillin
Ampicillin
Amoxicillin
Amoxicillin + clavulanate
Cefalosporins
Cefadroxil
Cefalexin
Cefazolin
Cefuroxim
Ceftriaxone
Macrolides
Erythromycin
Azithromycin
Clarithromycin
Roxithromycin
Spiramycin
Telithromycin
Tetracyclines
Doxycycline
Lymecycline
Minocycline
Clindamycine
Lincomycine
Fluoroquinolones

Ciprofloxacin
Levofloxacin
Moxifloxacin
Norfloxacin
Ofloxacin
Co-trimoxazole
sulphamethoxazole + trimethoprim
Urinary antibacterial agents
Nitrofurantoin
Nifurtoinol
Trimethoprim
Topical antibiotics (otitis)
Ciprofloxacin
Topical antibiotics (ophtalmology)
Fusidic acid
Chloramphenicol
Fluoroquinolones: ciprofloxacin, moxifloxacin, ofloxacin
Tetracyclines: chlortetracycline
Tobramycin
bacitracin + neomycin
oxytetracycline + polymyxin
Topical antibiotics (dermatology)
Fusidic acid
mupirocin
chloramphenicol
bacitracin + polymyxin B
oxytetracycline + polymyxin B
Probiotics
Saccharomyces boulardii
Lactobacillus acidophilus

Information of all these drugs will be obtained from RCTs.

Quinolones will also be researched in observational studies for safety endpoints.

3.1.2.3 Comparisons

To give an answer to different research questions, the following comparisons will be searched and reported.

<u>For all infections listed above</u>

* Is antibiotic treatment necessary? Efficacy/safety/tolerability of antibiotic treatment
    - Systemic antibiotic versus placebo or no treatment
    - Systemic antibiotic versus symptomatic treatment
    - Systemic antibiotic immediate start versus postponed prescription
* Which antibiotic is the best choice?
    - Antibiotic A versus antibiotic B

* What is the recommended dose and dosing schedule of antibiotic for a certain infection
    - Antibiotic (lower) dose A versus same antibiotic (higher) dose B
    - Schedule A versus schedule B
* What is the optimal duration of antibiotic treatment
    - Antibiotic (shorter) duration A versus same antibiotic (longer) duration B
*What is the recommended non-antibiotic treatment? (guidelines only, no literature search)

<u>For Sore throat</u>
Prevention of recurrent tonsillitis (only from guidelines or systematic reviews)

<u>For otitis media with tympanostomy tubes</u>
* Is a local antibiotic a treatment option?
    - Local antibiotics versus placebo or no treatment
    - Local antibiotics versus symptomatic treatment
    - Local antibiotics versus other local antibiotics
    - Local antibiotics versus oral antibiotics

<u>Community acquired pneumonia</u>
* Is hospitalisation needed (and when)
    - IV antibiotics versus oral antibiotics (in-hospital setting)

<u>Urinary tract infections</u>
* Is hospitalisation needed (and when)with pyelonefritis
    - IV antibiotics versus oral antibiotics (in-hospital setting)
*Can prophylactic antibiotics prevent infections in children with vesicoureteral reflux
    - Systemic antibiotics versus placebo
    - Systemic antibiotics versus surgery
* Is treatment necessary with covert bacteriuria (culture-proven UTI and no urinary symptoms at the time of diagnosis)
    - Systemic antibiotics versus placebo
*How to collect a urine sample (guidelines only, no literature search)

<u>Skin infections</u>
Local antibiotics versus placebo/symptomatic treatment
Local antibiotics versus other local antibiotics
Local antibiotics versus systemic antibiotics

<u>Conjunctivitis</u>
(No detailed information needed on systemic treatment)
    - Local antibiotics versus placebo
    - Local antibiotics versus other local antibiotics

<u>Gastro-intestinal infection</u>
*Are probiotics effective/safe/well tolerated in the treatment of acute gastro-intestinal infection?
    - Probiotics versus placebo

- Probiotics versus antibiotics

*Are probiotics effective/safe/well tolerated in the prevention and treatment of antibiotic-induced diarrhoea?

- Probiotics versus placebo

3.1.2.4 Endpoints

In order to be selected for review, studies need to report at least one clinical endpoint, such as:

- mortality
- need for hospitalisation
- number of sick days/ number of days until symptoms disappear
- 'clinical success'/'treatment success'/'treatment failure' (a composite outcome defined by the study authors that includes relevant disease parameters)
- complications of original infection
- recurrent infection
- adverse events related to treatment

3.1.2.5 Study criteria

To be included in our review, the selected studies need to meet certain criteria.

Meta-analyses and systematic reviews

- Research question matches research question for this literature review
- Systematic search
- Systematic reporting of results
- Inclusion of randomised controlled trials
- Reporting of clinically relevant outcomes

RCT's

- Blinded studies are preferred, but we will not exclude unblinded trials
- Duration: any duration accepted
- Minimum number of participants: 40 per study-arm. For studies with multiple treatment arms, we will look at the number of participants in comparisons relevant to our search.
- Phase III trials (no phase II trials)

Observational studies (to evaluate the safety of quinolones in children)

- Large cohort studies (>1000 participants)

Other sources for safety and dosing

- Belgisch Centrum voor Farmacotherapeutische Informatie (BCFI), Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten (FAGG), European Medicines Agency (EMA), Meyler's Side Effects of Drugs (15th edition),-Folia Pharmacotherapeutica

Some publications will be excluded for practical reasons:

- Publications unavailable in Belgian libraries
- Publications in languages other than Dutch, French, German and English

3.1.2.6 Guidelines

Only guidelines from 2010 onwards are to be selected.
Only guidelines that report levels of evidence/recommendation are to be selected.
Guidelines were selected and agreed upon through discussion with the organising committee, based on relevance for the Belgian situation. Because so little European guidelines are available according to the above criteria, we have allowed a little leniency:

- we have included older NICE guidelines if they report an appraisal of the current literature with a decision not to update, because of lack of new evidence, within the last 5 years.
- NHG guidelines are evolving to a more transparent approach in which levels of evidence and grades of recommendation can be found (see https://www.nhg.org/sites/default/files/content/nhg_org/uploads/handleiding_standaarden_2015.pdf for more information). Therefore we have included NHG guidelines, even though

in the guidelines prior to 2015-2014, this approach has not been applied yet, or has not been adequately reported.

- Because the BAPCOC 2012 guideline does not provide a detailed description of its methodology, we did not have sufficient information to assess this guideline with AGREE. As it is *the* reference guide for antibiotic use in first line in Belgium, we do report its recommendations.

Similarities and discrepancies between guidelines are to be reported.

The literature group will also report whether the guideline was developed together with other stakeholders (other healthcare professionals: pharmacists, nurses,… or patient representatives) and whether these guidelines are also targeting these groups.

In order to make an assessment on the rigour of development of the guidelines, guidelines will be scored according to Agree II score, for the domain "Rigour of development". More information can be found on http://www.agreetrust.org/.

Table 1 gives an overview of the items assessed in this domain according to the Agree II score.

No.	**Description of the item**
7	Systematic methods were used to search for evidence
8	The criteria for selecting the evidence are clearly described
9	The strengths and limitations of the body of evidence are clearly described
10	The methods for formulating the recommendations are clearly described
11	Health benefits, side effects, and risks have been considered in formulating the recommendations.
12	There is an explicit link between the recommendations and the supporting evidence.
13	The guideline has been externally reviewed by experts prior to its publication
14	A procedure for updating the guideline is provided

Table 2. Items assessed by the domain "Rigour of development" in AgreeII score.

Domain scores are calculated by summing up all the scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score for that domain. The domain score "Rigour of development" can be used to assess the process used to gather and synthesize the evidence, the methods to formulate the recommendations, and to update them, though be careful with the interpretation because this scoring is also subjective and the resulting scores can thus be disputable.

In the section about the guidelines, the Domain scores as assessed by the literature group, are given for each guideline.

3.2 Search strategy

3.2.1 Principles of systematic search

Relevant literature was searched in a stepwise approach.

- Firstly, sources that report and discuss data from systematic reviews, meta-analyses and original trials, like Clinical Evidence[1] were consulted. Guidelines were consulted to look up additional relevant references.
- In a second step we have searched for large systematic reviews from reliable EMB-producers (NICE, AHRQ, the Cochrane library) that answer our research questions. One or more systematic reviews were selected as our basic source. From these sources, references of relevant publications were screened manually.
- In a third step, we conducted a systematic search for randomised controlled trials (RCTs), meta-analyses and smaller systematic reviews that were published after the search date of our selected systematic reviews.
- To answer the question about quinolone safety, we conducted a search for systematic reviews that included RCTs and/or observational studies, followed by a systematic search for RCTs and observational studies published after the search date of the selected SR.

The following electronic databases have been searched

- Medline (PubMed)
- Cochrane Library

A number of other sources were consulted additionally: relevant publications, indices of magazines available in the library of vzw Farmaka asbl: mainly independent magazines that are a member of the International Society of Drug Bulletins (ISDB) such as Geneesmiddelenbulletin (The Netherlands), Folia Pharmacotherapeutica (Belgium), La Revue Prescrire (France), Drug & Therapeutics Bulletin (UK), Therapeutics Letter (Canada), Geneesmiddelenbrief (Belgium), Arzneimittelbrief (Germany),…

Guidelines were searched through the link “evidence-based guidelines” on the website of vzw Farmaka asbl (www.farmaka.be) and on the website of CEBAM (www.cebam.be). These contain links to the national and most frequently consulted international guidelines, as well as links to ‘guideline search engines’, like National Guideline Clearinghouse and G-I-N.

3.2.2 Search strategy details

As a source document to search for relevant publications, the following systematic reviews or meta-analyses were selected.

Acute sore throat

1. Spinks A, Glasziou Paul P, Del Mar Chris B. Antibiotics for sore throat. Cochrane Database of Systematic Reviews [Internet]. 2013; (11).
2. van Driel Mieke L, De Sutter An IM, Keber N, et al. Different antibiotic treatments for group A streptococcal pharyngitis. Cochrane Database of Systematic Reviews [Internet]. 2013; (4).
3. Altamimi S, Khalil A, Khalaiwi Khalid A, et al. Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children. Cochrane Database of Systematic Reviews [Internet]. 2012; (8).
4. Ng Gareth JY, Tan S, Vu Anh N, et al. Antibiotics for preventing recurrent sore throat. Cochrane Database of Systematic Reviews [Internet]. 2015; (7).

Acute otitis media

5. Venekamp Roderick P, Sanders Sharon L, Glasziou Paul P, et al. Antibiotics for acute otitis media in children. Cochrane Database of Systematic Reviews [Internet]. 2015; (6).
6. Shekelle PG, Takata GS, Newberry SJ, et al. Management of Acute Otitis Media: Update. Evidence Report/Technology Assessment No. 198. 2010.
7. Kozyrskyj Anita L, Klassen Terry P, Moffatt M, et al. Short-course antibiotics for acute otitis media. Cochrane Database of Systematic Reviews [Internet]. 2010; (9).
8. Thanaviratananich S, Laopaiboon M, Vatanasapt P. Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media. Cochrane Database of Systematic Reviews [Internet]. 2013; (12).

Acute rhinosinusitis

9. Kenealy T, Arroll B. Antibiotics for the common cold and acute purulent rhinitis. Cochrane Database of Systematic Reviews [Internet]. 2013; (6).
10. Smith MJ. Evidence for the diagnosis and treatment of acute uncomplicated sinusitis in children: a systematic review. Pediatrics 2013;132:e284-96, Jul. DOI: 10.1542/peds.2013-1072.

Acute bronchitis

11. Smith Susan M, Fahey T, Smucny J, et al. Antibiotics for acute bronchitis. Cochrane Database of Systematic Reviews [Internet]. 2014; (3).
12. Wark P. Bronchitis (acute). BMJ Clin Evid 2015;2015.
13. Laopaiboon M, Panpanich R, Swa Mya K. Azithromycin for acute lower respiratory tract infections. Cochrane Database of Systematic Reviews [Internet]. 2015; (3).

Acute bronchiolitis

14. National Collaborating Centre for Women's and Children's Health. Bronchiolitis: diagnosis and management of bronchiolitis in children. 2015.
15. Farley R, Spurling Geoffrey KP, Eriksson L, et al. Antibiotics for bronchiolitis in children under two years of age. Cochrane Database of Systematic Reviews [Internet]. 2014; (10).

Community acquired pneumonia
16. Lassi Zohra S, Kumar R, Das Jai K, et al. Antibiotic therapy versus no antibiotic therapy for children aged two to 59 months with WHO-defined non-severe pneumonia and wheeze. Cochrane Database of Systematic Reviews [Internet]. 2014; (5).
17. Lodha R, Kabra Sushil K, Pandey Ravindra M. Antibiotics for community-acquired pneumonia in children. Cochrane Database of Systematic Reviews [Internet]. 2013; (6).
18. Gardiner Samantha J, Gavranich John B, Chang Anne B. Antibiotics for community-acquired lower respiratory tract infections secondary to Mycoplasma pneumoniae in children. Cochrane Database of Systematic Reviews [Internet]. 2015; (1).
19. Haider Batool A, Lassi Zohra S, Bhutta Zulfiqar A. Short-course versus long-course antibiotic therapy for non-severe community-acquired pneumonia in children aged 2 months to 59 months. Cochrane Database of Systematic Reviews [Internet]. 2008; (2).

Urinary tract infections
20. Fitzgerald A, Mori R, Lakhanpaul M, et al. Antibiotics for treating lower urinary tract infection in children. Cochrane Database of Systematic Reviews [Internet]. 2012; (8).
21. Strohmeier Y, Hodson Elisabeth M, Willis Narelle S, et al. Antibiotics for acute pyelonephritis in children. Cochrane Database of Systematic Reviews [Internet]. 2014; (7).
22. Williams G, Craig Jonathan C. Long-term antibiotics for preventing recurrent urinary tract infection in children. Cochrane Database of Systematic Reviews [Internet]. 2011; (3).
23. Larcombe J. Urinary tract infection in children: recurrent infections. BMJ Clin Evid 2015;2015.

Acute gastro-enteritis
24. Christopher Prince RH, David Kirubah V, John Sushil M, et al. Antibiotic therapy for Shigella dysentery. Cochrane Database of Systematic Reviews [Internet]. 2010; (8).
25. National Collaborating Centre for Women's and Children's Health. Diarrhoea and vomiting caused by gastroenteritis - diagnosis, assessment and management in children younger than 5 years. 2009.
26. Allen Stephen J, Martinez Elizabeth G, Gregorio Germana V, et al. Probiotics for treating acute infectious diarrhoea. Cochrane Database of Systematic Reviews [Internet]. 2010; (11).
28. Johnston Bradley C, Goldenberg Joshua Z, Vandvik Per O, et al. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. Cochrane Database of Systematic Reviews [Internet]. 2011; (11).

Impetigo
29. Koning S, van der Sande R, Verhagen Arianne P, et al. Interventions for impetigo. Cochrane Database of Systematic Reviews [Internet]. 2012; (1).
Cellulitis and erysipelas
30. Morris AD. Cellulitis and erysipelas. BMJ Clin Evid 2008;2008.
31. Kilburn Sally A, Featherstone P, Higgins B, et al. Interventions for cellulitis and erysipelas. Cochrane Database of Systematic Reviews [Internet]. 2010; (6).

Conjunctivitis
32. Sheikh A, Hurwitz B, van Schayck Constant P, et al. Antibiotics versus placebo for acute bacterial conjunctivitis. Cochrane Database of Systematic Reviews [Internet]. 2012; (9).

33. Epling J. Bacterial conjunctivitis. BMJ Clin Evid 2012;2012.

Quinolones

34. Adefurin 2011(301) “Ciprofloxacin safety in paediatrics; a systematic review”

A search strategy was developed in Pubmed to find relevant RCTs that appeared after the search date of above publications (http://www.ncbi.nlm.nih.gov/pubmed/).
In some cases, when the selected systematic reviews were not sufficient (e.g. no search for all drugs), an additional search was conducted for RCTs that appeared before the search date of the selected systematic review.

The details of the search strategy can be found in appendix I

3.3 Selection procedure

Selection of relevant references was conducted by two researchers independently. Differences of opinion were resolved through discussion. A first selection of references was done based on title and abstract. When title and abstract were insufficient to reach a decision, the full article was read to decide on inclusion or exclusion.

In– and exclusion criteria of the different types of studies are found in chapter 3.1.2 with relevant populations, interventions, endpoints and study criteria.

3.4 Assessing the quality of available evidence

To evaluate the quality of the available evidence, the GRADE system was used. In other systems that use 'levels of evidence', a meta-analysis is often regarded as the highest level of evidence. In the GRADE system, however, only the quality of the original studies is assessed. Whether the results of original studies were pooled in a meta-analysis is of no influence to the quality of the evidence.
The GRADE-system is outcome-centric. This means that quality of evidence is assessed for each endpoint, across studies.

The GRADE system[2,3,4] assesses the following items:

Study design		+ 4	RCT
		+ 2	Observational
		+ 1	Expert opinion
Study quality		- 1	Serious limitation to study quality
		- 2	Very serious limitation to study quality
Consistency		- 1	Important inconsistency
Directness		- 1	Some uncertainty about directness
		- 2	Major uncertainty about directness
Imprecision		- 1	Imprecise or sparse data
Publication bias		- 1	High probability of publication bias
For observational studies	Evidence of association	+ 1	Strong evidence of association (RR of >2 or <0.5)
		+ 2	Very strong evidence of association (RR of >5 or <0.2)
	Dose response gradient	+ 1	Evidence of a dose response gradient (+1)
	Confounders	+ 1	All plausible confounders would have reduced the effect
SUM		4	HIGH quality of evidence
		3	MODERATE quality of evidence
		2	LOW quality of evidence
		1	VERY LOW quality of evidence

Table 3. Items assessed by the GRADE system

In this literature review the criteria 'publication bias' has not been assessed. The GRADE system has only been used in this literature review to assess RCT's, so the criteria specifically intended for observational studies (see table above) has not been assessed. This adapted version of GRADE therefore evaluates the following criteria:

Study design	+ 4	RCT
Study quality	- 1	Serious limitation to study quality
	- 2	Very serious limitation to study quality
Consistency	- 1	Important inconsistency
Directness	- 1	Some uncertainty about directness
	- 2	Major uncertainty about directness
Imprecision	- 1	Imprecise or sparse data
SUM	4	HIGH quality of evidence
	3	MODERATE quality of evidence
	2	LOW quality of evidence
	1	VERY LOW quality of evidence

Table 4 GRADE system adapted by literature group

In assessing the different criteria, we have applied the following rules:

Study design

In this literature review RCT's and observational studies are included but GRADE was only applied to the RCT's.

Study quality

To assess the methodological quality of RCT's, we considered the following criteria:

- **Randomization**: If the method of generating the randomization sequence was described, was it adequate (table of random numbers, computer-generated, coin tossing, etc.) or inadequate (alternating, date of birth, hospital number, etc.)?
- **Allocation concealment:** If the method of allocation was described, was it adequately concealed (central allocation, …) or inadequate (open schedule, unsealed envelopes, etc.)?
- **Blinding**: Who was blinded? Participants/personnel/assessors. If the method of blinding was described, was it adequate (identical placebo, active placebo, etc.) or inadequate (comparison of tablet vs injection with no double dummy)?
- **Missing outcome data:** Follow-up, description of exclusions and drop-outs, ITT
- **Selective outcome reporting**

If a meta-analysis or a systematic review is used, quality of included studies was assessed. It is not the quality of the meta-analysis or systematic review that is considered in GRADE assessment, but only the quality of RCTs that were included in the meta-analysis/systematic review.

Application in GRADE:
Points were deducted if one of the above criteria was considered to generate a high risk of bias for a specific endpoint.
For example:

- Not blinding participants will not decrease validity of the results when considering the endpoint 'mortality', but will decrease validity when considering a subjective endpoint such as pain, so for the endpoint pain, one point will be deducted.
- A low follow-up when no ITT analysis is done, will increase risk of bias, so one point will be deducted in this case.

Consistency

Good "consistency" means that several studies have a comparable or consistent result. If only one study is available, consistency cannot be judged. This will be mentioned in the synthesis report as "NA" (not applicable).

Consistency is judged by the literature group and the reading committee based on the total of available studies, whilst taking into account

- Statistical significance
- Direction of the effect if no statistical significance is reached.
- For meta-analyses: Statistical heterogeneity.

Directness

Directness addresses the extent in which we can generalise the data from a study to the real population (external validity). If the study population, the studied intervention and the control group or studied endpoint are not relevant, points can be deducted here. When indirect comparisons are made, a point is also deducted.

Imprecision

A point is deducted for imprecision if the 95%-confidence interval crosses both the point of appreciable harm AND the point of appreciable benefit (e.g. RR 95%CI ≤0.5 to ≥1.5).

Application of GRADE when there are many studies for 1 endpoint:

Points are only deducted if the methodological problems have an important impact on the result. If 1 smaller study of poor quality confirms the results of 2 large good quality studies, no points are deducted.

More information on the GRADE Working Group website: http://www.gradeworkinggroup.org

3.5 Synopsis of study results

The complete report contains per research question

- (Comprehensive) summary of selected guidelines
- Evidence tables (English) of systematic reviews or RCT's on which the answers to the study questions are based
- A short synopsis, consisting of a summary table and a text, with a quality assessment using an adjusted version of the GRADE system (English)

The synopsis report contains per research question

- (Brief) summary of selected guidelines
- A short synopsis, consisting of a summary table and a text, with a quality assessment using an adjusted version of the GRADE system.

The conclusions have been discussed and adjusted through discussions between the authors of the literature search and the reading committee of the literature group.

1. Clinical Evidence. A compendium of the best available evidence for effective health care. Website: http://clinicalevidence.bmj.com
2. GRADE working group. http://www.gradeworkinggroup.org
3. GRADE working group. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490.
4. Guyatt G, Oxman A, Kunz R et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6

4 Critical reflections of the reading committee and the literature group

A number of general remarks can be made on the studies selected for this review of the literature.

Literature in general
Regarding the studies in general, a number of them are quite old, dating from the fifties or sixties. This has an impact on the conclusions that can be drawn from those trials for a number or reasons. They were conducted in a different clinical context, where sometimes consequences from untreated infections could be much worse. Also, the resistance problematic was different back then. In part due to resistance, the microbiology has shifted since; some pathogens that were very common then are now less so, or others have arisen. For some pathologies, diagnostic criteria have shifted in the course of time.
Studies on 100% child populations tend to be older as well. Some of the very old trials pre-date the declaration of Helsinki of 1964[1], and awareness of bioethics and the necessity to strongly regulate medical trials has grown a lot since. Trials with children are stringently evaluated by ethics committees these days, which might not have been the case back then.

We reported many meta-analyses. Although a meta-analysis allows for a more robust point estimate than an individual RCT, one should be cautious when interpreting the results. Results from clinically heterogenous studies are often combined. RCTs employing different diagnostic criteria (e.g. clinical or microbiological diagnosis), different definitions of outcomes (e.g. “clinical cure”), including different populations (e.g. adults and children), and using different interventions (grouping of many different antibiotics), as well as RCTs of differing methodological quality, are sometimes pooled. It can be misleading to generalize these pooled results to the entire population.

Regarding population, a lot of trials have a mixed population consisting of both adults and children, and there are not always subanalyses according to age. Most of the time, it was not clear what proportion of subjects were children.

This is however less of a problem for certain topics such as AOM or sometimes not at all, such as in the case of bronchiolitis, since only children can have the disease.
Also, another remark concerning the population is that the way they are selected does not always reflect clinical practice. For example, if a study on sinusitis only selected patients with complaints for more than 10 days, this will be a different population than the one seen in a general practice, in this case a population where antibiotics might be more effective.
A last remark concerning the population is that often patients with a high risk profile such as immunocompromised patients, patients with comorbidities, etc. are excluded from the study population. However it is often recommended to give those patients antibiotics, even though antibiotics are not recommended in the rest of the population. This consensus conference did not focus on high-risk group so we did not report on those populations.

[1] Declaration of Helsinki: http://www.wma.net/en/30publications/10policies/b3/index.html

Regarding the interventions used in those studies, two remarks can be made. First, when antibiotics are compared, often a new or lesser widely used antibiotic is compared to a more common one. There is a lack of studies comparing well-known antibiotics with each other. Secondly, sometimes the dosage of these antibiotics can be quite low. This is especially the case for studies with amoxicillin[2].

Regarding the outcomes used, a lot of the studies do not report adverse events, or do not report them well. This is a problem when evaluating benefits and risks of a specific intervention.

Another problem with outcomes is that the primary outcome is often being symptom-free or cured after a number of days of treatment, but it is not always clearly established what the right amount of time would be to evaluate the effectivity of a treatment. This sometimes leads to similar studies having different endpoints, one looking at the amount of people cured by day 7, another looking at the amount of people cured by day 10. Sometimes those studies are pooled together in meta-analyses, where different antibiotics are compared to each other.

Bacterial eradication is mentioned in many studies but not reported in this review of the literature, since we focused on clinical endpoints.

We reported some trials that compared a standard dosing scheme of three daily administrations of amoxicillin with a twice or even once daily regimen. Although the clinical outcomes of these different dosing schemes seem comparable, we do have some concerns regarding the long-term impact of once or twice daily dosing on bacterial resistance patterns. We do not have data on this.

International context
A couple of remarks can also be made on differences between countries. First of all, not all existing antibiotics are on the market in Belgium, and we had to exclude a number of studies due to this. Secondly, resistance patterns can differ between countries, as well as recommendations and prescribing habits.

Guidelines
There is also difference in general trends between American guidelines and European ones. While not an absolute rule, often American guidelines seem to put a lot of emphasis on the diagnosis and recommend antibiotics when a bacterial pathogen is confirmed. European guidelines are in general more reluctant to push diagnostic tests and antibiotics. An article by Chiappini et al. comparing guidelines regarding pharyngitis highlights some of these trends {Chiappini, 2011 #368}.
Not all guidelines pay the same amount of attention to non-antibiotic treatments.
Several guidelines use grades of recommendations that must be deduced from their phrasing, which makes interpretation less straightforward.
Some guidelines recommend alternative choices of antibiotics in case of penicillin allergy. Often these choices are not ideal in terms of resistance patterns, adverse effects, or effectivity. There is a problem with overdiagnosis of penicillin allergy by relying on word of mouth of the patient or the parent. This could possibly lead to overuse of these alternative choices.

[2] For the reference dosages in Belgium, see BAPCOC guidelines. The kinderformularium (https://www.kinderformularium.nl/) can also be interesting but is Dutch, not Belgian.

Sore throat

Specifically for the chapter on sore throat, one can make the following remarks:

First, a number of studies date from the fifties, where the risk of severe complications (such as acute rheumatic fever) was much higher.

A lot of studies were open label, and were of low quality.

There are both adults and children in the study population and there are not always subanalyses, or sometimes only for one outcome.

Sore throat is a symptom of many different pathologies. In Belgium, it is common (and recommended) in first line to treat sore throat (whether with antibiotics or not) according to the severity of the illness without microbiologically confirming the presence, type, or absence of bacterial infection. Selection of the patients in trials is not always done in the same way. Some RCTs include patients based on clinical symptoms; some only include GABHS positive patients. Although this allows for a more straightforward comparison of effectivity of different antibiotics, it does not reflect the clinical practice in Belgium.

Acute otitis media

Populations selected for acute otitis media in the studies all consists of children, but the upper age limit differs (12, 14 or 16 are taken as cut-offs).

The pathogens causing acute otitis media have shifted according to Shekelle 2010{Shekelle, 2010 #81}: "*Since PCV7's introduction, AOM microbiology has shifted significantly, with Streptococcus pneumoniae becoming less prevalent and Haemophilus influenzae (HF) increasing in importance."*

It is unclear whether the clinical course of an acute otitis media is different than it used to be, and more importantly, if we can apply conclusion about antibiotics' effectiveness based on studies from decades ago, before the microbiological shift.

Furthermore, recent studies have employed more stringent diagnostic criteria than older ones.

Acute rhinosinusitis

All studies selected were on children only. Some meta-analyses pooled studies with different outcomes (cure at 10 days and cure at 14 days) and different antibiotics, and thus there is high heterogeneity.

Acute Bronchitis / cough

Certain studies operate under the following definition for acute bronchitis: "*Acute bronchitis is a clinical diagnosis for an acute cough {Smith Susan, 2014 #203}*", whereas acute cough can be due to a number of other causes. The studies and meta-analyses selected were done on both adults and children and didn't always provide sub-analyses for children. In one case the intervention in a pediatric study was different from the interventions in other studies (no placebo in the pediatric study).

Bronchiolitis

Due to the nature of the disease studies can only include children. There is a slight difference in the definition of bronchiolitis between America and Europe, so the definition has always been reported in the evidence tables. Interventions pooled consist of both oral and intravenous antibiotics.

Community acquired pneumonia

This is one of the larger chapters. Studies tend to be about 15-20 years old. On a number of outcomes (shorter versus longer duration of treatment, different dose regiments) the upper age limit is 59 months, so there is a lack of information on those comparisons in older children and adolescents. The diagnosis of pneumonia is diagnosed clinically in some trials, while others required radiological confirmation. Some trials included only non-severe CAP (as defined by WHO), others only severe CAP. There is some concern that the pooled results of these trials are not applicable to all patients.

UTI

A large majority of the patients enrolled in the studies is female, due to a higher prevalence of UTIs in girls and women. Age range is quite different across the studies, sometimes there is a cut-off at 18 years, sometimes 12 or 7. Causes for infection or for recurring UTIs can be vastly different between a 6 year old child and a sexually active teenager.
The population is younger for studies on VUR.

Acute Gastro-enteritis

A lot of the studies included in the meta-analyses had very small sample sizes and were not reported here. Ages of the participants tend to be rather young (with upper limits at 13 years). This was especially the case in studies on probiotics, where participants were even younger (sometimes ≤48 months).

Impetigo

Little evidence was found; only one guideline gave recommendations on the treatment of impetigo in children. Studies are older (one from the 1970's, several from the 1980's) and do not always give specifics about the age of the participants or whether they were adults or children.

Cellulitis

Here as well little evidence was found, in total only 155 patients are reported on.

5 Acute sore throat (pharyngitis/tonsillitis)

5.1 Guidelines

5.1.1 Method of reporting of the recommendations and notes

Formal recommendations, that are supplied with grades of recommendations or levels of evidence, are written in **bold**.

Text taken directly from the guidelines, that is not graded but provides supplemental information or a clarification of the formal recommendations, is written in *italics*.

Comments by the bibliography group are written in plain text.

5.1.2 General information on selected guidelines

5.1.2.1 Selected guidelines

The selected guidelines and their abbreviations as used in this report can be found in Table 5.

Abbreviation	Guideline
BAPCOC 2012{BAPCOC, 2012 #3}	BAPCOC - Belgische gids voor anti-infectieuze behandeling in de ambulante praktijk; editie 2012/ Guide Belge des traitements anti-infectieux en pratique ambulatoire; édition 2012
IDSA strep throat 2012{Shulman, 2012 #17}	Shulman S., et al.: Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America
NHG sore throat 2015{NHG - Dutch College of General Practitioners, 2015 #16}	NHG- Dutch College of General Practitioners: Acute keelpijn (M11)
NICE respiratory tract 2008{National Institute for Health and Clinical Excellence, 2008 #10}	National Institute for Health and Clinical Excellence: Respiratory tract infections – antibiotic prescribing. 2008.
SIGN sore throat 2010{SIGN - Scottish Intercollegiate Guidelines Network, 2010 #18}	SIGN – Scottish Intercollegiate Guidelines Network: Management of sore throat and indications for tonsillectomy (SIGN CPG 117) - 2010

Table 5: Selected guidelines and their abbreviations as used in this report.

5.1.2.2 Grades of recommendation

Grades of recommendation and levels of evidence as defined in each guideline, can be found in Table 6 - Table 10.

BAPCOC 2012		
Grades of recommendation:	1	Strong recommendation
	2	Weak recommendation
Levels of evidence	A	High degree of evidence; RCTs without limitations or strong, compelling evidence from observational studies
	B	Medium level of evidence; RCTs with limitations or strong evidence from observational studies
	C	(very) low degree of evidence; observational studies or case studies

Table 6: Grades of recommendation and Level of evidence of the BAPCOC 2012 guideline.

IDSA strep throat 2012		
Grades of recommendation:	Strong	Desirable effects clearly outweigh undesirable effects, or vice versa
	Weak	Desirable effects closely balanced with undesirable effects *(when paired with high or moderate quality evidence)* OR Uncertainty in the estimates of desirable effects, harms, and burden; desirable effects, harms, and burden may be closely balanced *(when paired with low quality evidence)* OR Major uncertainty in the estimates of desirable effects, harms, and burden; desirable effects may or may not be balanced with undesirable effects *(when paired with verly low quality evidence)*
Levels of evidence	High	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies
	Moderate	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from unbiased observational studies
	Low	Evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence
	Very Low	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence

Table 7: Grades of recommendation and Level of evidence of IDSA strep throat 2012 guideline.

The NHG guidelines do not explicitly attribute grades of recommendation or levels of evidence to their recommendations. They do perform a GRADE- evaluation of the included evidence on which the recommendations are based. They also express the grade of recommendation in the wording of the recommendation itself (i.e. strongly or weakly recommended). (see https://www.nhg.org/sites/default/files/content/nhg_org/uploads/handleiding_standaarden_2015.pdf)

NHG sore throat 2015		
Grades of recommendation:	Strong; Expressed in the wording of the recommendation	/
	Weak; Expressed in the wording of the recommendation	This often means there is not enough evidence to recommend a specific option and that medical professionals, together with their patient, make a choice from different options.
Levels of evidence	High	The true effect lies close to the estimated effect
	Moderate	The true effect probably lies close to the estimated effect, but the possibility exists that it differs substantially from it.
	Low	The true effect can differ substantially from the estimated effect.
	Very Low	The true effect probably differs substantially from the estimated effect.

Table 8: Grades of recommendation and Level of evidence of NHG sore throat 2015 guideline.

The NICE respiratory tract infections 2008 guideline did not attribute grades of recommendation or levels of evidence to its recommendations. However, they did assign a level to the evidence for the purpose of developing the recommendations.

NICE respiratory tract 2008		
Levels of evidence	1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
	1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
	1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
	2++	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
	2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability

		that the relationship is causal
	2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
	3	Non-analytic studies, eg case reports, case series
	4	Expert opinion

Table 9: Grades of recommendation and Level of evidence of NICE respiratory tract 2008 guideline.

SIGN sore throat 2010		
Grades of recommendation: *"Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation."*	A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
	B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
	C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
	D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
Levels of evidence	1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
	1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
	1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
	2++	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
	2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
	2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
	3	Non-analytic studies, eg case reports, case series

	4	Expert opinion
Good practice points	✔	Recommended best practice based on the clinical experience of the guideline development group

Table 10: Grades of recommendation and Level of evidence of SIGN sore throat 2010 guideline.

5.1.2.3 Agree II score

Information about the Agree II score can be found in the section "Methodology".

A summary of the assessment by the literature group of the individual items of the domain score for each guideline can be found in Table 11. The total domain score is also reported in this table.

Rigour of development item	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Total**	**Domain score**
BAPCOC 2012{BAPCOC, 2012 #3}	2	2	5	2	4	3	5	1	**24**	**43%**
IDSA strep throat 2012{Shulman, 2012 #17}	4	4	5	3	5	6	4	6	**37**	**66%**
NHG sore throat 2015{NHG - Dutch College of General Practitioners, 2015 #16}	7	3	5	2	6	7	6	2	**38**	**68%**
NICE respiratory tract 2008{National Institute for Health and Clinical Excellence, 2008 #10}	7	7	7	6	5	7	5	5	**49**	**88%**
SIGN sore throat 2010{SIGN - Scottish Intercollegiate Guidelines Network, 2010 #18}	7	6	6	2	7	7	5	6	**46**	**82%**

Table 11: AGREE score of selected guidelines on item "Rigour of development", see methodology for a description of the items.

5.1.2.4 Included populations – interventions – main outcomes

In Table 12 to Table 16, the populations, interventions and main outcomes considered in the selected guidelines are represented.

BAPCOC 2012	
Population	Ambulant care patients
Interventions	Antibiotic treatment (indication, choice, dose, duration)
Outcomes	Not specified

Table 12: Included population, intervention and main outcomes of BAPCOC 2012 guideline.

IDSA strep throat 2012	
Population	Adult and pediatric patients with group A streptococcal pharyngitis
Interventions	Diagnosis, treatment (antibiotics, adjunctive therapy)

Outcomes	Not specified

Table 13: Included population, intervention and main outcomes of IDSA strep throat 2012 guideline

NHG sore throat 2015	
Population	Patient with sore throat <14 days of a presumed infective cause
Interventions	Diagnosis, treatment
Outcomes	Not specified

Table 14: Included population, intervention and main outcomes of the NHG sore throat 2015 guideline

NICE respiratory tract 2008	
Population	Adults and children (3 months and older) in whom immediate antibiotic prescribing is not indicated
Interventions	Assessment, antibiotic management strategies (delayed treatment, no treatment), advice
Outcomes	• the presence, duration and severity of symptoms such as fever, pain and malaise • the risk of complications from not prescribing antibiotics • adverse events from prescribing antibiotics (for example, diarrhoea, vomiting, rashes, abdominal pain) • the level of antibiotic prescribing, including antibiotic prescriptions consumed or collected • resource use (including reconsultation rates and rates of referral to secondary care) • patient satisfaction and health-related quality of life.

Table 15: Included population, intervention and main outcomes of the NICE respiratory tract 2008 guideline

SIGN sore throat 2010	
Population	Children and adults with sore throat
Interventions	Diagnosis, pain management, antibiotic use, indications for surgical management and postoperative care
Outcomes	Not specified

Table 16: Included population, intervention and main outcomes of SIGN sore throat 2010 guideline.

5.1.2.5 Members of development group – target audience

Members of the development group that produced the guidelines, and the target audience for whom the guidelines are intended, can be found in Table 17 to Table 21.

BAPCOC 2012	
Development group	General practitioners, microbiologists, pneumologists, infectiologists, paediatricians, pharmacists
Target audience	Physicians working in ambulant care

Table 17: Members of the development group and target audience of the BAPCOC 2012 guideline.

IDSA strep throat 2012	
Development group	Internists and pediatricians, including adult and pediatric infectious disease specialists and a general pediatrician.
Target audience	healthcare providers who care for adult and pediatric patients with group A streptococcal pharyngitis

Table 18: Members of the development group and target audience of the IDSA strep throat 2012 guideline.

NHG sore throat 2015	
Development group	General practitioners
Target audience	General practitioners

Table 19: Members of the development group and target audience of the NHG sore throat 2015 guideline.

NICE respiratory tract 2008	
Development group	General practitioners, pediatricians, pharmacists, microbiologists, patient representative, consultant in respiratory medicine
Target audience	Primary care and community settings. These will include general practices, community pharmacies, NHS walk-in centres and primary medical and nursing care provided in emergency departments.

Table 20: Members of the development group and target audience of the NICE respiratory tract 2008 guideline.

SIGN sore throat 2010	
Development group	Specialists (ENT, paediatricians, surgeons, anaesthetist), general practitioners, nurses,pharmacists, lay representatives
Target audience	General practitioners, nurses, paediatricians, pharmacists, otolaryngologists, anaesthetists, public health specialists, patients with recurrent sore throat and their carers

Table 21: Members of the development group and target audience of the SIGN sore throat 2010 guideline.

5.1.3 Definition

5.1.3.1 Summary

Three out of five guidelines define the term “sore throat”. It encompasses acute pharyngitis in all cases and acute tonsillitis twice. The IDSA strep throat 2012 limits its definition to microbiologically confirmed Group A streptococcal pharyngitis.

5.1.3.2 BAPCOC 2012

The guideline doesn’t define this term.

5.1.3.3 IDSA strep throat 2012

The IDSA strep throat 2012 guideline concerns the treatment of microbiologically confirmed Group A streptococcal (GAS) pharyngitis.

5.1.3.4 NHG sore throat 2015

Pharyngitis: an infection of the throat.

Tonsillitis: an infection of the mucosa and parenchyma of the tonsils. Tonsillitis can occur as an isolated infection or as part of a pharyngitis. The distinction between the two is not always clear, both clinically and in the literature. It is often referred to as an acute pharyngotonsillitis.

5.1.3.5 NICE respiratory tract 2008

The guideline doesn't define this term.

5.1.3.6 SIGN sore throat 2010

Acute pharyngitis, tonsillitis, or acute exudative tonsillitis may all cause sore throat. For the purpose of non-surgical management, these are considered together under the term 'sore throat'.

5.1.4 Indications for antibiotic treatment

5.1.4.1 Summary

Four out of five guidelines mention explicitly that antibiotics are not systematically indicated (strong recommendation and high level of evidence where mentioned).

Severely ill patients or those with a high risk of complications due to comorbidity can be eligible for antibiotic therapy. For NICE respiratory tract 2008 exudate can be a factor to opt for antibiotics, while for SIGN sore throat 2010, suppurative complications are not a specific indication.

The SIGN sore throat 2010 guideline mentions the use of antibiotics to prevent an outbreak of GABHS in closed communities, not in the general public. BAPCOC 2012 also states that antibiotics can be indicated for a streptococcal outbreak in a closed community.

5.1.4.2 BAPCOC 2012

In acute sore throat, antibiotics are generally not indicated (Grade 1A) except in:

- **patients at risk- malignancy, a history of acute rheumatic fever, immunological deficiency; or**
- **severely ill patients - throat infection with severe malaise, pronounced sore throat and difficulty swallowing, and severe limitations in daily functioning; or**
- **a streptococcal outbreak in a closed community**

5.1.4.3 IDSA strep throat 2012

Patients with acute GAS pharyngitis should be treated with an appropriate antibiotic at an appropriate dose for a duration likely to eradicate the organism from the pharynx […]. (continued below, in "choice of antibiotic")

5.1.4.4 NHG sore throat 2015

Antibiotics are indicated (unless there is reason to refer) in:

• patients with a suspected peritonsillar infiltration;
• cervical lymphadenitis;
• pharyngotonsillitis in a severely ill patient;
• pharyngotonsillitis in a patient at an increased risk of complications (see *) depending on severity of immunological dysfunction, clinical appearance and the course of previous infections.

**Check whether there is an increased risk of complications such as in:*

use of oral corticosteroids, DMARDs, biologicals, antithyroid drugs, phenytoin, neuroleptics; chemo- or radiotherapy, malignancy, history of acute rheumatic fever, diabetes mellitus, immunological disorders, HIV infection with reduced number of T cells, sickle cell disease, severe alcohol abuse, iv drug use, functional asplenia.

5.1.4.5 NICE respiratory tract 2008

A no antibiotic prescribing strategy or a delayed antibiotic prescribing strategy should be agreed for patients with the following conditions:

- **acute sore throat/acute pharyngitis/acute tonsillitis**

Depending on clinical assessment of severity, patients in the following subgroups can also be considered for an immediate antibiotic prescribing strategy (in addition to a no antibiotic or a delayed antibiotic prescribing strategy):

- **acute sore throat/acute pharyngitis/acute tonsillitis when three or more Centor criteria are present.**

Centor criteria are: presence of tonsillar exudate, tender anterior cervical lymphadenopathy or lymphadenitis, history of fever and an absence of cough

An immediate antibiotic prescription and/or further appropriate investigation and management should only be offered to patients (both adults and children) in the following situations:

- **if the patient is systemically very unwell**
- **if the patient has symptoms and signs suggestive of serious illness and/or complications (particularly pneumonia, mastoiditis, peritonsillar abscess, peritonsillar cellulitis, intraorbital and intracranial complications)**
- **if the patient is at high risk of serious complications because of pre-existing comorbidity. This includes patients with significant heart, lung, renal, liver or neuromuscular disease, immunosuppression, cystic fibrosis, and young children who were born prematurely**

For these patients, the no antibiotic prescribing strategy and the delayed antibiotic prescribing strategy should not be considered.

5.1.4.6 SIGN sore throat 2010

Antibiotics should not be used to secure symptomatic relief in sore throat. (A)

In view of increases in healthcare-acquired infections and antibiotic resistance in the community, unnecessary prescribing of antibiotics for minor self-limiting illness should be avoided. (✔)

In severe cases, where the practitioner is concerned about the clinical condition of the patient, antibiotics should not be withheld. (Penicillin V 500 mg four times daily for 10 days is the dosage used in the majority of studies. A macrolide can be considered as an alternative first line treatment, in line with local guidance.) (✔)

In certain unusual circumstances, such as epidemics, more widespread prescription of antibiotics may be recommended and the relevant public health guidance should be followed. (✔)

Sore throat should not be treated with antibiotics specifically to prevent the development of rheumatic fever and acute glomerulonephritis. (C)

The prevention of suppurative complications is not a specific indication for antibiotic therapy in sore throat. (✔)

Antibiotics may prevent cross infection with GABHS in closed institutions (such as barracks, boarding schools) but should not be used routinely to prevent cross infection in the general community. (C)

5.1.5 Choice of antibiotic, dose and duration

5.1.5.1 Summary

If antibiotics need to be prescribed, all guidelines except NICE respiratory tract 2008 (which doesn't mention any) recommend a penicillin-type antibiotic; those recommendations are strong, with a high level of evidence in most cases. Two guidelines out of those four explicitly mention phenoxymethylpenicillin as first choice.
For non-IgE mediated allergies two guidelines recommend a first generation cephalosporin.
For IgE-mediated allergies, clarithromycin is recommended by two guidelines and azithromycin by three as alternative choice. Recommendation strength is weak, levels of evidence are moderate.
One guideline makes a difference between antibiotics for a pharyngotonsillitis and for suspected peritonsillar infiltration, recommending amoxicillin with clavulanate potassium in case of the latter.

5.1.5.2 BAPCOC 2012

First choice: (GRADE 1B)

- phenoxymethylpenicillin
Child: 50 000 IU / kg per day in 3 to 4 doses for 7d

Alternative in case of unavailability of phenoxymethylpenicillin or non-IgE-mediated penicillin allergy (GRADE 1C)
- cefadroxil
Child: 30 mg / kg per day in 2 to 3 doses for 7d

Alternative in case of IgE-mediated penicillin allergy (GRADE 1C)
- clarithromycin
Child: 15 mg / kg per day in 2 doses for 7d
- azithromycin
Child: 10 mg / kg per day in one dose for 3d; or the first day 10 mg / kg in 1 dose, then 5 mg / kg per day in one dose for 4d

5.1.5.3 IDSA strep throat 2012

Patients with acute GAS pharyngitis should be treated with an appropriate antibiotic at an appropriate dose for a duration likely to eradicate the organism from the pharynx (usually 10 days). Based on their narrow spectrum of activity, infrequency of adverse reactions, and modest cost, penicillin or amoxicillin is the recommended drug of choice for those non-allergic to these agents (strong, high).

Treatment of GAS pharyngitis in penicillin-allergic individuals should include a first generation cephalosporin (for those not anaphylactically sensitive) for 10 days, clindamycin or clarithromycin for 10 days, or azithromycin for 5 days (strong, moderate).

5.1.5.4 NHG sore throat 2015

pharyngotonsillitis		
Feneticilline or phenoxymethylpenicillin, Seven days	> 10 y 2-10 y <2 y	500 mg 3 times daily 250 mg 3 times daily 125 mg 3 times daily
In case of penicillin allergy: azithromycin, 3 days	> 10 y <10 y	500 mg 1 dose daily 10-20 mg / kg, 1 dose daily, max. 500 mg / day
In case of penicillin allergy and pregnancy or lactation: erythromycin, 7 days		500 mg 4 times daily
In case of suspected peritonsillar infiltration, cervical lymphadenitis or no effect of first antibiotic		
Amoxicillin / clavulanate potassium, 7 days	children	13.3 / 3.3 mg / kg, 3 times daily, max 500/125 mg 3 times daily

In case of penicillin allergy: consult with ENT doctor about antibiotic and need for culture (puncture)

Table 22: Choice of antibiotics in NHG sore throat 2015.

5.1.5.5 NICE respiratory tract 2008

No information found in this guideline.

5.1.5.6 SIGN sore throat 2010

In severe cases, where the practitioner is concerned about the clinical condition of the patient, antibiotics should not be withheld. (Penicillin V 500 mg four times daily for 10 days is the dosage used in the majority of studies. A macrolide can be considered as an alternative first line treatment, in line with local guidance.) (✔)

Ampicillin-based antibiotics, including co-amoxiclav, should not be used for sore throat because these antibiotics may cause a rash when used in the presence of glandular fever. (✔)

5.1.6 Antibiotic profylaxis for recurrent sore throat

5.1.6.1 Summary

Only the SIGN sore throat 2010 made mention of antibiotic profylaxis for recurrent sore throat. It was not recommended.

5.1.6.2 BAPCOC 2012

No information found in this guideline.

5.1.6.3 IDSA strep throat 2012

No information found in this guideline.

5.1.6.4 NHG sore throat 2015

No information found in this guideline.

5.1.6.5 NICE respiratory tract 2008

No information found in this guideline.

5.1.6.6 SIGN sore throat 2010

Antibiotic prophylaxis for recurrent sore throat is not recommended (✔)

5.1.7 Non-antibiotic treatment

5.1.7.1 Summary

Three out of five guidelines give information for treatment aside from antibiotic treatment. Those three guidelines mention pain relief and the use of an analgesic / antipyretic medication. Paracetamol and ibuprofen are mentioned as options by IDSA strep throat 2012 and SIGN sore throat 2010, but the SIGN sore throat guideline does not recommend ibuprofen routinely. Aspirin and corticosteroids are advised against by IDSA sore throat 2012 guideline, Echinacea purpura is advised against by SIGN sore throat 2010.

5.1.7.2 BAPCOC 2012

No information found on other treatment than antibiotics in this guideline.

5.1.7.3 IDSA strep throat 2012

Patients with acute GAS pharyngitis should be treated with an appropriate antibiotic at an appropriate dose for a duration likely to eradicate the organism from the pharynx […]. (continued below, in "choice of antibiotic")

Adjunctive therapy may be useful in the management of GAS pharyngitis.

- **If warranted, use of an analgesic/antipyretic agent such as acetaminophen** (=paracetamol) **or an NSAID for treatment of moderate to severe symptoms or control of high fever associated with GAS pharyngitis should be considered as an adjunct to an appropriate antibiotic (strong, high).**

- **Aspirin should be avoided in children (strong, moderate).**

- **Adjunctive therapy with a corticosteroid is not recommended (weak, moderate).**

5.1.7.4 NHG sore throat 2015

For pain relief, see the NHG guideline Pain.

[The NHG Guideline Pain recommends to provide adequate pain relief at fixed times; paracetamol is recommended as a first step in a dose if 15 mg/kg 4 times daily, ibuprofen (5 mg/kg 4 times a day with a maximum of 30 mg/kg/day for 3 days) is recommended as a possible second step.]

5.1.7.5 NICE respiratory tract 2008

No information found in this guideline.

5.1.7.6 SIGN sore throat 2010

In children with sore throat, an adequate dose of paracetamol should be used as first line treatment for pain relief. (✔)

Ibuprofen can be used as an alternative to paracetamol in children. (A)

Ibuprofen should not be given routinely to children with or at risk of dehydration. (D)

Echinacea purpurea is not recommended for treatment of sore throat. (B)

5.1.8 Referrals

5.1.8.1 Summary

Only two guidelines mention when to refer a patient, consult an internist or further investigate: in case of a (suspected) aggravating comorbidity, a suspected serious illness or possible complication, in case of a severely ill or very unwell patient, and in case of frequent tonsillitis (4 to 6 times a year). The NHG sore throat 2015 guideline provides a choice aid for the physician to help discuss tonsillectomy with the parents of the child.

5.1.8.2 BAPCOC 2012

No information found in this guideline.

5.1.8.3 IDSA strep throat 2015

No information found in this guideline

5.1.8.4 NHG sore throat 2015

Referral is indicated in:

- **impending upper airway obstruction, a (suspected) epiglottis;**
- **suspicion of a peritonsillar abscess or infiltration in a severely ill patient, difficulty swallowing or increased risk of complications* and in case of insufficient improvement or worsening during the treatment;**
- **cervical lymphadenitis: abcedation or a severely ill patient;**
- **severe abnormalities of laboratory investigations: such as agranulocytosis, or leukemia;**
- **frequent episodes of tonsillitis**.**

Consult an internist in case of a history of rheumatic and in severely immunocompromised patients.

**Check whether there is an increased risk of complications such as in:*

use of oral corticosteroids, DMARDs, biologicals, antithyroid drugs, phenytoin, neuroleptics; chemo- or radiotherapy, malignancy, history of acute rheumatic fever, diabetes mellitus, immunological disorders, HIV infection with reduced number of T cells, sickle cell disease, severe alcohol abuse, iv drug use, functional asplenia.

***In a throat infection the general practitioner distinguishes between a tonsillitis or pharyngitis. Often, there will be a mix of both. The distinction has no consequences for the antibiotic policy, but is relevant in case of frequent recurrences, when a tonsillectomy is being considered.*
If a tonsillitis causes problems (absenteeism, serious malaise or trouble sleeping), a tonsillectomy is indicated in children with very frequent recurrent episodes of tonsillitis (seven or more per year or five per year in each of the past two years or three in each of the past three years) and may be considered when there are four to six episodes of tonsillitis each year). Wait in children with less frequent episodes of tonsillitis or with less severe symptoms.

In the conversation with parents about the decision of whether or not to operate on children, the choice aid can be used to discuss the pros and cons of a tonsillectomy, see Table 23.

	Advantage	Disadvantage
Surgery	In the group with very frequent episodes of tonsillitis there are fewer episodes of acute sore throat in the first years after tonsillectomy. The size of the effect is estimated to average 0.6 episodes of sore throat per year less compared with conservative management.	Complications of surgery, such as: • nausea / vomiting • sore throat / pain when swallowing • fever • Temporarily altered voice • altered taste (8% after six months) • speech problems (very rarely) • very rare complications such as luxation of the tooth or mandible, osteomyelitis, mediastinitis and subcutaneous emphysema • delayed bleeding (2 to 4%). In about half of these cases, a revision surgery is necessary. Bleeding may still occur until 2 to 3 weeks after surgery. Any bleeding is cause for re-evaluation by the ENT doctor.
	Absenteeism: an annual average of 2.3 fewer missed school days compared to conservative management.	Higher costs
Conservative management	The child can stay at home, no hospitalization, surgery or anesthesia.	Slightly more episodes of tonsillitis: *See advantage surgery.*
	The quality of life is probably as high as when one chose surgery	. A few days more of absenteeism *see advantage surgery.*
	Many children grow out of it without surgery.	

Table 23: Choice aid in the conversation with parents about tonsillectomy in their child, from the NHG sore throat 2015 guideline

5.1.8.5 NICE respiratory tract 2008

An immediate antibiotic prescription and/or further appropriate investigation and management should only be offered to patients (both adults and children) in the following situations:

- **if the patient is systemically very unwell**
- **if the patient has symptoms and signs suggestive of serious illness and/or complications (particularly pneumonia, mastoiditis, peritonsillar abscess, peritonsillar cellulitis, intraorbital and intracranial complications)**
- **if the patient is at high risk of serious complications because of pre-existing comorbidity. This includes patients with significant heart, lung, renal, liver or neuromuscular disease, immunosuppression, cystic fibrosis, and young children who were born prematurely.**

5.1.8.6 SIGN sore throat 2010

No information found in this guideline.

5.2 Evidence tables and conclusions

5.2.1 Antibiotics versus placebo or no treatment

5.2.1.1 Clinical evidence profile

Meta-analysis: Cochrane Spinks 2013{Spinks, 2013 #72} "Antibiotics for sore throat"

Inclusion criteria: RCT's and quasi-RCT's; patients presenting to primary care facilities with symptoms of sore throat; antibiotics or placebo control
Search strategy: Cochrane Central Register of Controlled Trials (CENTRAL) 2013, Issue 6, part of The Cochrane Library, www.thecochranelibrary.com (accessed 11 July 2013), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register,MEDLINE (May 2011 to July week 1, 2013) and EMBASE (May 2011 to July 2013).There were no language or publication restrictions.
Assessment of quality of included trials: yes
ITT analysis: yes
Other methodological remarks: The systematic review included patients of all ages, both adults and children. A subanalysis with children was reported for one outcome only.

We will report the analysis in which (only) children were included.
Additionally, we will report analyses in a mixed (children and adults) populations. Of these analyses, we will only report the detailed information of the studies that included children.

Table 24

SUBGROUP ANALYSIS: CHILDREN <13 y

Ref	Comparison	N/n	Outcomes	Result (95%CI)

Spinks 2013{Spinks, 2013 #72} Design: SR + MA Search date: (July 2013)	Antibiotics versus placebo	N= 2 n= 61 (Krober 1985, Nelson 1984)	Symptom of fever on day 3	Crude absolute risk: 12/32 vs 10/29+ RR 1.27 (0.76 to 2.13) NS *+note: there were 0 cases in both groups in the Krober 1985 trial*

Table 25

* Characteristics of included studies: see below

MIXED POPULATION: ADULTS AND CHILDREN

RCT's including children are marked with "+": see below for characteristics of these studies

Ref	Comparison	N/n	Outcomes	Result (95%CI)
Spinks 2013{Spinks, 2013 #72} Design: SR + MA Search date: (July 2013)	Antibiotics versus placebo	N= 15 n= 3621 (Chapple 1956+, De Meyere 1992+, Brumfitt 1957, Zwart 2000, Little 1997+, Dagnelie 1996+, Denny 1953, Brink 1951, El-Daher 1991+, Landsman 1951+, MacDonald 1951, Middleton 1988+, Peterson 1997, Whitfield 1981+, Zwart 2003+)	Symptom of sore throat on day 3	Crude absolute risk: 1009/2066 vs 1031/1555 **RR 0.68 (0.59 to 0.79)** **SS in favour of AB**
		N= 13 n= 2974 (Bennike 1951+, De Meyere 1992+, Brumfitt 1957, Zwart 2000, Little 1997+, Dagnelie 1996+, Denny 1953, Brink 1951, Landsman 1951+, MacDonald 1951, Peterson 1997, Taylor 1977+, Zwart 2003+)	Symptom of sore throat at one week (6-8 days)	Crude absolute risk:246/1839 vs 206/1135 **RR 0.49 (0.32 to 0.76)** **SS in favour of AB**
		N= 7 n= 1334 (Brumfitt 1957, Brink 1951, Landsman 1951+, Middleton 1988+, Whitfield 1981+, Krober 1985+, Nelson 1984+)	Symptom of fever on day 3	Crude absolute risk:87/712 vs 114/622 RR 0.71 (0.45 to 1.10) NS
		N= 3 n= 777 (Brink 1951, Denny 1950, Landsman 1951+)	Symptom of fever at 1 week (6-8 days)	Not estimable; zero cases in intervention and control groups

		N= 3 n= 911 (Brink 1951, Denny 1953, El-Daher 1991+)	Symptom of headache on day 3	Crude absolute risk:122/552 vs 147/359 **RR 0.44 (0.27 to 0.71)** **SS in favour of AB**
		N= 16 n= 10101 (Chapple 1956+, De Meyere 1992+, Bennike 1951+, Brumfitt 1957, Zwart 2000, Little 1997+, Dagnelie 1996+, Pichichero 1987+, Leelarasamee 2000+, Chamovitz 1954, Denny 1950, Wannamaker 1951, Siegel 1961+, Brink 1951, Denny 1953, Catanzaro 1954)	Incidence of acute rheumatic fever within 2 months	Crude absolute risk: 37/5656 vs 74/4445 **RR 0.27 (0.12 to 0.60)** **SS in favour of AB**
		N= 11 n= 3778 (Chapple 1956*, De Meyere 1992+, Bennike 1951+, Zwart 2000, Little 1997+, Dagnelie 1996+, Pichichero 1987+, Chamovitz 1954, Brink 1951, Denny 1953, Taylor 1977+)	Incidence of otitis media within 14 days	Crude absolute risk: 11/2325 vs 28/1435 **RR 0.30 (0.15 to 0.58)** **SS in favour of AB**
		N= 8 n= 2387 (Landsman 1951, De Meyere 1992+, Zwart 2000, Little 1997+, Dagnelie 1996+, Pichichero 1987+, Chamovitz 1954, Brink 1951, Denny 1953)	Incidence of sinusitis within 14 days	Crude absolute risk: 4/1545 vs 4/842 RR 0.48 (0.08 to 2.76) NS
		N= 8 n= 2433 (Bennike 1951+, Dagnelie 1996+, Howe 1997, Landsman 1951+, De Meyere 1992+, Zwart 2000, Little 1997+, Pichichero 1987+)	Incidence of quinsy within 2 months	Crude absolute risk: 2/1438 vs 23/995 **0.15 (0.05 to 0.47)** **SS in favour of AB**

		N= 10 n= 5147 (Bennike 1951+, Dagnelie 1996+, Zwart 2000, Little 1997+, Brink 1951, Brumfitt 1957, Chamovitz 1954, Chapple 1956+, Leelarasamee 2000+, Siegel 1961+)	Incidence of acute glomerulonephritis within 1 month	Crude absolute risk: 0/2927 vs 2/2220 0.22 (0.02 to 2.08) NS

Table 26

MIXED POPULATION: ADULTS AND CHILDREN: SUBGROUP ANALYSES: GABHS +; GABHS -; untested

RCT's including children are marked with "+": see below for characteristics of these studies

Ref	Comparison	N/n	Outcomes	Result (95%CI)
Spinks 2013{Spinks, 2013 #72} Design: SR + MA Search date: (July 2013)	Antibiotics versus placebo	N= 11 n= 1839 (Brink 1951, Brumfitt 1957, Chapple 1956+, Dagnelie 1996+, De Meyere 1992+, Denny 1953, El-Daher 1991+, MacDonald 1951, Middleton 1988+, Zwart 2000, Zwart 2003+)	**Symptom of sore throat on day 3**; SUBGROUP: GABHS-positive throat swab	Crude AR 471/1073 vs 544/766 **RR 0.58 (0.48 to 0.71)** **SS**
		N= 6 n= 736 (Chapple 1956+, Dagnelie 1996+, MacDonald 1951, Petersen 1997, Zwart 2000, Zwart 2003+)	**Symptom of sore throat on day 3**; SUBGROUP: GABHS-negative throat swab	Crude AR 262/458 vs 202/278 **RR 0.78 (0.63 to 0.97)** **SS**
		N= 3 n= 1025 (Landsman 1951+, Little 1997+, Whitfield 1981+)	**Symptom of sore throat on day 3**; SUBGROUP: untested for GABHS culture or combined inseparable data	Crude AR 270/523 vs 294/502 RR 0.89 (0.80 to 1.00) NS
		N= 7 n= 1117 (Brink 1951, Brumfitt 1957, Dagnelie	**Symptom of sore throat at one week**; SUBGROUP: GABHS-positive	Crude AR 22/650 vs 57/467 **RR 0.29 (0.12 to 0.70)** **SS**

		1996+, De Meyere 1992+, Denny 1953, MacDonald 1951, Zwart 2003+)	throat swab	
		N= 5 n= 541 (Dagnelie 1996+, MacDonald 1951, Petersen 1997, Taylor 1977+, Zwart 2003+)	**Symptom of sore throat at one week**; SUBGROUP: GABHS-negative throat swab	Crude AR 42/315 vs 43/226 RR 0.73 (0.50 to 1.07) NS
		N= 3 n= 866 (Bennike 1951+, Landsman 1951+, Little 1997+)	**Symptom of sore throat at one week**; SUBGROUP: GABHS untested	Crude AR 66/540 vs 42/326 RR 0.35 (0.03 to 4.47) NS

Table 27

MIXED POPULATION: ADULTS AND CHILDREN: SUBGROUP ANALYSES: pre-1975; post-1975

RCT's including children are marked with "+": see below for characteristics of these studies

Ref	Comparison	N/n	Outcomes	Result (95%CI)
Spinks 2013{Spinks, 2013 #72} Design: SR + MA Search date: (July 2013)	Antibiotics versus placebo	N= 10 n= 7617 (Bennike 1951+, Brink 1951, Brumfitt 1957, Catanzaro 1954, Chamovitz 1954, Chapple 1956+, Denny 1950, Denny 1953, Siegel 1961+, Wannamaker 1951)	**Incidence of acute rheumatic fever within 2 months** SUBGROUP pre-1975 studies	Crude AR 37/4208 vs 74/3409 **RR 0.27 (0.12 to 0.60)** **SS**
		N= 6 n= 2484 (Dagnelie 1996+, De Meyere 1992+, Leelarasamee 2000+, Little 1997+, Pichichero 1987+, Zwart 2000)	**Incidence of acute rheumatic fever within 2 months** SUBGROUP post-1975 studies	Crude AR 0/1448 vs 0/1036 RR Not estimable
		N= 5 n= 1837	**Incidence of otitis media within 14 days**	Crude AR **RR 0.30 (0.15 to 0.62)**

		(Bennike 1951+, Brink 1951, Chamovitz 1954, Chapple 1956+, Denny 1953)	SUBGROUP pre-1975 studies	**SS**
		N= 6 n= 1923 (De Meyere 1992+, Little 1997+, Pichichero 1987+, Taylor 1977+, Zwart 2000)	**Incidence of otitis media within 14 days** SUBGROUP post-1975 studies	Crude AR RR 0.28 (0.03 to 2.74) NS

Table 28

Characteristics of included studies

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Cochrane group)
Bennike 1951{Bennike, 1951 #27} Open study, quasi-randomised	669	patients aged from less than 1 year to older than 50 years of age. Research was divided into 3 studies: ordinary tonsillitis, “phlegmonous” tonsillitis and “ulcerative” tonsillitis. Participants were excluded if they had a complication of tonsillitis on admission or if they had previous antibiotic treatment for the present sore throat		Age-adjusted intramuscular penicillin twice daily for 6 days or no treatment as a control Condition	RANDOM SEQUENCE GENERATION: high risk (Participants allocated to alternate conditions on alternate Days) ALLOCATION CONCEALMENT: high risk (No concealment of allocation present) BLINDING: high risk (no blinding of participants or assessments) INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: unclear risk(No antipyretics were administered to the control group. The use of antipyretics to participants in the treatment group was unstated)
Chapple 1956{Chapple, 1956	308	older than 2 years.	Follow-up 3 and 10-14	Age-adjusted oral penicillin, sulphadimidine or barium	RANDOM SEQUENCE GENERATION Low risk (Participants randomised

#28} Double-blind, placebo-controlled trial			days after the start of treatment	sulphate (placebo) administered for 5 days	by random bottle dispensing) ALLOCATION CONCEALMENT Low risk BLINDING Low risk INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk (All relevant outcomes reported)
Dagnelie 1996{Dagnelie, 1996 #31} Randomised, double-blind, placebo-controlled trial	239	Patients aged 4 to 60, presenting with sore throat to 37 General Practices in the Netherlands, who were clinically suspected of GABHS	Follow-up after 2 days After 14 days, existing complaints were registered by the general practitioner. Encounters which had taken place for sore throat and related conditions were registered with a questionnaire after 6 months.	Treatment with either penicillin V or placebo	RANDOM SEQUENCE GENERATION Low risk (Computer-generated random sequence) ALLOCATION CONCEALMENT Low risk BLINDING Low risk (Double-blind study design) INCOMPLETE OUTCOME DATA Low risk (No attrition of participants) SELECTIVE REPORTING Low risk (All relevant outcomes reported)

De Meyere 1992{De Meyere, 1992 #32} Double-blind, placebo-controlled trial	173	participants aged 5 to 50 years, from the Gent region of Belgium Data were obtained from 173 participants on days 1 and 3 Data were obtained from 131 participants on days 2, 4, 5, 6 and 7 Participants excluded if they: produced aGABHS-negative throat swab, had a sore throat for greater than 5 days, had a previous history of acute rheumatic fever, had an allergy to beta-lactam antibiotics, had received any antibiotics within the past 14 days, were in any high-risk situation as determined by the physician	Data were obtained from 173 participants on days 1 and 3 Data were obtained from 131 participants on days 2, 4, 5, 6 and 7	Oral penicillin or oral placebo 3 times a day	RANDOM SEQUENCE GENERATION Unclear risk (Randomisation method not documented) ALLOCATION CONCEALMENT Low risk BLINDING Low risk (Double-blind study design) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk (All relevant outcomes reported)
El-Daher 1991{el-Daher, 1991 #35} Double-blinded, randomised controlled trial	229	children with positive culture for GABHS	Data on day 3 Follow-up after 3 weeks Patients were instructed to report to the clinic in case of symptoms during the next 4 months	Early treatment with oral penicillin for 10 days versus oral placebo for 2 days followed by oral penicillin for 8 days	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk BLINDING Low risk (Double-blind study design) INCOMPLETE OUTCOME DATA Low risk (No attrition of participants) SELECTIVE REPORTING Low risk (All relevant outcomes reported)
Krober 1985{Krober, 1985 #40} Double-blind placebo trial	44	children presenting to a paediatric clinic. 26 of these participants yielded GABHS-positive throat swabs Participants were excluded if: the duration of symptoms was greater	Data at 24, 48 and 72 hours	Oral penicillin or similar looking and tasting oral placebo for the control condition, 3 times a day for 3 days	RANDOM SEQUENCE GENERATION Low risk (Participants were randomised by table of random numbers) ALLOCATION CONCEALMENT

		than 72 hours; they had received oral antibiotics within the past 72 hours or intramuscular antibiotics within the past 30 days; they had history of penicillin allergy; they had a rash suggestive of scarlet fever; they had a concurrent infection that required antibiotics other than penicillin; or if they had severe illness requiring immediate penicillin treatment Participants who produced GABHS-negative throat swabs were excluded fromthe study			Low risk BLINDING Low risk (Double-blind study design) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Unclear risk (Antipyretic use was not documented)
Landsman 1951{Landsman, 1951 #41} Double-blind, randomised, placebo-controlled trial	95	participants who presented to general practice complaining of sore throat		Oral sulphonamide or similar looking and tasting oral placebo, for the control condition	RANDOM SEQUENCE GENERATION Unclear risk (Randomised by random numbering of bottles) ALLOCATION Low risk BLINDING Low risk (Double-blind study design) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Unclear risk (Antipyretic use was not documented)
Leelarasamee 2000{Leelarasamee, 2000 #42} Double-blind, randomised, placebo-controlled trial	1217	patients aged over 5 years presenting to 4 community-based medical centres with complaints of fever or sore throat of less than 10 days duration	Data on day 4; follow-up after 18 and 60 days	Participants were randomised to receive either amoxycillin or placebo for 7 days	RANDOM SEQUENCE GENERATION Low risk (Computer-generated random sequence) ALLOCATION CONCEALMENT Low risk BLINDING Low risk (Double-blind study

					design) INCOMPLETE OUTCOME DATA Unclear risk (Some loss to follow-up occurred) SELECTIVE REPORTING Low risk (All relevant outcomes reported)
Little 1997{Little, 1997 #44} Unblinded randomised trial	716	patients aged 4 years and over, presenting to their GP with a sore throat, with an abnormal physical finding localised to the throat (e.g. inflamed tonsils or pharynx, etc.)		Participants were randomised to 3 groups. Participants in the first group were given an antibiotic for 10 days; those in the second group were given no prescription; and in the third group were given an offer of antibiotic prescription if the symptoms were not starting to settle after 3 days	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT High risk BLINDING High risk (No blinding of participants or assessors was performed) INCOMPLETE OUTCOME DATA Low risk (No attrition of participants) SELECTIVE REPORTING Low risk (All relevant outcomes reported)
Middleton 1988{Middleton, 1988 #46} Multicentre, double-blind, randomised, placebo-controlled	178	participants aged 4 to 29 years with streptococcal pharyngitis. Participants had symptom duration of less than 4 days. Results reported for 57 participants with severe illness only	Data on day 3	8 individual doses of penicillin or placebo	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk BLINDING Low risk (Double-blind study design used) INCOMPLETE OUTCOME DATA Low risk (No attrition of participants) SELECTIVE REPORTING Low risk (All relevant outcomes

					reported)
Nelson 1984{Nelson, 1984 #48} An oral placebo was used to single-blind participants, however outcome was not determined blind	51	children aged 5 to 11 years. Sixteen participants were excluded because they did not produce GABHS-positive throat swabs, leaving 35 participants. Children with history of penicillin hypersensitivity were also excluded	Data on day 3	Intramuscular penicillin or oral syrup placebo as a control group	RANDOM SEQUENCE GENERATION Unclear risk (Participants randomised to conditions by hospital number allocation) ALLOCATION High risk BLINDING Unclear risk (An oral placebo was used to single-blind participants. However outcome was not determined blind) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk (All relevant outcomes reported)
Pichichero 1987{Pichichero, 1987 #52} Single-blind, randomised, placebo-controlled trial	114	GABHS-positive children aged 4 to 18 years. Children were excluded from the study if: a throat swab was negative for GABHS; were allergic to penicillin; had received penicillin in past 7 days; had another acute illness within 7 days, had a GABHS-positive swab in past month, or had another concurrent infection that required antibiotics	Follow-up at 3 weeks after enrollment	Oral penicillin for 48 hours or an identical-looking and tasting oral placebo used for the control condition	RANDOM SEQUENCE GENERATION Low risk (Computer-generated random sequence) ALLOCATION CONCEALMENT Low risk BLINDING Low risk (Single-blind study design) INCOMPLETE OUTCOME DATA Low risk (No participant attrition) SELECTIVE REPORTING Low risk (All relevant outcomes reported)
Siegel 1961{Siegel, 1961 #60} Randomised controlled trial	1213	children aged 3 to 16 years. Suppurative complications occurring in participants in the control condition were treated		Intramuscular penicillin or no treatment for the controls	RANDOM SEQUENCE GENERATION Unclear risk (Participants randomised by bed chart number) ALLOCATION CONCEALMENT

		with sulphonamides. Participants were excluded if they had a complication on admission			High risk BLINDING High risk INCOMPLETE OUTCOME DATA (Low risk SELECTIVE REPORTING Unclear risk (Antipyretic use was not documented)
Taylor 1977{Taylor, 1977 #63} Double-blind, randomised, placebo-controlled trial	122	children aged 2 to 10 years. Children with positive Streptococcus throat swabs were excluded 9 children were excluded during trial because of pre-existing suppurative complications	Follow-up after seven days	Oral amoxycillin, oral cotrimoxazole or an oral placebo was administered by parents 3 times a day for 5 days	RANDOM SEQUENCE GENERATION Unclear risk (The method of randomisation to groups was not documented) ALLOCATION CONCEALMENT Low risk BLINDING Low risk (Double-blind study design) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Unclear risk (Antipyretic use was not documented)
Whitfield 1981{Whitfield, 1981 #64} Double-blind, randomised, placebo-controlled trial	745	Participants were people who presented to the General Practitioner with sore throat, aged more than 10 years. 745 participants were commenced on the study. Only 528 returned questionnaires. Participants were excluded if the General Practitioner thought the participant would demonstrate poor compliance; if they had previous reaction to penicillin; or a previous episode of		Oral penicillin 4 times a day for 5 days or identical-looking and tasting oral lactose placebo 4 times a day for 5 days	RANDOM SEQUENCE GENERATION Low risk(Randomised by pre-determined random order) ALLOCATION CONCEALMENT Low risk BLINDING Low risk (Double-blind study design) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING

		rheumatic fever or acute nephritis			Unclear risk (Antipyretic use was not documented)
Zwart 2003{Zwart, 2003 #65} Double-blind, randomised, placebo-controlled trial	156	children aged 4 to 15 years presenting with sore throat of less than 7 days duration with at least 2 of 4 Centor criteria	Follow up after seven days and 6 months	Penicillin V for 7 days, penicillin V for 3 days followed by 4 days of placebo or placebo or 7 days	RANDOM SEQUENCE GENERATION Low risk (Computer-generated random sequence ALLOCATION CONCEALMENT Low risk BLINDING Low risk INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk (All relevant outcomes reported)

Table 29

Author's remarks:

NOTE: these remarks pertain to a mixed population of adults and children

The authors of the Cochrane review state the following regarding relative versus absolute benefit on complications: "*Antibiotics are effective at reducing the relative complication rate of people suffering sore throat. However, the relative benefit exaggerates the absolute benefit because complication rates are low and the illness is short-lived. Interpretation of these data is aided by estimating the absolute benefit, which we attempt below.*

In these trials, conducted mostly in the 1950s, for every 100 participants treated with antibiotics rather than placebo, there was one fewer case of acute rheumatic fever, two fewer cases of acute otitis media and three fewer cases of quinsy. These figures need to be adapted to current circumstances and individuals. For example, the complication rate of acute otitis media among those with sore throats before 1975 was 3%. A NNTB of about 50 to prevent one case of acute otitis media can be estimated from the data. After 1975, this complication rate fell to 0.7% and applying the odds of reducing the complication with antibiotics from the data table yields a NNTB of nearly 200 to prevent one case of acute otitis media. Clinicians will have to exercise judgement in applying these data to their patients.

In particular, in high-income countries (where absolute rates of complications are lower) the NNTB will rise above a rate at which it might be regarded as worthwhile to treat. In low-income countries where the absolute rate may be much higher, the lower NNTB will mean antibiotics are more likely to be effective."

5.2.1.2 Summary and conclusions

Antibiotics versus placebo in sore throat in children			
Bibliography: Cochrane Spinks 2013{Spinks, 2013 #72}			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Symptom of fever on day 3	61 (2 studies)	RR 1.27 (0.76 to 2.13) NS	⊕⊕⊕⊖: **MODERATE** Study quality: ok Consistency: ok Directness: -1; both studies excluded GABHS-negative patients Imprecision:ok

Table 30

Antibiotics versus placebo in sore throat in children and adults			
Bibliography: Cochrane Spinks 2013{Spinks, 2013 #72}			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Symptom of sore throat on day 3	3621 (15 studies)	**RR 0.68 (0.59 to 0.79)** **(less symptom of sore throat on day 3 with AB)**	⊕⊕⊖⊖: **MODERATE** Assessed by Cochrane group as High level of evidence Directness: -1 (mixed population)
Symptom of sore throat at one week (6-8 days)	2974 (13 studies)	**RR 0.49 (0.32 to 0.76)** **(less symptom of sore throat at one week)**	⊕⊕⊖⊖: **MODERATE** Assessed by Cochrane group as High level of evidence Directness: -1 (mixed population
Symptom of fever on day 3	1334 (7 studies)	RR 0.71 (0.45 to 1.10) NS	⊕⊕⊖⊖: **MODERATE** Study quality: ok Consistency: ok Directness: -1 (mixed population) Imprecision:ok
Symptom of fever at 1 week (6-8 days)	777 (3 studies)	Not estimable; zero cases in intervention and control groups	Insufficient data
Symptom of headache on day 3	911 (3 studies)	**RR 0.44 (0.27 to 0.71)** **SS in favour of AB**	⊕⊕⊖⊖: **MODERATE** Study quality: ok Consistency: ok Directness: -1 (mixed population) Imprecision:ok
Incidence of acute rheumatic fever within 2 months	10101 (16 studies)	**RR 0.27 (0.12 to 0.60)** **(lower incidence of acute rheumatic fever with AB)**	⊕⊕⊖⊖: **MODERATE** Assessed by Cochrane group as High level of evidence Directness: -1 (mixed population)
Incidence of otitis media within 14 days	3778 (11 studies)	**RR 0.30 (0.15 to 0.58)** **(lower incidence of otitis media with AB)**	⊕⊕⊖⊖: **MODERATE** Assessed by Cochrane group as High level of evidence Directness: -1 (mixed population)
Incidence of sinusitis within 14 days	2387 (8 studies)	RR 0.48 (0.08 to 2.76) NS	⊕⊕⊖⊖: **LOW** Study quality: ok Consistency: ok Directness: -1 (mixed population)

			Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Incidence of quinsy within 2 months	2433 (8 studies)	**0.15 (0.05 to 0.47)** **(Lower incidence of quinsy with AB)**	⊕⊕⊖⊖: **MODERATE** Assessed by Cochrane group as High level of evidence Directness: -1 (mixed population)
Incidence of acute glomerulonephritis within 1 month	5147 (10 studies)	0.22 (0.02 to 2.08) NS	⊕⊖⊖⊖: **VERY LOW** Assessed by Cochrane group as Low level of evidence Directness: -1 (mixed population)

Table 31

Antibiotics versus placebo in sore throat in children and adults **SUBGROUP ANALYSES: GABHS +; GABHS -; untested**			
Bibliography: Cochrane Spinks 2013{Spinks, 2013 #72}			
Outcomes	**N° of participants (studies)** **Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Symptom of sore throat on day 3	1839 (11 studies) SUBGROUP: GABHS-positive throat swab	**RR 0.58 (0.48 to 0.71)** **SS** **(less symptom of sore throat on day 3 with AB)**	⊕⊕⊖⊖: **LOW** Study quality: ok Consistency: -1 (I^2>80%) Directness: -1 (mixed population) Imprecision: ok
	736 (6 studies) SUBGROUP: GABHS-negative throat swab	**RR 0.78 (0.63 to 0.97)** **SS** **(less symptom of sore throat on day 3 with AB)**	⊕⊕⊕⊖: **MODERATE** Study quality: ok Consistency: ok Directness: -1 (mixed population) Imprecision: ok
	1025 (3 studies) SUBGROUP: untested for GABHS culture or combined inseparable data	RR 0.89 (0.80 to 1.00) NS	⊕⊕⊕⊖: **MODERATE** Study quality: ok Consistency: ok Directness: -1 (mixed population) Imprecision: ok
Symptom of sore throat at one week (6-8 days)	1117 (7 studies) SUBGROUP: GABHS-positive throat swab	**RR 0.29 (0.12 to 0.70)** **SS** **(less symptom of sore throat at one week with AB)**	⊕⊕⊕⊖: **MODERATE** Study quality: ok Consistency: ok Directness: -1 (mixed population) Imprecision: ok
	541 (5 studies) SUBGROUP: GABHS-negative throat swab	RR 0.73 (0.50 to 1.07) NS	⊕⊕⊕⊖: **MODERATE** Study quality: ok Consistency: ok Directness: -1 (mixed population) Imprecision: ok
	866 (3 studies) SUBGROUP: GABHS untested	RR 0.35 (0.03 to 4.47) NS	⊕⊖⊖⊖: **VERY LOW** Study quality: -1 (no blinding in 2 trials) Consistency: ok Directness: -1 (mixed population) Imprecision: -1 (95%-CI crosses

			both the point of appreciable harm AND the point of appreciable benefit)

Table 32

Antibiotics versus placebo in sore throat in children and adults SUBGROUP ANALYSES: pre-1975; post-1975			
Bibliography: Cochrane Spinks 2013{Spinks, 2013 #72}			
Outcomes	**N° of participants (studies) Follow up**	**Results (RR(95%CI))**	**Quality of the evidence (GRADE)**
Incidence of acute rheumatic fever within 2 months	7617 (10 studies) SUBGROUP pre-1975 studies	**RR 0.27 (0.12 to 0.60) SS (lower incidence of acute rheumatic fever with AB)**	⊕⊕⊕⊖: **MODERATE** Study quality: ok Consistency: ok Directness: -1 (mixed population) Imprecision: ok
	2484 (6 studies) SUBGROUP post-1975 studies	Not estimable; zero cases in intervention and control groups	Insufficient data
Incidence of otitis media within 14 days	1837 (5 studies) SUBGROUP pre-1975 studies	**RR 0.30 (0.15 to 0.62) SS (lower incidence of otitis media with AB)**	⊕⊕⊕⊖: **MODERATE** Study quality: ok Consistency: ok Directness: -1 (mixed population) Imprecision: ok
	1923 (6 studies) SUBGROUP post-1975 studies	RR 0.28 (0.03 to 2.74) NS	⊕⊕⊖⊖: **LOW** Study quality: ok Consistency: ok Directness: -1 (mixed population) Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)

Table 33

In this Cochrane systematic review and meta-analysis, RCTs and quasi-RCTs that compared antibiotics with placebo in patients presenting to primary care with symptoms of sore throat were included.

This review included trials in patients with sore throat from different causes. Some trials recruited only patients with group A beta-hemolytic streptococcal pharyngitis (either clinically suspected or microbiologically confirmed), some trials excluded GABHS-positive patients, and others recruited patients with sore throat regardless of cause. Subgroup analyses were performed in patients testing positive for GABHS, in patients testing negative, and in patients untested for GABHS. The effectiveness of antibiotics seems to be increased in people testing positive for GABHS.

The systematic review included patients of all ages, both adults and children. A subanalysis was made containing only RCTs in children younger than 13 years. However, as this subanalysis was only performed for one outcome (symptom of fever on day 3), we have chosen to report the outcomes based on the results of a mixed child-adult population as well. Of the27 studies included in the review, 7 included only children (El-Daher 1991{el-Daher, 1991 #35}, Krober 1985{Krober, 1985 #40},

Nelson 1984{Nelson, 1984 #48}, Pichichero 1987{Pichichero, 1987 #52}, Siegel 1961{Siegel, 1961 #60}, Taylor 1977{Taylor, 1977 #63}, Zwart 2003{Zwart, 2003 #65}), 9 recruited both adults and children (Bennike 1951{Bennike, 1951 #27}, Chapple 1956{Chapple, 1956 #28}, Dagnelie 1996{Dagnelie, 1996 #31}, De Meyere 1992{De Meyere, 1992 #32}, Landsman 1951{Landsman, 1951 #41}, Leelarasamee 2000{Leelarasamee, 2000 #42}, Little 1997{Little, 1997 #44}, Middleton 1988{Middleton, 1988 #46}, Whitfield 1981{Whitfield, 1981 #64}), and 11 recruited adults only. We do not know the percentage of children in these studies.

The antibiotic used by most trials was oral penicillin, but amoxicillin and sulphonamides were given as well.

The authors of the Cochrane review stress the importance of relative versus absolute benefit on complications for interpreting the data. Most of the trials were conducted in the 1950s, when complication rates were much higher. This meant that the NNT to prevent a complication was relatively low (the authors estimate an NNT of 50 to prevent one case of acute otitis media before 1975). The complication rate fell after 1975, and applying the same relative risk to these numbers raises the NNT (with the same example the authors calculated an NNT of 200 to prevent one case of otitis media). In the trials after 1975, not one case of rheumatic fever was recorded. Particularly in high-income countries, clinicians will have to take absolute rates of complications into account, to determine whether it is worthwhile to treat sore throat with antibiotics.

Subgroup analyses were made for studies conducted before and after 1975.

This review was unable to present the adverse effects of antibiotic use because of inconsistencies in recording these symptoms.

In children with sore throat, a treatment with antibiotics, compared to placebo, **did not** result in a statistically significant difference in symptoms of *fever on day 3*.
GRADE: MODERATE quality of evidence

In children and adults with sore throat, a treatment with antibiotics, compared to placebo, resulted in a statistically significant **decrease** in *sore throat on day 3*, *sore throat at one week*, *headache on day 3*, *incidence of acute rheumatic fever*, *otitis media and quinsy*.
We have no information for a purely paediatric population
GRADE: MODERATE quality of evidence (when applied to a paediatric population)

In children and adults with sore throat, a treatment with antibiotics, compared to placebo, **did not** result in a statistically significant difference in *fever on day 3*.
GRADE: MODERATE quality of evidence (when applied to a paediatric population)

In children and adults with sore throat, there is insufficient data to determine whether a treatment with antibiotics, compared to placebo, will result in a statistically significant difference in *fever after one week.*
GRADE: insufficient data

In children and adults with sore throat, a treatment with antibiotics, compared to placebo, **did not** result in a statistically significant difference in *incidence of sinusitis within 14 days*.
We have no information for a purely paediatric population
GRADE: LOW quality of evidence (when applied to a paediatric population)

In children and adults with sore throat, a treatment with antibiotics, compared to placebo, **did not** result in a statistically significant difference in incidence of *acute glomerulonephritis within 1 month*.
We have no information for a purely paediatric population
GRADE: VERY LOW quality of evidence (when applied to a paediatric population)

In children and adults with sore throat testing positive for GABHS, a treatment with antibiotics, compared to placebo, **did** result in a statistically significant **decrease** in *symptom of sore throat on day 3.*
We have no information for a purely paediatric population
GRADE: LOW quality of evidence (when applied to a paediatric population)

In children and adults with sore throat testing positive for GABHS, a treatment with antibiotics, compared to placebo, **did** result in a statistically significant **decrease** in *symptom of sore throat at one week.*
We have no information for a purely paediatric population
GRADE: MODERATE quality of evidence (when applied to a paediatric population)

In children and adults with sore throat testing negative for GABHS, a treatment with antibiotics, compared to placebo, **did** result in a statistically significant **decrease** in *symptom of sore throat on day 3.*
We have no information for a purely paediatric population
GRADE: MODERATE quality of evidence (when applied to a paediatric population)

In children and adults with sore throat testing negative for GABHS, a treatment with antibiotics, compared to placebo, **did not** result in a statistically significant difference in *symptom of sore throat at one week.*
We have no information for a purely paediatric population
GRADE: MODERATE quality of evidence (when applied to a paediatric population)

In children and adults with sore throat untested for GABHS, a treatment with antibiotics, compared to placebo, **did not** result in a statistically significant difference in *symptom of sore throat on day 3.*
We have no information for a purely paediatric population
GRADE: MODERATE quality of evidence (when applied to a paediatric population)

In children and adults with sore throat untested for GABHS, a treatment with antibiotics, compared to placebo, **did not** result in a statistically significant difference in *symptom of sore throat at one week.*
We have no information for a purely paediatric population
GRADE: VERY LOW quality of evidence (when applied to a paediatric population)

In children and adults with sore throat in a trial before 1975, a treatment with antibiotics, compared to placebo, **did** result in a statistically significant **decrease** in *incidence of rheumatic fever within 2 months* and *incidence of otitis media within 14 days*.
We have no information for a purely paediatric population
GRADE: MODERATE quality of evidence (when applied to a paediatric population)

In children and adults with sore throat in a trial after 1975, a treatment with antibiotics, compared to placebo, **did not** result in a statistically significant difference in *incidence of otitis media within 14 days*.
We have no information for a purely paediatric population
GRADE: LOW quality of evidence (when applied to a paediatric population)

In children and adults with sore throat in a trial after 1975, there is insufficient data to determine whether a treatment with antibiotics, compared to placebo, will result in a statistically significant difference in *incidence of rheumatic fever within 2 months.*
We have no information for a purely paediatric population
GRADE: Insufficient data

5.2.2 Antibiotic A versus antibiotic B for group A streptococcal pharyngitis

5.2.2.1 Cephalosporin versus penicillin in confirmed GABHS infection

5.2.2.1.1 Clinical evidence profile

Meta-analysis: Cochrane Van Driel 2013{van Driel, 2013 #73} "Different antibiotic treatments for group A streptococcal pharyngitis"

Inclusion criteria: double blind RCTs comparing different antibiotics and reporting at least one of the following: clinical cure, clinical relapse, complications, adverse events. Participants: Adults and children of all ages presenting with symptoms of sore throat and with an infection caused by GABHS confirmed by a throat culture and/or rapid test.
Search strategy: Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 10, (accessed 19 October 2012, MEDLINE (1966 to October week 4, 2012), EMBASE(1974 to October 2012) and Web of Science (2010 to October 2012).
Assessment of quality of included trials: yes
ITT analysis: yes, 'if possible'
Other methodological remarks: Both adults and children were included in this SR. Separate analyses for children were reported by the Cochrane authors.

We will report only the analyses in which children were included.
Studies that include only adults or studies that include antibiotics not available in Belgium will not be reported, except when included in a meta-analysis with other RCTs that meet our inclusion criteria and when no separate analysis is available.
A lot of the RCT's including adults started inclusion age at > 12y.

Table 34

Cephalosporin vs penicillin in confirmed GABHS infection

Ref	Comparison	N/n	Outcomes	Results (95% CI)
ref* Cochrane Van Driel 2013{van Driel, 2013 #73}	Cephalosporin vs penicillin	N= 3 n= 855 (Disney 1992a, Henness 1982a, Reed 1991)	**Resolution of symptoms (subgroup children)** **post-treatment** (cure or improvement of signs and symptoms, such as sore throat, fever, feeling ill, etc.)	ITT analysis AR 68/437 (15.6%) vs 70/418 (16,7%) OR 0.83 (0.40, 1.73) NS see note on sensitivity analysis Evaluable participants

Design: SR + MA Search date: (oct 2012)				AR 20/389 (5.1%) vs 43/391 (11.0%) OR 0.46 (0.14, 1.52) NS see note on sensitivity analysis
		N= 1 n= 138 Randolph 1985	**Resolution of symptoms (children) within 24 hours of treatment** (cure or improvement of signs and symptoms, such as sore throat, fever, feeling ill, etc.)	ITT analysis AR 8/70 (11,4%) vs 8/68 (11,8%) OR 0.97 [0.34, 2.74] NS
		N=2 n=616 (Disney 1992a, Reed 1991)	**Incidence of relapse (subgroup children)**	Evaluable participants AR 8/308 (2.6%) vs 9/308 (2.9%) OR 0.89 [0.33, 2.43] NS
			Adverse events/complications	Not reported in trials that include children and that include cephalosporins available in Belgium

Table 35

Note: A sensitivity analysis revealed that in the ITT analysis the trial by Disney 1992a contributed to the heterogeneity of the analysis in children. However, removing this trial from the forest plot did not result in a significant change in the overall outcome. In a similar analysis for the evaluable patients only, the trial by Reed 1991 appeared to contribute most to the heterogeneity. After removing this trial, the I2 statistic was no longer important. Pooling of the two remaining trials in children then showed a statistically significant benefit in favour of cephalosporins in children.

Characteristics of included studies (that include children): see below

Ref + design	n	Population	Duration	Comparison	Methodology (assessed by Cochrane authors)
Disney 1992a{Disney, 1992 #33} - RCT - Double-blinded	525	- Setting: 7 paediatric practices in USA - Age: 4 to 17 yrs - Clinical tonsillopharyngitis and throat cultures strongly positive for GABHS - Exclusion criteria: concurrent enrolment of siblings, 2 ormore sore throats in previous	Treatment: 10 days Follow-up 32 to 35 days	cephalexin 27 mg/kg/day (divided over 4 doses) versus penicillin 27 mg/kg/d (divided over 4 doses)	ALLOCATION CONC:unclear RANDO: unclear BLINDING : Adequate INCOMPLETE OUTCOME DATA: high risk of bias, no description of dropouts

		6 months, treated with AB in previous 2 weeks, throat culture negative for GABHS			SELECTIVE REPORTING: high risk of bias, only clinical (and bacteriological) failure reported, no symptoms specified. No reporting of adverse events ITT:yes FUNDING: not reported
Hennes 1982a{Henness, 1982 #38} - RCT - Double-blinded	214	- Setting: private paediatric practices in USA - Age: 1 to 16 yrs - Diagnosis: throat culture - Inclusion criteria: acute untreated tonsillopharyngitis - Exclusion criteria: not reported	Treatment: 10 days, follow-up 27 to 43 days	penicillin V suspension 8mg/kg every 6 hours versus cefadroxil suspension 15 mg/kg twice daily	ALLOCATION CONC:unclear RANDO: unclear BLINDING : unclear INCOMPLETE OUTCOME DATA unclear risk: 52 participants discontinued (cefadroxil 35 and penicillin 17); reasons: negative culture (total 47; cefadroxil 31 and penicillin 16), lost to follow-up (total 3; cefadroxil 2 and penicillin 1), other (total 2; cefadroxil 2 and penicillin 0) ITT: No ITT analysis for clinical outcomes FUNDING: not mentioned, author employee of Mead Johnson Pharmaceutical Division, Evansville, USA
Randolph 1985{Randolph, 1985 #55} - RCT - Double-blinded	194	Setting: a private paediatric office - Age: 2 to 20 years - Diagnosis: throat culture - Inclusion criteria: clinically suggestive GABHS pharyngitis	Treatment: 10 days Follow-up: 4 weeks (only results from	cefadroxil 250 mg in 3 doses over next 18 to 24 hours (n = 70); penicillin V 250 mg in 3 doses	ALLOCATION CONC: low risk RANDO: low risk BLINDING : low risk INCOMPLETE OUTCOME DATA: low

		-Exclusion criteria: history of hypersensitivity to penicillin or cephalosporins, ABwithin previous 72 hours	examination 18 to 24 hours after initiation of treatment reported)	over next 18 to 24 hours (n = 68); placebo (n = 56)	risk of bias, no dropouts SELECTIVE REPORTING: unclear risk of bias, Specific signs and symptoms reported; No reporting of adverse events ITT:yes FUNDING: Mead Johnson and Company
Reed 1991{Reed, 1991 #56} *- RCT* *- Double-blinded*	*116*	*- Setting: 4 primary care offices in USA* *- Age: > 1 month* *- Diagnosis: rapid test, throat culture* *- Inclusion criteria: sore throat or poor eating, rapid test positive for GABHS* *- Exclusion criteria: allergy to penicillin or cephalosporins, pregnancy, history of renal or hepatic impairment, significant underlying disease or concomitant infection that could preclude evaluation of response to treatment, AB in the previous 3 days* *approximately 80% of participants were under 15 years of age (Reed 1991) and therefore included in the subgroup analysis for children*	*Treatment: 10 days* *Follow-up: 28 to 30 days post-therapy*	*cefaclor 20mg/kg/d in 3 doses (n = 60)* *versus* *penicillin VK 20mg/kg/d in 3 doses (n = 56)* ** no longer available in Belgium*	*ALLOCATION CONC: low risk* *RANDO: unclear risk (not described)* *BLINDING : low risk* *INCOMPLETE OUTCOME DATA: unclear risk of bias, Dropouts 23: no GABHS on culture (cefaclor 6 and peni-cillin 2), insufficient therapy (cefaclor 0 and penicillin 1), no follow-up culture (cefaclor 3 and penicillin 0), other an-tibiotic (cefaclor 1 and penicillin 2), unevaluable according to investigator (cefaclor 3 and penicillin 5)* *SELECTIVE REPORTING: unclear risk of bias, Only clinical (and bacteriological) outcome reported, no specific symptom outcomes reported* *Adverse events reported; no ITT analysis*

					ITT: No ITT analysis in original RCT, but ITT performed by cochrane *FUNDING: Eli Lily & Company, Indianapolis, Indiana USA*

Table 36

Remarks:

Adverse events were not always reported by the RCTs included in this Cochrane review. No RCTs that included cephalosporins available in Belgium that were studied in children reported adverse events.

All the identified studies were carried out in populations in high-income countries with a low risk of streptococcal complications.

Excluded studies

Fifty-three references were excluded from analysis. The most common reason for exclusion (37 trials) was no or inadequate blinding (Adam 1994; Adam 1995; Adam 1996; Adam 2000a; Adam 2000b; Adam 2001; Aujard 1995; Bottaro 2012; Cohen 2002;Denny 1953;Dykhuizen 1996; Esposito 2002; Feder 1999; Gerber 1986; Gooch 1993; Hamill 1993; Holm 1991; Howe 1997; Lennon 2008; McCarty 1992b;McCarty 1994;Milatovic 1991; Milatovic 1993; Pacifico 1996; Perkins 1969; Pichichero 2000; Pichichero 2008; Portier 1990; Portier 1994; Sanofi Aventis 2010; Sakata 2008; Shapera 1973; Shvartzman 1993; Stillerman 1986; Tack 1997; Tack 1998; Uysal 2000). Seven trials did not compare at least two different classes of antibiotics (Breese 1974; Disney 1979;Matsen 1974;McIsaac 2004; Rimoin 2011; Siegel 1961; Zwart 2000). In two trials the included participants did not exclusively have acute GABHS tonsillopharyngitis (Davies 1995; Standaert 1997) and one trial included patients with recurrent tonsillitis (Roos 1997). One trial did not report any clinical outcomes (Gerber 1999a) but was used as an additional reference; one reference was a meta-analysis (Cruz 2011) and four trials were not randomised controlled trials (RCTs) (DelMar 2008; De Meyere 1992; Granizio 2008; Haverkorn 1971)

Cochrane author's conclusions:

"*Evidence is insufficient to show clinically meaningful differences between antibiotics for GABHS tonsillopharyngitis.* "

"*Data on complications are too scarce to draw conclusions. Based on these results and considering the low cost and absence of resistance, penicillin can still be recommended as first choice*."

5.2.2.1.2 Summary and conclusions

Cephalosporin versus penicillin for group A streptococcal pharyngitis			
Bibliography: Cochrane Van Driel 2013{van Driel, 2013 #73}			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Clinical efficacy Resolution of symptoms post-treatment	855 (3 studies) 27 to 43 days	(subgroup children) ITT analysis OR 0.83 (0.40, 1.73) NS Evaluable participants 0.46 (0.14, 1.52) NS *note: heterogeneity disappeared when excluding 1 trial. Pooling of the remaining trials showed SS benefit of cephalosporin.*	⊕⊖⊖⊖: **VERY LOW** Study quality:-1 Consistency: -1 heterogeneity, see note Directness: ok Imprecision:-1 95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit
Clinical efficacy Resolution of symptoms within 24h	138 (1 study)	(children) ITT analysis OR 0.97 [0.34, 2.74] NS	⊕⊕⊕⊖: **MODERATE** Study quality: ok Consistency: NA Directness: ok Imprecision: -1 95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit
Incidence of relapse	616 (2 studies) 28 to 35 days	(subgroup children) Evaluable participants OR 0.89 [0.33, 2.43] NS note: this endpoint was SS in the adult population in favour of cephalosporin	⊕⊕⊖⊖: **LOW** Study quality: -1 unclear rando, unclear or problematic reporting Consistency: ok Directness: ok Imprecision:-1 95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit
Adverse events		Not reported in RCTs that included children	**Not applicable**

Table 37

This Cochrane review compared cephalosporin to penicillin for 10 days in the treatment of confirmed GABHS infection of the throat (confirmed by throat culture and/or rapid test). Only double blind RCTs were included. Participants included in this review were both adults and children. We will report only the outcomes for which information in a (predominantly) paediatric population is available. The upper age limit in the trials that included 'children' ranged from 16 to 20 in 3 trials. 1 trial (Reed 1991{Reed, 1991 #56} included children as well as adults, but since 80% of participants were <15y, this trials was included in the subanalysis for children.

The cephalosporins used in the trials were first-generation (cephalexin, cefadroxil) and second-generation (cefaclor).

The dose of the antibiotics differed between studies. In one study the dose of penicillin was markedly lower than usually recommended in Belgium.

The Cochrane authors included only double blind RCTs in an effort to achieve higher quality of the evidence. However, the quality of the included trials was still somewhat disappointing, mainly due to inadequately addressing incomplete outcome data and selectively reporting outcomes.

In children with group A streptococcal pharyngitis, there is no statistically significant difference between 10 days of cephalosporin and 10 days of penicillin for the resolution of symptoms post-treatment.
GRADE: VERY LOW quality of evidence

In children with group A streptococcal pharyngitis, there is no statistically significant difference between cephalosporin and penicillin for the resolution of symptoms within 24 hours.
GRADE: MODERATE quality of evidence

In children with group A streptococcal pharyngitis, there is no statistically significant difference between cephalosporin and penicillin for relapse rates.
GRADE: LOW quality of evidence

Sadly, none of the included trials reported complications or adverse events. The fact that this information is lacking limits our ability to make a proper risk/benefit assessment for cephalosporin compared to penicillin for the treatment of group A streptococcal pharyngitis.
GRADE: not applicable

5.2.2.2 *Azithromycin versus penicillin in confirmed GABHS infection*

5.2.2.2.1 Clinical evidence profile

Meta-analysis: Cochrane Van Driel 2013{van Driel, 2013 #73} "Different antibiotic treatments for group A streptococcal pharyngitis" Inclusion criteria: double blind RCTs comparing different antibiotics and reporting at least one of the following: clinical cure, clinical relapse, complications, adverse events. Participants: Adults and children of all ages presenting with symptoms of sore throat and with an infection caused by GABHS confirmed by a throat culture and/or rapid test. Search strategy: Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 10, (accessed 19 October 2012, MEDLINE (1966 to October week 4, 2012), EMBASE(1974 to October 2012) and Web of Science (2010 to October 2012). Assessment of quality of included trials: yes ITT analysis: yes, 'if possible' Other methodological remarks: Both adults and children were included in this SR. Separate analyses for children were reported by the Cochrane authors. We will report only the analyses in which (only) children were included. Studies that include only adults or studies that include antibiotics not available in Belgium will not be reported, except when included in a meta-analysis with other RCTs that meet our inclusion criteria and when no separate analysis is available. A lot of the RCT's including adults started inclusion age at > 12y.

Table 38

Ref	Comparison	N/n	Outcomes	Result (95% CI)
ref* Cochrane Van Driel 2013{van Driel, 2013 #73}	azithromycin versus penicillin	N= 1 n= 489 O'Doherty 1996	**Resolution of symptoms (children)** post-treatment (cure or improvement of signs and symptoms, such as sore throat, fever, feeling ill, etc.) mostly measured between five to 10 days following the end of	ITT analysis OR=1.25 [0.85, 1.84] Evaluable participants (n= 358) OR= 0.64 [0.36, 1.11]

Design: SR + MA Search date: (oct 2012))			antibiotic treatment	
		N= 1 n= 307 O'Doherty 1996	**Incidence of relapse (children)** The definition of clinical relapse varies slightly between trials; from "pretreatment signs & symptoms resolved but reappeared" or "initial improvement or alleviation of symp- toms, but subsequent worsening or recurrence" to "new infection with different serotype"	Evaluable participants OR= 3.10 [0.67, 14.25]
		N= 1 n= 489 O'Doherty 1996	**Adverse events (children)**	ITT analysis OR=2.33 [1.06, 5.15]

Table 39

* Characteristics of included studies (that include children): see below

Ref + design	n	Population	Duration	Comparison	Methodology (as reported by Cochrane authors)
O'Doherty 1996{O'Doherty, 1996 #49} - RCT - Double-blinded - Double-dummy	489	- Setting: 19 outpatient clinical centres (Europe) - Age: 2 to 13 years - Diagnosis: clinical examination, rapid antigen test - Inclusion criteria: clinical signs and symptoms suggestive of GABHS	- Duration of treatment: azithromycin 3 days; penicillin V 10 days - Duration of	azithromycin suspension single oral dose 10 mg/kg versus azithromycin suspension one single dose 20mg/kg	ALLOCATION CONC: unclear RANDO: unclear BLINDING : Adequate

		pharyngitis/ tonsillitis, rapid antigen test positive for GABHS - Exclusion criteria: within 72 hours prior to the study other AB which could interfere with evaluation of therapy,hypersensitivity tomacrolide or beta-lactamantibiotic, termi- nal illness or other serious disease, any gastrointestinal condition that might affect drug absorption, other investigational drug in the previous month or long-acting penicillin injections within the previous 6 weeks	follow-up: 28 to 30 days	versus penicillin V solution 125-250mg orally 4 times daily (total daily dose 500 to 1000 mg)	INCOMPLETE OUTCOME DATA unclear risk of bias: Dropout 131 participants: absence of pathogen (azithromycin 20 mg = 36; azithromycin 10mg = 30; penicillin = 26), deviation from protocol (azithromycin 20 mg = 10; azithromycin 10 mg = 8; penicillin = 3), adverse event (azithromycin 20 mg = 11; azithromycin 10 mg = 5; penicillin = 2) SELECTIVE REPORTING: unclear risk of bias: Only clinical (and bacteriological) cure reported, no specific symptoms in outcome analysis ITT:not performed in original RCT, but performed by Cochrane authors. FUNDING: not reported

Table 40

Remarks:

This Cochrane review found 6 double blind RCTs comparing macrolides to penicillin. Only 1 RCT included only children. The other RCTs included subjects ≥12y;≥13y; ≥15y. No separate analyses for the children in these studies were provided.

Cochrane author's conclusions:

"*Evidence is insufficient to show clinically meaningful differences between antibiotics for GABHS tonsillopharyngitis.*"

"*Data on complications are too scarce to draw conclusions. Based on these results and considering the low cost and absence of resistance, penicillin can still be recommended as first choice.*"

5.2.2.2.2 Summary and conclusions

Azithromycin vs penicillin in confirmed GABHS infection			
Bibliography: Cochrane Van Driel 2013{van Driel, 2013 #73}			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR[95%CI])**	**Quality of the evidence (GRADE)**
Resolution of symptoms (5 to 10 days after treatment)	489 (1 study)	(subgroup children) ITT analysis OR=1.25 [0.85, 1.84] NS Evaluable participants (n= 358) OR= 0.64 [0.36, 1.11]	⊕⊕⊕⊖: **MODERATE** Study quality:-1 (unclear rando, >20% dropout Consistency: na Directness: ok Imprecision:ok
Incidence of relapse	307 (1 study)	(subgroup children) Evaluable participants OR= 3.10 [0.67, 14.25] NS	⊕⊕⊕⊖: **MODERATE** Study quality: 1 (unclear rando, >20% dropout Consistency: na Directness: ok Imprecision: ok
Adverse events *Not specified*	489 (1 study)	(subgroup children) **ITT analysis** **OR=2.33 [1.06, 5.15]** **(more adverse events with azithromycin)**	⊕⊕⊕⊖: **MODERATE** Study quality: 1 (unclear rando, >20% dropout Consistency: na Directness: ok Imprecision:ok

Table 41

This Cochrane review compared treatment with azithromycin versus penicillin in confirmed GABHS infection of the throat (confirmed by throat culture and/or rapid test). Only double blind RCTs were included. Participants included in this review were both adults and children. We will report only the outcomes for which information in a paediatric population is available

Of the trials that reported on this comparison, only one was performed in a paediatric population. O' Doherty 1996{O'Doherty, 1996 #49}included children aged 2 to 13 and compared 3 days of azithromycin in two different doses (10 or 20 mg/kg) to 10 days of penicillin V at a total daily dose of 500 to 1000 mg.

The azithromycin dose of 20 mg/kg/day is higher than usually recommended in Belgium.

In children with group A streptococcal pharyngitis, treatment with azithromycin, compared to penicillin, **did not** result in a statistically significant difference in the *resolution of symptoms 5 to 10 days after treatment* or in the *incidence of relapse.*
GRADE: MODERATE quality of evidence

In children with group A streptococcal pharyngitis, treatment with azithromycin, compared to penicillin, resulted in a statistically significant **increase** of adverse events (not specified).
GRADE: MODERATE quality of evidence

5.2.3 Antibiotic A short duration versus antibiotic B longer duration

5.2.3.1 Azithromycin 10 mg/kg (3 days) vs penicillin (10 days)

5.2.3.1.1 Clinical evidence profile

Meta-analysis: Cochrane Altamimi 2012{Altamimi, 2012 #68} "Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children"

Inclusion criteria: Randomized controlled trials (RCTs) comparing short duration oral antibiotics (2-6 d)to standard duration (10 d)oral penicillin in children aged 1 to 18 years with acute GABHS pharyngitis based on a positive rapid antigen testing or positive throat swab culture for GABHS, conducted in the emergency department or physician's office (general practitioner, paediatrician or otolaryngologist).We excluded studies on GABHS carriers and studies using tools other than rapid antigen testing or throat swab culture to document GABHS pharyngitis. We selected 10 days of penicillin to be the control as it remains the recommended standard care due to its proven efficacy, narrow spectrum and low cost.

Search strategy: Cochrane Central Register of Controlled Trials (CENTRAL 2012, Issue 3) which contains the Cochrane Acute Respiratory Infections Group's Specialized Register, MEDLINE (January 1966 to March week 3, 2012) and EMBASE (January 1990 to April 2012)
Assessment of quality of included trials: yes
ITT analysis: All studies were analyzed by treatment received rather than by an intention- to-treat analysis
Other methodological remarks: /

Table 42

Ref	Comparison	N/n	Outcomes	Result (95% CI)
ref* Cochrane Altamimi 2012{Altamimi, 2012 #68} Design: SR +	Azithromycin 10 mg/kg for 3d vs penicillin V for 10 d	N= 6 n= 1366 (Cohen 2002a Hamill 1993 O'Doherty 1996a Pacifico 1996	**Early clinical treatment failure** defined as persistent sore throat, fever or both in the first two weeks after completion of antibiotic treatment.	Crude absolute rates 39/676 vs 38/690 OR 1.05 [0.66, 1.66] NS

MA Search date: (march/april 2012)		Schaad 1996 Schaad 2002)		
		N= 4 n= 869 (Cohen 2002a, O'Doherty 1996a Pacifico 1996 Schaad 2002)	**Late clinical recurrence** defined as recurrence of sore throat, fever or both after initial resolution, beyond the two-week period immediately after completion of antibiotic treatment	Crude absolute risk 33/428 vs 22/441 OR 1.62 [0.93, 2.83] NS
		N= 6 n= 1538 Cohen 2002a Hamill 1993 O'Doherty 1996a Pacifico 1996 Schaad 1996 Schaad 2002	**Side effects**	Crude absolute risk 83/772 vs 40/766 **OR 2.20 [1.49, 3.24]** **SS (more side effects with azithromycin)** *All reported adverse events were mild to moderate and self-limiting, most of the events involved the gastrointestinal system in both treatment groups.*
		Cohen 2002a	Compliance	see forest plot below
		Schaad 2002	Complications	see forest plot below

Table 43

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Altamimi 2012)
Cohen 2002a{Cohen, 2002 #30}	336	children aged 2 to 12 years; mean age 6 years. 181 males; 155 females	Early follow-up: on day 14 +/- 2 of the study	1. Penicillin 15 mg/kg/dose tds for 10 days 2. Azithromycin 10	ALLOCATION CONC: high risk of bias RANDO:

Prospective, comparative, randomized, multicenter trial			Late follow-up: on day 30 +/- 4 of the study	mg/kg/day od for 3 days	Adequate BLINDING : Participants/personnel high risk of bias No blinding or incomplete blinding and the outcome is likely to be influenced by lack of blinding BLINDING : outcome assessors high risk of bias No blinding of outcome assessment and the outcome measurement is likely to be influenced by lack of blinding INCOMPLETE OUTCOME DATA Low risk of bias SELECTIVE REPORTING low risk of bias ITT: no FUNDING: NR
Hamill 1993{Hamill, 1993 #37} Prospective, randomized, multicenter study	96	children aged 2 to 12 years; mean age 7.4 years. 51 males; 45 females	Early follow-up: at days 2 to 3 and 9 to 11 of the study Late follow-up: at day 29 to 31 of the study	1. Penicillin V 125 or 250 mg qds for 10 days 2. Azithromycin 10 mg/kg once a day for 3 days	ALLOCATION CONC: unclear risk (not mentioned) RANDO: unclear risk BLINDING : Participants/personnel high risk of bias No blinding BLINDING : outcome assessors high risk of bias No blinding INCOMPLETE OUTCOME DATA Low risk of bias SELECTIVE REPORTING low risk of bias

					ITT: no FUNDING: NR
O'Doherty 1996a{O'Doherty, 1996 #49} - RCT - Double-blinded - Double-dummy	489	children aged 2 to 13 years; mean age 7.7 years. 236 males; 253 females	Early follow-up: 2 to 4 days after completion of antibiotics Late follow-up: 28 to 30 days after completion of antibiotics	1. Penicillin V 125 to 250 mg qds for 10 days 2. Azithromycin 10 mg/kg od for 3 days	ALLOCATION CONC: unclear RANDO: unclear BLINDING : Adequate INCOMPLETE OUTCOME DATA unclear risk of bias: Dropout 131 participants: absence of pathogen (azithromycin 20 mg = 36; azithromycin 10mg = 30; penicillin = 26), deviation from protocol (azithromycin 20 mg = 10; azithromycin 10 mg = 8; penicillin = 3), adverse event (azithromycin 20 mg = 11; azithromycin 10 mg = 5; penicillin = 2) SELECTIVE REPORTING: unclear risk of bias: Only clinical (and bacteriological) cure reported, no specific symptoms in outcome analysis ITT: no FUNDING: not reported
Pacifico 1996{Pacifico, 1996 #51} Prospective,	183	children aged 3 to 12 years. 75 males; 79 females	Follow-up: at baseline, day 4 to 5, day 12 to 14 and day 34 to 36	1. Penicillin V 50,000 IU/kg/day in 2 divided doses for 10 days 2. Azithromycin 10	ALLOCATION CONC: unclear RANDO: low risk of bias

randomized, open study				mg/kg/day od for 3 days	BLINDING : high risk of bias INCOMPLETE OUTCOME DATA high risk of bias For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate SELECTIVE REPORTING: low risk of bias ITT: no FUNDING: not reported
Schaad 1996{Schaad, 1996 #57} Open, comparative, multicenter study	343	children aged 6 months to 14 years; mean age 7 years. 171 males; 172 females	Follow-up 10 to 14 and 20 to 30 days after the start of treatment	1. Penicillin V 100,000 IU = 56 mg/kg tid for 10 days 2. Azithromycin 10 mg/kg od for 3 days	ALLOCATION CONC: high risk RANDO: low risk of bias BLINDING : high risk of bias INCOMPLETE OUTCOME DATA low risk of bias For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate SELECTIVE REPORTING: low risk of bias ITT: no FUNDING: not reported
Schaad 2002{Schaad, 2002 #58}	292	children aged 2 to 12 years	Follow-up at study days 14 and 28	1. Penicillin V 100,000 IU/kg/day tid for 10 days 2. Azithromycin 10	ALLOCATION CONC: high risk of bias RANDO:

Multicenter, randomized, comparative, open-label study				mg/kg/day od for 3 days	unclear BLINDING : participants and personnel high risk of bias outcome assessors: low risk of bias INCOMPLETE OUTCOME DATA low risk of bias SELECTIVE REPORTING: low risk of bias ITT: no FUNDING: not reported

Table 44

5.2.3.1.2 Summary and conclusions

Azithromycin 10 mg/kg short duration (3 days) vs penicillin standard duration (10 days) in GABHS			
Bibliography: Cochrane Altamimi 2012{Altamimi, 2012 #68}			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Early clinical treatment failure	1366 (6 studies)	OR 1.05 [0.66, 1.66] NS	⊕⊕⊕⊖: **MODERATE** Study quality:-1 (no or inadequate blinding, no ITT) Consistency: ok Directness: ok Imprecision:ok
Late clinical recurrence	869 (4 studies)	OR 1.62 [0.93, 2.83] NS	⊕⊕⊕⊖: **MODERATE** Study quality: 1 (no or inadequate blinding, no ITT) Consistency: ok Directness: ok Imprecision:ok
Adverse effects	1538 (6 studies)	**OR 2.20 [1.49, 3.24]** **SS (more side effects with azithromycin)**	⊕⊕⊕⊖: **MODERATE** Study quality: 1 (no or inadequate blinding, no ITT) Consistency: ok Directness: ok Imprecision:ok

Table 45

In this Cochrane systematic review and meta-analysis, RCT's comparing short duration oral antibiotics (2-6 days) versus a standard treatment of 10 days of oral penicillin in children with confirmed GABHS pharyngitis were included. This subanalysis investigated the effect of azithromycin 10 mg/kg for 3 days versus a standard treatment of penicillin for 10 days.

In contrast to Cochrane Van Driel{van Driel, 2013 #73}, which also compared the treatment effect of azithromycin versus penicillin, this systematic review included unblinded studies in addition to those that were blinded. Most of the trials included children aged 2 to 12-13; one trial included children older than 6 months.

Most trials were inadequately blinded, and none were analysed by intention to treat.

In children with confirmed GABHS pharyngitis, a treatment with azithromycin 10 mg/kg for 3 days, compared to penicillin for 10 days, **did not** result in a statistically significant difference in early clinical treatment failure, or in late clinical recurrence.
GRADE: MODERATE quality of evidence

In children with confirmed GABHS pharyngitis, a treatment with azithromycin 10 mg/kg for 3 days, compared to penicillin for 10 days, resulted in a statistically significant **increase** of adverse effects.
GRADE: MODERATE quality of evidence

5.2.3.2 Azithromycin 20 mg/kg (3days) vs penicillin (10 days)

5.2.3.2.1 Clinical evidence profile

Meta-analysis: Cochrane Altamimi 2012{Altamimi, 2012 #68} "Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children"

Inclusion criteria: Randomized controlled trials (RCTs) comparing short duration oral antibiotics (2-6 d) to standard duration (10 d) oral penicillin in children aged 1 to 18 years with acute GABHS pharyngitis based on a positive rapid antigen testing or positive throat swab culture for GABHS, conducted in the emergency department or physician's office (general practitioner, paediatrician or otolaryngologist).We excluded studies on GABHS carriers and studies using tools other than rapid antigen testing or throat swab culture to document GABHS pharyngitis. We selected 10 days of penicillin to be the control as it remains the recommended standard care due to its proven efficacy, narrow spectrum and low cost.

Search strategy: Cochrane Central Register of Controlled Trials (CENTRAL 2012, Issue 3) which contains the Cochrane Acute Respiratory Infections Group's Specialized Register, MEDLINE (January 1966 to March week 3, 2012) and EMBASE (January 1990 to April 2012)

Assessment of quality of included trials: yes
ITT analysis: All studies were analyzed by treatment received rather than by an intention- to-treat analysis
Other methodological remarks: /

Table 46

Ref	Comparison	N/n	Outcomes	Result (95% CI)
ref* Cochrane Altamimi 2012{Altamimi, 2012 #68} Design: SR + MA	Azithromycin 20 mg/kg for 3 d vs penicillin for 10 d	N= 2 n= 520 Cohen 2002b O'Doherty 1996b	**Early clinical treatment failure** defined as persistent sore throat, fever or both in the first two weeks after completion of antibiotic treatment.	Crude absolute rates 0/242 vs 12/278 **OR 0.08 [0.01, 0.64]** **SS in favour of azithromycine**
		N= 2 n= 465 Cohen 2002b O'Doherty	**Late clinical recurrence** defined as recurrence of sore throat, fever or both after initial resolution, beyond the two-week period	Crude absolute rates 12/227 vs 13/238 OR 0.94 [0.42, 2.09] NS

Search date: (march/april 2012)		1996b	immediately after completion of antibiotic treatment	
		N= 2 n= 653 Cohen 2002b O'Doherty 1996b	**Side effects**	Crude absolute rates 57/324 vs 13/329 **OR 5.13 [2.76, 9.54]** **SS (more side effects with azithromycin)**
		Cohen 2002b	Compliance	see forest plot below

Table 47

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Cohen 2002b{Cohen, 2002 #30} Prospective, comparative, randomized, multicenter trial	332	children aged 2 to 12 years. 175 males; 165 females	Early follow-up day 14 +/- 2 of the study Late follow-up on day 30 +/- 4 of the study	1. Penicillin 15 mg/kg/dose tds for 10 days 2. Azithromycin 20 mg/kg/day od for 3 days	ALLOCATION CONC: high risk of bias RANDO: Adequate BLINDING : Participants/personnel high risk of bias No blinding or incomplete blinding and the outcome is likely to be influenced by lack of blinding BLINDING : outcome assessors high risk of bias No blinding of outcome assessment and the outcome measurement is likely to be influenced by lack of blinding INCOMPLETE OUTCOME DATA Low risk of bias

					SELECTIVE REPORTING low risk of bias ITT: no FUNDING: NR
O'Doherty 1996b{O'Doherty, 1996 #49} - RCT - Double-blinded - Double-dummy	489	children aged 2 to 13 years; mean age 7.7 years. 236 males; 253 females	Early follow-up: 2 to 4 days after completion of antibiotics Late follow-up: 28 to 30 days after completion of antibiotics	1. Penicillin V 125 to 250 mg qds for 10 days 2. Azithromycin 20 mg/kg od for 3 days	ALLOCATION CONC: unclear RANDO: unclear BLINDING : Adequate INCOMPLETE OUTCOME DATA unclear risk of bias: Dropout 131 participants: absence of pathogen (azithromycin 20 mg = 36; azithromycin 10mg = 30; penicillin = 26), deviation from protocol (azithromycin 20 mg = 10; azithromycin 10 mg = 8; penicillin = 3), adverse event (azithromycin 20 mg = 11; azithromycin 10 mg = 5; penicillin = 2) SELECTIVE REPORTING: unclear risk of bias: Only clinical (and bacteriological) cure reported, no specific symptoms in outcome analysis ITT: no FUNDING: not reported

Table 48

5.2.3.2.2 Summary and conclusions

Azithromycin 20 mg/kg short duration (3 days) vs penicillin standard duration (10 days) in GABHS			
Bibliography: Cochrane Altamimi 2012{Altamimi, 2012 #68}			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Early clinical treatment failure	520 (2studies)	**OR 0.08 [0.01, 0.64] SS (fewer early clinical treatment failures with azithromycin)**	⊕⊖⊖⊖: **VERY LOW** Study quality:-1 (no blinding, no ITT) Consistency: -1 Directness: -1 (high dose) Imprecision:ok
Late clinical recurrence	465 (2 studies)	OR 0.94 [0.42, 2.09] NS	⊖⊖⊖⊖: **VERY LOW** Study quality: 1 (no blinding, no ITT) Consistency: -1 Directness: -1 (high dose) Imprecision:-1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Adverse effects	653 (2 studies)	**OR 5.13 [2.76, 9.54] SS (more side effects with azithromycin)**	⊕⊕⊖⊖: **LOW** Study quality: -1 (no blinding, no ITT) Consistency: ok Directness: -1 (high dose) Imprecision:ok

Table 49

In this Cochrane systematic review and meta-analysis, RCT's comparing short duration oral antibiotics (2-6 days) versus a standard treatment of 10 days of oral penicillin in children with confirmed GABHS pharyngitis were included. This subanalysis investigated the effect of azithromycin 20 mg/kg for 3 days versus a standard treatment of penicillin for 10 days.

In contrast to Cochrane Van Driel{van Driel, 2013 #73}, which also compared the treatment effect of azithromycin versus penicillin, this systematic review included unblinded studies in addition to those that were blinded. The trials included children aged 2 to 12-13.

A dose of 20mg/kg/day is a higher dose than usually recommended in Belgium.

One trial was unblinded and none were analysed by intention to treat.

In children with confirmed GABHS pharyngitis, a treatment with azithromycin 20 mg/kg for 3 days, compared to penicillin for 10 days, resulted in a statistically significant **decrease** in *early clinical treatment failure*.
GRADE: VERY LOW quality of evidence

In children with confirmed GABHS pharyngitis, a treatment with azithromycin 20 mg/kg for 3 days, compared to penicillin for 10 days, **did not** result in a statistically significant difference in *late clinical recurrence.*
GRADE: VERY LOW quality of evidence

In children with confirmed GABHS pharyngitis, a treatment with azithromycin 20 mg/kg for 3 days, compared to penicillin for 10 days, resulted in a statistically significant **increase** of adverse effects.
GRADE: LOW quality of evidence

5.2.3.3 Clarithromycin (different doses) short duration (5 days) vs penicillin standard duration (10 days)

5.2.3.3.1 Clinical evidence profile

Meta-analysis: Cochrane Altamimi 2012{Altamimi, 2012 #68} "Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children"

Inclusion criteria: Randomized controlled trials (RCTs) comparing short duration oral antibiotics (2-6 d) to standard duration (10 d) oral penicillin in children aged 1 to 18 years with acute GABHS pharyngitis based on a positive rapid antigen testing or positive throat swab culture for GABHS, conducted in the emergency department or physician's office (general practitioner, paediatrician or otolaryngologist).We excluded studies on GABHS carriers and studies using tools other than rapid antigen testing or throat swab culture to document GABHS pharyngitis. We selected 10 days of penicillin to be the control as it remains the recommended standard care due to its proven efficacy, narrow spectrum and low cost.

Search strategy: Cochrane Central Register of Controlled Trials (CENTRAL 2012, Issue 3) which contains the Cochrane Acute Respiratory Infections Group's Specialized Register, MEDLINE (January 1966 to March week 3, 2012) and EMBASE (January 1990 to April 2012)

Assessment of quality of included trials: yes
ITT analysis: All studies were analyzed by treatment received rather than by an intention- to-treat analysis
Other methodological remarks: /

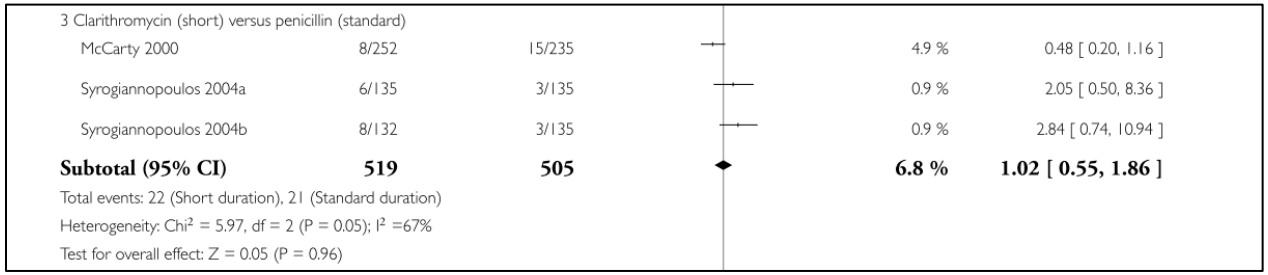
Table 50

Ref	Comparison	N/n	Outcomes	Result (95% CI)
ref* Cochrane Altamimi 2012{Altamimi, 2012 #68} Design: SR + MA	Clarithromycin 15 or 30mg/kg/d bid for 5 days vs penicillin for 10 d	N= 3 n= 1024 (McCarty 2000 Syrogiannopoulos 2004a Syrogiannopoulos 2004b)	**Early clinical treatment failure** defined as persistent sore throat, fever or both in the first two weeks after completion of antibiotic treatment.	Crude absolute rates 22/519 vs 21/505 OR 1.02 [0.55, 1.86] NS
		N= 3	**Late clinical recurrence**	Crude absolute rates 63/473 vs 49/459

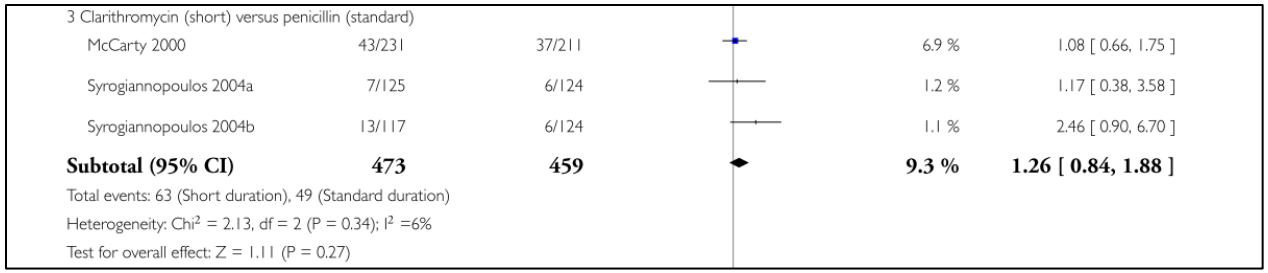
Search date: (march/april 2012)		n= 932 McCarty 2000 Syrogiannopoulos 2004a Syrogiannopoulos 2004b	defined as recurrence of sore throat, fever or both after initial resolution, beyond the two-week period immediately after completion of antibiotic treatment	OR 1.26 [0.84, 1.88] NS
		N= 3 n= 1157 McCarty 2000 Syrogiannopoulos 2004a Syrogiannopoulos 2004b	**Side effects**	Crude absolute rates 81/581 vs 48/576 **OR 1.77 [1.22, 2.58]** **SS (more side effects with clarithromycin)** *All reported adverse events were mild to moderate and self-limiting, most of the events involved the gastrointestinal system in both treatment groups.*
		McCarty 2000	Compliance	see forest plot below

Table 51

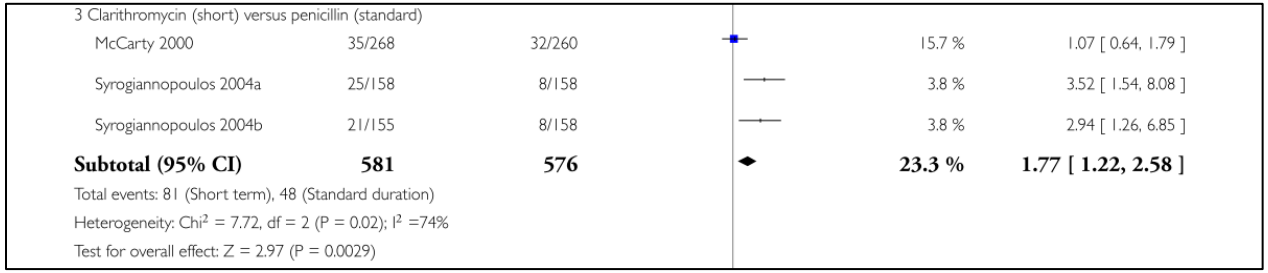
* Characteristics of included studies: see below



Figuur 1Clarithromycin short versus penicillin standard: early clinical treatment failure



Figuur 2 Clarithromycin short versus penicillin standard: late clinical recurrence



Figuur 3Clarithromycin short versus penicillin standard: side effects

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by the Cochrane authors)
McCarty 2000{McCarty, 2000 #45} Randomized, comparative, multicenter study	528	children aged 6 months to 12 years; mean age 90 months. 289 males; 239 females	Early follow-up: at 1 to 4 days after completion of the antibiotic duration Late follow-up: at 28 to 32 days after completion of the antibiotic duration	1. Penicillin V 13.3 mg/kg tid for 10 days 2. Clarithromycin 7.5 mg/kg bid for 5 days	ALLOCATION CONC: unclear risk RANDO: unclear risk BLINDING : Participants/personnel high risk of bias BLINDING : outcome assessors high risk of bias INCOMPLETE OUTCOME DATA High risk of bias For dichotomous outcome data, the proportion of missing outcomes comparedwith observed event risk enough to induce clinically relevant bias in intervention effect estimate SELECTIVE REPORTING low risk of bias ITT: no FUNDING: NR
Syrogiannopoulos 2004a{Syrogiannopoulos, 2004 #61} Multicenter, randomized, comparative, open-label study	316	children aged 2 to 15 years	Follow-up: day 4 to 8 and 21 to 28 after completion of therapy	1. Penicillin V 30 mg/kg/day tid for 10 days 2. Clarithromycin 30 mg/kg/day in 2 divided doses (max. 500 mg/dose) for 5 days	ALLOCATION CONC: high risk RANDO: unclear risk BLINDING : Participants/personnel high risk of bias BLINDING : outcome assessors high risk of bias INCOMPLETE OUTCOME DATA Low risk of bias SELECTIVE REPORTING

					low risk of bias ITT: no FUNDING: NR
Syrogiannopoulos 2004b{Syrogiannopoulos, 2004 #61} Multicenter, randomized, comparative, open-label study	313	children aged 1 to 17 years	Follow-up:day 4 to 8 and 21 to 28 after completion of therapy	1. Penicillin V 30 mg/kg/day in 3 divided doses for 10 days 2. Clarithromycin 15 mg/kg/day bid (max. 250 mg/bid) for 5 days	ALLOCATION CONC: high risk RANDO: unclear risk BLINDING : Participants/personnel high risk of bias BLINDING : outcome assessors high risk of bias INCOMPLETE OUTCOME DATA Low risk of bias SELECTIVE REPORTING low risk of bias ITT: no FUNDING: NR

Table 52

5.2.3.3.2 Summary and conclusions

Clarithromycin (different doses) short duration (5 days) vs penicillin standard duration (10 days) in GABHS			
Bibliography: Cochrane Altamimi 2012{Altamimi, 2012 #68}			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Early clinical treatment failure	1024 (3 studies)	OR 1.02 [0.55, 1.86] NS	⨁⨁⨁⊖: **MODERATE** Study quality: -1 (no blinding, no ITT) Consistency: ok Directness: ok Imprecision:ok
Late clinical recurrence	932 (3 studies)	OR 1.26 [0.84, 1.88] NS	⨁⨁⨁⊖: **MODERATE** Study quality: -1 (no blinding, no ITT) Consistency: ok Directness: ok Imprecision:ok
Adverse effects	1157 (3 studies)	**OR 1.77 [1.22, 2.58]** **SS (more side effects with clarithromycin)**	⨁⨁⊖⊖: **LOW** Study quality: -1 (no blinding, no ITT) Consistency: -1 Directness: ok Imprecision:ok

Table 53

In this Cochrane systematic review and meta-analysis, RCTs comparing short duration oral antibiotics (2-6 days) versus a standard treatment of 10 days of oral penicillin in children with confirmed GABHS pharyngitis were included. This subanalysis investigated the effect of clarithromycin for 5 days versus a standard treatment of penicillin for 10 days.

In one trial, the clarithromycin dose was 30 mg/kg/day, while in the other two trials the dose was 15 mg/kg/day. The trials included children aged 6 months to 17 years.

None of the trials were blinded, and none were analysed by intention to treat.

In children with confirmed GABHS pharyngitis, a treatment with clarithromycin for 5 days, compared to penicillin for 10 days, **did not** result in a statistically significant difference in early clinical treatment failure, or in late clinical recurrence.
GRADE: MODERATE quality of evidence

In children with confirmed GABHS pharyngitis, a treatment with clarithromycin for 5 days, compared to penicillin for 10 days, resulted in a statistically significant **increase** of adverse effects.
GRADE: LOW quality of evidence

5.2.3.4 Cefuroxime 20 - 40 mg/kg/d short duration (4 - 5 days) vs penicillin standard duration (10 days)

5.2.3.4.1 Clinical evidence profile

Meta-analysis: Cochrane Altamimi 2012{Altamimi, 2012 #68} "Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children"

Inclusion criteria: Randomized controlled trials (RCTs) comparing short duration oral antibiotics (2-6 d) to standard duration (10 d) oral penicillin in children aged 1 to 18 years with acute GABHS pharyngitis based on a positive rapid antigen testing or positive throat swab culture for GABHS, conducted in the emergency department or physician's office (general practitioner, paediatrician or otolaryngologist).We excluded studies on GABHS carriers and studies using tools other than rapid antigen testing or throat swab culture to document GABHS pharyngitis. We selected 10 days of penicillin to be the control as it remains the recommended standard care due to its proven efficacy, narrow spectrum and low cost.

Search strategy: Cochrane Central Register of Controlled Trials (CENTRAL 2012, Issue 3) which contains the Cochrane Acute Respiratory Infections Group's Specialized Register, MEDLINE (January 1966 to March week 3, 2012) and EMBASE (January 1990 to April 2012)

Assessment of quality of included trials: yes
ITT analysis: All studies were analyzed by treatment received rather than by an intention- to-treat analysis
Other methodological remarks: /

Table 54

Ref	Comparison	N/n	Outcomes	Result (95% CI)
ref* Cochrane Altamimi 2012{Altamimi, 2012 #68} Design: SR + MA	Cefuroxime short duration vs penicillin 10 d	N=2 n= 2152 (Aujard 1995 Scholz 2004)	**Early clinical treatment failure** defined as persistent sore throat, fever or both in the first two weeks after completion of antibiotic treatment.	Crude absolute rates 20/539 vs 103/1559 **OR 0.49 [0.30, 0.81]** **SS in favour of cefuroxime**
		N= 1 n= 158 Aujard 1995	**Late clinical recurrence** defined as recurrence of sore throat, fever or both after initial resolution, beyond the two-week period immediately after completion of	Crude absolute rates 5/72 vs 3/86 OR 2.06 [0.48, 8.95] NS

Search date: (march/april 2012)			antibiotic treatment	
		N= 2 n= 2331 Aujard 1995 Scholz 2004	**Side effects**	Crude absolute rates 16/641 vs 21/1690 OR 1.88 [0.97, 3.62] NS *All reported adverse events were mild to moderate and self-limiting, most of the events involved the gastrointestinal system in both treatment groups.*
		Aujard 1995	Compliance	see forest plot below
		Scholz 2004	Complications	see forest plot below

Table 55

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Aujard 1995{Aujard, 1995 #26}	308	children aged 2 to 15 years; mean age 6.9 years. 92 males; 108 females	Early follow-up: 2 to 4 days after completion of therapy Late follow-up: 28 to 32 days after completion of therapy	1. Penicillin V 45 mg/kg/day, in 3 divided doses for 10 days 2. Cefuroxime axetil 20 mg/kg/dose bid for 4 days	ALLOCATION CONC: high risk RANDO: low risk BLINDING : Participants/personnel high risk of bias BLINDING : outcome assessors high risk of bias INCOMPLETE OUTCOME DATA High risk of bias For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant

					bias in intervention effect estimate SELECTIVE REPORTING low risk of bias ITT: no FUNDING: NR
Scholz 2004{Scholz, 2004 #59} Multicenter, randomized, open-label, comparative study	1975	children aged 1 to 17 years	Follow-up: Day 7 to 9 and 12 to 14 in short duration group Day 12 to 14 and 17 to 19 in control group	1. Penicillin V 50,000 IU/kg/day (30 mg/kg) tid for 10 days 2. Cefuroxime axetil 20 mg/kg/day (max 500 mg) bid for 5 days	ALLOCATION CONC: high risk RANDO: unclear risk BLINDING : Participants/personnel high risk of bias BLINDING : outcome assessors high risk of bias INCOMPLETE OUTCOME DATA Low risk of bias SELECTIVE REPORTING low risk of bias ITT: no FUNDING: NR

Table 56

5.2.3.4.2 Summary and conclusions

Cefuroxime 20 - 40 mg/kg/d short duration (4 - 5 days) vs penicillin standard duration (10 days) in GABHS			
Bibliography: Cochrane Altamimi 2012{Altamimi, 2012 #68}			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Early clinical treatment failure	2152 (2 studies)	**OR 0.49 [0.30, 0.81]** **SS** **(fewer early clinical treatment failures with cefuroxime)**	⨁⨁⨁⨀: **MODERATE** Study quality: -1 (no blinding, no ITT) Consistency: ok Directness: ok Imprecision: ok
Late clinical recurrence	158 (1 study)	OR 2.06 [0.48, 8.95] NS	⨁⨁⨀⨀: **LOW** Study quality: -1 (no blinding, no ITT) Consistency: not applicable Directness: ok Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Adverse effects	2331 (2 studies)	OR 1.88 [0.97, 3.62] NS	⨁⨁⨁⨀: **MODERATE** Study quality: -1 (no blinding, no ITT) Consistency: ok Directness: ok Imprecision: ok

Table 57

In this Cochrane systematic review and meta-analysis, RCTs comparing short duration oral antibiotics (2-6 days) versus a standard treatment of 10 days of oral penicillin in children with confirmed GABHS pharyngitis were included. This subanalysis investigated the effect of cefuroxime for 4-5 days versus a standard treatment of penicillin for 10 days.

In one trial, the cefuroxime dose was 20 mg/kg/day, while in the other trial the dose was 40 mg/kg/day. The trials included children aged 1 to 17 years.

None of the trials were blinded, and none were analysed by intention to treat.

In children with confirmed GABHS pharyngitis, a treatment with cefuroxime for 4-5 days, compared to penicillin for 10 days, resulted in a statistically significant **decrease** in early clinical treatment failure.
GRADE: MODERATE quality of evidence

In children with confirmed GABHS pharyngitis, a treatment with cefuroxime for 4-5 days, compared to penicillin for 10 days, **did not** result in a statistically significant difference in late clinical recurrence.
GRADE: LOW quality of evidence

In children with confirmed GABHS pharyngitis, a treatment with cefuroxime for 4-5 days, compared to penicillin for 10 days, **did not** result in a statistically significant difference in adverse effects.
GRADE: MODERATE quality of evidence

5.2.3.5 Erythromycin 40 mg/kg (5 days) vs penicillin V standard duration (10 days)

5.2.3.5.1 Clinical evidence profile

Meta-analysis: Cochrane Altamimi 2012{Altamimi, 2012 #68} "Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children"

Inclusion criteria: Randomized controlled trials (RCTs) comparing short duration oral antibiotics (2-6 d) to standard duration (10 d) oral penicillin in children aged 1 to 18 years with acute GABHS pharyngitis based on a positive rapid antigen testing or positive throat swab culture for GABHS, conducted in the emergency department or physician's office (general practitioner, paediatrician or otolaryngologist). We excluded studies on GABHS carriers and studies using tools other than rapid antigen testing or throat swab culture to document GABHS pharyngitis. We selected 10 days of penicillin to be the control as it remains the recommended standard care due to its proven efficacy, narrow spectrum and low cost.

Search strategy: Cochrane Central Register of Controlled Trials (CENTRAL 2012, Issue 3) which contains the Cochrane Acute Respiratory Infections Group's Specialized Register, MEDLINE (January 1966 to March week 3, 2012) and EMBASE (January 1990 to April 2012)

Assessment of quality of included trials: yes
ITT analysis: All studies were analyzed by treatment received rather than by an intention- to-treat analysis
Other methodological remarks:

Table 58

Ref	Comparison	N/n	Outcomes	Result (95% CI)
ref* Cochrane Altamimi 2012{Altamimi, 2012 #68} Design: SR + MA	Erythromycin 40 mg/kg/d 5 days vs penicillin V 50,000 IU/kg/d 10 days	N=1 n= 227 Adam 1996	**Early clinical treatment failure** defined as persistent sore throat, fever or both in the first two weeks after completion of antibiotic treatment.	per protocol analysis absolute rates 2/102 vs 2/99 OR 0.97 [0.13, 7.02] NS
		N= 1 n= 227 Adam 1996	**Late clinical recurrence** defined as recurrence of sore throat, fever or both after initial resolution, beyond the two-week period immediately after completion of	per protocol analysis absolute rates 10/102 vs 6/99 OR 1.68 [0.59, 4.83] NS

Search date: (march/april 2012)			antibiotic treatment	
		N= 1 n= 227 Adam 1996	Side effects	absolute rates 10/115 vs 8/112 OR 1.24 [0.47, 3.26] NS *All reported adverse events were mild to moderate and self-limiting, most of the events involved the gastrointestinal system in both treatment groups.*
		N= 1 n= 227 Adam 1996	Compliance	see forest plot below

Table 59

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Cochrane Altamimi 2012)
Adam 1996{Adam, 1996 #24} Multicenter, randomized, open-label, controlled study	227	participants aged from 1 to 17 years; mean age 7.1 years. 103 males; 98 females	Early follow-up: 1 to 3 days after the end of therapy Late follow-up: 6 +/- 2 weeks after the end of therapy	1. Penicillin V 50,000 IU/kg/d (30 mg/kg/d in three divided doses for ten days) 2. Erythromycin estolate (40 mg/kg/d in two divided doses for five days)	ALLOCATION CONC: high risk RANDO: low risk BLINDING : Participants/personnel high risk of bias BLINDING : outcome assessors high risk of bias INCOMPLETE OUTCOME DATA Low risk of bias SELECTIVE REPORTING low risk of bias ITT: no FUNDING: NR

Table 60

5.2.3.5.2 Summary and conclusions

Erythromycin 40 mg/kg (5 days) vs penicillin V standard duration (10 days)			
Bibliography: Cochrane Altamimi 2012{Altamimi, 2012 #68}			
Outcomes	**N° of participants (studies) Follow up**	**Results (OR[95%CI])**	**Quality of the evidence (GRADE)**
Early clinical treatment failure *defined as persistent sore throat, fever or both in the first two weeks after completion of antibiotic treatment.*	227 (1 study)	OR 0.97 [0.13, 7.02] NS	⨁⨁⨀⨀: **LOW** Study quality:-1 (no blinding) Consistency: na Directness: ok Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Late clinical recurrence *defined as recurrence of sore throat, fever or both after initial resolution, beyond the two-week period immediately after completion of antibiotic treatment*	277 (1 study)	OR 1.68 [0.59, 4.83] NS	⨁⨁⨁⨀: **MODERATE** Study quality: -1 (no blinding) Consistency: na Directness: ok Imprecision: ok
Adverse events	277 (1 study)	OR 1.24 [0.47, 3.26] NS	⨁⨁⨀⨀: **LOW** Study quality: 1 (no blinding) Consistency: na Directness: ok Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)

Table 61

In this Cochrane systematic review and meta-analysis, RCTs comparing short duration oral antibiotics (2-6 days) versus a standard treatment of 10 days of oral penicillin in children with confirmed GABHS pharyngitis were included. In one study, a 5-day course of erythromycin was compared to 10 days of penicillin.

This trial included children aged 1 to 17 years.

As there is only one RCT with methodological flaws (no blinding) that investigated this comparison, our confidence in the outcome effects is limited.

In children with confirmed GABHS pharyngitis, a treatment with erythromycin for 5 days, compared to penicillin for 10 days, **did not** result in a statistically significant difference in *late clinical recurrence*.
GRADE: MODERATE quality of evidence

In children with confirmed GABHS pharyngitis, a treatment with erythromycin for 5 days, compared to penicillin for 10 days, **did not** result in a statistically significant difference in *early clinical treatment failur*e, nor in *adverse effects*.
GRADE: LOW quality of evidence

5.2.3.6 Amoxicillin 50 mg/kg/d short duration (6 days) vs penicillin standard duration (10 days)

5.2.3.6.1 Clinical evidence profile

Meta-analysis: Cochrane Altamimi 2012{Altamimi, 2012 #68} "Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children"

Inclusion criteria: Randomized controlled trials (RCTs) comparing short duration oral antibiotics (2-6 d) to standard duration (10 d) oral penicillin in children aged 1 to 18 years with acute GABHS pharyngitis based on a positive rapid antigen testing or positive throat swab culture for GABHS, conducted in the emergency department or physician's office (general practitioner, paediatrician or otolaryngologist).We excluded studies on GABHS carriers and studies using tools other than rapid antigen testing or throat swab culture to document GABHS pharyngitis. We selected 10 days of penicillin to be the control as it remains the recommended standard care due to its proven efficacy, narrow spectrum and low cost.

Search strategy: Cochrane Central Register of Controlled Trials (CENTRAL 2012, Issue 3) which contains the Cochrane Acute Respiratory Infections Group's Specialized Register, MEDLINE (January 1966 to March week 3, 2012) and EMBASE (January 1990 to April 2012)

Assessment of quality of included trials: yes
ITT analysis: All studies were analyzed by treatment received rather than by an intention- to-treat analysis
Other methodological remarks:

Table 62

Ref	Comparison	N/n	Outcomes	Result (95% CI)
ref* Cochrane Altamimi 2012{Altamimi, 2012 #68} Design: SR + MA	Amoxicillin 25 mg/kg/dose bid for 6 days vs penicillin V 15 mg/kg/day tds for 10	N=1 n= 321 Cohen 1996	**Early clinical treatment failure** defined as persistent sore throat, fever or both in the first two weeks after completion of antibiotic treatment.	per protocol analysis absolute rates 13/141 vs 15/136 OR 0.82 [0.37, 1.79] NS
		N=1 n= 321 Cohen 1996	**Late clinical recurrence** defined as recurrence of sore throat, fever or both after initial resolution, beyond the two-week period	per protocol analysis absolute rates9/111 vs 6/105 OR 1.46 [0.50, 4.24] NS

Search date: (march/april 2012)	days		immediately after completion of antibiotic treatment	
		N=1 n= 321 Cohen 1996	**Side effects**	absolute rates 4/160 vs 8/158 OR 1.82 [0.65, 5.10] NS *All reported adverse events were mild to moderate and self-limiting, most of the events involved the gastrointestinal system in both treatment groups.*
		N=1 n= 321 Cohen 1996	Compliance	see forest plot below

Table 63

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Cohen 1996{Cohen, 1996 #29} Prospective, comparative, open, randomized multicenter trial	321	patients aged 3 to 15 years; mean age 5.9. 153 males; 165 females	Early follow-up: 4 days after completion of therapy Late follow-up: 1 month after completion of therapy	1. penicillin V (45 mg/kg/day divided into three doses/day) 2. amoxicillin (50 mg/kg/day divided twice daily)for 6 days	ALLOCATION CONC: high risk RANDO: low risk BLINDING : Participants/personnel high risk of bias BLINDING : outcome assessors high risk of bias INCOMPLETE OUTCOME DATA High risk of bias Reason for missing outcome data is likely to be related to true outcome, with either imbalance in numbers of reasons for missing data across intervention groups

					SELECTIVE REPORTING low risk of bias ITT: no FUNDING: NR

Table 64

5.2.3.6.2 Summary and conclusions

Amoxicillin 50 mg/kg/d short duration (6 days) vs penicillin standard duration (10 days) in GABHS			
Bibliography: Cochrane Altamimi 2012{Altamimi, 2012 #68}			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Early clinical treatment failure	321 (1 study)	OR 0.82 [0.37, 1.79] NS	⨁⨁⨀⨀: **LOW** Study quality: -1 (no blinding, no ITT) Consistency: not applicable Directness: ok Imprecision:-1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Late clinical recurrence	321 (1 study)	OR 1.46 [0.50, 4.24] NS	⨁⨁⨀⨀: **LOW** Study quality: -1 (no blinding, no ITT) Consistency: not applicable Directness: ok Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Adverse effects	321 (1 study)	OR 1.82 [0.65, 5.10] NS	⨁⨁⨁⨀: **MODERATE** Study quality: -1 (no blinding, no ITT) Consistency: not applicable Directness: ok Imprecision: ok

Table 65

In this Cochrane systematic review and meta-analysis, RCTs comparing short duration oral antibiotics (2-6 days) versus a standard treatment of 10 days of oral penicillin in children with confirmed GABHS pharyngitis were included. In one study, a 6-day course of amoxicillin was compared to 10 days of penicillin.

This trial included children aged 3 to 15 years.

As there is only one RCT with serious methodological flaws (no blinding, no intention to treat analysis, incomplete outcome data) that investigated this comparison, our confidence in the outcome effects is severely limited.

In children with confirmed GABHS pharyngitis, a treatment with amoxicillin for 6 days, compared to penicillin for 10 days, **did not** result in a statistically significant difference in *adverse effects*.
GRADE: MODERATE quality of evidence

In children with confirmed GABHS pharyngitis, a treatment with amoxicillin for 6 days, compared to penicillin for 10 days, **did not** result in a statistically significant difference in *early clinical treatment failure* or *late clinical recurrence*.

GRADE: LOW quality of evidence

5.2.3.7 Amoxicilline/clavulanate short duration (5days) vs penicillin standard duration (10 days)

5.2.3.7.1 Clinical evidence profile

Meta-analysis: Cochrane Altamimi 2012{Altamimi, 2012 #68} "Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children"

Inclusion criteria: Randomized controlled trials (RCTs) comparing short duration oral antibiotics (2-6 d) to standard duration (10 d) oral penicillin in children aged 1 to 18 years with acute GABHS pharyngitis based on a positive rapid antigen testing or positive throat swab culture for GABHS, conducted in the emergency department or physician's office (general practitioner, paediatrician or otolaryngologist).We excluded studies on GABHS carriers and studies using tools other than rapid antigen testing or throat swab culture to document GABHS pharyngitis. We selected 10 days of penicillin to be the control as it remains the recommended standard care due to its proven efficacy, narrow spectrum and low cost.

Search strategy: Cochrane Central Register of Controlled Trials (CENTRAL 2012, Issue 3) which contains the Cochrane Acute Respiratory Infections Group's Specialized Register, MEDLINE (January 1966 to March week 3, 2012) and EMBASE (January 1990 to April 2012)

Assessment of quality of included trials: yes
ITT analysis: All studies were analyzed by treatment received rather than by an intention- to-treat analysis
Other methodological remarks:

Table 66

Ref	Comparison	N/n	Outcomes	Result (95% CI)
ref* Cochrane Altamimi 2012{Altamimi, 2012 #68} Design: SR + MA	Amoxicillin/clavulanate (43.8/6.2 mg/kg/day) bid (max. 1 g bid) for 5 days vs Penicillin V 30 mg/kg/day tid for 10 days	N=1 n= 313 Syrogiannopoulos 2004c	**Early clinical treatment failure** defined as persistent sore throat, fever or both in the first two weeks after completion of antibiotic treatment.	absolute rates 4/135 vs 3/135 OR 1.34 [0.29, 6.12] NS
			Late clinical recurrence defined as recurrence of sore throat, fever or both after initial resolution,	absolute rates 8/130 vs 6/124 OR 1.29 [0.43, 3.83] NS

Search date: (march/april 2012)			beyond the two-week period immediately after completion of antibiotic treatment	
			Side effects	absolute rates 23/155 vs 8/158 **OR 3.27 [1.41, 7.55]** **SS (more side effects with amoxicillin/clavulanate)** *All reported adverse events were mild to moderate and self-limiting, most of the events involved the gastrointestinal system in both treatment groups.*

Table 67

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Syrogiannopoulos 2004c{Syrogiannopoulos, 2004 #61} Multicenter, randomized, comparative, open-label study	313	children aged 1 to 17 years	Follow-up: day 4 to 8 and 21 to 28 after completion of therapy	1. Penicillin V 30 mg/kg/day tid for 10 days 2. Amoxicillin/clavulanate (43.8/6.2 mg/kg/day) bid (max. 1 g bid) for 5 days	ALLOCATION CONC: high risk RANDO: unclear risk BLINDING : Participants/personnel high risk of bias BLINDING : outcome assessors high risk of bias INCOMPLETE OUTCOME DATA Low risk of bias SELECTIVE REPORTING low risk of bias ITT: no FUNDING: NR

Table 68

5.2.3.7.2 Summary and conclusions

Amoxicilline/clavulanate short duration (5days) vs penicillin standard duration (10 days)			
Bibliography: Cochrane Altamimi 2012{Altamimi, 2012 #68}			
Outcomes	**N° of participants (studies) Follow up**	**Results (OR[95%CI])**	**Quality of the evidence (GRADE)**
Early clinical treatment failure *defined as persistent sore throat, fever or both in the first two weeks after completion of antibiotic treatment.*	313 (1 study)	OR 1.34 [0.29, 6.12] NS	⊕⊕⊖⊖: **LOW** Study quality:-1 (inadequate rando, no blinding) Consistency: na Directness: ok Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Late clinical recurrence *defined as recurrence of sore throat, fever or both after initial resolution, beyond the two-week period immediately after completion of antibiotic treatment*	313 (1 study)	OR 1.29 [0.43, 3.83] NS	⊕⊕⊖⊖: **LOW** Study quality: -1 (inadequate rando, no blinding) Consistency: na Directness: ok Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Adverse events	313 (1 study)	**OR 3.27 [1.41, 7.55]** **SS** **(more side effects with amoxicillin/clavulanate**	⊕⊕⊕⊖: **MODERATE** Study quality: 1 (inadequate rando, no blinding) Consistency: na Directness: ok Imprecision:ok

Table 69

In this Cochrane systematic review and meta-analysis, RCTs comparing short duration oral antibiotics (2-6 days) versus a standard treatment of 10 days of oral penicillin in children with confirmed GABHS pharyngitis were included. In one study, a 5-day course of amoxicillin/clavulanate was compared to 10 days of penicillin.

This trial included children aged 1 to 17 years.

As there is only one RCT with serious methodological flaws (no blinding, unclear allocation concealment and randomization) that investigated this comparison, our confidence in the outcome effects is severely limited.

In children with confirmed GABHS pharyngitis, a treatment with amoxicillin/clavulanate for 5 days, compared to penicillin for 10 days, **did not** result in a statistically significant difference in early clinical treatment failure or in late clinical recurrence.
GRADE: LOW quality of evidence

In children with confirmed GABHS pharyngitis, a treatment with amoxicillin/clavulanate for 5 days, compared to penicillin for 10 days, resulted in a statistically significant **increase** in adverse effects.
GRADE: MODERATE quality of evidence

5.2.3.8 Short-term late-generation antibiotics versus penicillin 10 days

5.2.3.8.1 Clinical evidence profile

Meta-analysis: Cochrane Altamimi 2012{Altamimi, 2012 #68} "Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children"

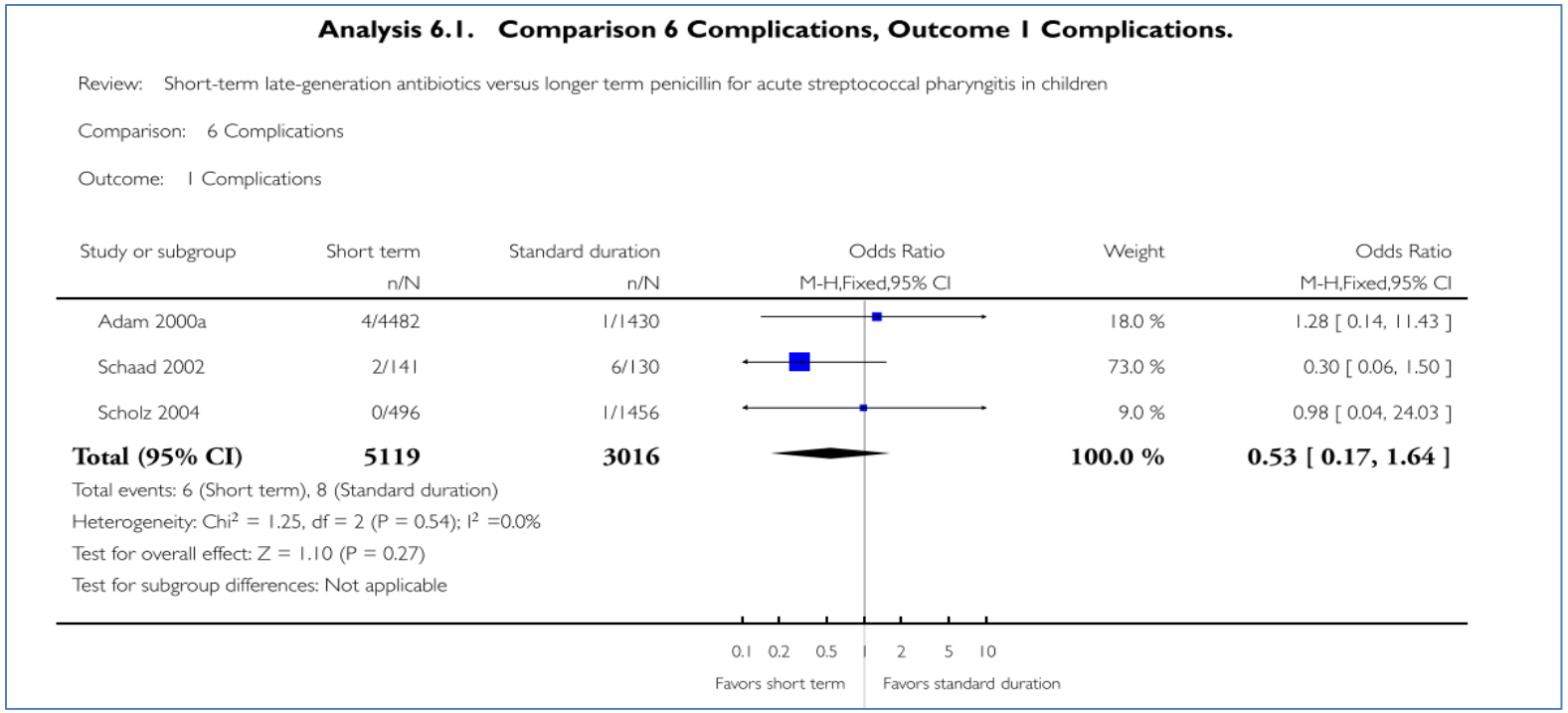
Inclusion criteria: Randomized controlled trials (RCTs) comparing short duration oral antibiotics (2-6 d) to standard duration (10 d) oral penicillin in children aged 1 to 18 years with acute GABHS pharyngitis based on a positive rapid antigen testing or positive throat swab culture for GABHS, conducted in the emergency department or physician's office (general practitioner, paediatrician or otolaryngologist).We excluded studies on GABHS carriers and studies using tools other than rapid antigen testing or throat swab culture to document GABHS pharyngitis. We selected 10 days of penicillin to be the control as it remains the recommended standard care due to its proven efficacy, narrow spectrum and low cost.

Search strategy: Cochrane Central Register of Controlled Trials (CENTRAL 2012, Issue 3) which contains the Cochrane Acute Respiratory Infections Group's Specialized Register, MEDLINE (January 1966 to March week 3, 2012) and EMBASE (January 1990 to April 2012)

Assessment of quality of included trials: yes
ITT analysis: All studies were analyzed by treatment received rather than by an intention- to-treat analysis
Other methodological remarks:

Table 70

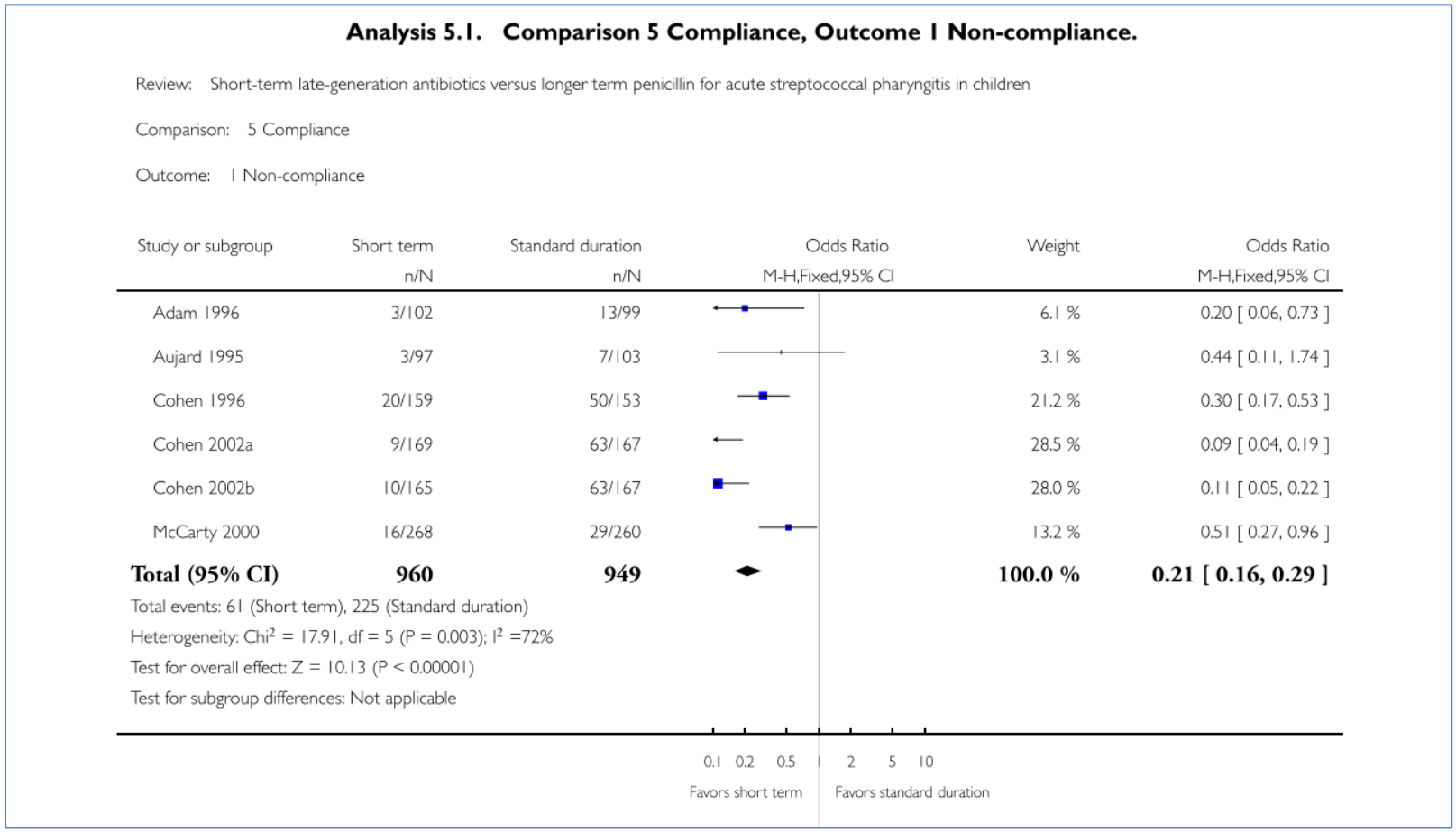
5 days other antibiotic vs 10 days penicillin: complications



Figuur 4 short term of a late-generation antibiotic versus standard duration penicillin: outcome Complications

Nb: Adam 2000a was not included in our report because it pooled 6 different antibiotics compared to penicillin

Short duration of late-generation antibiotics vs standard duration penicillin (10 days): compliance



Figuur 5 : short term late generation antibiotics versus standard duration penicillin. Outcome: compliance

5.2.3.8.2 Summary and conclusions

Short-term late-generation antibiotics vs 10 days penicillin in GABHS			
Bibliography: Cochrane Altamimi 2012{Altamimi, 2012 #68}			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Non-compliance	1909 (6 studies)	**OR 0.21 [0.16 to 0.29]** **(les non-compliance with short-term AB)**	⊕⊕⊕⊖: **MODERATE** Study quality: -1 (no or inadequate blinding) Consistency: ok Directness: ok Imprecision: ok
Complications	8135 (3 studies)	OR 0.53 [0.17 to 1.64] NS	⊕⊕⊖⊖: **LOW** Study quality: -1 (no or inadequate blinding) Consistency: ok Directness: ok Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)

Table 71

In this Cochrane systematic review and meta-analysis, RCTs comparing short duration oral antibiotics (2-6 days) versus a standard treatment of 10 days of oral penicillin in children with confirmed GABHS pharyngitis were included. For this subanalysis, all trials comparing short-term treatment with late-generation antibiotics with a 10 day course of penicillin that reported non-compliance or complication rate, were included.

These short-term, late-generation antibiotics included amoxicillin, amoxicillin +clavulanate, azithromycin, erythromycin, clarithromycin, ceftibuten, cefuroxime axetil and lorcabecef.

In children with confirmed GABHS pharyngitis, short-term treatment with late-generation antibiotics, compared to penicillin for 10 days, resulted in a statistically significant **decrease** of non-compliance.
GRADE: MODERATE quality of evidence

In children with confirmed GABHS pharyngitis, short-term treatment with late-generation antibiotics, compared to penicillin for 10 days, **did not** result in a statistically significant difference in complications.
GRADE: LOW quality of evidence

5.2.3.9 Amoxicillin/clavulanate 3 days versus amoxicillin 10 days in children with confirmed GABHS pharyngolaryngitis or tonsillitis

5.2.3.9.1 Clinical evidence profile

"Comparison of clinical efficacy between 3-day combined clavulanate/amoxicillin preparation treatment and 10-day amoxicillin treatment in children with pharyngolaryngitis or tonsillitis"

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Kuroki 2013{Kuroki, 2013 #70} Design: RCT OL PG multicenter Duration of follow-up: 1–2 weeks after completion or discontinuation of treatment	n= 119 ranged from 2 to 13 y Mean age: 5.6 y 100% Japanese Pretreatment disease severity: 98% mild <u>Inclusion</u> children with pharyngolaryngitis or tonsillitis, aged less than 15 years, who tested positive on the instantaneous Group A Streptococcus infection diagnosis kit <u>Exclusion</u>	3-day treatment with a combined CVA/AMPC preparation a dose level of 96.4 mg/kg/day (CVA6.4mg/kg/day, AMPC90mg/kg/day) in two divided doses Vs 10-day treatment with AMPC at a dose level of 30 mg/kg/day in three divided doses	Efficacy		RANDO: unclear: 'simple randomisation' ALLOCATION CONC: unclear BLINDING : Participants: no Personnel: no Assessors: unclear, not stated FOLLOW-UP: 10 patients in the CVA/AMPC group and 12 patients in the AMPC group were excluded because of lack of follow-up Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes ITT: no
			Clinical efficacy (PO) rated on a four-category scale (markedly effective, effective, slightly effective, or ineffective) using the Criteria for Judgment in Clinical Studies of Antimicrobial Drugs in the Field of Pediatrics	Markedly effective CVA/AMPC: 50/54 (92.6%) AMPC: 37/42 (88.1%) NS (Chi-square test) Markedly effective + effective CVA/AMPC: 53/54 (98.1%) AMPC: 39/42 (92.9%) NS	
			Safety		
			Diarrhea	CVA/AMPC: 22/47 (46.8%) AMPC: 5/39 (12.8%) SS: more diarrhea with CVA/AMPC p<0.01	
			Urinary adverse events (1-2w post treatment)	There was no sign of abnormality or of acute glomerulonephritis in any patient	

			Other adverse events	Urticaria and eruption (one case each) were noted in the CVA/AMPC group, and upper airway inflammation (one case) was seen in the AMPC group. None of these adverse reactions was severe. Discontinuation of test drug treatment because of an adverse reaction occurred in one patient (urticaria) from the CVA/AMPC group and one patient (diarrhea) from the AMPC group	SELECTIVE REPORTING: no Other important methodological remarks : no calculation of sample size/power Sponsor: The lead author received financial aid from Glaxo-SmithKline K.K

Table 72

Note: bacteriological efficacy also reported by authors (eradiction higher with AMPC)

5.2.3.9.2 Summary and conclusions

Amoxicillin/clavulanate 96.4mg/kg/day in 2 divided doses for 3 days versus amoxicillin 30 mg/kg/day in 3 divided doses for 10 days in children with GABHS pharyngolaryngitis or tonsillitis			
Bibliography: Kuroki 2013{Kuroki, 2013 #70}			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Clinical efficacy rated on a four-category scale (markedly effective, effective, slightly effective, or ineffective)	119 (1 study) 24 days	Markedly effective 92.6% vs 88.1% NS Markedly effective + effective 98.1% vs 92.9% NS	⊕⊖⊖⊖: **VERY LOW** Study quality:- 2 open label, unclear rando and allocation concealment, no power calculation Consistency: NA Directness: -1 (low dose in one arm) Imprecision: ok
Diarrhea	119 (1 study) 24 days	**46.8% vs 12.8%** **SS** **(more diarrhea with CVA/AMPC p<0.01)**	⊕⊕⊖⊖: **LOW** Study quality:-1 unclear rando and allocation concealment Consistency: NA Directness: -1 (low dose in one arm) Imprecision:ok
Urinary adverse events (1-2w post treatment)	119 (1 study) 24 days	0 vs 0	Insufficient data
Other adverse events	119 (1 study) 24 days	Rare and none reached a statistically significant difference	⊕⊖⊖⊖: **VERY LOW** Study quality:-1 Consistency: NA Directness: -1 (low dose in one arm) Imprecision:-1 small sample size

Table 73

In this RCT, 119 japanese children under the age of 15 y (mean age 5.6 y), with clinically mild GABHS pharyngolaryngitis or tonsillitis were randomized to either a 3-day treatment of clavulanate/amoxicillin (96.4mg/kg/day in 2 divided doses) or a 10-day treatment of amoxicillin (30 mg/kg/day in 3 divided doses).

The amoxicillin dose in the 10-day treatment is much lower than usually recommended in Belgium. The dosis interval in the amoxicillin/clavulanate (2x/day) is also not usually recommended in Belgium.

This trial was unblinded and the methods were reported rather poorly.

In children with confirmed GABHS pharyngolaryngitis or tonsillitis, a treatment with clavulanate/amoxicillin for 3 days, compared to amoxicillin for 10 days, **did not** result in a statistically significant difference in *clinical efficacy*.

GRADE: VERY LOW quality of evidence

In children with confirmed GABHS pharyngolaryngitis or tonsillitis, a treatment with clavulanate/amoxicillin for 3 days caused **more** diarrhea compared to amoxicillin for 10 days.
GRADE: LOW quality of evidence

In children with confirmed GABHS pharyngolaryngitis or tonsillitis, there is insufficient data to determine whether a treatment with clavulanate/amoxicillin for 3 days, compared to amoxicillin for 10 days will result in a statistically significant difference in urinary endpoints
GRADE: insufficient data

In children with confirmed GABHS pharyngolaryngitis or tonsillitis, a treatment with clavulanate/amoxicillin for 3 days, compared to amoxicillin for 10 days, **did not** result in a statistically significant difference in other adverse events.
GRADE:VERY LOW quality of evidence

5.2.4 Antibiotic A short duration versus antibiotic A longer duration

5.2.4.1 Short course (5-7 days) versus long-course (10 days) of the same antibiotic for GABHS tonsillopharyngitis

5.2.4.1.1 Clinical evidence profile

Meta-analysis: Falagas 2008{Falagas, 2008 #69} "Effectiveness and Safety of Short-Course vs Long-Course Antibiotic Therapy for Group A β-Hemolytic Streptococcal Tonsillopharyngitis: A Meta-analysis of Randomized Trials"

Inclusion criteria: Randomized controlled trials were considered eligible for inclusion in this meta-analysis if they enrolled at least 25 patients in each relevant treatment arm; involved patients of any age who had been diagnosed as having GAS tonsillopharyngitis (see other methodological remarks below); compared antibiotic treatment with the same agents, administered at the same daily dosage, but for different durations (a short-course [・7 days] and a long-course [at least 2 days longer than the short-course] treatment arm); and reported specific data on the effectiveness or safety of treatment

Search strategy: PubMed and the Cochrane Central Register of Controlled Trials, both last accessed on November 14, 2007. Bibliographies of relevant articles were also carefully reviewed

Assessment of quality of included trials: yes
Jadad criteria were used to assess the methodological quality of the included RCTs. According to these criteria, randomization, blinding, and data regarding study withdrawals are valued at 1 point each. One point is awarded or subtracted depending on the appropriateness of the randomization and blinding procedures. The highest that a trial can score is 5 points. A score higher than 2 points was used to denote a trial of adequate methodological quality
ITT analysis: yes/no
Other methodological remarks: 11 RCTs were eligible for inclusion. Seven RCTs exclusively enrolled children or adolescents (one of which enrolled patients aged 3 to 25 years, with a mean age of 9.8 years (Gerber 1987)). Two enrolled both children and adults. One enrolled adolescents or adults (NR), and one did not specify age selection criteria (Siananian 1972).
The reported RCTs below exclusively enrolled patients with GAS tonsillopharyngitis that had been verified by throat culture alone or throat culture in addition to rapid antigen detection tests (5 RCTs) serology (antistreptolysin-O) (1 RCT).

The primary outcome of this meta-analysis was microbiological eradication of GAS from the throat at end-of-therapy evaluation. The secondary outcomes of the meta-analysis included clinical success, defined as complete or substantial resolution of symptoms and signs of the disease at end-of-therapy evaluation; bacteriological relapse, defined as the growth in throat culture of the same type of GAS as the initial isolate after prior microbiological

eradication at the end of therapy; bacteriological recurrence, defined as the growth in throat culture of a different type of GAS than the initial isolate after prior microbiological eradication at the end of therapy; total adverse events reported in the population of the included RCTs; study withdrawals due to adverse events; as well as immunologic complications of tonsillopharyngitis. All outcomes of the meta-analysis referred to the respective evaluable populations

Table 74

Ref	Comparison	N/n	Outcomes	Result (95% CI)
ref* Falagas 2008{Falagas, 2008 #69} Design: SR + MA Search date: (nov 2007)	Short course (5-7 days) versus long course (10 days) therapy with the same antibiotic	N= 5 n= 1217 (Stromberg 1988 Peixoto 1993 Pichichero 1994 Mehra 1998 Esposito 2001)	**Clinical success (mainly children and adolescents)**	**OR 0.49 (0.25-0.96)** **SS in favour of long course** ***see forest plot below***
		N= 6 n= 1258 (Schwartz 1981 Gerber 1987 Peixoto 1993 Pichichero 1994 Mehra 1998 Esposito 2001)	**Microbiological eradication (children and adolescents)**	**OR 0.63 (0.40-0.98)** **SS in favour of long course**
		N= 3 n= 879 (Mehra 1998 Esposito 2001 Sinanian 1972)	**Adverse events**	OR 0.97(0.57-1.66) NS
		N=1 n=144 Stromberg 1988	**Immunologic complications including arthritis, myocarditis and exacerbation of psoriasis (children and adults)**	Short course 2.8% Long course 6.9% NT

		N=1 n=361 Peixoto 1993	**Proteinuria (children and adults)**	End of therapy: 4% in both treatment arms Follow-up: 0% in both treatment arms NT

Table 75

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology as evaluated by Falagas 2008
Esposito 2001{Esposito, 2001 #278} *Open-label* *RCT*	*120*	*3-12y* *GAS tonsillopharyngitis* *Diagnosis clinical + microbiological (throat culture)*	*follow-up 14 d*	*Cefaclor (oral) 25 mg/kg twice daily* *5 days versus 10 days* *nb. No longer available in Belgium*	*Jadad score 3*
Gerber 1987{Gerber, 1987 #36} Open-label RCT	172	3-25 y, GAS tonsillopharyngitis; Diagnosis clinical + microbiological (throat culture)	follow-up 16 d	Penicillin V (oral) 250 mg 3 times daily 5 days versus 10 days	Jadad score 2
Mehra 1998{Mehra, 1998 #74} Multicenter Open-label RCT	520	3-13y GAS tonsillopharyngitis; Diagnosis clinical + microbiological (throat culture, RADT)	follow up 38 d	Cefuroxime (oral) 10mg/kg 5 days versus 10 days	Jadad score 2
Peixoto 1993{Peixoto, 1993 #277} *Multicenter* *Open-label* *RCT*	*361 total of which 186 children*	*1-80y* *GAS tonsillopharyngitis* *Diagnosis clinical + microbiological (throat culture, RADT) or serological (ASO)*	*NR*	*Cefetamet (oral)* *Adults: 500 mg twice daily* *Children: 10mg/kg twice daily* *7 days versus 10 days* *nb. Not available in Belgium*	*Jadad score 2*
Pichichero 1994{Pichichero, 1994 #53} *Multicenter* *Investigator-blinded*	*247*	*2-17y* *GAS tonsillopharyngitis* *Diagnosis clinical + microbiological (throat culture, RADT)*	*follow-up 38 days*	*Cefpodoxime (oral) 10mg/kg per day (max 200mg/d)* *5 days versus 10 days* *nb. Not available in Belgium*	*Jadad score 2*

RCT					
Schwartz 1981{Schwartz, 1981 #77} Open-label RCT	191	1-18y GAS tonsillopharyngitis Diagnosis clinical + microbiological (throat culture)	follow-up 16 days	Penicillin V (oral) weight, <50 kg, 20mg/kg 3 times daily weight, > 50 kg, 15mg/d daily 7 days versus 10 days	Jadad score 2
Sinanian 1972{Sinanian, 1972 #78} Double blind RCT	90	No age stated GAS tonsillopharyngitis Diagnosis clinical + microbiological (throat culture)	follow-up 30 days	Clindamycin (oral) <55lbs, 75mg once daily to 150 mg 3 times daily 55-75lbs, 150 mg 3 to 4 times daily >75lbs, 150-300 mg 4 times daily 5 days versus 10 days	Jadad score 2
Stromberg 1988{Stromberg, 1988 #76} Double blind RCT		7-70y GAS tonsillopharyngitis Diagnosis clinical + microbiological (throat culture, RADT)	follow up 2 months	Penicillin V (oral) 7-12y: 400 mg twice daily 13-70y 800 mg twice daily 5d vs 10 d	Jadad score 5

Table 76

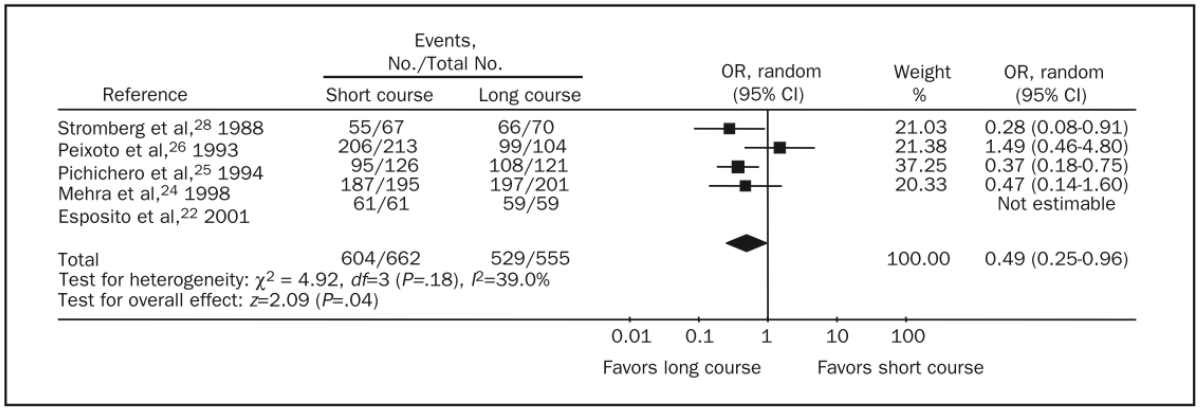


FIGURE 4. Meta-analysis of clinical success in patients with group A β-hemolytic streptococcal tonsillopharyngitis treated with short-course (5-7 days) vs long-course (10 days) therapy with the same antibiotic. The vertical line is the "no difference" line between compared treatments. The squares represent the point-estimates, and their size reflects the weight of the study in the meta-analysis. Horizontal lines represent 95% confidence intervals (CIs). The diamond shape shows the pooled odds ratios (ORs) plus 95% CIs.

Figure 1 Meta-analysis of outcome "clinical success" in Falagas 2008

Remarks:

The primary outcome of this meta-analysis was microbiological eradication. Recurrence/relapse was only recorded through microbiological testing and did not rely on clinical parameters. Since our review focusses on clinical endpoints, this meta-analysis is not very useful to us.

There were no cases of rheumatic fever reported in the trials included in this meta-analysis.

Author's conclusions (Falagas 2008):

Short-course treatment for GAS tonsillopharyngitis, particularly with penicillin V, is associated with inferior bacteriological eradication rates.

- most data refer to penicillin
- in the RCTs included in the meta-analysis, the determination of clinical effectiveness may have been made earlier in the course of the disease in the short-course treatment arms, thus potentially confounding outcomes by not allowing adequate time for some of the symptoms to subside in comparison with the long-course treatment arms. Moreover, the rates of end-of-therapy clinical success in patients treated with short-course regimens were greater than 90% and differed little from those obtained with longcourse treatment. Given this small degree of difference and the mainly self-remitting natural history of the

disease, it can be assumed that clinical success rates in patients treated with short-course regimens would have reached those of patients treated with long-course regimens if assessed at an equally distant time point.
- Because the trials included in this meta-analysis focused primarily on bacteriological relapses, they did not adequately examine the association of inferior microbiological eradication with clinical relapses.

5.2.4.1.2 Summary and conclusions

Shorter duration versus longer duration of the same antibiotic for GABHS tonsillopharyngitis			
Bibliography: SR Falagas 2008{Falagas, 2008 #69}			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Clinical success	1217 (5 studies)	**OR 0.49 (0.25-0.96)** **SS** **(less clinical success with short course)**	⊕⊕⊖⊖: **LOW** Study quality: -1 Consistency: ok Directness: -1 (mixed children and adults) Imprecision:ok
Microbiological eradication	1258 (6 studies)	**OR 0.63 (0.40-0.98)** **SS** **(less microbiological eradication with short course)**	⊕⊕⊖⊖: **LOW** Study quality:-1 Consistency: ok Directness: -1 (mixed children and adults) Imprecision:ok
Adverse events	879 (3 studies)	OR 0.97(0.57-1.66) NS	⊕⊕⊕⊖: **MODERATE** Study quality:-1 Consistency: ok Directness: ok Imprecision:ok
Immunologic complications (including arthritis, myocarditis and exacerbation of psoriasis)	144 (1 study)	Short course 2.8% Long course 6.9% NT	Not applicable

Table 77

This systematic review and meta-analysis included RCTs that compared different treatment durations of the same antibiotic in the same dose in patients of all ages with GABHS tonsillopharyngitis. A short course was defined as less than 7 days, while a long course was at least 2 days longer than the short course.

Even though the systematic review included people of all ages, most trials were performed in children and adolescents. Only one trial was performed exclusively in adults, but this trial was not included in the meta-analysis. 6 trials were performed exclusively in a paediatric population, and 3 in a mixed population of children and adults. In one trial the age of participants was not clear, but it can be assumed children were included as antibiotic doses for patients weighing less than 55 lbs were described.

The types of antibiotic differed between studies and included penicillin V, cefaclor, cefuroxime, clindamycin, cefpodoxime, and cefetamet. Cefpodoxime and cefetamet are not available in Belgium.

The authors of the review remark that the evaluation of the endpoint clinical success may have been performed at an earlier time point in the short-course treatment arms, compared with the long-

course arms. This could be a potential confounder in favor of the long-course, where patients had more time to recover.

No cases of rheumatic fever were reported in the trials included in this meta-analysis.

In children and adults with GABHS tonsillopharyngitis, a shorter antibiotic treatment duration, compared with a longer treatment, resulted in a statistically significant **decrease** in clinical success.
We have no information for a purely paediatric population.
GRADE: LOW quality of evidence (when applied to a paediatric population)

In children and adults with GABHS tonsillopharyngitis, a shorter antibiotic treatment duration, compared with a longer treatment, resulted in a statistically significant **decrease** in microbiological eradication.
We have no information for a purely paediatric population.
GRADE: LOW quality of evidence (when applied to a paediatric population)

In children and adults with GABHS tonsillopharyngitis, a shorter antibiotic treatment duration, compared with a longer treatment, **did not** result in a statistically significant difference in adverse effects.
We have no information for a purely paediatric population.
GRADE: MODERATE quality of evidence (when applied to a paediatric population)

5.2.5 Delayed versus immediate antibiotics in acute sore throat

5.2.5.1 Clinical evidence profile

Systematic review: Spurling 2013{Spurling Geoffrey, 2013 #204} "Delayed antibiotics for respiratory infections"
Inclusion criteria: "Randomised controlled trials (RCTs) involving participants of all ages defined as having an ARTI, where delayed antibiotics were compared to antibiotics used immediately or no antibiotics."
Search strategy: "We searched CENTRAL (The Cochrane Library 2013, Issue 2), which includes the Acute Respiratory Infection Group's Specialised Register; Ovid MEDLINE (January 1966 to February Week 3 2013); Ovid MEDLINE In-Process & Other Non-Indexed Citations (28 February 2013); EMBASE (1990 to 2013 Week 08); Science Citation Index - Web of Science (2007 to May 2012) and EBSCO CINAHL (1982 to 28 February 2013)."
Assessment of quality of included trials: GRADE
Other methodological remarks:

Table 78

Ref	Comparison	N/n	Outcomes	Results (95% CI)
ref* Spurling 2013{Spurling Geoffrey, 2013 #204} Design: SR + MA	Delayed vs. immediate antibiotics	N= 1 n= 229 (El-Daher 1991)	**Pain on day 3**	Crude AR 106/118 vs 42/111 **OR 14.51 (7.14 to 29.50)** **SS** **(More pain on day 3 with delayed antibiotics)**
		N= 1 n= 114 (Pichichero 1987)	**Pain severity on day 3**	MD 0.30 (-0.15 to 0.75) NS
		N= 1 n= 229 (El-Daher 1991)	**Malaise on day 3**	Crude AR 45/118 vs 4/111 **OR 16.49 (5.68 to 47.83)** **SS** **(More malaise on day 3 with delayed antibiotics)**
		N= 1 n= 114 (Pichichero 1987)	**Malaise severity**	MD 0.20 (-0.11 to 0.51) NS
		N= 2 n=343	**Fever severity on day 3**	**Std. MD 0.53 (0.31 to 0.74)** **SS**

		(El-Daher 1991, Pichichero 1987)		**(More fever severity on day 3 with delayed antibiotics)**
		N= 2 n=343 (El-Daher 1991, Pichichero 1987)	**Fever severity on day 1**	Std. MD -0.07 (-0.29 to 0.14) NS

Table 79

Characteristics of included studies (that include children): see below

Ref + design	n	Population	Duration	Comparison	Methodology (assessed by Cochrane authors)
El-Daher 1991{el-Daher, 1991 #35}	229	children with positive culture for GABHS	Data on day 3 Follow-up after 3 weeks Patients were instructed to report to the clinic in case of symptoms during the next 4 months	Early treatment with oral penicillin for 10 days versus oral placebo for 2 days followed by oral penicillin for 8 days	RANDOM SEQUENCE GENERATION Unclear risk (not described) ALLOCATION CONCEALMENT High risk (not described) BLINDING Low risk INCOMPLETE OUTCOME DATA High risk (drop-outs not described) SELECTIVE REPORTING Low risk
Pichichero 1987	114	Children with sore throat (suspected group A beta haemolytic Streptococcus) 2-17y	Follow-up at 3 weeks after enrollment	Delayed antibiotics (48 hours) versus immediate antibiotics (penicillin 250 mg tds for 10 days)	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT High risk (not used) BLINDING Low risk INCOMPLETE OUTCOME DATA Low risk

					SELECTIVE REPORTING Low risk

Table 80

5.2.5.2 Summary and conclusions

Delayed antibiotics versus immediate antibiotics for acute sore throat			
Bibliography: Spurling 2013{Spurling Geoffrey, 2013 #204}			
Outcomes	**N° of participants (studies) Follow up**	**Results (95%CI)**	**Quality of the evidence (GRADE)**
Pain on day 3	229 (1 study)	**OR 14.51 (7.14 to 29.50)** **SS** **(More pain on day 3 with delayed antibiotics)**	⊕⊕⊖⊖: **LOW** Study quality: -1 (unclear rando, allocation concealment, dropout) Consistency: na Directness: -1 (delayed AB with placebo) Imprecision: ok
Pain severity on day 3	114 (1 study)	MD 0.30 (-0.15 to 0.75) NS	⊕⊕⊖⊖: **LOW** Study quality: -1 (unclear allocation concealment) Consistency: na Directness: -1 (delayed AB with placebo) Imprecision: ok
Malaise on day 3	229 (1 study)	**OR 16.49 (5.68 to 47.83)** **SS** **(More malaise on day 3 with delayed antibiotics)**	⊕⊕⊖⊖: **LOW** Study quality: -1 (unclear rando, allocation concealment, dropout Consistency: na Directness: -1 (delayed AB with placebo) Imprecision: ok
Malaise severity	114 (1 study)	MD 0.20 (-0.11 to 0.51) NS	⊕⊕⊖⊖: **LOW** Study quality: -1 (unclear allocation concealment) Consistency: na Directness: -1 (delayed AB with placebo) Imprecision: ok
Fever severity on day 3	343 (2 studies)	**Std. MD 0.53 (0.31 to 0.74)** **SS** **(More fever severity on day 3 with delayed antibiotics)**	⊕⊕⊖⊖: **LOW** Study quality: -1 (unclear rando, allocation concealment, dropout Consistency: ok Directness: -1 (delayed AB with placebo) Imprecision: ok
Fever severity on day 1	343 (2 studies)	Std. MD -0.07 (-0.29 to 0.14) NS	⊕⊕⊖⊖: **LOW** Study quality: -1 (unclear rando, allocation concealment, dropout Consistency: ok Directness: -1 (delayed AB with placebo) Imprecision: ok

Table 81

In this meta-analysis, treatment of acute sore throat in children with delayed antibiotics was compared to immediate antibiotics.

In one trial only children with a positive GABHS culture were included, in the other trial children with suspected GABHS were included.

The antibiotic used in the trials was penicillin. In the immediate antibiotic group this was given for 10 days, while in the delayed group the children were given two days of placebo followed by 8 days of penicillin treatment.

In children *with acute sore throat*, a treatment with delayed penicillin, compared to immediate penicillin, **did** result in a statistically significant **increase** in *pain on day 3, malaise on day 3 and fever severity on day 3.*
GRADE: LOW quality of evidence

In children *with acute sore throat*, a treatment with delayed penicillin, compared to immediate penicillin, **did not** result in a statistically significant **difference** in *pain severity on day 3, malaise severity, or fever severity on day 1.*
GRADE: LOW quality of evidence

5.2.6 Prevention of recurrent sore throat

5.2.6.1 Clinical evidence profile

Meta-analysis: Cochrane Ng 2015{Ng, 2015 #71} "Antibiotics for preventing recurrent sore throat" Inclusion criteria: Randomised controlled trials (RCTs) of antibiotics in adults and children suffering from pre-existing recurrent sore throat, defined as three or more sore throats in a year, examining the incidence of sore throat recurrence, with follow-up of at least 12 months post-antibiotic therapy Search strategy: TheCochrane Ear,Nose and ThroatDisordersGroup (CENTDG) Trials SearchCo-ordinator searched theCENTDG Trials Register; Central Register of Controlled Trials (CENTRAL 2015, Issue 5); PubMed; EMBASE; CINAHL;Web of Science; Clinicaltrials.gov; ICTRP and additional sources for published and unpublished trials. The date of the search was 25 June 2015

Table 82

No trials could be included in this review.
Ng 2015 formally excluded four studies following review of the full-text report, because either tonsillectomy was used for treatment before follow-up was complete, or no placebo was used or results were uninterpretable)

Cochrane Ng 2015 conclusions:
"There is insufficient evidence to determine the effectiveness of antibiotics for preventing recurrent sore throat. This finding must be balanced against the known adverse effects and cost of antibiotic therapy, when considering antibiotics for this purpose. There is a need for high quality RCTs that compare the effects of antibiotics versus placebo in adults and children with pre-existing recurrent sore throat on the following outcomes: incidence of sore throat recurrence, adverse effects, days off work and absence from school, and the incidence of complications. Future studies should be conducted and reported according to the CONSORT statement"

6 Acute otitis media

6.1 Guidelines

6.1.1 Method of reporting of the recommendations and notes

Formal recommendations, that are supplied with grades of recommendations or levels of evidence, are written in **bold**.

Text taken directly from the guidelines, that is not graded but provides supplemental information or a clarification of the formal recommendations, is written in *italics*.

Comments by the bibliography group are written in plain text.

6.1.2 General information on selected guidelines

6.1.2.1 Selected guidelines

The selected guidelines and their abbreviations as used in this report can be found in Table 83.

Abbreviation	Guideline
AAP AOM 2013{Lieberthal, 2013 #8}	Lieberthal A., Carroll A., Chonmaitree et al.; American Academy of Pediatrics: The diagnosis and management of acute otitis media; 2013
BAPCOC 2012{BAPCOC, 2012 #3}	BAPCOC - Belgische gids voor anti-infectieuze behandeling in de ambulante praktijk; editie 2012/ Guide Belge des traitements anti-infectieux en pratique ambulatoire; édition 2012
NHG AOM 2014{NHG - Dutch College of General Practitioners, 2014 #13}	NHG - Dutch College of General Practitioners – Otitis media acuta bij kinderen (M09); 2014
NICE respiratory tract 2008{National Institute for Health and Clinical Excellence, 2008 #10}	National Institute for Health and Clinical Excellence: Respiratory tract infections – antibiotic prescribing. 2008. (reaffirmed 2012)
UoM AOM 2013{University of Michigan Health System, 2013 #20}	University of Michigan Health System – Otitis Media; 2013

Table 83: Selected guidelines and their abbreviations as used in this report

6.1.2.2 Grades of recommendation

Grades of recommendation and levels of evidence as defined in each guideline, can be found in Table 84 to Table 88.

6.1.2.2.1 AAP AoM 2013

AAP AOM 2013		
Grades of recommendation	Strong Recommendation	A strong recommendation in favor of a particular action is made when the anticipated benefits of the recommended intervention clearly exceed the harms (as a strong recommendation against an action is made when the anticipated harms clearly exceed the benefits) and the quality of the supporting evidence is excellent. In some clearly identified circumstances, strong recommendations may be made when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms
	Recommendation	A recommendation in favor of a particular action is made when the anticipated benefits exceed the harms, but the quality of evidence is not as strong. Again, in some clearly identified circumstances, recommendations may be made when high quality evidence is impossible to obtain but the anticipated benefits outweigh the harms.
	Option	Options define courses that may be taken when either the quality of evidence is suspect or carefully performed studies have shown little clear advantage to 1 approach over another.
	No Recommendation	No recommendation indicates that there is a lack of pertinent published evidence and that the anticipated balance of benefits and harms is presently unclear.
Levels of evidence	A	Well-designed RCTs or diagnostic studies on relevant population
	B	RCTs or diagnostic studies with minor limitations; overwhelmingly consistent evidence from observational studies
	C	Observational studies (case-control and cohort design)
	D	Expert opinion, case reports, reasoning from first principles
	X	Exceptional situations in which validating studies cannot be performed and there is a clear preponderance of benefit or harm

Table 84: Grades of recommendation and Level of evidence of AAP AOM 2013 guideline.

6.1.2.2.2 BAPCOC 2012

BAPCOC 2012		
Grades of recommendation:	1	Strong recommendation
	2	Weak recommendation
Levels of evidence	A	High degree of evidence; RCTs without limitations or strong, compelling evidence from observational studies
	B	Medium level of evidence; RCTs with limitations or strong evidence from observational studies
	C	(very) low degree of evidence; observational studies or case studies

Table 85

6.1.2.2.3 NHG AOM 2014

The NHG guidelines do not explicitly attribute grades of recommendation or levels of evidence to their recommendations. They do perform a GRADE- evaluation of the included evidence on which the recommendations are based. They also express the grade of recommendation in the wording of the recommendation itself (i.e. strongly or weakly recommended). (see https://www.nhg.org/sites/default/files/content/nhg_org/uploads/handleiding_standaarden_2015.pdf)

NHG AOM 2014		
Grades of recommendation:	Strong; Expressed in the wording of the recommendation	/
	Weak; Expressed in the wording of the recommendation	This often means there is not enough evidence to recommend a specific option and that medical professionals, together with their patient, make a choice from different options.
Levels of evidence	High	The true effect lies close to the estimated effect
	Moderate	The true effect probably lies close to the estimated effect, but the possibility exists that it differs substantially from it.
	Low	The true effect can differ substantially from the estimated effect.
	Very Low	The true effect probably differs substantially from the estimated effect.

Table 86: Grades of recommendation and Level of evidence of NHG AOM 2014 guideline.

6.1.2.2.4 NICE respiratory tract 2008

NICE respiratory tract 2008

Levels of evidence	1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
	1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
	1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
	2++	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
	2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
	2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
	3	Non-analytic studies, eg case reports, case series
	4	Expert opinion

Table 87: Grades of recommendation and Level of evidence of NICE respiratory tract 2008 guideline.

6.1.2.2.5 UoM AOM 2013

UoM AOM 2013		
Grades of recommendation	I	Generally should be performed
	II	May be reasonable to perform
	III	Generally should not be performed
Levels of evidence	A	Randomized controlled trials
	B	Controlled trials, no randomization
	C	Observational trials
	D	Opinion of expert panel

Table 88: Grades of recommendation and Level of evidence of the UoM AOM 2013.

6.1.2.3 Agree II score

Information about the Agree II score can be found in the section “Methodology”.

A summary of the assessment by the literature group of the individual items of the domain score for each guideline can be found in **Table 89**.The total domain score is also reported in this table.

Rigour of development item	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Total**	**Domain score**
AAP AOM 2013	6	7	7	5	7	7	5	6	**50**	**89%**

NHG AOM 2014	7	3	5	2	6	7	6	2	**39**	**70%**
NICE respiratory tract 2008	7	7	7	6	5	7	5	5	**49**	**88%**
UoM AOM 2013	5	4	5	4	6	5	5	2	**36**	**64%**

Table 89: AGREE score of selected guidelines on item "Rigour of development", see 1.1.2.6 for a description of the items.

6.1.2.4 Included populations – interventions – main outcomes

In Table 90 to Table 94, the populations, interventions and main outcomes considered in the selected guidelines are represented.

AAP AOM 2013	
Population	Children from 6 months through 12 years of age with uncomplicated AOM
Interventions	Pain management, initial observation versus antibiotic treatment, appropriate choices of antibiotic agents, preventive measures. It also addresses recurrent AOM.
Outcomes	• Parent satisfaction • Duration of symptoms/illness • Treatment failure, mastoiditis, bacteremia, clinical cure, bacteriologic cure • Disease recurrence • Harms: Antibiotic resistance, Diarrhea/vomiting

Table 90: Included population, intervention and main outcomes of guideline.

BAPCOC 2012	
Population	Ambulant care patients
Interventions	Antibiotic treatment (indication, choice, dose, duration)
Outcomes	Not specified

Table 91: Included population, intervention and main outcomes of guideline

NHG AOM 2014	
Population	Children and adolescents up to 18 years of age, with acute otitis media
Interventions	Patient education, drug treatment (symptomatic and antimicrobial treatment)
Outcomes	Not specified

Table 92: Included population, intervention and main outcomes of guideline.

NICE respiratory tract 2008	
Population	Adults and children (3 months and older) in whom immediate antibiotic prescribing is not indicated
Interventions	Assessment, antibiotic management strategies (delayed treatment, no

	treatment), advice
Outcomes	• the presence, duration and severity of symptoms such as fever, pain and malaise • the risk of complications from not prescribing antibiotics • adverse events from prescribing antibiotics (for example, diarrhoea, vomiting, rashes, abdominal pain) • the level of antibiotic prescribing, including antibiotic prescriptions consumed or collected • resource use (including reconsultation rates and rates of referral to secondary care) • patient satisfaction and health-related quality of life.

Table 93 Included population, intervention and main outcomes of guideline.

UoM AOM 2013	
Population	Pediatric patients (>2 months old) and adults with acute otitis media or otitis media with effusion
Interventions	Analgesia, Antibiotic therapy (indication, dosing, duration)
Outcomes	Not specified

Table 94 Included population, intervention and main outcomes of guideline.

6.1.2.5 Members of development group – target audience

Members of the development group that produced the guidelines, and the target audience for whom the guidelines are intended, can be found in Table 95 toTable 99.

AAP AOM 2013	
Development group	Paediactricians, informatician, family physicians, otolaryngologists, epidemiologist, methodologist
Target audience	Primary care clinicians

Table 95: Members of the development group and target audience of the AAP AOM 2013 guideline.

BAPCOC 2012	
Development group	General practitioners, microbiologists, pneumologists, infectiologists, paediatricians, pharmacists
Target audience	Physicians working in ambulant care

Table 96: Members of the development group and target audience of the BAPCOC 2012 guideline.

NHG AOM 2014	
Development group	General practitioners, epidemiologists
Target audience	General practitioners

Table 97: Members of the development group and target audience of the NHG AOM 2014 guideline.

NICE respiratory tract 2008	
Development group	General practitioners, paediatricians, pharmacists, microbiologists, patient representative, consultant in respiratory medicine

Target audience	Primary care and community settings. These will include general practices, community pharmacies, NHS walk-in centres and primary medical and nursing care provided in emergency departments.

Table 98: Members of the development group and target audience of the NICE respiratory tract 2008 guideline.

UoM AOM 2013	
Development group	Pediatricians, family physicians, otolaryngologists
Target audience	University of Michigan Health System physicians providing ambulatory care

Table 99: Members of the development group and target audience of the UoM AOM 2013 guideline.

6.1.3 Definition

6.1.3.1 Summary

Two guidelines define acute otitis media as an acute inflammation of the middle ear but classify into different subtypes for different severities.
For recurrent AOM, the two aforementioned guidelines speak of 3 or more episodes in the preceding 6 months, or 4 episodes a year.

6.1.3.2 AAP AOM 2013

AOM—the rapid onset of signs and symptoms of inflammation in the middle ear

Uncomplicated AOM—AOM without otorrhea

Severe AOM—AOM with the presence of moderate to severe otalgia or fever equal to or higher than 39°C

Nonsevere AOM—AOM with the presence of mild otalgia and a temperature below 39°C

Recurrent AOM—3 or more well documented and separate AOM episodes in the preceding 6 months or 4 or more episodes in the preceding 12 months with at least 1 episode in the past 6 months

6.1.3.3 BAPCOC 2012

The guideline doesn't define this term.

6.1.3.4 NHG AOM 2014

Acute otitis media: an infectious inflammation of the middle ear with a duration of less than 3 weeks.

Recurrent acute otitis media: frequently recurring acute otitis media (3 or more episodes in 6 months or 4 episodes a year)

Acute otitis media can be distinguished from otitis media with effusion by the features of an acute infection.

6.1.3.5 NICE respiratory tract infection 2008

The guideline doesn't define this term.

6.1.3.6 UoM AOM 2013

The guideline doesn't define this term.

6.1.4 Indications for antibiotic treatment

6.1.4.1 Summary

All guidelines define cases in which antibiotic therapy should be started immediately and cases in which it should be delayed or not prescribed.
BAPCOC 2012 and NICE respiratory tract 2008 clearly state, with high levels of evidence, that immediate antibiotic use is not recommended for uncomplicated acute otitis media. Continued observation of the patient or delayed prescription is an option. Antibiotics can be considered for a unilateral AOM lasting more than 3 days for two guidelines, for example through a delayed prescription.

All guidelines agree that antibiotic use can be indicated when one, or several aggravating factors are present. Those factors can be:

- Age (usually divided in children <6 months, children between 6 and 24 months, children >24m). Younger children tend to get recommended antibiotics.
- Being severely ill (including sustained high fever, defined by two guidelines as above 39°C)
- Bilateral otitis
- Ottorhea and eardrum perforation
- Being part of a high risk group

Levels of evidence for these recommendations are moderate to high.

6.1.4.2 AAP AOM 2013

Severe AOM: The clinician should prescribe antibiotic therapy for AOM (bilateral or unilateral) in children 6 months and older with severe signs or symptoms (ie, moderate or severe otalgia or otalgia for at least 48 hours or temperature 39°C [102.2°F] or higher). (Evidence Quality: Grade B. Strength: Strong Recommendation.)

Nonsevere bilateral AOM in young children: The clinician should prescribe antibiotic therapy for bilateral AOM in children 6 months through 23 months of age without severe signs or symptoms (ie, mild otalgia for less than 48 hours and temperature less than 39°C [102.2°F]). (Evidence Quality: Grade B. Strength: Recommendation.)

Nonsevere unilateral AOM in young children: The clinician should either prescribe antibiotic therapy or offer observation with close follow-up based on joint decision-making with the parent(s)/caregiver for unilateral AOM in children 6 months to 23 months of age without severe signs or symptoms (ie, mild otalgia for less than 48 hours and temperature less than 39°C [102.2°F]). When observation is used, a mechanism must be in place to ensure follow-up and begin

antibiotic therapy if the child worsens or fails to improve within 48 to 72 hours of onset of symptoms. (Evidence Quality: Grade B. Strength: Recommendation.)

Nonsevere AOM in older children: The clinician should either prescribe antibiotic therapy or offer observation with close follow-up based on joint decision-making with the parent(s)/ caregiver for AOM (bilateral or unilateral) in children 24 months or older without severe signs or symptoms (ie, mild otalgia for less than 48 hours and temperature less than 39°C [102.2°F]). When observation is used, a mechanism must be in place to ensure follow-up and begin antibiotic therapy if the child worsens or fails to improve within 48 to 72 hours of onset of symptoms. (Evidence Quality: Grade B. Strength: Recommendation.)

Clinicians should not prescribe prophylactic antibiotics to reduce the frequency of episodes of AOM in children with recurrent AOM. (Evidence Quality: Grade B. Strength: Recommendation.)

6.1.4.3 BAPCOC 2012

In acute middle ear infection , antibiotics are not indicated in most cases (GRADE 1A) except in:

- **children younger than 6 months at the time of diagnosis ; or**
- **children between six months and two years if the patient appears very ill (check signs of complications - see below) or if the course of the illness is atypical (no improvement after two days AND clinically confirmed diagnosis) ; or**
- **children older than 2 years if there is no improvement after 3 days, with recurrence within 12 months , or the patient appears very ill (check signs of complication - see below); or**
- **patients at risk - Down syndrome , cleft palate , immunological deficiency; or**
- **persistent otorrhea .**

If the physician wants both to respect the above recommendations and to avoid unnecessary consultations , it is possible to utilize a delayed antibiotic prescription

6.1.4.4 NHG AOM 2014

Initiate oral antimicrobial therapy immediately in:

- **risk groups (including infants < 6 months with acute otitis media) ;**
- **patients appearing severely ill , regardless of whether there is also discharge from a spontaneously perforated eardrum or a grommet .**

Consider oral antimicrobial therapy in:

- **children younger than 2 years with bilateral acute otitis media ;**
- **children who first present with ear discharge during an episode of acute otitis media as a result of a spontaneous eardrum perforation , and also present with fever and/ or pain;**
- **children with acute otitis media in whom no improvement has occurred after three days of pain medication in sufficiently high dosage and frequency.**

6.1.4.5 NICE respiratory tract 2008

A no antibiotic prescribing strategy or a delayed antibiotic prescribing strategy should be agreed for patients with the following conditions:

- **acute otitis media**

Depending on clinical assessment of severity, patients in the following subgroups can also be considered for an immediate antibiotic prescribing strategy (in addition to a no antibiotic or a delayed antibiotic prescribing strategy):

- **bilateral acute otitis media in children younger than 2 years**
- **acute otitis media in children with otorrhoea**

An immediate antibiotic prescription and/or further appropriate investigation and management should only be offered to patients (both adults and children) in the following situations:

- **if the patient is systemically very unwell**
- **if the patient has symptoms and signs suggestive of serious illness and/or complications (particularly pneumonia, mastoiditis, peritonsillar abscess, peritonsillar cellulitis, intraorbital and intracranial complications)**
- **if the patient is at high risk of serious complications because of pre-existing comorbidity. This includes patients with significant heart, lung, renal, liver or neuromuscular disease, immunosuppression, cystic fibrosis, and young children who were born prematurely**

For these patients, the no antibiotic prescribing strategy and the delayed antibiotic prescribing strategy should not be considered

6.1.4.6 UoM AOM 2013

Consider deferring antibiotic therapy for lower risk children with AOM [II, A]

When antibiotic therapy is deferred, facilitate patient access to antibiotics if symptoms worsen (e.g., a "back-up" prescription given at visit or a convenient system for subsequent call-in) [I, C].

6.1.5 Choice of antibiotic, dose and duration

6.1.5.1 Summary

All guidelines except NICE respiratory tract 2008 recommend specific antibiotics.

Four guidelines recommend amoxicillin as first choice (in general a strong recommendation but with moderate or low levels of evidence). They also all mention switching to amoxicillin + clavulanate potassium if the patient doesn't improve within three days, except NHG AOM 2014 which recommends amoxicillin + clavulanate potassium if there are no improvements within 48h. Only one guideline specifies dosage.

In case of allergies or aggravating factors (such as purulent conjunctivitis) different second choice antibiotics are mentioned. Two guidelines mention azithromycin.

In case of a failure of treatment, UoM AOM 2013 mentions a third group cephalosporin (ceftriaxone) as first choice, with caveats regarding resistance building.

6.1.5.2 AAP AOM 2013

Clinicians should prescribe amoxicillin for AOM when a decision to treat with antibiotics has been made and the child has not received amoxicillin in the past 30 days or the child does not have concurrent purulent conjunctivitis or the child is not allergic to penicillin.
Evidence Quality: Grade B. Strength: Recommendation.

Clinicians should prescribe an antibiotic with additional β-lactamase coverage for AOM when a decision to treat with antibiotics has been made, and the child has received amoxicillin in the last 30 days or has concurrent purulent conjunctivitis, or has a history of recurrent AOM unresponsive to amoxicillin.
Evidence Quality: Grade C. Strength: Recommendation.

Clinicians should reassess the patient if the caregiver reports that the child's symptoms have worsened or failed to respond to the initial antibiotic treatment within 48 to 72 hours and determine whether a change in therapy is needed.
Evidence Quality: Grade B. Strength: Recommendation.

6.1.5.3 BAPCOC 2012

- **First choice: (GRADE 1B) - amoxicillin: 75-100 mg / kg per day in 3 to 4 gifts for 5-7d**

- **Alternatively, in case of non - IgE - mediated penicillin allergy : (GRADE 1C) –**
  - **cefuroxime axetil: 30-50 mg / kg per day in 3 doses for 5-7d**

- **Alternative for IgE-mediated penicillin allergy (GRADE 1C) –**
  - **cotrimoxazole 1-5 years : 40/8 mg / kg per day in two doses for 5-7d 6-12: 800/160 mg per day in two gifts for 5-7d**
  - **azithromycin: 10 mg / kg per day in one gift for 3d ; or the first day 10 mg / kg in 1 gift , then 5 mg / kg per day in one gift during 4d**
  - **Clarithromycin: 15 mg / kg per day in two doses for 5-7d**

If no improvement occurs within three days (persisting symptoms and signs): half of the daily dose of amoxicillin is replaced by amoxicillin-clavulanate: 37.5 to 50 mg / kg amoxicillin + 37.5 to 50 mg / kg amoxicillin- clavulanate

6.1.5.4 NHG AOM 2014

When an oral antimicrobial treatment is indicated, amoxicillin is first-choice drug.

Cotrimoxazole may be prescribed if amoxicillin is contraindicated.

If, 48 hours after initiating amoxicillin, no improvement has occurred, the physician can prescribe amoxicillin / clavulanate potassium or refer the child.

Treat ear discharge in children with grommets with eardrops containing antibiotics and corticosteroids.

6.1.5.5 NICE respiratory tract infection 2008

No information found in this guideline.

6.1.5.6 UoM AOM 2013

Amoxicillin is the first choice of antibiotic therapy for all cases of AOM.
Children:

- **Dosing: < 4 years, 80 mg/kg/day divided BID; ≥ 4 years, 40- 60 mg/kg/day [I, C].**
- **Duration 5-10 days: 5 days is usually sufficient at lower cost and fewer side effects, although 10 days reduces clinical failure [A]. Consider 10-day course for children: with significant early URI symptoms and <2 years old, with possible sinusitis, and with possible strep throat [II, D].**

Treat AOM that is clinically unresponsive to amoxicillin after 72 hours of therapy with amoxicillin/clavulanate (Augmentin ES; amoxicillin component 80 mg/kg/day divided BID) for 10 days or with azithromycin (Zithromax) 20 mg/kg daily for 3 days [II, C].

Patients with significant, persistent symptoms on high-dose amoxicillin/clavulanate (Augmentin ES) or azithromycin (Zithromax) may respond to IM ceftriaxone (Rocephin; 1-3 doses) [II, C]. The decision to use ceftriaxone (Rocephin) should take into account the negative impact it will have on local antibiotic resistance patterns.

6.1.6 Non-antibiotic treatment

6.1.6.1 Summary

All guidelines who cover treatment outside of antibiotics mention the need for analgesia. The NHG AOM 2014 guideline explicitly mentions paracetamol as first choice and advises against xylometazoline and lidocaine ear drops.

6.1.6.2 AAP AOM 2013

The management of AOM should include an assessment of pain. If pain is present, the clinician should recommend treatment to reduce pain. (Evidence Quality: Grade B. Strength: Strong Recommendation.)

6.1.6.3 BAPCOC 2012

No information outside of the antibiotic treatment given in this guideline.

6.1.6.4 NHG AOM 2014

Always provide adequate pain relief for the treatment of acute otitis media.

In all cases, the general practitioner advises adequate short-term pain relief. Paracetamol in a sufficiently high dose and frequency is the first choice. The doctor advises the caregivers to give the child paracetamol at fixed times. A more rapid analgesic effect is achieved when administered orally (about 30 minutes after ingestion, maximum plasma concentration is achieved 0.5 to 2 hours after administration) than after rectal administration. In rectal administration the effect is less predictable. In young children, however, rectal administration is often preferred for practical reasons,.
When paracetamol in sufficiently high dosage and frequency gives insufficient results, this agent can be replaced with ibuprofen in children older than one year. Ibuprofen is contraindicated in children with renal impairment. Caution is recommended in children with signs of dehydration or diarrhea and in children with asthma.

Decongestant nose drops or nasal sprays are not recommended for the treatment of acute otitis media, because the effect on symptoms and cure of acute otitis media has not been established and because xylometazoline in children can have (rare) serious side effects. The use of nasal drops or nasal spray with physiological saline has no effect on the symptoms or cure of acute otitis media and is therefore not recommended.

Lidocaine ear drops are not recommended for pain relief in acute otitis media because the effect has not been established.

6.1.6.5 NICE respiratory tract infection 2008

For all antibiotic prescribing strategies, patients should be given advice about the usual natural history of the illness, including the

- *average total length of the illness (before and after seeing the doctor): acute otitis media: 4 days*
- *advice about managing symptoms, including fever (particularly analgesics and antipyretics).*

6.1.6.6 UoM AOM 2013

Recommend adequate analgesia for all children with AOM [I, D].

6.1.7 Referrals

6.1.7.1 Summary

Three out of five guidelines mention when to refer or consult a specialist (BAPCOC 2012, NHG AOM 2014, NICE respiratory tract 2008) .
Those guidelines advise referral to a pediatrician or ENT specialist in case of failed treatment or for (suspected) complications such as mastoiditis or meningitis, one also in the case of continued discharged, perforated eardrum after 6 weeks or recurring infections.
The BAPCOC guideline mentions hospitalization in case of a severely ill infant with IgE-mediated penicillin-allergy due to the resistance patterns in pneumococci against macrolides and co-trimoxazole.

6.1.7.2 AAP AOM 2013

No information found in this guideline.

6.1.7.3 BAPCOC 2012

When there are signs of complications such as mastoiditis and meningitis, the patient will be referred urgently.

Note: Macrolides and co-trimoxazole are not ideal alternatives because of the high proportion of antibiotic resistance in pneumococci and the risk of side effects. For children with IgE-mediated penicillin allergy that make a severely ill impression or if treatment has failed, hospitalization for intravenous therapy is recommended.

6.1.7.4 NHG AOM 2014

Alarm symptoms:

- **child younger than 1 month with fever;**
- **seriously ill child (drowsiness, drinks less than half of usual intake, rapid deterioration);**
- **suspected meningitis (neck stiffness, impaired consciousness, headache);**
- **suspected mastoiditis (tender mastoid region, ear turned forward).**

Refer children with alarm symptoms to a pediatrician or, in suspected mastoiditis, to an ENT specialist.

Consult with or refer to an ENT specialist in the following cases:

- **no improvement despite treatment with an oral antibiotic (amoxicillin or co-trimoxazole, possibly followed by amoxicillin / clavulanate potassium when there is inadequate effect of amoxicillin);**
- **persistence of ear discharge after treatment with an oral antibiotic and / or ear drops containing antibiotics and corticosteroids.**
- **persistence of a perforated eardrum six weeks after the onset of ear discharge.**

Refer children with frequent recurrences (three or more episodes per six months or four episodes per year) to an ENT specialist for further diagnosis and treatment, or to a pediatrician if an antibody deficiency disorder is suspected (this is more likely if there are also other bacterial infections , such as sinusitis, bronchitis, pneumonia).

6.1.7.5 NICE respiratory tract 2008

An immediate antibiotic prescription and/or further appropriate investigation and management should only be offered to patients (both adults and children) in the following situations:

- **if the patient is systemically very unwell**
- **if the patient has symptoms and signs suggestive of serious illness and/or complications (particularly pneumonia, mastoiditis, peritonsillar abscess, peritonsillar cellulitis, intraorbital and intracranial complications)**
- **if the patient is at high risk of serious complications because of pre-existing comorbidity. This includes patients with significant heart, lung, renal, liver or neuromuscular disease, immunosuppression, cystic fibrosis, and young children who were born prematurely**

6.1.7.6 UoM AOM 2013

No information found in this guideline.

6.2 Evidence tables and conclusions

6.2.1 Antibiotics versus placebo

6.2.1.1 Clinical evidence profile

Meta-analysis: Cochrane Venekamp 2015{Venekamp, 2015 #79} "Otitis for acute otitis media in children"

Inclusion criteria: RCTs of antimicrobial drugs versus placebo control and RCTs comparing immediate antibiotic versus expectant observation. Studies including children (aged from one month to 15 years) of either gender **without ventilation tubes**, suffering from AOM irrespective of the setting from which they were recruited.
Search strategy: the Cochrane Central Register of Controlled Trials (CENTRAL 2015, Issue 3) (accessed 26 April 2015), which contains the Acute Respiratory Infections (ARI) Group's Specialised Register, MEDLINE (October 2012 to April week 3, 2015), EMBASE (November 2012 to April 2015), Current Contents (2012 to April 2015), CINAHL (October 2012 to April 2015) and LILACS (2012 to April 2015).Our previous update using the same search strategies covered the period 2008 to November 2012.
Assessment of quality of included trials: yes
ITT analysis: yes

Table 100

Ref	Comparison	N/n	Outcomes	Result
Cochrane Venekamp 2015{Venekamp, 2015 #79} Design: MA of RCTs	Antibiotics vs placebo	N= 6 n= 1394 (Burke 1991, Le Saux 2005, Thalin 1985, Tähtinen 2011, van	Pain at 24 hours	Crude AR: 267/709 vs 292/685 RR: 0.89 (0.78 to 1.01) NS

Search date: (april 2015)		Buchem 1981a, van Buchem 1981b)		
		N= 7 n= 2320 (Appelman 1991, Halsted 1968, Kaleida 1991, Le Saux 2005, Mygind 1981, Thalin 1985, Tähtinen 2011)	Pain at 2 to 3 days	Crude AR: 138/1186 vs 180/1134 **RR: 0.70 (0.57 to 0.86)** **SS**
		N= 8 n= 1347 (Burke 1991, Damoiseaux 2000, Mygind 1981, Tapiainen 2014, Thalin 1985, Tähtinen 2011, van Buchem 1981a, van Buchem 1981b	Pain at 4 to 7 days	Crude AR: 119/680 vs 161/667 **RR: 0.76 (0.63 to 0.91)** **SS**
		N= 1 n= 278	Pain at 10 to 12 days	Crude AR: 10/139 vs 30/139 **RR: 0.33 (0.17 to 0.66)**

		(Hoberman 2011)		**SS**
		N= 8 n= 2107 (Burke 1991, Damoiseaux 2000, Hoberman 2011, Le Saux 2005, Mygind 1981, Tapiainen 2014, Thalin 1985, Tähtinen 2011)	Vomiting, diarrhoea or rash	Crude AR: 283/1044 vs 208/1063 **RR: 1.38 (1.19 to 1.59)** **SS**
		N=5 N= 1075 Tapiainen 2014, Hoberman 2011, Tähtinen 2011, Burke 1991, Mygind 1981	Tympanic membrane perforation	Crude AR: 9/533 vs. 26/542 **RR: 0.37 (0.18 to 0.76)** **SS**
		N= 4 n= 906 (Burke 1991, Hoberman 2011, Mygind 1981, Thalin	Contralateral otitis (in unilateral cases)	Crude AR: 48/453 vs 85/453 **RR: 0.49 (0.25 to 0.95)** **SS**

		1985)		
		N= 6 n= 2200 (Hoberman 2011, Kaleida 1991, Le Saux 2005, Mygind 1981, Thalin 1985, van Buchem 1981a)	Late AOM recurrences	Crude AR: 208/1138 vs 213/1062 RR: 0.93 (0.78 to 1.10) NS

Table 101

* Characteristics of included studies: see below

Ref + design	n	Population	Comparison	Methodology
Appelman 1991{Appelman, 1991 #145}	126	**Age** - between 6 months and 12 years **Setting** - general practice and secondary care in the Netherlands; confirmation of diagnosis and randomisation were done by otorhinolaryngologists **Inclusion criteria** - recurrence of acute otitis media (AOM) characterised by a (sub) acute onset, otalgia and otoscopic signs of middle-ear infection within 4 weeks to 12 months of the previous attack **Exclusion criteria** - antibiotic treatment < 4 weeks prior to randomisation,	**Tx** - amoxicillin/clavulanate (weight tailored dose) for 7 days; N = 70 (N = 67 included in analysis) **C** - matching placebo for 7 days; N = 56 (N = 54 included in analysis) **Use of additional medication** - each child was given analgesics (paracetamol) as long as earache was present and decongestive nose drops for 1 week	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk OTHER BIAS Unclear risk (ITT analysis - unclear, baseline characteristics- balanced) BLINDING OF PARTICIPANTS AND PERSONNEL Unclear risk (Identical taste and appearance to amoxicillin/clavulanate and placebo not described) INCOMPLETE OUTCOME DATA

		previous participation in this study, contraindication for penicillin, serious concurrent disease that necessitated antibiotic treatment **Baseline characteristics** – balanced		Low risk
Burke 1991{Burke, 1991 #146}	232	**Age** - between 3 and 10 years **Setting** - general practice; 48 general practitioners in 17 general practices in Southampton, Bristol and Portsmouth (UK) **Inclusion criteria** - acute earache and at least 1 abnormal eardrum **Exclusion criteria** - antibiotic treatment or acute otitis media (AOM) < 2 weeks prior to randomisation, strong indication for antibiotic treatment according to general practitioner, contraindication for amoxicillin, serious chronic conditions **Baseline characteristics** - slight imbalance in gender (boys treated with antibiotics versus boys treated with placebo = 52% versus 42%) and figure 1 appears to demonstrate that fewer children were crying at baseline (0 hours) in the amoxicillin arm compared with the placebo arm, suggesting a failure of randomisation	**Tx** - amoxicillin 125 mg 3 times a day for 7 days; N = 114 (N = 114 included in analysis for short-term outcome) **C** - matching placebo 3 times daily for 7 days; N = 118 (N = 118 included in analysis for short-term outcome) **Use of additional medication** - analgesics (paracetamol 120 mg/5 mL) for pain as needed	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk OTHER BIAS Unclear risk (ITT analysis - yes; baseline characteristics -imbalance for gender and crying) BLINDING OF PARTICIPANTS AND PERSONNEL Low risk INCOMPLETE OUTCOME DATA Unclear risk (Loss to follow-up - not described; all randomised patients included in short-outcome analysis)
Damoiseaux 2000{Damoiseaux, 2000 #147}	240 N = 212 children included	**Age** - between 6 months and 2 years **Setting** - general practice; 53 general practitioners (GPs) in the Netherlands **Inclusion criteria** - acute otitis media	**Tx** - amoxicillin suspension 40 mg/kg/day in 3 doses for 10 days; N = 117 (N = 107 included in analysis for	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk

	in analysis	(AOM) defined as infection of the middle ear of acute onset and a characteristic eardrum picture (injection along the handle of the malleus and the annulus of the tympanicmembrane or a diffusely red or bulging eardrum) or acute otorrhoea. In addition 1 or more symptoms of acute infection (fever, recent earache, general malaise, recent irritability) **Exclusion criteria** - antibiotic treatment < 4 weeks prior to randomisation, contraindication for amoxicillin, comprised immunity, craniofacial abnormalities, Down's syndrome or being entered in this study before **Baseline characteristics** - slight imbalance in the prevalence of recurrent AOM, regular attendance at a daycare centre and parental smoking; logistic regression was used to adjust for these imbalances	short-term outcome) **C** - matching placebo suspension for 10 days; N = 123 (N = 105 included in analysis for short-term outcome) **Use of additional medication** - all children received decongestive nose drops for 7 days; analgesics (paracetamol, children < 1 year: 120 mg suppository, > 1 year: 240 mg suppository) was allowed	OTHER BIAS Low risk BLINDING OF PARTICIPANTS AND PERSONNEL Low risk INCOMPLETE OUTCOME DATA Unclear risk (Loss to follow-up/exclusion from analysis(received other antibiotics or had grommets inserted) - treatment: N = 10 (9%) and placebo: N = 18 (15%). However, for primary analysis of symptoms at day 4 all randomised patients were included)
Halsted 1968{Halsted, 1968 #148}	106 89 children included in analysis	**Age** - between 2 months and 5.5 years **Setting** - secondary care: paediatric department of Cleveland (USA) Inclusion criteria - AOM based on otoscopic findings; most of the cases had bulging membrane with loss of normal light reflex and landmarks, in a few the eardrum was only diffusely red **Exclusion criteria** - antibiotic treatment < 10 days prior to randomisation,	**Tx 1** - ampicillin 100 mg/kg/day in 4 doses for 10 days; N = ? (N = 30 included in analysis) **Tx 2** - pheneticillin 30 mg/kg/day 4 daily and sulfisoxazole 150 mg/kg/day 4 daily for 10 days; N = ? (N = 32 included in analysis)	RANDOM SEQUENCE GENERATION Unclear risk (Pre-determined code, which was unknown to physician; method of random sequence generation unclear) ALLOCATION CONCEALMENT Unclear risk (Method not described) OTHER BIAS Unclear risk (ITT analysis - unclear,

		associated bacterial infection requiring antibiotic treatment, rupture of tympanic membrane, contraindication for study drugs **Baseline characteristics** - not described	**C** - placebo for 10 days; N = ? (N = 27 included in analysis) **Use of additional medication** - phenylephrine nose drops and aspirin for children over 6 months was prescribed as necessary; no other medications were employed	baseline characteristics- not described) BLINDING OF PARTICIPANTS AND PERSONNEL Unclear risk (Identical taste and appearance to antibiotics and placebo not described) INCOMPLETE OUTCOME DATA Unclear risk (Reasons described, unclear from which treatment group patients were excluded)
Hoberman 2011{Hoberman, 2011 #149}	291	**Age** - between 6 months and 2 years **Setting** - secondary care; children's hospital of Pittsburgh and a private paediatric clinic in Kittanning (USA) **Inclusion criteria** - children needed to have received at least 2 doses of pneumococcal conjugate vaccine and to have acute otitis media (AOM) as defined on the basis of 3 criteria: (a) the onset (i.e. within the preceding 48 hours) of symptoms that parents rated with a score of at least 3 on the acute otitis media - severity of symptoms (AOM-SOS) scale (on which scores range from0 to 14, with higher scores indicating greater severity of symptoms), (b) the presence of middle-ear effusion and (c) moderate or marked bulging of the tympanic membrane or slight bulging accompanied by either otalgia or marked erythema of the membrane All	**Tx** - amoxicillin-clavulanate 90-6.4 mg/kg daily in 2 doses for 10 days; N = 144 (N = 139 were assessed at day 4 to 5) **C** - matching placebo in 2 doses for 10 days; N = 147 (N = 142 were assessed at day 4 to 5) **Use of additional medication** - acetaminophen (paracetamol) as needed for symptom relief At each visit children were categorised as having met the criteria for either clinical success or clinical failure Children who met the criteria for clinical failure were treated with a standardised 10- day regimen of orally	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk OTHER BIAS Low risk BLINDING OF PARTICIPANTS AND PERSONNEL Low risk INCOMPLETE OUTCOME DATA Low risk

		the study clinicians were otoscopists who had successfully completed an otoscopic validation programme **Exclusion criteria** - antibiotic treatment < 96 hours prior to randomisation, concomitant acute illness (e.g. pneumonia) or a chronic illness (e.g. cystic fibrosis), contraindication to amoxicillin, presence of otalgia for more than 48 hours, perforation of the tympanic membrane **Baseline characteristics** - balanced	administered amoxicillin (90 mg/kg daily) and cefixime (8 mg/kg daily)	
Kaleida 1991{Kaleida, 1991 #150}	536	**Age** - between 7 months and 12 years Setting - secondary care: children's hospital and a private paediatric practice in Pittsburgh (USA) **Inclusion criteria** - AOM based on presence of middle-ear effusion, as determined otoscopically, in associationwith specified symptoms of acutemiddle-ear infection (fever, otalgia or irritability), or signs of acute infection (erythema or white opacification, or both, accompanied by fullness or bulging and impaired mobility), or both **Exclusion criteria** - children who recently received antibiotics, who had potential complicating or confounding conditions (e.g. eardrum perforation, asthma or chronic sinusitis) **Baseline characteristics** - balanced	Children were enrolled for a 1-year period. At entry each child was assigned randomly to a treatment regimen that specified consistent treatments for episodes of non-severe and severe AOM based on severity of otalgia and the presence of fever (> 39 °C orally or > 39.5 °C rectally within the 24-hour period before presentation) Non-severe AOM episodes were treated with: **Tx** - amoxicillin 40 mg/kg/day in 3 doses for 14 days; N = 522 (N = 488 included in primary analysis) **C** - placebo for 14 days; N = 527 (N = 492 included in primary analysis)	RANDOM SEQUENCE GENERATION Unclear risk (Method of randomisation not described) ALLOCATION CONCEALMENT Unclear risk (Method not described) OTHER BIAS Low risk BLINDING OF PARTICIPANTS AND PERSONNEL Unclear risk (Identical taste and appearance to amoxicillin and placebo not described) INCOMPLETE OUTCOME DATA Unclear risk (Follow-up/exclusion of nonsevere episodes for short-term outcome - treatment: N = 34 (7%) and placebo: N = 35 (7%). Reasons not described)

			Severe AOM episodes in children aged < 2 years were treated with: **Tx 1** - amoxicillin 40 mg/kg/day 3 times daily for 14 days **Tx 2** - amoxicillin 40 mg/kg/day 3 times daily for 14 days and myringotomy Severe AOM episodes in children aged ≥ 2 years were treated with: **Tx 1** - amoxicillin 40 mg/kg/day 3 times daily for 14 days **Tx 2** - amoxicillin 40 mg/kg/day 3 times daily for 14 days and myringotomy **Tx 3** - placebo and myringotomy	
Le Saux 2005{Le Saux, 2005 #152}	531 children (N = 512 children included in analysis;	**Age** - between 6 months and 5 years **Setting** - secondary care: emergency department in Ottawa (Canada) **Inclusion criteria** - new onset (< 4 days) of symptoms referable to the upper respiratory tract and either ear pain or fever (> 38 °C). In addition, all patients had to have evidence of middle-ear effusion, defined by ≥ 2 of the following signs: opacity, impaired mobility on the basis of pneumatic otoscopy and redness or bulging (or both) of the tympanic membrane	**Tx** - amoxicillin suspension (60 mg/kg) 3 times daily for 10 days; N = 258 (N = 253 included in analysis for day 3) **C** - matching placebo for 10 days; N = 254 (N = 246 included in analysis for day 3) **Use of additional medication** - parents were given a 5-day supply of antipyretic and	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk OTHER BIAS Low risk BLINDING OF PARTICIPANTS AND PERSONNEL Low risk INCOMPLETE OUTCOME DATA Low risk

		Exclusion criteria - antibiotic treatment < 2 weeks prior to randomisation, contraindication to amoxicillin or penicillin or sensitivity to ibuprofen or aspirin, presence of otorrhoea, co-morbid disease such as sinusitis or pneumonia, prior middle-ear surgery, placement of a ventilation tube, history of recurrent acute otitis media (more than 4 episodes in 12 months), compromised immunity, craniofacial abnormalities, or any chronic or genetic disorder **Baseline characteristics** - balanced	analgesic medication in the form of ibuprofen suspension as required for pain or fever and a 48-hour supply of codeine elixir to be given as required for pain and fever	
Mygind 1981{Mygind, 1981 #155}	158 children (N = 149 included in analysis)	**Age** - between 1 and 10 years **Setting** - general practice and secondary care: confirmation of diagnosis and trial recruitment were done by otorhinolaryngologists in Copenhagen (Denmark) **Inclusion criteria** - earache for 1 to 24 hours. The diagnosis was made if the child cried because of pain and if the tympanic membrane appeared to be red and inflamed **Exclusion criteria** - antibiotic treatment < 4 weeks prior to randomisation, other treatment apart fromacetylsalicylic acid already commenced, secretion in the external ear, suspected chronic otitis media, treatment for secretory otitis media within last 12 months, concurrent	**Tx** - penicillin 50 mg/mL 4 times daily; children aged 1 to 2 years: 10 mL daily, children between 3 and 5 years: 20 mL daily, children between 6 and 10 years: 30 mL daily for 7 days; N = ? (N = 72 included in analysis) **C** - placebo for 7 days; N = ? (N = 77 included in analysis) **Use of additional medication** - acetylsalicylic acid tablets (maximum of 50 mg/kg/day for 3 days) were supplied as the only supplementary treatment permitted	RANDOM SEQUENCE GENERATION Unclear risk (Method of randomisation not described) ALLOCATION CONCEALMENT Low risk OTHER BIAS Unclear risk (ITT analysis - unclear, baseline characteristics – balanced) BLINDING OF PARTICIPANTS AND PERSONNEL Unclear risk (Identical taste and appearance to amoxicillin and placebo not described) INCOMPLETE OUTCOME DATA Unclear risk (Patients not included in analysis - N = 9 (6%). Reasons described, unclear from which treatment group patients were excluded)

		disease (e.g. pneumonia or severe tonsillitis), suspected penicillin allergy **Baseline characteristics** - balanced		
Tähtinen 2011{Tahtinen, 2011 #157}	322 children (N = 319 children were included in analysis)	**Age** - between 6 months and 3 years **Setting** - general practice: healthcare centre of Turku (Finland) **Inclusion criteria** - acute otitis media (AOM) based on 3 criteria: (a) middle-ear fluid had to be detected by means of pneumatic otoscopic examination that showed at least 2 of the following tympanic membrane findings: bulging position, decreased or absent mobility, abnormal colour or opacity not due to scarring, or air fluid interfaces; (b) at least 1 of the following acute inflammatory signs in the tympanic membrane had to be present: distinct erythematous patches or streaks or increased vascularity over full, bulging, or yellow tympanic membrane; (c) presence of acute symptoms such as fever, otalgia or respiratory symptoms **Exclusion criteria** - ongoing antibiotic treatment; AOM with spontaneous perforation of the tympanic membrane; systemic or nasal steroid therapy within 3 preceding days; antihistamine, oseltamivir or a combination therapywithin 3 preceding days; contraindication to penicillin or amoxicillin; presence of ventilation tube; severe infection requiring	**Tx** - amoxicillin-clavulanate 40-5.7 mg/kg daily in 2 doses for 7 days; N = 162 (N = 161 included in analysis) **C** - matching placebo in 2 doses for 7 days; N = 160 (N = 158 included in analysis) **Use of additional medication** - the use of analgesics and antipyretic agents was encouraged and the use of analgesic ear drops and decongestive nose drops or sprays was allowed	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk OTHER BIAS Low risk BLINDING OF PARTICIPANTS AND PERSONNEL Low risk INCOMPLETE OUTCOME DATA Low risk

		antibiotic treatment; documented Epstein-Barr virus infection within 7 preceding days; Down's syndrome or other condition affecting middle-ear diseases; known immunodeficiency **Baseline characteristics** - balanced		
Tapiainen 2014{Tapiainen, 2014 #158}	84	**Age** - between 6 months and 15 years **Setting** - primary and secondary care: children in day care centres attending an AOM prevention trial at the Department of Pediatrics, Oulu University Hospital and children visiting the City of Oulu Health Care Center and Mehiläinen Pediatric Private Practice, Oulu (Finland) **Inclusion criteria** - acute symptoms of respiratory infection and/or ear-related symptoms and signs of tympanic membrane inflammation together with middle-ear effusion at pneumatic otoscopy performed by a study physician **Exclusion criteria** - ventilation tubes (grommets), AOM complication, amoxicillin allergy, Down syndrome, congenital craniofacial abnormality and immunodeficiency **Baseline characteristics** - balanced	**Tx** - amoxicillin-clavulanate for 7 days (amoxicillin 40 mg/kg/day divided into 2 daily doses); N = 42 (N = 42 included in analysis) **C** - matching placebo in 2 doses for 7 days; N = 42 (N = 42 included in analysis) **Use of additional medication** - not described	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk OTHER BIAS Low risk BLINDING OF PARTICIPANTS AND PERSONNEL Low risk INCOMPLETE OUTCOME DATA Low risk
Thalin 1985{Thalin A, 1985 #161}	293	**Age** - between 2 and 15 years **Setting** - secondary care: department of otorhinolaryngology in Halmstad (Sweden) **Inclusion criteria** - purulent acute otitis media (AOM) (no further	**Tx** - phenoxymethyl penicillin 50 mg/kg/day twice daily for 7 days; N = 159 (N = 159 included in analysis)	RANDOM SEQUENCE GENERATION Unclear risk (Block randomisation, method of random sequence generation not described) ALLOCATION CONCEALMENT

		criteria described) **Exclusion criteria** - antibiotic treatment or AOM episode < 4 weeks prior to randomisation, suspected penicillin allergy, presence of ventilation tubes, sensorineural hearing loss, existence of concomitant infection for which antibiotic treatment was required and chronic diseases **Baseline characteristics** - not described	**C** - matching placebo in 2 doses for 7 days; N = 158 (N = 158 included in analysis) **Use of additional medication** - all children were given nose drops containing oxymetazoline chloride and, if needed, analgesics (paracetamol)	Low risk OTHER BIAS Unclear risk (ITT analysis - unclear; baseline characteristics - not described) BLINDING OF PARTICIPANTS AND PERSONNEL Low risk INCOMPLETE OUTCOME DATA Low risk
van Buchem 1981a{van Buchem, 1981 #159}	202 children (N = 171 children included in analysis	**Age** - between 2 and 12 years **Setting** - both general practice and secondary care: 12 general practitioners in or near Tilburg (the Netherlands) recruited patients and referred them to 1 of the 3 otorhinolaryngologists, which excluded those cases where there was disagreement with the diagnosis **Inclusion criteria** - acute otitis media (AOM) was based on history and clinical picture (i.e. diffuse redness, bulging of the eardrum, or both) **Exclusion criteria** - antibiotic treatment < 2 weeks prior to randomisation, chronic otitis or otitis media serosa, contraindication for antibiotic treatment **Baseline characteristics** - balanced	**Tx** - sham myringotomy and amoxicillin 250 mg 3 times daily for 7 days; N = 47 **C** - sham myringotomy and matching placebo for 7 days; N = 40 **Use of additional medication** - all participants were allowed to use decongestive nose drops and analgesic suppositories (i.e. children aged 2 to 7 years: acetylsalicylic acid 50 mg, phenacetin 50 mg, phenobarbitone 15 mg, codeine phosphate 2.5 mg, caffeine 1. 25 mg; children aged 8 to 12 years: acetylsalicylic acid 100 mg, phenacetin 100 mg, phenobarbitone 30 mg, codeine phosphate 5 mg, caffeine 2.5 mg	RANDOM SEQUENCE GENERATION Unclear risk (Method of randomisation not described) ALLOCATION CONCEALMENT Low risk OTHER BIAS Unclear risk (ITT analysis - unclear, baseline characteristics- balanced) BLINDING OF PARTICIPANTS AND PERSONNEL Low risk INCOMPLETE OUTCOME DATA Unclear risk (Loss to follow-up/exclusions - N = 31 (15%). Reasons not described)

van Buchem 1981b{van Buchem, 1981 #159}	202 children (N = 171 children included in analysis	**Age** - between 2 and 12 years **Setting** - both general practice and secondary care: 12 general practitioners in or near Tilburg (the Netherlands) recruited patients and referred them to 1 of the 3 otorhinolaryngologists who excluded those cases where there was disagreement with the diagnosis **Inclusion criteria** - acute otitis media (AOM) was based on history and clinical picture (i.e. diffuse redness, bulging of the eardrum, or both) **Exclusion criteria** - antibiotic treatment < 2 weeks prior to randomisation, chronic otitis or otitis media serosa, contraindication for antibiotic treatment **Baseline characteristics** - balanced	**Tx** - myringotomy and amoxicillin 250 mg 3 times daily for 7 days; N = 48 **C** - myringotomy and matching placebo for 7 days; N = 36 **Use of additional medication** - all participants were allowed to use decongestive nose drops and analgesic suppositories (i.e. children aged 2 to 7 years: acetylsalicylic acid 50 mg, phenacetin 50 mg, phenobarbitone 15 mg, codeine phosphate 2.5 mg, caffeine 1. 25 mg; children aged 8 to 12 years: acetylsalicylic acid 100 mg, phenacetin 100 mg, phenobarbitone 30 mg, codeine phosphate 5 mg, caffeine 2.5 mg	RANDOM SEQUENCE GENERATION Unclear risk (Method of randomisation not described) ALLOCATION CONCEALMENT Low OTHER BIAS Unclear risk (ITT analysis - unclear, baseline characteristics – balanced) BLINDING OF PARTICIPANTS AND PERSONNEL Low risk INCOMPLETE OUTCOME DATA Unclear risk (Loss to follow-up/exclusions - N = 31 (15%). Reasons not described)

Table 102

Author's conclusions: This review reveals that antibiotics have no early effect on pain, a slight effect on pain in the days following and only a modest effect on the number of children with tympanic perforations, contralateral otitis episodes and abnormal tympanometry findings at two to four weeks and at six to eight weeks compared with placebo in children with AOM. In high-income countries, most cases of AOM spontaneously remitwithout complications.The benefits of antibioticsmust beweighed against the possible harms: for every 14 children treated with antibiotics one child experienced an adverse event (such as vomiting, diarrhoea or rash) that would not have occurred if antibiotics were withheld. Therefore clinical management should emphasise advice about adequate analgesia and the limited role for antibiotics. Antibiotics are most useful in children under two years of age with bilateral AOM, or with both AOM and otorrhoea. For most other children with mild disease in high-income countries, an expectant observational approach seems justified.

Remarks: The included studies cover a period of 30 years (see chapter 4 for a reflection on how this might influence results)

In one of the studies (van Buchem 1981) sham myringotomy was performed in both arms.

6.2.1.2 Summary and conclusions

Antibiotics versus placebo for acute otitis media			
Bibliography: Cochrane Venekamp 2015{Venekamp, 2015 #79}			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Pain at 24 hours	1394 (6 studies)	RR: 0.89 (0.78 to 1.01) NS	⊕⊕⊕⊖: **MODERATE** High: As assessed by Cochrane group Directness: -1 (low dose)
Pain at 2 to 3 days	2320 (7 studies)	**RR: 0.70 (0.57 to 0.86) SS (less pain with AB)**	⊕⊕⊕⊖: **MODERATE** High: As assessed by Cochrane group Directness: -1 (low dose)
Pain at 4 to 7 days	1347 (8 studies)	**RR: 0.76 (0.63 to 0.91) SS (less pain with AB)**	⊕⊕⊕⊖: **MODERATE** High: As assessed by Cochrane group Directness: -1 (low dose)
Pain at 10 to 12 days	278 (1 study)	**RR: 0.33 (0.17 to 0.66) SS (less pain with AB)**	⊕⊕⊕⊖: **MODERATE** As assessed by Cochrane group
Tympanic membrane perforation	1075 (5 studies)	**RR: 0.37 (0.18 to 0.76) SS (less tympanic membrane perforation with AB)**	⊕⊕⊕⊖: **MODERATE** Study quality:ok Consistency: ok Directness: -1 (low dose) Imprecision:ok
Contralateral otitis (in unilateral cases)	906 (4 studies)	**RR: 0.49 (0.25 to 0.95) SS (less contralateral otitis with AB)**	⊕⊕⊖⊖: **LOW** Study quality:-1; unclear randomization, unclear ITT Consistency: ok Directness: -1 (low dose) Imprecision: ok
Late AOM recurrences	2200 (6 studies)	RR: 0.93 (0.78 to 1.10) NS	⊕⊕⊖⊖: **LOW** Study quality: -1 unclear randomization, unclear ITT Consistency: ok Directness: -1 (low dose) Imprecision: ok
Vomiting, diarrhoea or rash	2107 (8 studies)	**RR: 1.38 (1.19 to 1.59) SS (more vomiting, diarrhoea or rash with AB)**	⊕⊕⊕⊖: **MODERATE** High: As assessed by Cochrane group Directness: -1 (low dose)

Table 103

In this meta-analysis of 12 trials, a treatment with antibiotics was compared to placebo in children with acute otitis media.

The children included in the twelve trials were aged between two months and 15 years. The antibiotics used were penicillin for seven days (two trials), amoxicillin for seven to 14 days (6 trials), amoxicillin/clavulanate for seven to 10 days(4 trials),and ampicillin for 10 days (1 trial).

In many of the trials using amoxicillin, the administered dose was lower than usually recommended in Belgium (dose in these trials was 40 mg/kg/day while 75-100 mg/kg/day is recommended by

BAPCOC). In some trials the dose was divided into 2 administrations per day, while it is usually recommended to give 3 to 4 daily doses.

There were very few reported cases of serious complications (e.g. mastoiditis, meningitis), so this outcome was not analysed.

In children *with acute otitis media*, a treatment with antibiotics, compared to placebo, **did not** result in a statistically significant difference in *pain at 24 hours.*
GRADE: MODERATE quality of evidence

In children *with acute otitis media*, a treatment with antibiotics, compared to placebo, **did** result in a statistically significant **decrease** in *pain at 2 to 3 days, pain at 4 to 7 days, pain at 10 to 12 days,* and in *tympanic membrane perforation.*
GRADE: MODERATE quality of evidence

In children *with acute otitis media*, a treatment with antibiotics, compared to placebo, **did** result in a statistically significant **decrease** in *contralateral otitis.*
GRADE: LOW quality of evidence

In children *with acute otitis media*, a treatment with antibiotics, compared to placebo, **did not** result in a statistically significant difference in *late acute otitis media recurrences.*
GRADE: LOW quality of evidence

In children *with acute otitis media*, a treatment with antibiotics, compared to placebo, **did** result in a statistically significant **increase** in *vomiting, diarrhoea or rash.*
GRADE: MODERATE quality of evidence

6.2.2 Antibiotic A versus antibiotic B

6.2.2.1 Ampicillin or amoxicillin (7-10d) vs ceftriaxone(single dose) for acute otitis media

6.2.2.1.1 Clinical evidence profile

Meta-analysis: Shekelle 2010{Shekelle, 2010 #81} AHRQ Evidence Report/Technology Assessment "Management of acute otitis media: update"

Inclusion criteria: SR, RCT, CCT, uncomplicated AOM in average risk children
Search strategy: This is an update of a 2001 report. Searches of PubMed and the Cochrane databases were conducted from January 1998 July 2010 using the same search strategies used for the 2001 report, with the addition of terms not considered in the 2001 review. The Web of Science was also searched for citations of the 2001 report and its peer-reviewed publications
Assessment of quality of included trials: yes: Jadad for RCTs, AMSTAR for SRs, GRADE for overall evaluation
ITT analysis: yes/no

Table 104

Ref	Comparison	N/n	Outcomes	Result (95% CI)
ref* Shekelle 2010{Shekelle, 2010 #81} Design: SR+ MA Search date: (july 2010)	Ampicillin or amoxicillin vs ceftriaxone	N= 4 n= 571 Varsano 1988 Green 1993 Kara 1998 Zhang 2003	**Treatment success** *(not defined)*	Risk Difference= 0% (-7 to 7) NS *moderate heterogeneity (I^2 50,7%)*
			Adverse events	Shekelle 2010 states that adverse events were either not reported in the individual trials or, when reported, no statistically significant difference was found.

Table 105

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by Shekele 2010
Varsano 1988{Varsano, 1988 #119}	52	see figure below mean age 23 months	see figure below	Amoxicillin37.5 mg/kg/day in 3 doses a day for 7 days vs ceftriaxone 50mg/kg IM single dose	Jadad score 4 No access to original article
Green 1993{Green, 1993 #120}	233	see figure below	see figure below	amoxicillin 40mg/kg per day divided in 3 doses for 10 days vs ceftriaxone 50mg/kg IM single dose	Jadad score 4 note: Description of adverse events in original publication: 4 cases of allergic reaction with amoxi vs 1 case with ceftriaxone.
Kara 1998{Kara, 1998 #121}	75 (3 groups)	see figure below	see figure below	amoxicillin 40 mg/kg/day in 3 doses per os for 10 days vs cefuroxime axetil 30 mg/kg/day in two doses per os for 10 days; vs ceftriaxone 50 mg/kg single-dose i.m	Jadad score 1 No access to original article
Zhang 2003{Zhang, 2003 #122}	236	see figure below	see figure below	Amoxicillin 40 mg/kg/day in 3 doses for 10 days vs Ceftriaxone 50 mg/kg/day for 1 day	Jadad score 2 Adverse events not reported by therapy arm according to Shekelle 2010

Table 106

Table 13. Ampicillin/Amoxicillin vs. Ceftriaxone; Outcome Indicator: Treatment Success Rate

Author, Year	Age	Definition of outcome	Amoxicillin/ Ampicillin Sample Size	Ceftriaxone Sample Size	Amoxicillin Success Rate (%)	Ceftriaxone Success Rate (%)	Rate Difference In %	95% CI of Rate Difference In %
Varsano, 1988[110]	6 mos-8 yrs	Success at day 7	22	22	86.4	81.8	4.5	-17.0, 26.1
Green, 1993[111]	5 mos-5 yrs	Success at day 10	107	105	97.2	94.3	2.9	-2.5, 8.3
Kara, 1998[112]	6 mos-6 yrs	Success at day 5	25	25	92.0	84.0	8.0	-9.9, 25.9
Zhang, 2003[68]	6 mos-12 yrs	Success at day 10-14	106	106	90.6	97.2	-6.6	-13.0, -0.2
Random effects estimates			260	258	93.1	93.4	0	-6.9, 7.0
Test of heterogeneity Chi-square test value							6.09	
Test of heterogeneity Chi-square test p-value							0.107	
Test of heterogeneity I-squared							50.7%	
Test of publication bias, Egger's asymmetry test p-value							0.70	

Figuur 6. RCTs included by Shekelle 2010, description and outcomes

Author's conclusions:
Caution is advised in interpreting overall summary measures. The two higher quality studies showed no difference in effect between amoxicillin and ceftriaxone, whereas one of the lower quality studies showed no difference and the other favored ceftriaxone.
The quality of evidence for this conclusion is moderate, meaning that further high quality research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

Remarks: very limited information on adverse events available in Shekelle 2010.
As the outcome "treatment succes" is not defined, it is difficult to interpret.

6.2.2.1.2 Summary and conclusions

Amoxicillin vs ceftriaxone for acute otitis media			
Bibliography: Shekelle 2010{Shekelle, 2010 #81}			
Outcomes	**N° of participants (studies) Follow up**	**Results (95%CI)**	**Quality of the evidence (GRADE)**
Treatment success	571 (4 studies) 5 – 14 d	Risk Difference= 0% (-7 to 7) NS	⨁⨁⨀⨀: **LOW** Study quality:-1 low JADAD in 2/4 studies Consistency: problems, but no points deducted Directness: -1 (low dose) Imprecision:ok
Adverse events	571 (4 studies) 5 – 14 d	No numbers available *(not reported or NS)*	Not estimable

Table 107

This systematic review + meta-analysis compared amoxicillin (+/- 40 mg/kg/d for 7-10 days) to a single IM dose of ceftriaxone (50 mg/kg for 1 day) in children with acute otitis media. 4 RCTs were found, including a total of 571 children. The children were aged between 6 months and 12 years.

The amoxicillin dose in these trials was much lower than the dose usually recommended in Belgium (75-100 mg/kg/day).

In children *with acute otitis media*, a treatment with amoxicillin for 7-10 days, compared to ceftriaxone for 1 day, **did not** result in a statistically significant difference in *treatment success.*
GRADE: LOW quality of evidence

We have no information on recurrence rates.

There was very limited reporting of adverse events. No conclusions can be made for this endpoint.
GRADE: Not estimable

We cannot make a valid risk-benefit assessment for the comparison of amoxicillin to ceftriaxone in the treatment of acute otitis media in children, due to the lack of data on adverse events.

6.2.2.2 Amoxicillin - clavulanate (10d) vs ceftriaxone (single dose) for acute otitis media

6.2.2.2.1 Clinical evidence profile

Meta-analysis: Shekelle 2010{Shekelle, 2010 #81} AHRQ Evidence Report/Technology Assessment "Management of acute otitis media: update"

Inclusion criteria: SR, RCT, CCT, uncomplicated AOM in average risk children
Search strategy: This is an update of a 2001 report. Searches of PubMed and the Cochrane databases were conducted from January 1998 July 2010 using the same search strategies used for the 2001 report, with the addition of terms not considered in the 2001 review. The Web of Science was also searched for citations of the 2001 report and its peer-reviewed publications
Assessment of quality of included trials: yes: Jadad for RCTs, AMSTAR for SRs, GRADE for overall evaluation
ITT analysis: yes/no

Table 108

Ref	Comparison	N/n	Outcomes	Result (95% CI)
ref* Shekelle 2010{Shekelle, 2010 #81} Design: SR+ MA Search date: (july 2010)	amoxicilline/clavulanate vs ceftriaxone	N= 5 n=1590 Bauchner 1996 Varsano 1997 Cohen 1999 Wang 2004 Biner 2007	**Treatment success** *(not defined)*	Absolute Risk Difference= 3% (-2 to 7) NS *no statistical heterogeneity (I^2 22.9%)*
		N=1 n=513 Cohen 1999	**Overall adverse events**	**Absolute risk difference= 16% (9%, 24%)** **SS** **Amoxicillin-clavulanate associated with greater overall AE rate**

		N=1 n=513 Cohen 1999	**Diarrhea**	**Absolute risk difference= 13% (6%, 20%)** **SS** **Amoxicillin clavulanate associated with greater rate of diarrhea**

Table 109

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by Shekele 2010
Bauchner 1996{Bauchner, 1996 #123}	648	see figure below	see figure below	amoxicillin clavulanate (dose not reported in Shekele 2010 or in abstract) for 10 days vs ceftriaxone IM for 1 day ((dose not reported in Shekele 2010 or in abstract)	Jadad score 2
Varsano 1997{Varsano, 1997 #124}	215	see figure below	see figure below	amoxicillin-clavulanate 12.5mg tid for 10 days vs ceftriaxone 50mg/kg IM single dose (second dose if unsatisfactory response after 48 h or history of recurrent AOM)	Jadad score 3
Cohen 1999{Cohen, 1999 #125}	513	see figure below	see figure below	amoxicillin – clavulanate 80/10 mg/kg/day in three divided doses for 10 days vs cefuroxime axetil 30 mg/kg bid per os for 10 days; vs ceftriaxone 50 mg/kg	Jadad score 3

				single-dose i.m	
Wang 2004{Wang, 2004 #126}	110	mean age of 30.73 +/- 20.79 month see figure below	see figure below	Amoxicillin –clavulanate 45 mg/kg/day, in 3 divided doses for 10 days vs Ceftriaxone 50 mg/kg/day for 1 day	Jadad score 2
Biner 2007{Biner, 2007 #127}	104	mean age of 3.8 (2.3) years see figure below	see figure below	amoxicillin/clavulanate (90/6.4 mg/kg/day in 2 doses) vs Ceftriaxone 50 mg/kg/day for 1 day	Jadad score 1

Table 110

Table 14. Amoxicillin-Clavulanate (7-10 Days) vs. Ceftriaxone (single Dose); Outcome Indicator: Treatment Success Rate

Author, Year	Age	Definition of outcome	Amox-clav Sample Size	Ceftriaxone Sample Size	Amox-clav Success Rate (%)	Ceftriaxone Success Rate (%)	Rate Difference In %	95% CI of Rate Difference In %
Bauchner, 1996[113]	3 mos-6 yrs	Success at day 14-16	271	267	89.7	81.3	8.4	2.5, 14.3
Varsano, 1997[110]	6 mos-8 yrs	Success at day 11	106	109	95.3	95.4	-0.1	-5.8, 5.5
Cohen, 1999[77]	4-30 mos	Success at day 12-14	228	235	48.2	49.4	-1.1	-10.2, 8.0
Wang, 2004[78]	3 mos-6 yrs	Success at day 10	32	41	78.1	75.6	2.5	-16.9, 22.0
Biner, 2007[71]	6 mos-10 yrs	Success at day 3	39	34	87.2	85.3	1.9	-14.0, 17.8
Random effects estimates			676	686	79.8	77.4	2.8	-1.6, 7.2
Test of heterogeneity Chi-square test value							5.19	
Test of heterogeneity Chi-square test p-value							0.27	
Test of heterogeneity I-squared							22.9%	
Test of publication bias, Egger's asymmetry test p-value							0.78	

Figuur 7. RCTs included by Shekelle 2010, description and outcomes

Author's conclusions:
The quality of evidence for this conclusion (treatment success) is moderate, meaning that further high quality research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

Remarks: information on adverse events is reported unclearly in Shekelle 2010. It is unclear whether all AEs were pooled.
As the outcome "treatment succes" is not defined, it is difficult to interpret.

6.2.2.2.2 Summary and conclusions

Amoxicillin – clavulanate for 10 days vs ceftriaxone single dose for acute otitis media			
Bibliography: Shekelle 2010{Shekelle, 2010 #81}			
Outcomes	**N° of participants (studies) Follow up**	**Results (95%CI)**	**Quality of the evidence (GRADE)**
Treatment success	1590 (5 studies)	Absolute RD= 3% (-2 to 7) NS	⊕⊕⊕⊖: **MODERATE** Study quality:-1 open label, low jaded in 2/5 Consistency: OK Directness: OK Imprecision:OK
Overall adverse events	513 (1 study)	**Absolute RD= 16% (9% to 24%)** **SS** **Amoxicillin-clavulanate associated with greater overall AE rate**	⊕⊕⊖⊖: **LOW** Study quality: -2 open label, selective reporting (no information from 4 other trials) Consistency: N/A Directness: ok Imprecision:ok
Diarrhea	513 (1 study)	**Absolute RD= 13% (6% to 20%)** **SS** **Amoxicillin clavulanate associated with greater rate of diarrhea**	⊕⊕⊖⊖: **LOW** Study quality: -2 open label, selective reporting (no information from 4 other trials) Consistency: N/A Directness: ok Imprecision:ok

Table 111

This systematic review + meta-analysis compared amoxicillin - clavulanate for 10 days to a single IM dose of ceftriaxone (50 mg/kg) in children with acute otitis media. 5 RCTs were found, including a total of 1590 children. The dose of amoxicillin-clavulanate differed considerably between the trials. In one trial, the single dose of ceftriaxone could be followed by a second dose after 48 hours in case of inadequate treatment response. The children were aged between 3 months and 10 years. Information on adverse events could only be obtained from 1 trial.

In children *with acute otitis media*, a treatment with amoxicillin – clavulanate for 10 days, compared to ceftriaxone for 1 day, **did not** result in a statistically significant difference in *treatment success.*
GRADE: MODERATE quality of evidence

No information on recurrence rates was available.

In children *with acute otitis media*, a treatment with amoxicillin – clavulanate for 10 days resulted in a statistically significantly higher rate of *overall adverse events* when compared to a treatment with ceftriaxone for 1 day.
GRADE: LOW quality of evidence

In children *with acute otitis media*, a treatment with amoxicillin – clavulanate for 10 days resulted in a statistically significantly higher rate of *diarrhea* when compared to a treatment with ceftriaxone for 1 day.

GRADE: LOW quality of evidence

6.2.2.3 Amoxicillin - clavulanate (10d) vs azithromycin (3-5d) for acute otitis media

6.2.2.3.1 Clinical evidence profile

Meta-analysis: Shekelle 2010{Shekelle, 2010 #81} AHRQ Evidence Report/Technology Assessment "Management of acute otitis media: update"

Inclusion criteria: SR, RCT, CCT, uncomplicated AOM in average risk children
Search strategy: This is an update of a 2001 report. Searches of PubMed and the Cochrane databases were conducted from January 1998 to July 2010 using the same search strategies used for the 2001 report, with the addition of terms not considered in the 2001 review. The Web of Science was also searched for citations of the 2001 report and its peer-reviewed publications
Assessment of quality of included trials: yes: Jadad for RCTs, AMSTAR for SRs, GRADE for overall evaluation
ITT analysis: yes/no

Table 112

Ref	Comparison	N/n	Outcomes	Result (95% CI)
ref* Shekelle 2010{Shekelle, 2010 #81} Design: SR+ MA Search date: (july 2010)	amoxicillin - clavulanate vs azithromycine	N= 9 n=2057	**Treatment success** *(not defined)*	Risk Difference= 0% (-7 to 6) NS (after exclusion of 1 outlier: RD= 2% (-3 to 7) NS *heterogeneity still present: I^2 70%*
		N=3 n=?	**Overall adverse events**	**Risk difference =19%(9%, 29%)** **SS (more overall AE with amoxicilline-clavulanate)**
		N=3 n=?	**Gastrointestinal adverse events**	**Risk difference:** 18% (8%, 28%) SS **(more gastrointestinal AE with amoxicilline-clavulanate)**

		N=1 n=373 Dunne 2003	**Vomiting**	**absolute risks 1% vs 2%** **NS**

Table 113

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by Shekelle 2010
Pestalozza 1992{Pestalozza, 1992 #128}	30	see figure below	see figure below	azithromycin (10 mg/kg administered as a single daily dose for 3 days) vs amoxycillin/clavulanic acid (50 mg/kg/day given b.i.d. for 10 days)	Jadad score 1
Daniel 1993{Daniel, 1993 #129}	159	see figure below	see figure below	Azithromycin (10 mg/kg/day) as a single dose for three days vs co-amoxiclav was given tid for ten days at a dosage according to the manufacturer's instructions for the country	Jadad score 2
Schaad 1993{Schaad, 1993 #130}	389	see figure below	see figure below	azithromycin was 10 mg/kg/day, in a single daily dose, administered for three days vs Co-amoxiclav was given at a dose of 13.3 mg/kg	Jadad score 2

				(amoxycillin equivalent) tid for ten days	
Principi 1995{Principi, 1995 #131}	484	see figure below	see figure below	once-daily azithromycin given for three days versus thrice-daily amoxicillin/clavulanic acid (CA) given for ten days	Jadad score 2
Arguedas 1996{Arguedas, 1996 #132}	238	see figure below	see figure below	azithromycin (10 mg/kg once daily for 3 days) vs amoxycillin/clavulanate potassium (40 mg/kg/day divided into three equal doses for 10 days)	Jadad score 3
Dagan 2000{Dagan, 2000 #133}	100	see figure below	see figure below	amoxicillin/clavulanate (45/6.4 mg/kg/day in two divided doses for 10 days) vs azithromycin (10 mg/kg on Day 1, then 5 mg/kg daily on Days 2 through 5)	Jadad score 2
Dunne 2003{Dunne, 2003 #134}	188+185	see figure below	see figure below	azithromycin 10 mg/kg/day x 3 days or co-amoxiclav 45 mg/kg/day x 10 days	Jadad score 5
Guven 2006{Guven, 2006 #135}	180	see figure below	see figure below	amoxicillin-clavulanate (45/6.4 mg/kg/day in two divided doses for 10 days) vs low dose azithromycin (10mg/kg/day for 3 days)	Jadad score 2
Biner 2007{Biner, 2007 #127}	104	see figure below	see figure below	5 days of azithromycin (10 mg/kg on day 1, then 5 mg/kg daily on days 2-5)	Jadad score 1

				vs 10-day course of amoxicillin/clavulanate (90/6.4 mg/kg/day in 2 doses)	

Table 114

Table 15. Amoxicillin-Clavulanate (7-10 Days) vs. Azithromycin (≤5 Days); Outcome Indicator: Treatment Success Rate

Author, Year	Age	Definition of outcome	Amox-clav Sample Size	Azithromycin Sample Size	Amox-clav Success Rate (%)	Azithromycin Success Rate (%)	Rate Difference In %	95% CI of Rate Difference In %
Pestalozza, 1992[115]	11 mos-9 yrs	Success at day 12-14	15	15	40.0	93.3	-53.3	-81.2, -25.5
Daniel, 1993[116]	2-8 yrs	Success at day 10-12	54	103	100.0	94.2	5.8	0.5, 11.1
Schaad, 1993[117]	6 mos-10.2 yrs	Success at day 7-20	189	192	97.4	93.8	3.6	-0.5, 7.7
Principi, 1995[118]	6 mos-12 yrs	Success at day 10-14	198	215	73.2	85.1	-11.9	-19.7, -4.1
Arguedas, 1996[119]	6 mos-12 yrs	Success at day 10-11	45	47	95.6	100.0	-4.4	-11.6, 2.7
Dagan, 2000[7]	6 mos-9 yrs	Success at day 12-14	70	73	85.7	69.9	15.9	2.5, 29.2
Dunne, 2003[70]	6 mos-12 yrs	Success at day 10	181	185	87.8	82.7	5.1	-2.1, 12.4
Guven, 2006[52]	6 mos-12 yrs	Success at day 11-13	84	90	81.0	77.8	3.2	-8.8, 15.2
Biner, 2007[71]	6 mos-10 yrs	Success at day 3	39	31	87.2	87.1	0.1	-15.7, 15.9
Random effects estimates			875	951	86.1	86.4	-0.3	-6.5, 5.9
Test of heterogeneity Chi-square test value							39.8	
Test of heterogeneity Chi-square test p-value							<0.001	
Test of heterogeneity I-squared							79.9%	
Test of publication bias, Egger's asymmetry test p-value							0.28	

Figuur 8. RCTs included by Shekelle 2010, description and outcomes

Author's conclusions: The quality of evidence for this conclusion is moderate due to heterogeneity in the results of studies, meaning that further high quality research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.

Remarks: Unclear reporting of adverse events in Shekelle 2010. Not all AEs seem to be pooled.

As the outcome “treatment succes” is not defined, it is difficult to interpret.

6.2.2.3.2 Summary and conclusions

amoxicillin – clavulanate (10 days) vs azithromycine (3-5 days) for acute otitis media			
Bibliography: Shekelle 2010{Shekelle, 2010 #81}			
Outcomes	**N° of participants (studies) Follow up**	**Results (95%CI)**	**Quality of the evidence (GRADE)**
Treatment success	2057 (9 studies) 3-14 days	Absolute RD= 0% (-7 to 6) NS	⊕⊕⊕⊖: **MODERATE** Study quality: -1 low JADAD scores, heterogeneity present Consistency: see above Directness: ok Imprecision: ok
Overall adverse events	? (3 studies)	**Absolute RD =19%(9%, 29%)** **SS** **more overall AE with amoxicillin-clavulanate**	⊕⊕⊖⊖: **LOW** Study quality: : -2 low JADAD scores, selective reporting Consistency: ? Directness: ok Imprecision:ok
Gastrointestinal adverse events	? (3 studies)	**Absolute RD= 18% (8%, 28%)** **SS** **more gastrointestinal AE with amoxicillin-clavulanate**	⊕⊕⊖⊖: **LOW** Study quality: : -2 low JADAD scores, selective reporting Consistency: ? Directness: ok Imprecision:ok
Vomiting	373 (1 study) 10 days	Absolute risk 1% vs 2% NS	⊕⊕⊖⊖: **LOW** Study quality: : -2 low JADAD scores, selective reporting Consistency: N/A Directness: ok Imprecision: unclear

Table 115

This systematic review + meta-analysis compared amoxicillin-clavulanate for 10 days to azithromycin for 3 to 5 days in children with acute otitis media. 9 RCTs were found, including a total of 2057 children. The children were aged between 6 months and 12 years. There were some differences in dose of antibiotic between the trials, but in most trials, the dose of amoxicillin-clavulanate was +/- 45 mg/kg/day in 2 or 3 divided doses and the dose of azithromycin was 10mg/kg/day in 1 dose.

Most trials were open label.

In children *with acute otitis media*, a treatment with amoxicillin-clavulanate for 10 days, compared to azithromycin for 3-5 days **did not** result in a statistically significant difference in *treatment success.*
GRADE: MODERATE quality of evidence

We have no information on recurrence rates.

In children *with acute otitis media*, a treatment with amoxicillin-clavulanate for 10 days resulted in a statistically significantly higher rate of *overall adverse events and of gastro-intestinal adverse events* compared to azithromycin for 3-5 days.
GRADE: LOW quality of evidence

In children *with acute otitis media*, a treatment with amoxicillin-clavulanate for 10 days, compared to azithromycin for 3-5 days **did not** result in a statistically significant difference in *vomiting.*
GRADE: LOW quality of evidence

6.2.3 Duration of antibiotic treatment

6.2.3.1 Short course antibiotic > 48 hours (and <7 days) versus longer course (> 7 days) of same or other antibiotic

6.2.3.1.1 Clinical evidence profile

Meta-analysis: Cochrane Kozyrskyj 2010 {Kozyrskyj, 2010 #82} "Short-course antibiotics for acute otitis media"

Inclusion criteria: randomized controlled trials (RCTs) of the empiric treatment of AOM, comparing two antibiotic regimens of different durations
Intervention/control: We compared antibiotic therapy of a treatment arm for less than seven days (defined as the short course), with a treatment arm greater than or equal to seven days (defined as the long course). The antibiotic may be the same or different in the two treatment arms.
Population: children aged one month to 18 years, with a clinical diagnosis of AOM and no history of immediate antibiotic use, immune deficiency, chronic disease or head and neck abnormalities.
Search strategy: Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2009, issue 4) which contains the Cochrane Acute Respiratory Infections Group's Specialised Register; MEDLINE (1966 to November Week 1, 2009); EMBASE (1974 to November 2009); MEDLINE In-Process & Other Non-Indexed Citations (1966 to Week 1, 2009); International Pharmaceutical Abstracts (1970 to August Week 1, 2008); BIOSIS Previews (1969 to November 2009); CINAHL (1981 to November 2009); the NLM Gateway (1998 to August 2008); OCLC Papers First and Proceedings First (1997 to November 2009); ClinicalTrials.gov (1998 to August 2008); Proquest Dissertations and Theses (1861 to November 2009); and Current Controlled Trials (1997 to August 2008). We searched the following databases without any date restrictions in September 2007: the National Research Register; CRISP; the TRIP Database; Scirus; and Google Scholar. We imposed no language or publication restrictions
Assessment of quality of included trials: yes

Table 116

Ref	Comparison	N/n	Outcomes	Result OR (95% CI)
Cochrane Kozyrskyj 2010 {Kozyrskyj, 2010 #82}	**Short-acting antibiotic > 48 hours (and <7 days) versus > 7 days**	N=16 n= 5093 (Adam 1996, Adam 2000, Block 2000, Block 2004, Boulesteix	Treatment failure at 1 month or less *(which included lack of clinical resolution, relapse or recurrence of AOMduring a one-month period following the initiation of therapy)*	Crude AR: 486/2376 vs 475/2717 **1.34 [1.15, 1.55]** **SS**

		1995, Catania 2004, Cohen 1997, Cohen 1998, Cohen 2000, Gooch 1996, Hendrickse 1988, Hoberman 1997, Ingvarsson 1982, Kafetzis 1997, Pessey 1999, Ploussard 1984)		
		N=11 n=3932 (Adam 2000, Block 2000, Block 2004, Boulesteix 1995, Catania 2004, Cohen 1997, Cohen 1998, Cohen 2000, Hendrickse 1988, Hoberman 1997, Pessey 1999)	Treatment failure at 8 to 19 days	Crude AR: 340/1892 vs 293/2040 **1.37 [1.15, 1.64]** **SS**

		N=9 n=2476 (Adam 1996, Block 2004, Cohen 1997, Gooch 1996, Ingvarsson 1982, Kafetzis 1997, Pessey 1999, Ploussard 1984)	Treatment failure at 20 to 30 days	Crude AR: 238/1141 vs 271/1335 1.16 [0.94, 1.42] NS
		N=7 n=2068 (Block 2000, Boulesteix 1995, Cohen 1998, Cohen 2000, de Saintongue 1982, Hendrickse 1988, Hoberman 1997)	Treatment failure at 3 months or less	Crude AR: 391/973 vs 399/1095 1.18 [0.98, 1.41] NS
		N=2 n=207 (de Saintongue 1982, Hendrickse 1988)	Treatment failure at 90 days	Crude AR: 36/100 vs 35/107 1.16 [0.65, 2.06] NS

		N=5 n=1861 (Block 2000, Boulesteix 1995, Cohen 1998, Cohen 2000, Hoberman 1997)	Treatment failure at 30 to 45 days	Crude AR: 355/873 vs 364/988 1.18 [0.97, 1.43] NS
		N=13 N=4918 (Adam 1996, Adam 2000, Block 2000, Block 2004, Boulesteix 1995, Catania 2004, Cohen 1997, Cohen 1998, Gooch 1996, Hendrickse 1988, Hoberman 1997, Kafetzis 1997, Ploussard 1984)	Gastrointestinal adverse effects	Crude AR: 206/2221 vs 369/2697 **0.72 (0.60 to 0.87)** **SS**
			SUBGROUP ANALYSES	
		N=5 n=570 (Block 2000, Block 2004,	SUBGROUP <2 years old Treatment failure at 1 month or less	Crude AR: 99/296 vs 85/274 1.09 [0.76, 1.57] NS

		Ingvarsson 1982, Pessey 1999, Ploussard 1984)		
		N=6 n= 1064 (Block 2000, Block 2004, Catania 2004, Ingvarsson 1982, Pessey 1999, Ploussard 1984)	SUBGROUP =>2 years old Treatment failure at 1 month or less	Crude AR: 74/530 vs 86/534 0.85 [0.60, 1.21] NS
		N= 1 n= 27 (Hendrickse 1988)	SUBGROUP perforated eardrum Treatment failure at 1 month or less	Crude AR: 10/15 vs 4/12 3.62 [0.81, 16.06] NS
		N=1 n=101 (Hendrickse 1988)	SUBGROUP non- perforated eardrum Treatment failure at 1 month or less	Crude AR: 10/47 vs 11/54 1.06 [0.40, 2.75] NS

Table 117

* Characteristics of included studies: see below

Ref + design	n	Population	Duration (last follow-up)	Comparison	Methodology scored by authors of review
Adam 1996{Adam,	96	children 3 months to 6 years old	3 weeks	Cefpodoxime 40 mg to 60	BLINDING

1995 #280}			after study entry	mg twice daily for 5 days versus cefaclor 40 mg/kg/day 3 times daily for 10 days	High risk INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk OTHER BIAS Unclear risk (Funding not reported)
Adam 2000{Adam, 2000 #281}	212	children aged 2 to 14 years	Day 28	Cefixime 8 mg/kg/day for 5 days versus same treatment for 10 days	BLINDING Low risk INCOMPLETE OUTCOME DATA High risk SELECTIVE REPORTING High risk OTHER BIAS Unclear risk (Funding not reported)
Block 2000{Block, 2000 #283}	373	children aged 6 months through 12 years	Day 38-45	Cefdinir 14 mg/kg/day twice daily for 5 days versus cefprozil 30 mg/kg twice daily for 10 days	BLINDING High risk (Only investigators blinded) OTHER BIAS Low risk
Block 2004{Block, 2004 #284}	324	children aged 6 months through 6 years	Day 25-28	Cefdinir 14 mg/kg twice daily for 5 days versus amoxicillin/clavulanate 45/6.4 mg/kg twice daily for 10 days	BLINDING High risk (Only investigator blinded) SELECTIVE REPORTING High risk OTHER BIAS Low risk
Boulesteix 1995{Boulesteix, 1995 #282}	242	children 6 months to 6 years old	Day 30-40	Cefpodoxime 4 mg/kg twice daily for 5 days versus cefixime 4 mg/kg twice daily for 8 days	ALLOCATION CONCEALMENT Low risk BLINDING High risk INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING

					Low risk OTHER BIAS Unclear risk (Funding not declared)
Catania 2004{Catania, 2004 #294}	400	children 2 to 6 years	Day 15-20	Cefaclor 40 mg/kg/day for 5 days versus cefaclor 40 mg/kg/day for 10 days	INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk OTHER BIAS Unclear risk (No funding declared)
Cohen 1997{Cohen, 1997 #295}	334	children 4 months to 3 years old	Day 20-30	Cefpodoxime 8 mg/kg/day twice daily for 5 days versus amoxil-clavulanate 80 mg/kg/day 3 times daily for 8 days	ALLOCATION CONCEALMENT Low risk BLINDING High risk INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk OTHER BIAS Unclear risk (Funding not declared)
Cohen 1998{Cohen, 1998 #288}	378	children aged 4 to 30 months	Day 28-42	Amoxicillin/clavulanate 80/10 mg/kg/day 3 times daily for 5 days versus same treatment for 10 days	RANDOM SEQUENCE GENERATION Low risk BLINDING Low risk SELECTIVE REPORTING High risk OTHER BIAS Unclear risk (The only significant difference at baseline was diarrhea, but GI symptoms are an outcome; industry funding)
Cohen 2000{Cohen, 2000 #289}	448	children aged 4 to 30 months	Day 28-42	Cefpodoxime proxetil 8 mg/kg/day for 5 days versus	RANDOM SEQUENCE GENERATION Low risk BLINDING

				same regimen for 10 days	Low risk SELECTIVE REPORTING Low risk OTHER BIAS Low risk
De Saintongue 1982{Chaput de Saintongue, 1982 #296}	79	children 2 to 10 years old	12 weeks	Amoxicillin 125/250 mg 3 times daily for 3 days + placebo for 7 days versus amoxicillin 125/250 mg 3 times daily for 10 days	BLINDING Low risk INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk OTHER BIAS Low risk
Gooch 1996{Gooch, 1996 #291}	497	children 3 months to 12 years old	Day 14-18	Cefuroxime 30 mg/kg/day twice daily for 5 days + placebo twice daily for 5 days versus cefuroxime 30 mg/kg/day twice daily for 10 days	INCOMPLETE OUTCOME DATA High risk SELECTIVE REPORTING Low risk OTHER BIAS Low risk
Hendrickse 1988{Hendrickse, 1988 #292}	128	Children 1 month to 12 years old	Day 90	Cefaclor 40 mg/kg/day twice daily for 5 days + placebo for 5 days versus cefaclor 40 mg/kg/day twice daily for 10 days	RANDOM SEQUENCE GENERATION Low risk BLINDING Low risk INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk OTHER BIAS Low risk
Hoberman 1997{Hoberman, 1997 #164}	564	children 2 months to 12 years old	Day 32-38	Amoxil-clavulanate (new formulation) twice daily for 5 days versus	ALLOCATION CONCEALMENT Low risk BLINDING Unclear risk (Only investigators

				amoxil-clavulanate (new formulation) twice daily for 10 days or amoxil-clavulanate (old formulation) 3 times daily for 10 days	blinded) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk OTHER BIAS Unclear risk (Industry funding and authors from SmithKline Beecham, baseline differences in exposure to cigarette smoke)
Ingvarsson 1982{Ingvarsson, 1982 #287}	134	children 6 months to 7 years old	Day 28-30	Penicillin-V 25 mg/kg twice daily for 5 days versus penicillin-V 25 mg/kg twice daily for 10 days	BLINDING High risk (Not mentioned and no placebo) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk OTHER BIAS Unclear risk (Funding not reported)
Kafetzis 1997{Kafetzis, 1997 #286}	560	children 2 to 172 months old	Day 28-32	Cefprozil 30 mg/kg/day twice daily for 5 days versus cefprozil 30 mg/kg/day twice daily for 10 days	BLINDING High risk INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk OTHER BIAS Unclear risk (Funding not reported)
Pessey 1999{Pessey, 1999 #285}	347	Children aged 6 to 36 months	Day 21-28	Cefuroxime axetil 30 mg/kg/day twice daily for 5 days versus amoxicillin/clavulanate 40 mg/kg/day 3 times daily for	BLINDING High risk (Open study) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk

				10 days versus amoxicillin/clavulanate 80 mg/kg/day 3 times daily for 8 days	OTHER BIAS Unclear risk (Corresponding author from Glaxo, funding not reported)
Ploussard 1984{Ploussard, 1984 #297}	56	Children 5 months to 5 years old	Day 10-16	Cefaclor 40 mg/kg 3 times daily for 5 days versus amoxicillin 40 mg/kg 3 times daily for 10 days	RANDOM SEQUENCE GENERATION Low risk BLINDING High risk INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk OTHER BIAS Unclear risk (Funding not reported)

Table 118

Author's conclusions:

"Evidence is increasing for a wait and watch approach to AOM.We believe that this is the most prudent approach for most children who are older than six months or do not have serious or complicated disease. If treatment is warranted, the clinician must decide if treatment for 7 to 10 days is worth the slightly reduced risk of treatment failure in the short term (< 21 days). Shorter courses can also be safely used, resulting in few side effects and, perhaps, a lower risk of antibiotic resistant bacteria. Shorter courses may also be associated with higher levels of compliance."

"Statement 19/06/12:

As of 19 June 2012, this Cochrane Review is no longer being updated, as there is high quality evidence that treating children with acute otitis media with a short course (less than seven days) of antibiotics, compared to treatment with a long course (seven days or greater) of antibiotics, increases the likelihood of treatment failure in the short term, meaning further research is unlikely to change our confidence in the estimate of effect in our primary outcome. The review authors recommend that it is no longer necessary to update this review"

6.2.3.1.2 Summary and conclusions

Short course antibiotic > 48 hours (and <7 days) versus > 7 days for acute otitis media			
Bibliography: Cochrane Kozyrskyj 2010 {Kozyrskyj, 2010 #82}			
Outcomes	**N° of participants (studies) Follow up**	**Results (OR(95%CI))**	**Quality of the evidence (GRADE)**
Treatment failure at 1 month or less	5093 (16 studies)	**1.34 [1.15, 1.55] SS (more treatment failure with short course)**	⊕⊕⊖⊖: **LOW** Study quality:-1 (unclear blinding, selective reporting) Consistency: ok Directness: -1 (comparison; not the same antibiotics) Imprecision: ok
Treatment failure at 8 to 19 days	3932 (11 studies)	**1.37 [1.15, 1.64] SS (more treatment failure with short course)**	⊕⊕⊖⊖: **LOW** Study quality: 1 (unclear blinding, selective reporting) Consistency: ok Directness: -1 (comparison; not the same antibiotics) Imprecision: ok
Treatment failure at 20 to 30 days	2476 (9 studies)	1.16 [0.94, 1.42] NS	⊕⊕⊖⊖: **LOW** Study quality: 1 (unclear blinding, selective reporting) Consistency: ok Directness: -1 (comparison; not the same antibiotics) Imprecision: ok
Treatment failure at 3 months or less	2068 (7 studies)	1.18 [0.98, 1.41] NS	⊕⊕⊖⊖: **LOW** Study quality: 1 (unclear blinding, selective reporting) Consistency: ok Directness: -1 (comparison; not the same antibiotics) Imprecision: ok
Treatment failure at 90 days	207 (2 studies)	1.16 [0.65, 2.06] NS	⊕⊕⊕⊖: **MODERATE** Study quality: ok Consistency: ok Directness: ok Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Treatment failure at 30 to 45 days	1861 (5 studies)	1.18 [0.97, 1.43] NS	⊕⊕⊖⊖: **LOW** Study quality: 1 (unclear blinding, selective reporting) Consistency: ok Directness: -1 (comparison; not the same antibiotics) Imprecision: ok
Gastrointestinal adverse effects	4918 (13 studies)	**0.72 (0.60 to 0.87) SS (less adverse effects with short course)**	⊕⊕⊖⊖: **LOW** Study quality: 1 (unclear blinding, selective reporting) Consistency: ok Directness: -1 (comparison; not the same antibiotics) Imprecision: ok

Table 119

In this meta-analysis, a treatment with a short course of an antibiotic (more than 48 hours but less than 7 days) was compared to a longer antibiotic course of 7 days or more(with the same or a different antibiotic), in children with acute otitis media.

The children in these trials ranged from 1 month to 14 years old. The follow-up in these studies varied from 10 days to 3 months after treatment.

The antibiotics used in de short course arms were amoxicillin, amoxicillin+clavulanate, cefuroxime, penicillin V, cefaclor, cefdinir, cefixime, cefpodoxime, and cefprozil. In all studies but one, the duration of the short course was 5 days. Cefaclor, cefdinir, cefixime, cefpodoxime, cefprozil are not available in Belgium.

The antibiotics used in the long course arms were amoxicillin, amoxicillin+clavulanate, cefuroxime, penicillin V, cefaclor, cefixime, cefpodoxime, and cefprozil. The duration of the long course was 8-10 days.

In 10 out of 17 studies, the same antibiotics were used in both arms. A sensitivity analysis including only these studies was performed and is reported in the next section(see 6.2.3.2)

In children *with acute otitis media*, a treatment with a short course of an antibiotic (more than 48 hours but less than 7 days) , compared to a longer antibiotic course of 7 days or more(with the same or a different antibiotic), **did** result in a statistically significant **increase** in *treatment failure at one month or less*, and *at 8 to 19 days.*
GRADE: LOW quality of evidence

In children *with acute otitis media*, a treatment with a short course of an antibiotic (more than 48 hours but less than 7 days) , compared to a longer antibiotic course of 7 days or more(with the same antibiotic), **did not** result in a statistically significant difference in *treatment failure at 90 days.*
GRADE: MODERATE quality of evidence

In children *with acute otitis media*, a treatment with a short course of an antibiotic (more than 48 hours but less than 7 days) , compared to a longer antibiotic course of 7 days or more(with the same or a different antibiotic), **did not** result in a statistically significant difference in *treatment failure at 20 to 30 days, at 3 months or less,* or *at 30 to 45 days.*
GRADE: LOW quality of evidence

In children *with acute otitis media*, a treatment with a short course of an antibiotic (more than 48 hours but less than 7 days) , compared to a longer antibiotic course of 7 days or more(with the same or a different antibiotic), **did** result in a statistically significant **decrease** in *gastrointestinal adverse events.*
GRADE: LOW quality of evidence

6.2.3.2 Short course antibiotic > 48 hours (and <7 days) versus longer course (> 7 days) of same antibiotic

6.2.3.2.1 Clinical evidence profile

Meta-analysis: Cochrane Kozyrskyj 2010 {Kozyrskyj, 2010 #82} "Short-course antibiotics for acute otitis media"

Inclusion criteria: randomized controlled trials (RCTs) of the empiric treatment of AOM, comparing two antibiotic regimens of different durations
Intervention/control: We compared antibiotic therapy of a treatment arm for less than seven days (defined as the short course), with a treatment arm greater than or equal to seven days (defined as the long course). The antibiotic may be the same or different in the two treatment arms.
Population: children aged one month to 18 years, with a clinical diagnosis of AOM and no history of immediate antibiotic use, immune deficiency, chronic disease or head and neck abnormalities.
Search strategy: Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2009, issue 4) which contains the Cochrane Acute Respiratory Infections Group's Specialised Register; MEDLINE (1966 to November Week 1, 2009); EMBASE (1974 to November 2009); MEDLINE In-Process & Other Non-Indexed Citations (1966 to Week 1, 2009); International Pharmaceutical Abstracts (1970 to August Week 1, 2008); BIOSIS Previews (1969 to November 2009); CINAHL (1981 to November 2009); the NLM Gateway (1998 to August 2008); OCLC Papers First and Proceedings First (1997 to November 2009); ClinicalTrials.gov (1998 to August 2008); Proquest Dissertations and Theses (1861 to November 2009); and Current Controlled Trials (1997 to August 2008). We searched the following databases without any date restrictions in September 2007: the National Research Register; CRISP; the TRIP Database; Scirus; and Google Scholar. We imposed no language or publication restrictions
Assessment of quality of included trials: yes

Table 120

Ref	Comparison	N/n	Outcomes	Result OR (95% CI)
Cochrane Kozyrskyj 2010 {Kozyrskyj, 2010 #82}	**Short course antibiotic > 48 hours (and <7 days) versus > 7 days**	N=9 n= 3321 (Adam 2000, Catania 2004, Cohen 1998, Cohen 2000, Gooch 1996, Hendrickse 1988,	Treatment failure at 1 month or less *(which included lack of clinical resolution, relapse or recurrence of AOMduring a one-month period following the initiation of therapy)*	Crude AR: 258/1482 vs 257/1839 **OR 1.65 [1.35, 2.01]** **SS**

		Hoberman 1997, Ingvarsson 1982, Kafetzis 1997)		
		N= 6 n= 2153 (Adam 2000, Catania 2004, Cohen 1998, Cohen 2000, Hendrickse 1988, Hoberman 1997)	Treatment failure at 8 to 19 days	Crude AR: 185/995 vs 134/1158 **OR 1.97 [1.54, 2.52]** **SS**
		N=4 n= 1319 (Gooch 1996, Hendrickse 1988, Ingvarsson 1982, Kafetzis 1997)	Treatment failure at 20 to 30 days	Crude AR:87/561 vs 129/758 OR 1.27 [0.92, 1.76] NS
		N= 5 n= 1492 (Cohen 1998, Cohen 2000, de Saintongue 1982, Hendrickse 1988, Hoberman 1997,)	Treatment failure at 3 months or less	Crude AR: 277/677 vs 293/815 OR 1.24 [1.00, 1.53] NS

		N= 2 n= 207 (de Saintongue 1982, Hendrickse 1988)	Treatment failure at 90 days	Crude AR: 36/100 vs 35/107 OR 1.16 [0.65, 2.06] NS
		N= 3 n= 1285 (Cohen 1998, Cohen 2000, Hoberman 1997)	Treatment failure at 30 to 45 days	Crude AR: 241/577 vs 258/708 OR 1.25 [1.00, 1.57] NS

Table 121

* Characteristics of included studies: see below

Ref + design	n	Population	Duration (last follow-up)	Comparison	Methodology scored by authors of review
Adam 2000{Adam, 2000 #281}	212	children aged 2 to 14 years	Day 28	Cefixime 8 mg/kg/day for 5 days versus same treatment for 10 days	BLINDING Low risk INCOMPLETE OUTCOME DATA High risk SELECTIVE REPORTING High risk OTHER BIAS Unclear risk (Funding not reported)
Catania 2004{Catania, 2004 #294}	400	children 2 to 6 years	Day 15-20	Cefaclor 40 mg/kg/day for 5 days versus cefaclor 40 mg/kg/day for 10 days	INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk OTHER BIAS

					Unclear risk (No funding declared)
Cohen 1998{Cohen, 1998 #288}	378	children aged 4 to 30 months	Day 28-42	Amoxicillin/clavulanate 80/10 mg/kg/day 3 times daily for 5 days versus same treatment for 10 days	RANDOM SEQUENCE GENERATION Low risk BLINDING Low risk SELECTIVE REPORTING High risk OTHER BIAS Unclear risk (The only significant difference at baseline was diarrhea, but GI symptoms are an outcome; industry funding)
Cohen 2000{Cohen, 2000 #289}	448	children aged 4 to 30 months	Day 28-42	Cefpodoxime proxetil 8 mg/kg/day for 5 days versus same regimen for 10 days	RANDOM SEQUENCE GENERATION Low risk BLINDING Low risk SELECTIVE REPORTING Low risk OTHER BIAS Low risk
De Saintongue 1982{Chaput de Saintongue, 1982 #296}	79	children 2 to 10 years old	12 weeks	Amoxicillin 125/250 mg 3 times daily for 3 days + placebo for 7 days versus amoxicillin 125/250 mg 3 times daily for 10 days	BLINDING Low risk INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk OTHER BIAS Low risk
Gooch 1996{Gooch, 1996 #291}	497	children 3 months to 12 years old	Day 14-18	Cefuroxime 30 mg/kg/day twice daily for 5 days + placebo twice daily for 5 days versus cefuroxime 30 mg/kg/day	INCOMPLETE OUTCOME DATA High risk SELECTIVE REPORTING Low risk OTHER BIAS

				twice daily for 10 days	Low risk
Hendrickse 1988{Hendrickse, 1988 #292}	128	Children 1 month to 12 years old	Day 90	Cefaclor 40 mg/kg/day twice daily for 5 days + placebo for 5 days versus cefaclor 40 mg/kg/day twice daily for 10 days	RANDOM SEQUENCE GENERATION Low risk BLINDING Low risk INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk OTHER BIAS Low risk
Hoberman 1997{Hoberman, 1997 #164}	564	children 2 months to 12 years old	Day 32-38	Amoxil-clavulanate (new formulation) twice daily for 5 days versus amoxil-clavulanate (new formulation) twice daily for 10 days or amoxil-clavulanate (old formulation) 3 times daily for 10 days	ALLOCATION CONCEALMENT Low risk BLINDING Unclear risk (Only investigators blinded) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk OTHER BIAS Unclear risk (Industry funding and authors from SmithKline Beecham, baseline differences in exposure to cigarette smoke)
Ingvarsson 1982{Ingvarsson, 1982 #287}	134	children 6 months to 7 years old	Day 28-30	Penicillin-V 25 mg/kg twice daily for 5 days versus penicillin-V 25 mg/kg twice daily for 10 days	BLINDING High risk (Not mentioned and no placebo) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk OTHER BIAS

					Unclear risk (Funding not reported)
Kafetzis 1997{Kafetzis, 1997 #286}	560	children 2 to 172 months old	Day 28-32	Cefprozil 30 mg/kg/day twice daily for 5 days versus cefprozil 30 mg/kg/day twice daily for 10 days	BLINDING High risk INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk OTHER BIAS Unclear risk (Funding not reported)

Table 122

Author's conclusions:

"Evidence is increasing for a wait and watch approach to AOM.We believe that this is the most prudent approach for most children who are older than six months or do not have serious or complicated disease. If treatment is warranted, the clinician must decide if treatment for 7 to 10 days is worth the slightly reduced risk of treatment failure in the short term (< 21 days). Shorter courses can also be safely used, resulting in few side effects and, perhaps, a lower risk of antibiotic resistant bacteria. Shorter courses may also be associated with higher levels of compliance."

"Statement 19/06/12:

As of 19 June 2012, this Cochrane Review is no longer being updated, as there is high quality evidence that treating children with acute otitis media with a short course (less than seven days) of antibiotics, compared to treatment with a long course (seven days or greater) of antibiotics, increases the likelihood of treatment failure in the short term, meaning further research is unlikely to change our confidence in the estimate of effect in our primary outcome. The review authors recommend that it is no longer necessary to update this review"

6.2.3.2.2 Summary and conclusions

Short course antibiotic > 48 hours (and <7 days) versus > 7 days with the same antibiotic for acute otitis media			
Bibliography: Cochrane Kozyrskyj 2010 {Kozyrskyj, 2010 #82}			
Outcomes	**N° of participants (studies) Follow up**	**Results (OR(95%CI))**	**Quality of the evidence (GRADE)**
Treatment failure at 1 month or less	3311 (9 studies)	**OR 1.65 [1.35, 2.01] SS (more treatment failure with short course)**	⊕⊕⊕⊖: **MODERATE** Study quality:-1 (unclear blinding, selective reporting) Consistency: ok Directness: ok Imprecision: ok
Treatment failure at 8 to 19 days	2153 (6 studies)	**OR 1.97 [1.54, 2.52] SS (more treatment failure with short course)**	⊕⊕⊕⊕:**HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
Treatment failure at 20 to 30 days	1319 (4 studies)	OR 1.27 [0.92, 1.76] NS	⊕⊕⊕⊖: **MODERATE** Study quality: 1 (unclear blinding) Consistency: ok Directness: ok Imprecision: ok
Treatment failure at 3 months or less	1492 (5 studies)	OR 1.24 [1.00, 1.53] NS	⊕⊕⊕⊕:**HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
Treatment failure at 90 days	207 (2 studies)	OR 1.16 [0.65, 2.06] NS	⊕⊕⊕⊖: **MODERATE** Study quality: ok Consistency: ok Directness: ok Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Treatment failure at 30 to 45 days	1285 (3 studies)	OR 1.25 [1.00, 1.57] NS	⊕⊕⊕⊖: **MODERATE** Study quality: -1 (selective reporting) Consistency: ok Directness: ok Imprecision: ok

Table 123

In this meta-analysis, a treatment with a short course of an antibiotic (more than 48 hours but less than 7 days) was compared to a longer antibiotic course of 7 days or more(with the same antibiotic), in children with acute otitis media.

The children in these trials ranged from 1 month to 14 years old. The follow-up in these studies varied from 14 days to 12 weeks after treatment.

The antibiotics used were amoxicillin, amoxicillin+clavulanate, cefaclor, cefixime, cefpodoxime, cefprozil, cefuroxime, and penicillin V. The duration of the short course was 5 days in all studies but one, and the long course was 10 days in all studies.

In children *with acute otitis media*, a treatment with a short course of an antibiotic (more than 48 hours but less than 7 days) , compared to a longer antibiotic course of 7 days or more(with the same antibiotic), **did** result in a statistically significant **increase** in *treatment failure at one month or less*.
GRADE: MODERATE quality of evidence

In children *with acute otitis media*, a treatment with a short course of an antibiotic (more than 48 hours but less than 7 days) , compared to a longer antibiotic course of 7 days or more(with the same antibiotic), **did** result in a statistically significant **increase** in *treatment failure at 8 to 19 days.*
GRADE: HIGH quality of evidence

In children *with acute otitis media*, a treatment with a short course of an antibiotic (more than 48 hours but less than 7 days) , compared to a longer antibiotic course of 7 days or more(with the same antibiotic), **did not** result in a statistically significant difference in *treatment failure at 20 to 30 days, at 90 days,* or *at 30 to 45 days.*
GRADE: MODERATE quality of evidence

In children *with acute otitis media*, a treatment with a short course of an antibiotic (more than 48 hours but less than 7 days) , compared to a longer antibiotic course of 7 days or more(with the same antibiotic), **did not** result in a statistically significant difference in *treatment failure at 3 months or less.*
GRADE: HIGH quality of evidence

6.2.4 Dose A versus dose B

6.2.4.1 One or two daily doses vs three daily doses amoxicillin with or without clavulanate

6.2.4.1.1 Clinical evidence profile

Meta-analysis: Cochrane Thanaviratananich{Thanaviratananich, 2013 #80} "Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media" Inclusion criteria: RCTs comparing two different dosing intervals of the same intervention, amoxicillin, with or without clavulanate. Participants aged 12 years or younger, with acute otitis media diagnosed by acute ear pain and an inflamed ear drum. Search strategy: were searched: the Cochrane Central Register of Controlled Trials (CENTRAL) 2013, Issue 2, part of The Cochrane Library, www.thecochranelibrary.com (accessed 15 March 2013), which contains the Acute Respiratory Infections (ARI) Group's Specialised Register, MEDLINE (January 1950 to March week 1, 2013), EMBASE (July 2010 to August 2012) and the Science Citation Index (2001 to March 2013). Assessment of quality of included trials:yes Other methodological remarks: ITT data analysis

Table 124

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Cochrane Thanaviratananich{Thanaviratananich, 2013 #80}	One or two daily doses versus three daily doses of amoxicillin, with or without clavulanate	N= 5 n= 1601 (Principi 1986, Murph 1993, Hoberman 1997, Behre 1997, Damrikarnlert 2000)	Clinical cure rate at the end of therapy *(resolution of otalgia, resolution of fever and bacteriological cure rate, if data are provided.)*	Crude AR: 716/805 vs. 688/796 RR: 1.03 (0.99 to 1.07) NS

		N= 2 n=448 (Murph 1993, Damrikarnlert 2000)	Clinical cure rate during therapy *(resolution of otalgia, resolution of fever.)*	Crude AR: 78/229 vs 73/219 RR: 1.06 (0.85 to 1.33) NS
		N= 4 n=1476 (Principi 1986, Hoberman 1997, Behre 1997, Damrikarnlert 2000)	Clinical cure rate at post-treatment *(resolution of middle ear effusion, as determined by tympanometry, assessed only in those who do not have recurrences of AOM after completion of therapy.)*	Crude AR: 567/733 to 557/743 RR: 1.02 (0.95 to 1.09) NS
		N= 3 n=1029 (Principi 1986, Hoberman 1997, Damrikarnlert 2000)	AOM complications: Recurrent AOM after completion of therapy	Crude AR: 62/516 vs 47/513 RR: 1.21 (0.52 to 2.81) NS
		N= 2 n=878 (Behre 1997, Damrikarnlert 2000)	Adverse reactions to medication (overall)	Crude AR: 136/440 vs 131/438 RR: 0.92 (0.52 to 1.63) NS
		N= 4 n=1563 (Principi 1986, Hoberman 1997, Behre	Specific adverse reactions to medication: Diarrhoea	Crude AR: 47/782 vs 67/781 RR: 0.70 (0.49 to 1.00) NS

		1997, Damrikarnlert 2000)		
		N= 3 n=1100 (Principi 1986, Hoberman 1997, Damrikarnlert 2000)	Specific adverse reactions to medication: Skin adverse events	Crude AR: 28/551 vs 38/549 RR: 0.74 (0.46 to 1.18) NS
		N= 4 n=1520 (Murph 1993, Hoberman 1997, Behre 1997, Damrikarnlert 2000)	Compliance rate	Crude AR: 655/760 vs 622/760 RR: 1.04 (0.98 to 1.10) NS

Table 125

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology assessed by Cochrane group
Behre 1997{Behre, 1997 #162}	463	AOM children aged 2 to 12 years	Follow-up at day 28	10 days with amoxicillin/clavulanate (70/10 mg/kg/day and 60/15 mg/kg/day for the 2 and 3 times daily groups, respectively)	RANDOM SEQUENCE GENERATION Unclear risk (Quote: "The patients were randomised to treatment" Comment: the authors did not describe the method of randomisation)

					ALLOCATION CONCEALMENT Unclear risk (Comment: the authors did not mention anything about allocation concealment) BLINDING Low risk INCOMPLETE OUTCOME DATA High risk (Quote: "This fall in the success rate is partly accounted for by increased numbers of patients lost to follow-up and those with an indeterminate outcome at follow-up who were categorised as failures" Comment: for robustness, 'loss to followup' and 'indeterminate outcome' should be counted as failure in the 2 times daily and success in the 3 times daily groups. If it was recalculated, success rate should be 185/ 231(80.1%) and 210/232 (90.5%) for the 2 times daily and 3 times daily groups, respectively) SELECTIVE REPORTING Low risk OTHER BIAS Low risk
Damrikarnlert 2000{Damrikarnlert, 2000 #163}	415	AOM children aged 2 months to 12 years	Follow-up on day 42	7 to 10 days (depending on national prescribing practice) with amoxicillin/clavulanate 45/6.4 mg/kg/day and 40/10 mg/kg/day (2 versus 3 times daily groups, respectively)	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Unclear risk (Comment: did not mention the method of allocation concealment)

					BLINDING Low risk INCOMPLETE OUTCOME DATA High risk (Quote: “The primary efficacy variable was the clinical response (success or failure) at the end of therapy (Day 7-12). Secondary efficacy variables were clinical response at follow-up (Day 38-42) and bacteriological response (success or failure) at the end of therapy. A tertiary efficacy variable was the clinical response at the on-therapy visit (Day 3-5)”) SELECTIVE REPORTING Low risk OTHER BIAS Low risk
Hoberman 1997{Hoberman, 1997 #164}	575	AOM children aged 2months to 12 years were included	Follow-up on day 31 and 38	10 days of amoxicillin/clavulanate 40/10 mg/kg/day 2 times daily versus 45/6.4 mg/kg/ day 3 times daily	RANDOM SEQUENCE GENERATION Unclear risk (Quote: “assigned randomly” Comment: method of randomisation was not mentioned) ALLOCATION CONCEALMENT Unclear risk (Quote: “Investigators were blinded to treatment assignments” Comment: no information on the allocation concealment) BLINDING Low risk INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING

					Low risk OTHER BIAS Low risk
Murph 1993{Murph, 1993 #165}	77	AOM children, aged 7 months to 12 years old	Follow-up 3 months	10 days of amoxicillin 40 mg/kg/day 1 versus 3 times daily	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Unclear risk (The authors did not mention allocation concealment) BLINDING Low risk INCOMPLETE OUTCOME DATA Unclear risk (Quote: "10 children (14.9%) could not be evaluated (failed to return for follow-up or withdrew from the study)" Comment: no information on whether those lost to follow-up or who withdrew were in the once or thrice daily dose group) SELECTIVE REPORTING High risk (Comments: clinical cure rate at follow-up (1 to 3 months) and AOM complications were not reported) OTHER BIAS Low risk
Principi 1986{Principi, 1986 #166}	110	AOM children, aged 6 months to 12 years	Follow-up at day 30, 60 and 90	10 days of amoxicillin 60 mg/kg/day 2 or 3 times daily	RANDOM SEQUENCE GENERATION Unclear risk (Quote: "randomly assigned" Comment: method of randomisation was not described) ALLOCATION CONCEALMENT Unclear risk (Comment: allocation concealment methods were not

					mentioned) BLINDING Unclear risk (Comment: no information) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk Comment OTHER BIAS Unclear risk (Comment: no report of compliance rate)

Table 126

Authors' conclusions:

"This review showed that the results of using once or twice daily doses of amoxicillin, with or without clavulanate, were comparable with three doses for the treatment of AOM."

6.2.4.1.2 Summary and conclusions

One or two daily doses vs three daily doses amoxicillin with or without clavulanate in acute otitis media			
Bibliography: Cochrane Thanaviratananich{Thanaviratananich, 2013 #80}			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Clinical cure rate at the end of therapy	1601 (5 studies)	RR: 1.03 (0.99 to 1.07) NS	⊕⊕⊕⊖: **MODERATE** Study quality: -1 (unclear rando, allocation concealment) Consistency: ok Directness: ok Imprecision:ok
Clinical cure rate during therapy	448 (2 studies)	RR: 1.06 (0.85 to 1.33) NS	⊕⊕⊕⊖: **MODERATE** Study quality: -1 (allocation concealment, selective reporting) Consistency: ok Directness: ok Imprecision:ok
Clinical cure rate at post-treatment	1476 (4 studies)	RR: 1.02 (0.95 to 1.09) NS	⊕⊕⊕⊖: **MODERATE** Study quality: -1 (unclear rando, allocation concealment) Consistency: ok Directness: ok Imprecision:ok
AOM complications: Recurrent AOM after completion of therapy	1029 (3 studies)	RR: 1.21 (0.52 to 2.81) NS	⊕⊕⊖⊖: **LOW** Study quality: -1 (unclear rando, allocation concealment) Consistency: ok Directness: ok Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Adverse reactions to medication (overall)	878 (2 studies)	RR: 0.92 (0.52 to 1.63) NS	⊕⊖⊖⊖: **VERY LOW** Study quality: -1 (unclear rando, allocation concealment) Consistency: -1 (I^2=80%) Directness: ok Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Specific adverse reactions to medication: Diarrhoea	1563 (4 studies)	RR: 0.70 (0.49 to 1.00) NS	⊕⊕⊕⊖: **MODERATE** Study quality: -1 (unclear rando, allocation concealment) Consistency: ok Directness: ok Imprecision: ok
Specific adverse reactions to medication: Skin adverse events	1100 (3 studies)	RR: 0.74 (0.46 to 1.18) NS	⊕⊕⊕⊖: **MODERATE** Study quality: -1 (unclear rando, allocation concealment) Consistency: ok Directness: ok Imprecision: ok
Compliance rate	1520 (4 studies)	RR: 1.04 (0.98 to 1.10) NS	⊕⊕⊕⊖: **MODERATE** Study quality: -1 (unclear rando, allocation concealment)

		Consistency: ok Directness: ok Imprecision: ok

Table 127

In this meta-analysis, treatment of acute otitis media in children with once or twice daily doses of amoxicillin, with or without clavulanate, was compared to three daily doses.
The 5 trials in this meta-analysis included children from 2 months to 12 years of age. Amoxicillin with clavulanate was used in three studies, amoxicillin alone in two studies. The duration of treatment was 10 days in four studies, and 7-10 days in one.

All of the included trials had some methodological issues: none of the trials mentioned allocation concealment and in three the method of randomization was not described. In some, there was also a risk of incomplete outcome data or selective reporting. This limits our confidence in the results.

In children *with acute otitis media*, a treatment with one or two daily doses of amoxicillin with or without clavulanate, compared to three daily doses, **did not** result in a statistically significant difference in *clinical cure rate at the end of therapy, clinical cure rate during therapy, clinical cure rate at post-treatment, diarrhoea, skin adverse effects, or compliance rate.*
GRADE: MODERATE quality of evidence

In children *with acute otitis media*, a treatment with one or two daily doses of amoxicillin with or without clavulanate, compared to three daily doses, **did not** result in a statistically significant difference in *recurrent AOM after completion of therapy.*
GRADE: LOW quality of evidence

In children *with acute otitis media*, a treatment with one or two daily doses of amoxicillin with or without clavulanate, compared to three daily doses, **did not** result in a statistically significant difference in *adverse reactions to medication (overall).*
GRADE: VERY LOW quality of evidence

6.2.4.2 One or two daily doses vs three daily doses amoxicillin only

6.2.4.2.1 Clinical evidence profile

Meta-analysis: Cochrane Thanaviratananich{Thanaviratananich, 2013 #80}"Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media"
Inclusion criteria: RCTs comparing two different dosing intervals of the same intervention, amoxicillin, with or without clavulanate. Participants aged 12 years or younger, with acute otitis media diagnosed by acute ear pain and an inflamed ear drum.
Search strategy: were searched: the Cochrane Central Register of Controlled Trials (CENTRAL) 2013, Issue 2, part of The Cochrane Library, www.thecochranelibrary.com (accessed 15 March 2013), which contains the Acute Respiratory Infections (ARI) Group's Specialised Register, MEDLINE (January 1950 to March week 1, 2013), EMBASE (July 2010 to August 2012) and the Science Citation Index (2001 to March 2013).
Assessment of quality of included trials:yes
Other methodological remarks: ITT data analysis

Table 128

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Cochrane Thanaviratananich{Thanaviratananich, 2013 #80}	One or two daily doses versus three daily doses of amoxicillin	N= 2 n=177 (Principi 1986, Murph 1993)	Clinical cure rate at the end of therapy *(resolution of otalgia, resolution of fever and bacteriological cure rate, if data are provided.)*	Crude AR: 76/88 vs 74/89 RR: 1.05 (0.82 to 1.34) NS
		N= 1 n=63 (Murph 1993)	Clinical cure rate during therapy *(resolution of otalgia, resolution of fever.)*	Crude AR: 30/30 vs 28/33 **RR: 1.17 (1.01 to 1.37)** **SS**
		N= 1 n=95 (Principi 1986)	Clinical cure rate at post-treatment *(resolution of middle ear effusion, as determined by tympanometry, assessed only in those who do not have recurrences of AOM after*	Crude AR: 42/46 vs 48/49 RR: 0.93 (0.85 to 1.03) NS

			completion of therapy.)	
		N= 1 n=100 (Principi 1986)	AOM complications: Recurrent AOM after completion of therapy	Crude AR: 4/49 vs 1/51 RR: 4.16 (0.48 to 35.95) NS
		N= 1 n=110 (Principi 1986)	Specific adverse reactions to medication: Diarrhoea	Crude AR: 1/55 vs 1/55 RR: 1.00 (0.06 to 15.59) NS
		N= 1 n=110 (Principi 1986)	Specific adverse reactions to medication: Skin adverse events	Crude AR: 3/55 vs 3/55 RR: 1.00 (0.21 to 4.74) NS
		N= 1 n=67 (Murph 1993)	Compliance rate	Crude AR: 33/33 vs 34/34 RR: 1.00 (0.94 to 1.06) NS

Table 129

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology assessed by Cochrane group
Murph 1993{Murph, 1993 #165}	77	AOM children, aged 7 months to 12 years old	Follow-up 3 months	10 days of amoxicillin 40 mg/kg/day 1 versus 3 times daily	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Unclear risk (The authors did not mention allocation concealment) BLINDING

					Low risk INCOMPLETE OUTCOME DATA Unclear risk (Quote: “10 children (14.9%) could not be evaluated (failed to return for follow-up or withdrew from the study)” Comment: no information on whether those lost to follow-up or who withdrew were in the once or thrice daily dose group) SELECTIVE REPORTING High risk (Comments: clinical cure rate at follow-up (1 to 3 months) and AOM complications were not reported) OTHER BIAS Low risk
Principi 1986{Principi, 1986 #166}	110	AOM children, aged 6 months to 12 years	Follow-up at day 30, 60 and 90	10 days of amoxicillin 60 mg/kg/day 2 or 3 times daily	RANDOM SEQUENCE GENERATION Unclear risk (Quote: “randomly assigned” Comment: method of randomisation was not described) ALLOCATION CONCEALMENT Unclear risk (Comment: allocation concealment methods were not mentioned) BLINDING Unclear risk (Comment: no information) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk Comment OTHER BIAS

					Unclear risk (Comment: no report of compliance rate)

Table 130

Authors' conclusions:

"This review showed that the results of using once or twice daily doses of amoxicillin, with or without clavulanate, were comparable with three doses for the treatment of AOM."

6.2.4.2.2 Summary and conclusions

One or two daily doses vs three daily doses amoxicillin in acute otitis media			
Bibliography: Cochrane Thanaviratananich{Thanaviratananich, 2013 #80}			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Clinical cure rate at the end of therapy	177 (2 studies)	RR: 1.05 (0.82 to 1.34) NS	⊕⊕⊖⊖: **LOW** Study quality: -1 (unclear rando, allocation concealment) Consistency: ok Directness: -1 (low dose) Imprecision: ok
Clinical cure rate during therapy	63 (1 study)	**RR: 1.17 (1.01 to 1.37)** **SS** **(higher clinical cure rate during therapy with one or two daily doses versus three)**	⊕⊕⊖⊖: **LOW** Study quality: -1 (unclear rando, allocation concealment) Consistency: na Directness: -1 (low dose) Imprecision: ok
Clinical cure rate at post-treatment	95 (1 study)	RR: 0.93 (0.85 to 1.03) NS	⊕⊖⊖⊖: **VERY LOW** Study quality: -1 (unclear rando, allocation concealment) Consistency: na Directness: -1 (low dose) Imprecision: ok
AOM complications: Recurrent AOM after completion of therapy	100 (1 study)	RR: 4.16 (0.48 to 35.95) NS	⊕⊖⊖⊖: **VERY LOW** Study quality: -1 (unclear rando, allocation concealment) Consistency: na Directness: -1 (low dose) Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Specific adverse reactions to medication: Diarrhoea	110 (1 study)	RR: 1.00 (0.06 to 15.59) NS	⊕⊖⊖⊖: **VERY LOW** Study quality: -1 (unclear rando, allocation concealment) Consistency: na Directness: -1 (low dose) Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Specific adverse reactions to medication: Skin adverse events	110 (1 study)	RR: 1.00 (0.21 to 4.74) NS	⊕⊖⊖⊖: **VERY LOW** Study quality: -1 (unclear rando, allocation concealment) Consistency: na Directness: -1 (low dose) Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Compliance rate	67 (1 study)	RR: 1.00 (0.94 to 1.06) NS	⊕⊕⊖⊖: **LOW** Study quality: -1 (unclear rando, allocation concealment) Consistency: na Directness: -1 (low dose) Imprecision: ok

Table 131

In this meta-analysis, treatment of acute otitis media in children with once or twice daily doses of amoxicillin (alone) was compared to three daily doses.

The 2 trials in this meta-analysis included children from 6 months to 12 years of age. The dose of amoxicillin was 40-60 mg/kg /day for 10 days, which is a lower dose than usually recommended in Belgium (75-100 mg/kg/day).

The included trials had some methodological issues: none of the trials mentioned allocation concealment and in one the method of randomization was not described. There was also a risk of incomplete outcome data and selective reporting. This limits our confidence in the results.

In children *with acute otitis media*, a treatment with one or two daily doses of amoxicillin, compared to three daily doses, **did not** result in a statistically significant difference in *clinical cure rate at the end of therapy, clinical cure rate at post-treatment, or compliance rate.*
GRADE: LOW quality of evidence

In children *with acute otitis media*, a treatment with one or two daily doses of amoxicillin, compared to three daily doses, did result in a statistically significant **increase** in *clinical cure rate during therapy.*
GRADE: LOW quality of evidence

In children *with acute otitis media*, a treatment with one or two daily doses of amoxicillin, compared to three daily doses, **did not** result in a statistically significant difference in *recurrent AOM after completion of therapy, diarrhoea,*or *skin adverse effects.*
GRADE: VERY LOW quality of evidence

6.2.4.3 One or two daily doses vs three daily doses amoxicillin/clavulanate

6.2.4.3.1 Clinical evidence profile

Meta-analysis: Cochrane Thanaviratananich{Thanaviratananich, 2013 #80}"Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media"
Inclusion criteria: RCTs comparing two different dosing intervals of the same intervention, amoxicillin, with or without clavulanate. Participants aged 12 years or younger, with acute otitis media diagnosed by acute ear pain and an inflamed ear drum.
Search strategy: were searched: the Cochrane Central Register of Controlled Trials (CENTRAL) 2013, Issue 2, part of The Cochrane Library, www.thecochranelibrary.com (accessed 15 March 2013), which contains the Acute Respiratory Infections (ARI) Group's Specialised Register, MEDLINE (January 1950 to March week 1, 2013), EMBASE (July 2010 to August 2012) and the Science Citation Index (2001 to March 2013).
Assessment of quality of included trials:yes
Other methodological remarks: ITT data analysis

Table 132

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Cochrane Thanaviratananich{Thanaviratananich, 2013 #80}	One or two daily doses versus three daily doses of amoxicillin/clavulanate	N= 3 n=1424 (Hoberman 1997, Behre 1997, Damrikarnlert 2000)	Clinical cure rate at the end of therapy *(resolution of otalgia, resolution of fever and bacteriological cure rate, if data are provided.)*	Crude AR: 640/717 vs 614/707 RR: 1.03 (0.99 to 1.07) NS
		N= 1 n=385 (Damrikarnlert 2000)	Clinical cure rate during therapy *(resolution of otalgia, resolution of fever.)*	Crude AR: 48/199 vs 45/186 RR: 1.00 (0.70 to 1.42) NS
		N= 3 n=1381 (Hoberman 1997, Behre	Clinical cure rate at post-treatment *(resolution of middle ear effusion, as determined by tympanometry,*	Crude AR: 525/687 vs 509/694 RR: 1.04 (0.98 to 1.10) NS

		1997, Damrikarnlert 2000)	*assessed only in those who do not have recurrences of AOM after completion of therapy.)*	
		N= 2 n=929 (Hoberman 1997, Damrikarnlert 2000)	AOM complications: Recurrent AOM after completion of therapy	Crude AR: 58/467 vs 46/462 RR: 1.01 (0.39 to 2.60) NS
		N= 2 n=878 (Behre 1997, Damrikarnlert 2000)	Adverse reactions to medication: Overall	Crude AR: 136/440 vs 131/438 RR: 0.92 (0.52 to 1.63) NS
		N= 3 n=1453 (Hoberman 1997, Behre 1997, Damrikarnlert 2000)	Specific adverse reactions to medication: Diarrhoea	Crude AR: 46/727 vs 66/726 RR: 0.70 (0.48 to 1.00) NS
		N= 2 n=990 (Hoberman 1997, Damrikarnlert 2000)	Specific adverse reactions to medication: Skin adverse events	Crude AR: 25/496 vs 35/494 RR: 0.72 (0.44 to 1.17) NS
		N= 3 n=1453 (Hoberman 1997, Behre 1997,	Compliance rate	Crude AR: 622/727 vs 588/726 RR: 1.05 (0.98 to 1.13) NS

		Damrikarnlert 2000)		

Table 133

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology assessed by Cochrane group
Behre 1997{Behre, 1997 #162}	463	AOM children aged 2 to 12 years	Follow-up at day 28	10 days with amoxicillin/clavulanate (70/10 mg/kg/day and 60/15 mg/kg/day for the 2 and 3 times daily groups, respectively)	RANDOM SEQUENCE GENERATION Unclear risk (Quote: "The patients were randomised to treatment" Comment: the authors did not describe the method of randomisation) ALLOCATION CONCEALMENT Unclear risk (Comment: the authors did not mention anything about allocation concealment) BLINDING Low risk INCOMPLETE OUTCOME DATA High risk (Quote: "This fall in the success rate is partly accounted for by increased numbers of patients lost to follow-up and those with an indeterminate outcome at follow-up who were categorised as failures" Comment: for robustness, 'loss to followup' and 'indeterminate outcome' should be counted as

					failure in the 2 times daily and success in the 3 times daily groups. If it was recalculated, success rate should be 185/ 231(80.1%) and 210/232 (90.5%) for the 2 times daily and 3 times daily groups, respectively) SELECTIVE REPORTING Low risk OTHER BIAS Low risk
Damrikarnlert 2000{Damrikarnlert, 2000 #163}	415	AOM children aged 2 months to 12 years	Follow-up on day 42	7 to 10 days (depending on national prescribing practice) with amoxicillin/clavulanate 45/6.4 mg/kg/day and 40/10 mg/kg/day (2 versus 3 times daily groups, respectively)	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Unclear risk (Comment: did not mention the method of allocation concealment) BLINDING Low risk INCOMPLETE OUTCOME DATA High risk (Quote: “The primary efficacy variable was the clinical response (success or failure) at the end of therapy (Day 7-12). Secondary efficacy variables were clinical response at follow-up (Day 38-42) and bacteriological response (success or failure) at the end of therapy. A tertiary efficacy variable was the clinical response at the on-therapy visit (Day 3-5)”) SELECTIVE REPORTING Low risk

					OTHER BIAS Low risk
Hoberman 1997{Hoberman, 1997 #164}	575	AOM children aged 2months to 12 years were included	Follow-up on day 31 and 38	10 days of amoxicillin/clavulanate 40/10 mg/kg/day 2 times daily versus 45/6.4 mg/kg/ day 3 times daily	RANDOM SEQUENCE GENERATION Unclear risk (Quote: "assigned randomly" Comment: method of randomisation was not mentioned) ALLOCATION CONCEALMENT Unclear risk (Quote: "Investigators were blinded to treatment assignments" Comment: no information on the allocation concealment) BLINDING Low risk INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk OTHER BIAS Low risk

Table 134

Authors' conclusions:

"This review showed that the results of using once or twice daily doses of amoxicillin, with or without clavulanate, were comparable with three doses for the treatment of AOM."

6.2.4.3.2 Summary and conclusions

One or two daily doses vs three daily doses amoxicillin/clavulanate in acute otitis media			
Bibliography: Cochrane Thanaviratananich{Thanaviratananich, 2013 #80}			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Clinical cure rate at the end of therapy	1424 (3 studies)	RR: 1.03 (0.99 to 1.07) NS	⊕⊕⊕⊖: **MODERATE** Study quality: -1 (unclear rando, allocation concealment) Consistency: ok Directness: ok Imprecision: ok
Clinical cure rate during therapy	385 (1 study)	RR: 1.00 (0.70 to 1.42) NS	⊕⊕⊕⊖: **MODERATE** Study quality: -1 (allocation concealment, risk incomplete outcome data) Consistency: na Directness: ok Imprecision: ok
Clinical cure rate at post-treatment	1381 (3 studies)	RR: 1.04 (0.98 to 1.10) NS	⊕⊕⊕⊖: **MODERATE** Study quality: -1 (unclear rando, allocation concealment) Consistency: ok Directness: ok Imprecision: ok
AOM complications: Recurrent AOM after completion of therapy	929 (2 studies)	RR: 1.01 (0.39 to 2.60) NS	⊕⊕⊖⊖: **LOW** Study quality: -1 (unclear rando, allocation concealment) Consistency: ok Directness: ok Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Adverse reactions to medication: Overall	878 (2 studies)	RR: 0.92 (0.52 to 1.63) NS	⊕⊖⊖⊖: **VERY LOW** Study quality: -1 (unclear rando, allocation concealment) Consistency: -1 (I^2=80%) Directness: ok Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Specific adverse reactions to medication: Diarrhoea	1453 (3 study)	RR: 0.70 (0.48 to 1.00) NS	⊕⊕⊕⊖: **MODERATE** Study quality: -1 (unclear rando, allocation concealment) Consistency: ok Directness: ok Imprecision: ok
Specific adverse reactions to medication: Skin adverse events	990 (2 studies)	RR: 0.72 (0.44 to 1.17) NS	⊕⊕⊕⊖: **MODERATE** Study quality: -1 (unclear rando, allocation concealment) Consistency: ok Directness: ok Imprecision: ok
Compliance rate	1453 (3 studies)	RR: 1.05 (0.98 to 1.13) NS	⊕⊕⊕⊖: **MODERATE** Study quality: -1 (unclear rando, allocation concealment)

		Consistency: ok Directness: ok Imprecision: ok

Table 135

In this meta-analysis, treatment of acute otitis media in children with once or twice daily doses of amoxicillin/clavulanate was compared to three daily doses.

The 3 trials in this meta-analysis included children from 2 months to 12 years of age. The dose of amoxicillin/clavulanate given varied between 40-70/6.4-15 mg/kg/day and the duration of treatment between 7 and 10 days.

The included trials had some methodological issues: none of the trials mentioned allocation concealment and in two the method of randomization was not described. There was also a risk of incomplete outcome data in two trials. This limits our confidence in the results.

In children *with acute otitis media*, a treatment with one or two daily doses of amoxicillin/clavulanate, compared to three daily doses, **did not** result in a statistically significant difference in *clinical cure rate at the end of therapy, clinical cure rate during therapy, clinical cure rate at post-treatment, diarrhoea, skin adverse effects,* or *compliance rate.*
GRADE: MODERATE quality of evidence

In children *with acute otitis media*, a treatment with one or two daily doses of amoxicillin/clavulanate, compared to three daily doses, **did not** result in a statistically difference in *recurrent AOM after completion of therapy.*
GRADE: LOW quality of evidence

In children *with acute otitis media*, a treatment with one or two daily doses of amoxicillin/clavulanate, compared to three daily doses, **did not** result in a statistically significant difference in *overall adverse reactions to medication.*
GRADE:VERY LOW quality of evidence

6.2.5 Immediate AB versus expectant observation

6.2.5.1 Clinical evidence profile

Meta-analysis: Cochrane Venekamp 2015{Venekamp, 2015 #79} "Otitis for acute otitis media in children" Inclusion criteria: RCTs of antimicrobial drugs versus placebo control and RCTs comparing immediate antibiotic versus expectant observation. Studies including children (aged from one month to 15 years) of either gender **without ventilation tubes**, suffering from AOM irrespective of the setting from which they were recruited. Search strategy: the Cochrane Central Register of Controlled Trials (CENTRAL 2015, Issue 3) (accessed 26 April 2015), which contains the Acute Respiratory Infections (ARI) Group's Specialised Register, MEDLINE (October 2012 to April week 3, 2015), EMBASE (November 2012 to April 2015), Current Contents (2012 to April 2015), CINAHL (October 2012 to April 2015) and LILACS (2012 to April 2015).Our previous update using the same search strategies covered the period 2008 to November 2012. Assessment of quality of included trials: yes ITT analysis: yes

Table 136

Ref	Comparison	N/n	Outcomes	Result
Cochrane Venekamp 2015{Venekamp, 2015 #79} Design: MA of RCTs Search date: (april 2015)	Immediate antibiotics versus expectant observation	N= 4 n= 959 (Little 2001, McCormick 2005, Neumark 2007, Spiro 2006)	Pain at 3 to 7 days	Crude AR: 141/478 vs 171/481 RR: 0.75 (0.50 to 1.12) NS
		N= 1 n= 247 (Spiro 2006)	Pain at 11 to 14 days	Crude AR: 75/123 vs 83/124 RR: 0.91 (0.75 to 1.10) NS
		N= 2	Vomiting, diarrhoea or rash	Crude AR: 77/268 vs 47/282

		n= 550 (Little 2001, Spiro 2006)		**RR: 1.71 (1.24 to 2.63)** **SS**
		N= 1 n= 179 Neumark 2007	Tympanic membrane perforation	Crude AR: 0/92 vs. 0/87 Not estimable
		N= 1 n= 209 (McCormick 2005)	AOM recurrences	Crude AR: 20/109 vs 13/100 RR: 1.41 (0.74 to 2.69) NS

Table 137

Ref + design	n	Population	Comparison	Methodology
Little 2001{Little, 2001 #153}	315 children (N = 285 children included in analysis) 36/150 of delayed prescription group used AB	**Age** - between 6 months and 10 years **Setting** - general practice; 42 general practitioners in 3 health authorities in south-west England **Inclusion criteria** - acute otalgia and otoscopic evidence of acute inflammation of the eardrum (dullness or cloudiness with erythema, bulging or perforation). When children were too young for otalgia to be specifically documented from their history (under 3 years old) then otoscopic evidence alone was a sufficient entry criterion **Exclusion criteria** - otoscopic appearances consistent with crying or a fever alone (pink drum alone), appearances and history more suggestive of otitis media with effusion	**Tx** - immediate treatment with antibiotics: amoxicillin syrup 125 mg/5mL 3 times daily for 7 days (children who were allergic to amoxicillin received erythromycin 125 mg/5 mL 4 times daily; N = 151 (N = 135 included in analysis) **C** - similar antibiotics were prescribed but parents were asked to wait for 72 hours before considering using the prescription. Parents were instructed that if their child still had substantial otalgia or fever after 72 hours, had discharge for > 10 days or	RANDOM SEQUENCE GENERATION Unclear risk (Method of randomisation not described) ALLOCATION CONCEALMENT Low risk OTHER BIAS Low risk BLINDING OF PARTICIPANTS AND PERSONNEL Unclear risk (Open-label trial, outcome assessment not blinded) INCOMPLETE OUTCOME DATA Low risk

		and chronic suppurative otitis media, serious chronic disease (such as cystic fibrosis, valvular heart disease), use of antibiotics < 2weeks prior to randomisation, previous complications (septic complications, hearing impairment) and if the child was unwell to be left to wait and see (e.g. high fever, floppy, drowsy, not responding to antipyretics) **Baseline characteristics** - balanced	was not starting to get better then they should collect the antibiotic prescription that was left at the practice; N = 164 (N = 150 included in analysis) **Use of additional medication** - for both groups doctors emphasised the importance of paracetamol in full doses for relief of pain and fever	
McCormick 2005{McCormick, 2005 #154}	223 children (N = 218 children included in analysis at day 12) 34% of watchful waiting group used AB	**Age** - between 6 months and 12 years **Setting** - secondary care: paediatric clinic of University of Texas Medical Branch (USA) **Inclusion criteria** - children were required to have (a) symptoms of ear infection; (b) otoscopic evidence of acute otitis media (AOM), including middle-ear effusion; (c) nonsevere AOM **Exclusion criteria** - co-morbidity requiring antibiotic treatment, anatomic defect of ear or nasopharynx, allergy to study medication, immunologic deficiency, major medical condition and/or indwelling ventilation tube or draining otitis in the affected ear(s) **Baseline characteristics** - balanced	**Tx** - immediate treatment with antibiotics: oral amoxicillin 90 mg/kg/day twice daily for 10 days; N = 112 (N = 110 included in analysis at day 12) **C** - expectant observation: no immediate antibiotics; N = 111 (N = 108 included in analysis at day 12) Children in the control group with AOM failure or recurrence received oral amoxicillin 90mg/kg/day; children in Tx group with AOM failure or recurrence received amoxicillinclavulanate (90 mg/kg/day of amoxicillin component) **Use of additional medication** - all parents	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Unclear risk (Method not described) OTHER BIAS Low risk BLINDING OF PARTICIPANTS AND PERSONNEL Unclear risk (Investigator-blinded study, parents not blinded) INCOMPLETE OUTCOME DATA Low risk

			received saline nose drops and/or cerumen removal drops (if needed), ibuprofen and over-the-counter decongestant/antihistamine to be given as needed	
Neumark 2007{Neumark, 2007 #160}	186 children (N = 179 patients were included in analysis; 18% of children in no AB-group revisited physician, 5% of these children received AB	**Age** - between 2 and 16 years **Setting** - general practice: 32 healthcare centres and 72 general practitioners in Sweden **Inclusion criteria** - acute otitis media (AOM) was based on direct inspection of the eardrum by pneumatic otoscope or preferably an aural microscope. Findings had to include a bulging, red eardrum displaying reduced mobility **Exclusion criteria** - perforation of the eardrum, chronic ear conditions or impaired hearing, previous adverse reactions to penicillin, concurrent disease that should be treated with antibiotics, recurrent AOM (3 or more AOM episodes during the past 6 months), children with immunosuppressive conditions, genetic disorders and mental disease or retardation **Baseline characteristics** - balanced	**Tx** - immediate treatment with antibiotics: phenoxymethylpenicillin 25 mg/kg twice daily for 5 days; N = 92 **C** - expectant observation: no immediate antibiotics; N = 87 The guardians received written information about how to act if the condition did not improve or got worse within 3 days after randomisation **Use of additional medication** - symptomatic treatment with paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs), drugs reducing the swelling of the nasal mucosa (e.g. decongestive nose drops) and nasal steroids were allowed	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Unclear risk (Method not described) OTHER BIAS Unclear risk (ITT analysis - unclear, baseline characteristics- balanced) BLINDING OF PARTICIPANTS AND PERSONNEL Unclear risk (Open-label trial, outcome assessment not blinded) INCOMPLETE OUTCOME Unclear risk (Patients not included in analysis - N =7 (4%). Reasons described, unclear from which treatment group patients were excluded)
Spiro 2006{Spiro, 2006 #156}	283 children (N = 265 children	**Age** - between 6 months and 12 years **Setting** - secondary care: paediatric emergency department of Yale-New Haven Hospital in New Haven (USA)	**Tx** - immediate treatment with antibiotics; N = 145 (N = 133 included in analysis at days 4 to 6)	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk

	included in analysis at days 4 to 6) 38% of the wait-and-see-prescription group used AB	**Inclusion criteria** - the diagnosis of acute otitis media (AOM) was made at the discretion of the clinician according to the diagnostic criteria in the evidence-based guideline published in Pediatrics 2004 **Exclusion criteria** - presence of additional intercurrent bacterial infection such as pneumonia, if the patient appeared to be "toxic" as determined by the clinician, hospitalisation, immunocompromised children, antibiotic treatment < 1 week prior to randomisation, children who had either myringotomy or a perforated tympanic membrane, uncertain access tomedical care (e.g. no telephone access), primary language of parents was neither English nor Spanish, previous enrolment in the study **Baseline characteristics** - balanced	**C** - participants randomised to delayed prescription were given written and verbal instructions "not to fill the antibiotic prescription unless your child either is not better or is worse 48 hours (2 days) after today's visit"; N = 138 (N = 132 included in analysis at days 4 to 6) **Use of additional medication** - all participants received complimentary bottles of ibuprofen suspension (100 mg/5 mL) and analgesic ear drops	OTHER BIAS Low risk BLINDING OF PARTICIPANTS AND PERSONNEL Unclear risk (Investigator-blinded study, parents not blinded) INCOMPLETE OUTCOME DATA Unclear risk (Loss to follow-up at day 4 to 6 treatment: N = 12 (8%) and expectant observation: N = 6 (4%))

Table 138

6.2.5.2 *Summary and conclusions*

Immediate antibiotics versus expectant observation			
Bibliography: Cochrane Venekamp 2015{Venekamp, 2015 #79}			
Outcomes	**N° of participants (studies) Follow up**	**Results (RR(95%CI))**	**Quality of the evidence (GRADE)**
Pain at 3 to 7 days	959 (4 studies)	RR: 0.75 (0.50 to 1.12) NS	⊕⊕⊕⊖**:MODERATE** Study quality: -1 (outcome assessor not blinded in 2 studies) Consistency: ok Directness: ok Imprecision: ok
Pain at 11 to 14 days	247 (1 study)	RR: 0.91 (0.75 to 1.10) NS	⊕⊕⊕⊕**:HIGH** Study quality: ok Consistency: na Directness: ok Imprecision: ok
Tympanic membrane perforation	179 (1 study)	Crude AR: 0/92 vs. 0/87 Not estimable	Insufficient data
AOM recurrences	209 (1 study)	RR: 1.41 (0.74 to 2.69) NS	⊕⊕⊕⊖: **MODERATE** Study quality: ok Consistency: na Directness: ok Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Vomiting, diarrhoea or rash	550 (2 studies)	**RR: 1.71 (1.24 to 2.63)** **SS** **(more vomiting, diarrhoea or rash with AB)**	⊕⊕⊕⊖**:MODERATE** Study quality: (outcome assessor not blinded in 1 study) Consistency: ok Directness: ok Imprecision: ok

Table 139

In this meta-analysis, an immediate treatment with antibiotics was compared to expectant observation in children with acute otitis media.

The children included in the four trials were 6 months to 16 years of age. In two trials an immediate antibiotic script was compared to an antibiotic script with instructions to wait 48 or 72 hours before considering filling the antibiotic prescription (if the child was not better, or worse). In the other trials, immediate antibiotics was compared to watchful waiting. In all cases, the parents were instructed to provide adequate analgesic treatment. Between 18-38% of the participants in the expectant observation groups filled their antibiotic prescription, or revisited the physician (depending on study protocol).

Amoxicillin was used in two trials, phenoxymethylpenicillin in one trial, and in one trial the antibiotic used was chosen by the physician.

In children *with acute otitis media*, an immediate treatment with antibiotics, compared to expectant observation, **did not** result in a statistically significant difference in *pain at 3 to7 days.*

GRADE: MODERATE quality of evidence

In children *with acute otitis media*, an immediate treatment with antibiotics, compared to expectant observation, **did not** result in a statistically significant difference in *pain at 11 to14 days.*
GRADE: HIGH quality of evidence

There is insufficient data to conclude whether or not an immediate treatment with antibiotics, compared to expectant observation in children *with acute otitis media*, resulted in a difference in tympanic membrane perforation.
GRADE: Insufficient data

In children *with acute otitis media*, an immediate treatment with antibiotics, compared to expectant observation, **did not** result in a statistically significant difference in *acute otitis media recurrences.*
GRADE: MODERATE quality of evidence

In children *with acute otitis media*, an immediate treatment with antibiotics, compared to expectant observation, **did** result in a statistically significant **increase** in *vomiting, diarrhoea or rash.*
GRADE: MODERATE quality of evidence

6.2.6 Acute treatment of persistent or recurrent AOM

6.2.6.1 Amoxicillin – clavulanate (10d) vs levofloxacin 10 d for the treatment of recurrent or persistent AOM

6.2.6.1.1 Clinical evidence profile

Meta-analysis: Shekelle 2010{Shekelle, 2010 #81} AHRQ Evidence Report/Technology Assessment "Management of acute otitis media: update"

Inclusion criteria: SR, RCT, CCT,
AOM Treatment Failure: infection within 14 days of last antibiotic dose or failure to improve after 48 hours
Persistent AOM: signs or symptoms of AOM after 48 hours of treatment
Search strategy: This is an update of a 2001 report. Searches of PubMed and the Cochrane databases were conducted from January 1998 July 2010 using the same search strategies used for the 2001 report, with the addition of terms not considered in the 2001 review. The Web of Science was also searched for citations of the 2001 report and its peer-reviewed publications
Assessment of quality of included trials: yes: Jadad for RCTs, AMSTAR for SRs, GRADE for overall evaluation
ITT analysis: yes/no

Table 140

Ref	Comparison	N/n	Outcomes	Result (95% CI)
ref* Shekelle 2010{Shekelle, 2010 #81} Design: SR+ MA Search date: (july 2010)	Amox-clav (45mg/kg bid, 10d) vs Levofloxacin (10mg/kg bid, 10d)	N=1 n=1650 Noel 2008	**Clinical success (cure and improved)** *(not defined)*	Success rate on day 2-5: Amox-clav: 91% Levofloxacin: 94% Risk difference= -3.2% (-6.2% to 0.2%) NS Success rate on day 10-17 Amox-clav: 80% Levofloxacin: 84% Risk difference= -3.2% (-7.2% to 0.8%) NS

			Adverse events	

	Levofloxacin	Amox-clav	Diff(95%CI)
1 or more up to visit 4	54% (448/827)	58% (475/823)	-4%(-8,1.3)
Arthralgia	1.5% (12/827)	0.7%(6/823)	0.8%(-0.2,1.8)
Arthralgia disorder	1.2% (10/827)	0.6% (5/823)	0.6%(-0.3,1.5)
Arthritis disorder	0.2% (2/827)	0% (0/823)	0.2%(-0.1,0.5)
Arthropathy	0% (0/827)	0.2% (2/823)	-0.2%(-0.5,0.1)
Dermatitis	13% (108/827)	16% (129/823)	-3%(-6, 0.8)
Diarrhea	13% (108/827)	20% (161/823)	-7%(-10, -3)
Fever	7% (60/827)	8% (64/823)	-1%(-3, 2)
Gait abnormality disorder	0.1% (1/827)	0% (0/823)	0.1%(-0.1,0.3)
Muscle weakness	0% (0/827)	0.1% (1/823)	-0.1%(-0.3,0.1)
Otitis media not related to treatment failure	5% (45/827)	4% (34/823)	1% (-0.8, 3.4)
Pathologic fracture	0% (0/827)	0.5% (4/823)	-0.5%(-1, 0)
Musculoskeletal disorder (DSMC)	1.5% (12/827)	0.6% (5/823)	1%(-0.1, 1.9)
Musculoskeletal adverse events	2.8% (23/827)	2.3% (19/823)	0.5%(-1, 2)
Rhinitis	5% (43/827)	5% (39/823)	0.5%(-1.6,2.6)
Synovitis	0.1% (1/827)	0% (0/823)	0.1%(-0.1,0.3)
URI	6% (53/827)	9% (78/823)	3%(-5.7,-0.5)
Vomiting	10% (81/827)	7% (61/823)	2%(-0.3, 5.1)

SS more diarrhea with amoxicillin-clavulanate

Table 141

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by Shekele 2010
Noel 2008{Noel, 2008 #137} Noninferiority RCT	1650	0.5-<5 years ROM and/or persistent AOM	follow up 17 d	Amox-clav (45mg/kg bid, 10d) vs Levofloxacin (10mg/kg bid, 10d)	Jadad score 3 conclusion: not enough evidence to conclude

Table 142

Remarks:

As the outcome “treatment succes” is not defined, it is difficult to interpret.

8 comparisons in this population were found, but only 2 compared antibiotics that are available in Belgium. Of these 8 comparisons, 3 studied children with tympanostomy tubes. None of these could be included.

6.2.6.1.2 Summary and conclusions

Amoxicillin – clavulanate 10d vs levofloxacin 10 d for the treatment of recurrent or persistent AOM			
Bibliography: Shekelle 2010{Shekelle, 2010 #81}			
Outcomes	**N° of participants (studies) Follow up**	**Results (95%CI)**	**Quality of the evidence (GRADE)**
Clinical success (cure and improved)	1650 (1 study) 17d	on day 10-17 Levoflox: 84% Amoxiclav:80% Absolute RD= -3.2% (-7.2 to 0.8) NS	⊕⊕⊖⊖: **LOW** Study quality:-1 open label Consistency: N/A Directness: ok Imprecision:-1 minimal clinically important difference not ruled out
Overall adverse events	1650 (1 study) 17d	Levoflox: 54% Amoxiclav: 58% Absolute RD= -4.2% (-8 to 1.3) NS	⊕⊕⊖⊖: **LOW** Study quality:-1 open label Consistency: N/A Directness: ok Imprecision:-1 minimal clinically important difference not ruled out
Diarrhea	1650 (1 study) 17d	Levoflox: 13% Amoxiclav: 20% **Absolute RD= -7% (-10 to -3)** **SS** **(More diarrhea with amoxicillin-clavulanate)**	⊕⊕⊖⊖: **LOW** Study quality:-1 open label Consistency: N/A Directness: ok Imprecision:-1 clinically unimportant difference not ruled out
Musculoskeletal adverse events	1650 (1 study) 17d	Levo: 2.8% Amoxiclav: 2.3% Absolute RD= 0.5%(-1 to 2) NS	⊕⊕⊖⊖: **LOW** Study quality:--2 open label, short follow-up Consistency: N/A Directness: ok Imprecision:ok

Table 143

This systematic review found 1 RCT that compared a 10 day treatment of amoxicillin-clavulanate (90mg/kg/day amoxicillin in 2 divided doses) to levofloxacin (20 mg/kg/day in 2 divided doses) in the treatment of recurrent or persistent otitis media. 1650 children were included, aged between 6 months and 5 years.

In children *with recurrent or persistent otitis media*, a 10 day treatment with amoxicillin-clavulanate, compared to levofloxacin **did not** result in a statistically significant difference in *treatment success.*
GRADE: LOW quality of evidence

In children *with recurrent or persistent otitis media*, a 10 day treatment with amoxicillin-clavulanate, compared to levofloxacin **did not** result in a statistically significant difference in *overall adverse events.*
GRADE: LOW quality of evidence

In children *with recurrent or persistent otitis media*, a 10 day treatment with amoxicillin-clavulanate resulted in a statistically significantly higher rate of *diarrhea* compared to levofloxacin.
GRADE: LOW quality of evidence

In children *with recurrent or persistent otitis media*, a 10 day treatment with amoxicillin-clavulanate, compared to levofloxacin **did not** result in a statistically significant difference in *musculoskeletal adverse events*
GRADE: LOW quality of evidence

6.2.6.2 Amoxicillin – clavulanate (10d) vs azithromycin (3d) for the treatment of recurrent or persistent AOM

6.2.6.2.1 Clinical evidence profile

"Management of acute otitis media: update"

<table>
<tr><th>Ref</th><th>Comparison</th><th>N/n</th><th>Outcomes</th><th>Result (95% CI)</th></tr>
<tr><td rowspan="2">ref* Shekelle 2010{Shekelle, 2010 #81}

Design: SR+ MA

Search date: (july 2010)</td><td rowspan="2">Amox-clav (95mg/kg, bid, 10d
vs
Azithromycin (20mg/kg, qd, 3d)</td><td rowspan="2">N=1
n=296

Arrieta 2003</td><td>Treatment success
(not defined)</td><td>Success rate on day 12-16:
Amox-clav: 84%
Azithromycin: 86%
Risk difference= -1.8% (-10.0% to 6.4%)
NS</td></tr>
<tr><td>Adverse events</td><td>
<table>
<tr><th></th><th>Amox-clav</th><th>Azithromycin</th><th>Diff(95%CI)</th></tr>
<tr><td>Any</td><td>42.2% (62/147)</td><td>32.0% (49/153)</td><td>10%(-0.7, 21)</td></tr>
<tr><td>Abd pain</td><td>2.0% (3/147)</td><td>3.9% (6/153)</td><td>-2%(-5.7, 2)</td></tr>
<tr><td>Anorexia</td><td>2.7% (4/147)</td><td>3.3% (6/153</td><td>-0.6%(-4, 3)</td></tr>
<tr><td>Dermatitis</td><td>2.0% (3/147)</td><td>0.7% (1/153)</td><td>1.3%(-1.3, 4)</td></tr>
<tr><td>Diarrhea</td><td>29.9% (44/147)</td><td>19.6% (30/153)</td><td>10%(0.5, 20)</td></tr>
<tr><td>Rash</td><td>4.8% (7/147)</td><td>3.3% (5/153)</td><td>1.5%(-3, 6)</td></tr>
<tr><td>Vomiting</td><td>8.2% (12/147)</td><td>5.2% (8/153)</td><td>3%(-2.6, 9)</td></tr>
</table>
SS more diarrhea with amoxicilline-clavulanate
</td></tr>
</table>

Table 144

Ref + design	n	Population	Duration	Comparison	Methodology scored by Shekele 2010
Arrieta 2003{Arrieta, 2003 #136} RCT	294	0.5-6 years ROM and/or persistent AOM	16d	Amox-clav (90-6,4mg/kg/d in 2 divided doses, 10d vs Azithromycin (20mg/kg, qd, 3d)	Jadad score 3 conclusion: not enough evidence to conclude

Table 145

Author's conclusions (Shekelle 2010): the evidence level for these comparisons is low.

Remarks:
8 comparisons in this population were found, but only 2 compared antibiotics that are available in Belgium. Of these 8 comparisons, 3 studied children with tympanostomy tubes. None of these could be included.

As the outcome "treatment succes" is not defined, it is difficult to interpret.

6.2.6.2.2 Summary and conclusions

Amoxicillin-clavulanate (10d) vs azithromycin (3d) for the treatment of recurrent or persistent AOM			
Bibliography: Shekelle 2010{Shekelle, 2010 #81}			
Outcomes	**N° of participants (studies) Follow up**	**Results (95%CI)**	**Quality of the evidence (GRADE)**
Treatment success	296 (1 study) 16d	Success rate on day 12-16: Amoxiclav: 84% Azithromycin: 86% Absolute RD= -1.8% (-10.0 to 6.4) NS	⊕⊕⊖⊖: **LOW** Study quality: -1 open label Consistency: N/A Directness: ok Imprecision:-1 95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit
Overall adverse events	296 (1 study) 16d	Amoxiclav: 42% Azithromycin: 32% Absolute RD= 10% (-0.7 to 21) NS	⊕⊕⊖⊖: **LOW** Study quality: -1 open label Consistency: N/A Directness: ok Imprecision:-1 95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit
Diarrhea	296 (1 study) 16d	Amoxiclav: 30% Azithromycin: 20% **Absolute RD= 10% (0.5 to 20)** **SS more diarrhea with amoxicillin-clavulanate**	⊕⊕⊖⊖: **LOW** Study quality: -1 open label Consistency: N/A Directness: ok Imprecision:-1 95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit
Other adverse events	296 (1 study) 16d	NS difference in abdominal pain, anorexia, dermatitis, Rash, vomiting	⊕⊕⊖⊖: **LOW** Study quality: -1 open label Consistency: N/A Directness: ok Imprecision:-1 95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit

Table 146

This systematic review found 1 RCT that compared 10 days of amoxicillin-clavulanate (95mg/kg/day in 2 divided doses) to 3 days of azithromycin (20 mg/kg/day in a single dose) in the treatment of recurrent or persistent otitis media. 296 children were included, aged between 6 months and 6 years.

In children *with recurrent or persistent otitis media*, a 10 day treatment with amoxicillin-clavulanate, compared to a 3 day treatment with azithromycin **did not** result in a statistically significant difference in *treatment success.*
GRADE: LOW quality of evidence

In children *with recurrent or persistent otitis media*, a 10 day treatment with amoxicillin-clavulanate, compared to a 3 day treatment with azithromycin **did not** result in a statistically significant difference in *overall adverse events.*

GRADE: LOW quality of evidence

In children *with recurrent or persistent otitis media*, a 10 day treatment with amoxicillin-clavulanate resulted in a statistically significantly higher rate of *diarrhea* compared to a 3 day treatment with azithromycin.
GRADE: LOW quality of evidence

6.2.7 Prophylactic AB for the prevention of recurrent AOM

6.2.7.1 Summary and conclusions

In this systematic review(Shekelle 2010{Shekelle, 2010 #81}), long-term (6 months to 2 years) prophylactic antibiotic therapy was compared to placebo or no treatment in children with recurrent acute otitis media.

Adverse effects were not evaluated. The quality of this systematic review is poor.

Because of problems with antibiotic resistance, long-term antibiotics are not considered to be a strategy of choice for recurrent acute otitis media in Belgium, according to the Organising Committee. Therefore we do not report this review in detail.

7 Acute rhinosinusitis

7.1 Guidelines

7.1.1 Method of reporting of the recommendations and notes

Formal recommendations, that are supplied with grades of recommendations or levels of evidence, are written in **bold**.

Text taken directly from the guidelines, that is not graded but provides supplemental information or a clarification of the formal recommendations, is written in *italics*.

Comments by the bibliography group are written in plain text.

7.1.2 General information on selected guidelines

7.1.2.1 Selected guidelines

The selected guidelines and their abbreviations as used in this report can be found in Table 147.

Abbreviation	Guideline
AAP sinusitis 2013{Wald, 2013 #22}	Wald E., Applegate K., et al.: American Academy of Pediatrics - Clinical Practice Guideline for the Diagnosis and Management of Acute Bacterial Sinusitis in Children Aged 1 to 18 Years - 2013
BAPCOC 2012{BAPCOC, 2012 #3}	BAPCOC - Belgische gids voor anti-infectieuze behandeling in de ambulante praktijk; editie 2012/ Guide Belge des traitements anti-infectieux en pratique ambulatoire; édition 2012
IDSA sinusitis 2012{Chow, 2012 #5}	Chow A., Benninger M., et al.: Infectious Disease Society of America - clinical practice guideline for acute bacterial rhinosinusitis in children and adults.
NHG sinusitis 2014{NHG - Dutch College of General Practitioners, 2014 #14}	NHG- Dutch College of General Practitioners – Standaard acute rhinosinusitis - 2014

Table 147: Selected guidelines and their abbreviations as used in this report

7.1.2.2 Grades of recommendation

Grades of recommendation and levels of evidence as defined in each guideline, can be found in Figure 2 to Figure 4 and Table 148 to Table 149.

AAP SINUSITIS 2013

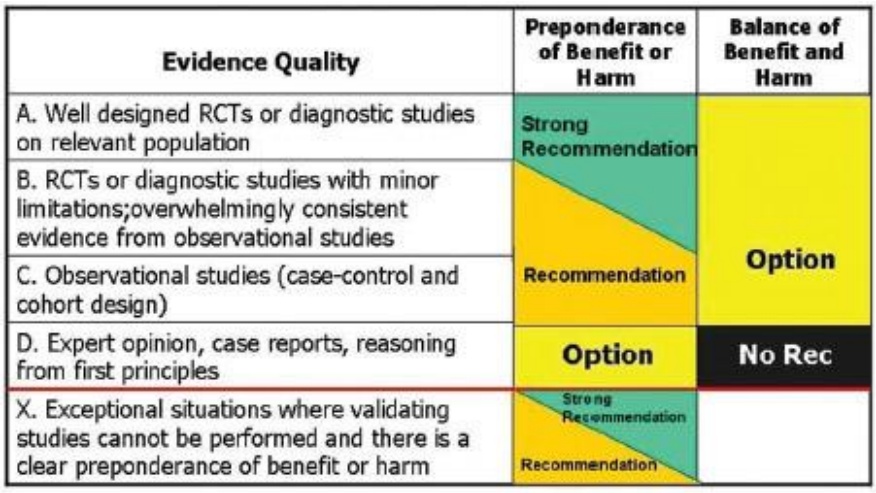


Figure 2: Strength of recommendation from the AAP sinusitis guideline

TABLE Guideline Definitions for Evidence-Based Statements

Statement	Definition	Implication
Strong recommendation	A strong recommendation in favor of a particular action is made when the anticipated benefits of the recommended intervention clearly exceed the harms (as a strong recommendation against an action is made when the anticipated harms clearly exceed the benefits) and the quality of the supporting evidence is excellent. In some clearly identified circumstances, strong recommendations may be made when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Recommendation	A recommendation in favor of a particular action is made when the anticipated benefits exceed the harms but the quality of evidence is not as strong. Again, in some clearly identified circumstances, recommendations may be made when high-quality evidence is impossible to obtain but the anticipated benefits outweigh the harms.	Clinicians would be prudent to follow a recommendation, but should remain alert to new information and sensitive to patient preferences.
Option	Options define courses that may be taken when either the quality of evidence is suspect or carefully performed studies have shown little clear advantage to one approach over another.	Clinicians should consider the option in their decision-making, and patient preference may have a substantial role.
No recommendation	No recommendation indicates that there is a lack of pertinent published evidence and that the anticipated balance of benefits and harms is presently unclear.	Clinicians should be alert to new published evidence that clarifies the balance of benefit versus harm.

Figure 3: Guideline definitions for evidence based statements in the AAP sinusitis 2013 guideline

BAPCOC 2012		
Grades of recommendation:	1	Strong recommendation
	2	Weak recommendation
Levels of evidence	A	High degree of evidence; RCTs without limitations or strong, compelling evidence from observational studies
	B	Medium level of evidence; RCTs with limitations or strong evidence from observational studies
	C	(very) low degree of evidence; observational studies or case studies

Table 148 Strength of recommendation and levels of evidence from the BAPCOC 2012 recommendation

IDSA SINUSITIS 2012

Table 1. Strength of Recommendations and Quality of the Evidence[a]

Strength of Recommendation and Quality of Evidence	Clarity of Balance Between Desirable and Undesirable Effects	Methodological Quality of Supporting Evidence (Examples)	Implications
Strong recommendation, high-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research is unlikely to change our confidence in the estimate of effect.
Strong recommendation, moderate-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Strong recommendation, low-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence	Recommendation may change when higher-quality evidence becomes available. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Strong recommendation, very low-quality evidence (very rarely applicable)	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence	Recommendation may change when higher-quality evidence becomes available; any estimate of effect for at least 1 critical outcome is very uncertain.
Weak recommendation, high-quality evidence	Desirable effects closely balanced with undesirable effects	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies	The best action may differ depending on circumstances or patients or societal values. Further research is unlikely to change our confidence in the estimate of effect.
Weak recommendation, moderate-quality evidence	Desirable effects closely balanced with undesirable effects	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from unbiased observational studies	Alternative approaches likely to be better for some patients under some circumstances. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Weak recommendation, low-quality evidence	Uncertainty in the estimates of Desirable effects, harms, and burden; desirable effects, harms, and burden may be closely balanced	Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence	Other alternatives may be equally reasonable Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Weak recommendation, very low-quality evidence	Major uncertainty in the estimates of desirable effects, harms, and burden; desirable effects may or may not be balanced with undesirable effects	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence	Other alternatives may be equally reasonable. Any estimate of effect, for at least 1 critical outcome, is very uncertain.

Abbreviation: RCT, randomized controlled trial.

[a] Based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [1–6].

Figure 4: Strength of recommendation and levels of evidence from the IDSA sinusitis guideline

NHG SINUSITIS 2014

The NHG guidelines do not explicitly attribute grades of recommendation or levels of evidence to their recommendations. They do perform a GRADE- evaluation of the included evidence on which the recommendations are based. They also express the grade of recommendation in the wording of the recommendation itself (i.e. strongly or weakly recommended (see https://www.nhg.org/sites/default/files/content/nhg_org/uploads/handleiding_standaarden_2015.pdf)

NHG sinusitis 2014		
Grades of recommendation:	Strong; Expressed in the wording of the recommendation	/

	Weak; Expressed in the wording of the recommendation	This often means there is not enough evidence to recommend a specific option and that medical professionals, together with their patient, make a choice from different options.
Levels of evidence	High	The true effect lies close to the estimated effect
	Moderate	The true effect probably lies close to the estimated effect, but the possibility exists that it differs substantially from it.
	Low	The true effect can differ substantially from the estimated effect.
	Very Low	The true effect probably differs substantially from the estimated effect.

Table 149: Grades of recommendation and levels of evidence as used in the NHG sinusitis 2014 guideline

7.1.2.3 Agree II score

Information about the Agree II score can be found in the section “Methodology”.

A summary of the assessment by the literature group of the individual items of the domain score for each guideline can be found inTable 150 The total domain score is also reported in this table.

Rigour of development item	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Total**	**Domain score**
AAP Sinusitis 2013	6	6	6	2	7	7	3	7	**44**	**79%**
IDSA sinusitis 2012	6	4	7	7	7	6	2	3	**42**	**75%**
NHG sinusitis 2014	6	3	5	2	6	7	7	2	**38**	**68%**

Table 150: AGREE score of selected guidelines on item “Rigour of development”, see 2.1.2.6 for a description of the items.

7.1.2.4 Included populations – interventions – main outcomes

In Table 151 to Table 154, the populations, interventions and main outcomes considered in the selected guidelines are represented.

AAP Sinusitis 2013	
Population	Children under 18 years of age, but above 1 year old in a variety of settings (office, emergency department, hospital)
Interventions	Diagnosis, imaging studies, antibiotics
Outcomes	Not specified

Table 151: Included population, intervention and main outcomes of guideline.

BAPCOC 2012	
Population	Ambulantory care patients

Interventions	Antibiotic treatment (indication, choice, dose, duration)
Outcomes	Not specified

Table 152: Included population, intervention and main outcomes of guideline.

IDSA sinusitis 2012	
Population	Children and adults in community and emergency department settings
Interventions	Diagnosis, antibiotics, other treatments (saline irrigation, intranasal corticosteroids, topical or oral decongestants)
Outcomes	Not Specified

Table 153: Included population, intervention and main outcomes of guideline.

NHG Sinusitis 2014	
Population	Adults and children with an acute rhinosinusitis due to an infectious agent (duration less than 12 weeks).
Interventions	Diagnosis, treatment (antibiotic and other)
Outcomes	Not specified

Table 154: Included population, intervention and main outcomes of guideline.

7.1.2.5 Members of development group – target audience

Members of the development group that produced the guidelines, and the target audience for whom the guidelines are intended, can be found in Table 155 to Table 158.

AAP Sinusitis 2013	
Development group	Physicians with expertise in the fields of primary care pediatrics, academic general pediatrics, family practice, allergy, epidemiology and informatics, pediatric infectious diseases, pediatric otolaryngology, radiology and pediatric emergency medicine
Target audience	Clinicians who treat pediatric patients in a variety of clinical settings

Table 155: Members of the developmental group and target audience of the AAP sinusitis 2013 guideline

BAPCOC 2012	
Development group	General practitioners, microbiologists, pneumologists, infectiologists, paediatricians, pharmacists
Target audience	Physicians working in ambulant care

Table 156: Members of the developmental group and target audience of the BAPCOC 2012 guideline

IDSA Sinusitis 2012	
Development group	Multidisciplinary experts: internists and pediatricians, infectious disease specialists, emergency physicians and an otolaryngologic

	specialist
Target audience	Primary care physicians in community and the emergency department settings, including family practitioners, internists, pediatricians and emergency physicians

Table 157: Members of the developmental group and target audience of the IDSA sinusitis 2012 guideline

NHG Sinusitis 2014	
Development group	General practitioners, professors in first line medicine, epidemiologist
Target audience	General practitioners

Table 158: Members of the development group and target audience of the NHG sinusitis 2014 guideline.

7.1.3 Definition

7.1.3.1 Summary

Only two guidelines define the term. IDSA Sinusitis 2012 speaks of an inflammation of the nasal passage and paranasal sinuses, NHG sinusitis speaks of rhinorrhea or blocked nose plus one other symptom of the face or sinuses, such as facial pain or pressure.

7.1.3.2 AAP Sinusitis 2013

The guideline doesn't define the term sinusitis, but gives diagnostic criteria for acute bacterial sinusitis.

7.1.3.3 BAPCOC 2012

The guideline doesn't define this term.

7.1.3.4 IDSA Sinusitis 2012

Acute rhinosinusitis is defined as an inflammation of the mucosal lining of the nasal passage and paranasal sinuses lasting up to 4 weeks. It can be caused by various inciting factors including allergens, environmental irritants, and infection by viruses, bacteria or fungi.

7.1.3.5 NHG Sinusitis 2014

Acute rhinosinusitis is described as rhinorrhea or a blocked nose, together with at least one other symptom of the nose or facial sinuses, such as pain or pressure felt in the face and diminished sense of smell. The pain can be felt in teeth or molars and can worsen when bending over.

7.1.4 Indications for antibiotic treatment

7.1.4.1 Summary

All the guidelines give a different message.
- Antibiotics are indicated for severe or worsening course acute bacterial sinusitis according to AAP Sinusitis 2013 guideline.
- Antibiotics are not indicated except for severe rhinosinusitis according to BAPCOC 2012 guideline.
- Antibiotics are indicated as soon as the diagnosis of acute bacterial sinusitis is established for IDSA sinusitis 2012 guideline.

- Antibiotics are only indicated for the small groups of patients with heightened risk or who are severely ill according to NHG sinusitis 2014.

Note: the BAPCOC 2012 and NHG sinusitis 2014 guidelines are intended for primary care, while the AAP Sinusitis 2013 and IDSA sinusitis 2012 guidelines has a wider target audience, including emergency or secondary care.

7.1.4.2 AAP Sinusitis 2013

The recommendation to start antibiotics depends on the type of sinusitis the physician has diagnosed before, according to the following action statement:
Clinicians should make a presumptive diagnosis of acute bacterial sinusitis when a child with an acute URI presents with the following:

- **Persistent illness, ie, nasal discharge (of any quality) or daytime cough or both lasting more than 10 days without improvement**
- **Worsening course, ie, worsening or new onset of nasal discharge, daytime cough, or fever after initial improvement**
- **Severe onset, ie, concurrent fever (temperature ≥39°C/102.2°F) and purulent nasal discharge for at least 3 consecutive days**

(Evidence Quality: B; Recommendation)

Indications for antibiotic treatments are based on this diagnosis:

"Severe onset and worsening course" acute bacterial sinusitis.
The clinician should prescribe antibiotic therapy for acute bacterial sinusitis in children with severe onset or worsening course (signs, symptoms, or both) (Evidence Quality: B; Strong Recommendation).

"Persistent illness." The clinician should either prescribe antibiotic therapy OR offer additional outpatient observation for 3 days to children with persistent illness (nasal discharge of any quality or
cough or both for at least 10 days without evidence of improvement) (Evidence Quality: B; Recommendation).

7.1.4.3 BAPCOC 2012

Antibiotics are generally not indicated (Grade 1A), except for patients with severe rhinosinusitis (a lot of pain, fever and being severely ill).

Treatment could be considered for patients with mild or moderate rhinosinusitis if the patient doesn't improve after 7 to 10 days (14 for children) of symptomatic treatment. However it needs to be stressed that the effect of treatment with antibiotics is limited in this group of patients as well and that it is preferable to wait for spontaneous remission.
Patients with post-nasal drip recover more slowly and often benefit from antibiotic treatment.

7.1.4.4 IDSA Sinusitis 2012

It is recommended that empiric anti-microbial therapy be initiated as soon as the clinical diagnosis of ABRS is established as defined in recommendation 1 (strong, moderate).

Recommendation 1 is which clinical presentations best identify patients with acute bacterial versus viral rhinosinusitis.

7.1.4.5 NHG Sinusitis 2014

An antibiotic is only indicated for the small group of patients with an increased risk of complications. The complications of rhinosinusitis are due to spreading of the infection to surrounding structures or intracranial expansion.
In a small amount of patients no improvement is seen after 14 days. There is no proof that an antibiotic quickens the recovery of those patients.

Antibiotics are generally not indicated because they only have a small effect on the mean duration of recovery. Their effect doesn't outweigh the frequency at which side effects occur. Antibiotics don't seem to prevent the (already very rare) complications. Moreover, the increase in resistant bacteria is another reason to avoid antibiotic use.

Antibiotics can be considered in the following patients:

- *Patients with diminished immunity (chronic corticosteroid use or use of other immunosuppressant medication, hiv-infection with lowered amount of T-cells) chemo- or radiotherapy, immune disorders, frail elderly and patients with diabetes mellitus*
- *Patients who have fever for more than 5 days and for whom fever reoccurs after a few fever-free days within one disease course*

Give an antibiotic to patients who are severely ill.

The effect of antibiotics in the aforementioned group isn't well known, because they are usually excluded from trials about the effect of antibiotics. It is not always necessary to give an antibiotic to those patients.

7.1.5 Choice of antibiotic, dose and duration

7.1.5.1 Summary

All four guidelines agree that the first choice is amoxicillin with or without clavulanic acid. In case of allergies other antibiotics are recommended. BAPCOC 2012 recommends cefuroxime axetil for non-IgE mediated, and cotrimoxazol for IgE-mediated allergy, even though they also remark that these alternatives are not ideal because of high resistance patterns of pneumococci. NHG sinusitis recommends doxycycline or cotrimoxazol in case of penicillin allergy.

7.1.5.2 AAP Sinusitis 2013

Clinicians should prescribe amoxicillin with or without clavulanic acid as first-line treatment when a decision has been made to initiate antibiotic treatment of acute bacterial sinusitis (Evidence Quality: B; Recommendation).

7.1.5.3 BAPCOC 2012

- **First choice in children (GRADE 1B): Amoxicilline, 75-100 mg/kg/day in 3 to 4 doses during 5-7days (GRADE 1B)**
- **Alternative in case of non-IgE-mediated penicillin allergy (GRADE 1C): Cefuroxime axetil, 30-50 mg/kg/d in 3 doses during 5-7 days**
- **Alternative in case of IgE-mediated penicillin allergy (GRADE 1C):**
    - **Co-trimoxazol:**
        - **1 to 5 years: 40/8 mg/kg/d in 2 doses during 5-7 days**
        - **6-12 years: 800/160 mg/d in 2 doses during 5-7 days**
    - **Azithromycine**
        - **10 mg/kg/d in 1 dose during 3 days or first day 10 mg/kg/d in 1 dose, then 5 mg/kg/d in 1 dose during 4 days**
    - **Clarithromycine**
        - **15 mg/kg/d in 2 doses during 5-7 days**

Remark: Macrolides and cotrimoxazole are not ideal alternatives because of the high resistance of pneumococci and the risk of adverse effects. A child with an IgE-mediated penicillin-allergy and a severely ill appearance, or in which the therapy has no effect, is preferable hospitalised for intravenous therapy.

7.1.5.4 IDSA Sinusitis 2012

Choice:

Amoxicillin-clavulanate rather than amoxicillin alone is recommended as empiric antimicrobial therapy for ABRS in children (Strong, moderate).

High-dose (2g orally twice daily or 90 mg/kg/d orally twice daily) amoxicillin-clavulanate is recommended for children and adults with ABRS from geographic regions with high endemic rates (≥10%) of invasive penicillin-nonsusceptible (PNS) S. pneumoniae, those with severe infection (eg, evidence of systemic toxicity with fever of 39°C [102°F] or higher, and threat of suppurative complications), attendance at daycare, age <2 or >65 years, recent hospitalization, antibiotic use within the past month, or who are immunocompromised (weak, moderate).

- **A b-lactam agent (amoxicillin-clavulanate) rather than a respiratory fluoroquinolone is recommended for initial empiric antimicrobial therapy of ABRS (weak, moderate).**
- **Macrolides are not recommended for empiric therapy due to high rates of resistance among S*. Pneumoniae* (~30%). Trimpethoprim-sulfamethoxazole (TMP/SMX) is not recommended for empiric therapy because of high rates of resistance among both *S. Pneumoniae* and *Haemophilus Influenzae* (~30-40%).**
- **Doxycycline may be used as an alternative regimen to amoxicillin-clavulanate for initial empiric antimicrobial therapy of ABRS in adults because it remains highly active against respiratory pathogens and has excellent pharmacokinetic/pharmacodynamics properties (weak, low)**
- **Second- and third-generation oral cephalosporins are no longer recommended for empiric monotherapy of ABRS due to variable rates of resistance among *S.Pneumoniae*. Combination therapy with a third-generation oral cephalosporin (cefixime of cefpodoxime)**

plus clindamycin may be used as a second-line therapy for children with non-type I penicillin allergy or from geographic regions with high endemic rates of PNS *S. Pneumoniae* (weak, moderate).

- **Levofloxacin is recommended for children with a history of type I hypersensitivity to penicillin; combination therapy with clindamycin plus a third-generation oral cephalosporin (cefixime or cefpodoxine) is recommended in children with a history of non-type I hypersensitivity to penicillin (weak, low).**

Duration:
In children with ABRS, the longer treatment duration of 10-14 days is still recommended (weak, low-moderate)

Note: Cefixime and cefpodoxime are not available in Belgium.

7.1.5.5 NHG Sinusitis 2014

When it has been decided to give an antibiotic:

- *First choice is amoxicillin during one week*
- *In case of penicillin allergy: replace amoxicillin by doxycycline during one week, except if the patient is pregnant or younger than 8 years, in that case replace amoxicillin by cotrimoxazol during one week*
- *The use of cotrimoxazol is limited by a number of factors:*
    - *Contra-indications: children younger than 1 month, or use of coumarin derivatives, phenytoin or methotrexate*

7.1.6 Non-antibiotic treatment

7.1.6.1 Summary

The AAP sinusitis 2013 guideline states there is no evidence to determine the effectiveness of intranasal corticosteroids, saline nasal solutions, topical or oral decongestants, antihistamines or nasal irrigation.
IDSA Sinusitis 2012 recommends intranasal saline irrigation in adults, but does not give a recommendation for children (weak, low-moderate LoE). Intranasal corticosteroids are recommended as add-on in the case of antibiotic therapy (weak, moderate LoE). Topical or oral decongestants are not recommended (strong, low-moderate LoE).
NHG sinusitis 2014 states that complaints can be lessened through saline solutions but they do not speed up recovery. Steaming is not recommended in children due to the presence of hot water.

7.1.6.2 AAP Sinusitis 2013

Potential adjuvant therapy for acute sinusitis might include intranasal corticosteroids, saline nasal irrigation or lavage, topical or oral decongestants, mucolytics, and topical or oral antihistamines. A recent Cochrane review on decongestants, antihistamines and nasal irrigation for acute sinusitis in

children found no appropriately designed studies to determine the effectiveness of these interventions.

7.1.6.3 BAPCOC 2012

Since the guideline only reports on antibiotics, no information on non-antibiotic treatment is to be found in the guideline.

7.1.6.4 IDSA Sinusitis 2012

Intranasal saline irrigation with either physiologic or hypertonic saline is recommended as an adjunctive treatment in adults with ABRS (weak, low-moderate).

Intranasal corticosteroids (INCs) are recommended as an adjunct to antibiotics in the empiric treatment of ABRS, primarily in patients with a history of allergic rhinitis (weak, moderate).

Neither topical nor oral decongestants and/or antihistamines are recommended as adjunctive treatment in patients with ABRS (strong, low-moderate).

7.1.6.5 NHG Sinusitis 2014

(Physiological) salt solutions
Complaints can be lessened by administering a (physiological) saline solution through nose drops or spray, or by steaming. Both options do not have an impact on the speed of recovery. A physiological saline solution can be bought or prepared, but it is advised to only use store-bought preparations for children younger than 6 years, who are more fragile, and not use solutions prepared at home. If one considers administering a saline solution to a child younger than 2 years, it needs to be taken into account that 40% of them refuse drops or sprays and that this doesn't help recovery.

Steaming
What is understood by steaming: taking a steam bath above a bowl of hot water (60°C maximum) twice or thrice daily. Additional products such as chamomile, salt or menthol have no proven additional benefit. The general practitioner should advise the patients for the risk of (severe) burns when using hot water. Because young children are more vulnerable, steaming is not recommended.

7.1.7 Referrals

7.1.7.1 Summary

Three guidelines mention an immediate referral in the case of complications (such as visual, orbital, meningeal or cerebral symptoms).
IDSA sinusitis 2012 recommends referral to a specialist for recurrent bouts of acute rhinosinusitis with clearing episodes in between.

7.1.7.2 AAP Sinusitis 2013

No information found in this guideline.

7.1.7.3 BAPCOC 2012

A patient with signs of complication (redness and swelling in the face, visual, orbital, meningeal or cerebral symptoms) should be referred immediately.

7.1.7.4 IDSA Sinusitis 2012

Patients who are seriously ill and immunocompromised, continue to deteriorate clinically despite extended course of antimicrobial therapy, or have recurrent bouts of acute rhinosinusitis with clearing between episodes should be referred to a specialist (such as an otolaryngologist, infectious disease specialist, or allergist) for consultation. As this is a "good clinical practice" statement rather than a recommendation, it is not further graded.

7.1.7.5 NHG Sinusitis 2014

Bacterial complications of rhinosinusitis:
(peri)orbital cellulitis or (peri)orbital abscess, infection of the ethmoidal bone, osteomyelitis frontalis, brain abscess, meningitis and cerebral venous sinus thrombosis. Those complications are very rare and warrant an immediate referral.

7.2 Evidence tables and conclusions

7.2.1 Antibiotics versus placebo or no treatment for acute rhinosinusitis

7.2.1.1 Clinical evidence profile

Systematic review: Cronin 2013{Cronin, 2013 #138} "The role of antibiotics in the treatment of acute rhinosinusitis in children: a systematic review."

Inclusion criteria:
Children between 1 and 18 / RCTs with patients diagnosed with acute sinusitis or acute rhinosinusitis / efficacy of antibiotics compared with placebo / analytical data available for children under 15 years of age / primary outcome of symptom improvement following the intervention
Exclusion criteria: patients with more than 30 days of symptoms.

Search strategy: "We searched Medline, Embase and the Cochrane controlled trials register up to October 2011 using the terms sinusitis, paranasal, rhinosinutis, purulent, rhinorrhea, sinus infection, randomised, randomised control trial, double blind method, random allocation, placebo, antibiotic, antimicrobial, animal, human, child, children and adolescent. No restriction was made based on language. MC, SK and SS each independently conducted a literature search and assessment for inclusion. We contacted authors where relevant data was not available in published sources."

Assessment of quality of included trials: yes
Other methodological remarks: /

Table 159

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Cronin 2013{Cronin, 2013 #138} Design: SR + MA	**antibiotics vs placebo**	N = 4 n = 382	**symptom improvement at 14 days**	**OR: 2 (95% CI: 1.16 – 3.47)** **SS (more symptom improvement with antibiotics)** I^2: 14.8%

Search: october 2011				

Table 160

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors
Wald 1986{Wald, 1986 #142} RCT DB	93	2-16 years seen at primary or secondary services. Clinical severity score and sinus radiographs. Symptoms for minimum of 10 days.	10 days	Amoxicillin 40 mg/kg/d in divided doses vs amoxicillin clavulonate 40 mg/kg/d (of amoxicillin) vs placebo	Randomization method not described. No intention to treat method. No detail regarding use of possible ancillary drugs. Use of sinus radiographs decrease external validity. Low risk of bias
Garbutt 2001{Garbutt, 2001 #298} RCT DB	161	1-18 years seen at primary care centers Clinical severity score. Symptoms for minimum of 10 days.	14 days	Amoxicillin 40 mg/kg/d in divided doses vs amoxicillin-clavulonate (45 mg/kg/day of amoxicillin) in divided doses vs placebo	Possible bias with exclusion of patients with more severe disease Low risk of bias
Kristo 2005{Kristo, 2005 #141} RCT DB	72	4-10 years seen at primary care centers Clinical severity score and sinus ultrasonography.	10 days	cefuroxime 125 mg twice daily vs placebo	No ITT Use of sinus ultrasonography Low risk of bias
Wald 2009{Wald, 2009 #143} RCT	56	1-10 years seen at primary and secondary centers Clinical severity score.	14 days	amoxicillin, in amoxicillin clavulonate 90 mg/kg/d in divided doses vs placebo	No detail regarding possible use of ancillary drugs Intended sample size not attained

DB					Low risk of bias

Table 161

Author's conclusions:
Evidence to support the routine use of antibiotics here remains unclear despite the positive findings of the statistical analysis

Remarks:
MA includes studies with small sample sizes. Another SR (Smith 2013{Smith, 2013 #140}) does not perform meta-analysis on the same studies because of heterogeneity in study design (different inclusion criteria).

7.2.1.2 Summary and conclusions

Antibiotics versus placebo or no treatment			
Bibliography: Cronin 2013{Cronin, 2013 #138}			
Outcomes	**N° of participants (studies) Follow up**	**Results (95%CI)**	**Quality of the evidence (GRADE)**
Symptom improvement at 14 days	382 (4)	OR (odds ratio): **2 (95% CI: 1.16 – 3.47) SS (more symptoms improvement with AB)**	⊕⊕⊕⊖: **MODERATE** Study quality: -1 Consistency: ok Directness: ok Imprecision: ok

Table 162

In this meta-analysis 4 studies comparing antibiotics with placebo were pooled regarding symptom improvement at 14 days. All patients were children (< 18 years old).

For the diagnosis of rhinosinusitis, all four studies used a clinical severity score. Two studies used additional diagnostic means: radiography in one study and ultrasonography in another.

In *children with rhinosinusitis*, a treatment with antibiotics, compared to placebo, **did** result in a statistically **increase** in *symptom improvement at 14 days*.
GRADE: MODERATE quality of evidence

In another SR (Smith 2013{Smith, 2013 #140}) with a different search strategy but the same research question, the same 4 studies were also found, but they were not pooled together there; the authors from the second study thought heterogeneity in study design was too important to allow pooling.

7.2.2 Antibiotics and nasal irrigation versus nasal irrigation for acute rhinosinusitis

7.2.2.1 Clinical evidence profile

"A comparison of the efficacy of amoxicillin and nasal irrigation in treatment of acute sinusitis in children" 2014
Amoxicillin versus nasal irrigation

Study details	n/Population	Comparison	Outcomes		Methodological
Khoshdel 2014 {Khoshdel, 2014 #139} Design: RCT DB Duration of follow-up:	n= 100 Mean age: 7.6 years <u>Inclusion</u> - children 4 to 15 years - recent upper respiratory infection, postnasal discharge and/or nasal congestion **for more than 10 days** and less than 30 days <u>Exclusion</u> - severe symptoms - chronic sinusitis, - history of any nasal or adenoid surgery and those with probably	amoxicillin 80 mg/kg/day in 3 divided doses per day + saline nasal irrigation 2-3 times a day* Vs Saline nasal irrigation 2-3 times a day* (* composition: saline normal 0.9% and nasal phenylephrin 0.25%; Saline nasal irrigation	Efficacy		RANDO: Inadequate, patient received number and would be allocated based on even or odd ALLOCATION CONC: Inadequate, according to odd or even numbers BLINDING : Participants: unclear Personnel: unclear Assessors: unclear Remarks on blinding method: study states double blind but doesn't mention nature of the placebo's FOLLOW-UP: 80% in efficacy analysis Drop-outs and Exclusions: • Described: yes • Balanced across groups: yes
			Clinical cure on third day of treatment	AB + nasal irrigation: 34/40 nasal irrigation: 15/40 p< 0.001 SS	
			Clinical cure at day 14 of treatment	AB + nasal irrigation: 39/40 Nasal irrigation: 38/40 p>0.05 NS	

	complications (e.g. per orbital swelling), cystic fibrosis - history of allergy to amoxicillin - GE reflux - palate defect	was administered using a disposable syringe filled about with 15–20 mL of NS 0.9% for each nostril and 1–3 times a day for five days. The saline normal solution were irrigated fast upward in a sitting or standing position, with the head pulled back to allow the secretions to flow down ward from the nose without the patient breathing them in)			ITT: NO SELECTIVE REPORTING: no Sponsor: Shahrekord Medical University of Sciences

Table 163

7.2.2.2 Summary and conclusions

Antibiotics versus nasal irrigation for acute rhinosinusitis			
Bibliography: Khoshdel 2014{Khoshdel, 2014 #139}			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Clinical cure on third day of treatment	100 (1)	**AB-group: 34/40** **Control: 15/40** **p>0.001** **SS** **(More clinical cure with AB)** (No HR given, only p value)	⊕⊕⊖⊖: **LOW** Study quality: -1, inadequate randomization, no ITT Consistency: NA Directness: ok Imprecision: -1, small number of participants
Clinical cure at day 14 of treatment	100 (1)	AB-group: 39/40 Control: 38/40 p > 0.05 NS (No HR given, only p value)	⊕⊕⊖⊖: **LOW** Study quality: -1, inadequate randomization, no ITT Consistency: NA Directness: ok Imprecision: -1, small number of participants

Table 164

For this comparison only one RCT was found.

In this RCT bij Khoshdel et al. the use of amoxicillin (80 mg/kg/day in 3 doses) plus phenylephrin saline nasal irrigation was compared with only the phenylephrine saline nasal irrigation. One hundred children with recent URTI or nasal congestion for more than 10 days were recruited (so children with a high chance of acute bacterial rhinosinusitis), mean age 7 years.

In *children with acute rhinosinusitis*, a treatment with amoxicillin and nasal irrigation compared with only nasal irrigation **did** result in a statistically significant **increase** in *the number of clinically cured patients on day 3.*
GRADE: LOW quality of evidence

In *children with acute rhinosinusitis*, a treatment with amoxicillin and nasal irrigation compared with only nasal irrigation **did not** result in a statistically significant difference in *the number of clinically cured patients on day 7.*
GRADE: LOW quality of evidence

7.2.3 Antibiotic A versus antibiotic B for acute rhinosinusitis

7.2.3.1 Clinical evidence profile

Systematic review: Smith 2013 {Smith, 2013 #140} "Evidence for the diagnosis and treatment of acute uncomplicated sinusitis in children: a SR
Inclusion criteria: randomized studies of sinusitis in children
Search strategy: "Searches of Pubmed were performed by using the same search term as the 2001 report ("sinusitis"). All searches were limited to English language and human studies. […] Web of Science was used to search for additional studies that cited the 2001 technical report and guidelines as well as citations of each double-blind, randomized controlled pediatric trial identified. The Cochrane Database of Systematic Reviews was also reviewed. Finally, clinicaltrials.gov was searched to identify results of unpublished or ongoing studies.
Until November 2012
Assessment of quality of included trials: Jadad scale
Other methodological remarks: /

Table 165

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Smith 2013{Smith, 2013 #140} SR (no MA)	**antibiotics vs other antibiotics**	N = 5 (*) n = 485	No MA performed due to high heterogeneity	/

Table 166

Remarks: No meta-analysis performed by the authors due to a too high heterogeneity. (*) Only one study out of those four was performed with antibiotics available in Belgium. See Ficnar 1997 in 7.2.4, Short duration antibiotic versus longer duration antibiotic.

7.2.3.2 Summary and conclusions

Antibiotic A versus antibiotic B for acute rhinosinusitis
Bibliography: Smith 2013{Smith, 2013 #140}

Table 167

In this systematic review by Smith{Smith, 2013 #140} 5 studies were identified comparing one antibiotic with another. However, 4 of those studies compared antibiotics which are not on the market in Belgium. The fifth study (Ficnar 1997{Ficnar, 1997 #144}) compares a short course of azithromycine with a longer course, and will be discussion in the section 7.2.4 on duration of treatment.

7.2.4 Different durations of the same antibiotic for acute rhinosinusitis

7.2.4.1 Azithromycin 10 mg/kg per day for 3 days versus azithromycin 10 mg/kg on day 1, then 5 mg/kg on days 2-5

7.2.4.1.1 Clinical evidence profile

Azithromycin 10 mg/kg/day in 1 dose for 3 days vs Azithromycin 10 mg/kg/day on day 1 and 5 mg/kg/day on day 2-5

Study details	n/Population	Comparison	Outcomes			Methodological
Ficnar 1997{Ficnar, 1997 #144} Design: RCT Open label	n= 371 Mean age: *unknown, no access to full paper* aged 6 months to 12 years <u>Inclusion</u> *no access to full paper* <u>Exclusion</u> *no access to full paper*	azithromycin 10 mg/kg/day in 1 dose for 3 days (n = 192) Vs azithromycin 10 mg/kg/day on day 1 and 5 mg/kg on days 2-5 (n=179)	Efficacy			Evaluated "1" on Jadad scale by Smith 2013{Smith, 2013 #140}
			Overal clinical cure rate (PO)	3-day azithromycin course: 95.7% cure rate 5 day azithromycin course: 96.1% cure rate		
			4x4 table (calculated by bibliography group)*			
				Clinically cured	*Not cured*	
			3 day azithromycin	*184*	*8*	
			5 day azithromycin	*172*	*7*	
				RR = 0.9973 (95% CI: 0.9566 – 1.0399) *p = 0.9* *NS*		
			Bacteriological eradication	3-day azithromycin course: 90.1% 5-day azithromycin course: 94.2%		
			4x4 table (calculated by bibliography group)*			
				Bacteriological eradication	*not eradicated*	
			3 day azithromycin	173	19	
			5 day azithromycin	169	10	

				RR = 0.9544 (95% CI: 0.8998-1.012) *p = 0.12* *NS*	

Table 168

**with help of the medcalc calculator (https://www.medcalc.org/calc/relative_risk.php)*

7.2.4.1.2 Summary and conclusions

Azithromycin short course vs azithromycin long course			
Bibliography: Ficnar 1997{Ficnar, 1997 #144}			
Outcomes	**N° of participants (studies) Follow up**	**Results (RR(95%CI)) *Calculated by bibliography group***	**Quality of the evidence (GRADE)**
Clinical cure	371 (1)	*RR = 0.9973* *(0.96 – 1.04)* *p = 0.9* *NS*	⨁⨁⨀⨀: **LOW** Study quality: -2 (Jadad score 1) Consistency: NA Directness: ok Imprecision: ok

Table 169

This open label RCT by Ficnar{Ficnar, 1997 #144} examined the difference between a 3-day course of azithromycin at 10 mg/kg/day in 1 dose, with a 5-day course of azithromycin (10 mg/kg/day on day 1 and 5 mg/kg/day on day 2 to 5), in 371 children aged 6 months to 12 years.

In *children with acute rhinosinusitis*, a treatment with a short course of azithromycin, compared to a treatment with a long course of azithromycin **did not** result in a difference *in clinical cure*.
GRADE: LOW quality of evidence

8 Acute laryngitis

8.1 Evidence tables and conclusions

8.1.1 Antibiotics versus placebo or no treatment for croup in children

8.1.1.1 Clinical evidence profile

Systematic review: Johnson 2009{Johnson, 2009 #279} “Croup”
Inclusion criteria: “we have included children up to the age of 12 years with croup; no attempt has been made to exclude spasmodic croup.
Study design criteria for inclusion in this review were: published systematic reviews of RCTs, RCTs, and observational studies (cohort studies, case studies, and case reports) in any language. There was no minimum length of follow-up required to include studies.”
Search strategy: “We searched: Medline, Embase, The Cochrane Library, and other important databases up to June 2008”
Assessment of quality of included trials: yes, GRADE evaluation

Table 170

No SRs, RCTs, or observational studies of sufficient quality evaluating antibiotics in children with mild, moderate or severe croup were found

8.1.1.2 Summary and conclusions

Antibiotics versus placebo or no treatment for croup in children
Bibliography: Johnson 2009{Johnson, 2009 #279}

Table 171

In this systematic review, SRs, RCTs and observational studies evaluating antibiotics in children with croup were sought.

No SRs, RCTs, or observational studies of sufficient quality (according to the review criteria of Johnson 2009) evaluating antibiotics in children with mild, moderate or severe croup were found

9 Acute tracheitis

We did not find any SRs or RCTs that met our inclusion criteria for this pathology.

10 Acute bronchitis

10.1 Guidelines

10.1.1 Method of reporting of the recommendations and notes

Formal recommendations, that are supplied with grades of recommendations or levels of evidence, are written in **bold**.

Text taken directly from the guidelines, that is not graded but provides supplemental information or a clarification of the formal recommendations, is written in *italics*.

Comments by the bibliography group are written in plain text.

10.1.2 General information on selected guidelines

10.1.2.1 Selected guidelines

The selected guidelines and their abbreviations as used in this report can be found in Table 172.

Abbreviation	Guideline
BAPCOC 2012{BAPCOC, 2012 #3}	BAPCOC - Belgische gids voor anti-infectieuze behandeling in de ambulante praktijk; editie 2012/ Guide Belge des traitements anti-infectieux en pratique ambulatoire; édition 2012
DM acute cough 2011{Coenen S., 2008 #6}	Domus Medica acute hoest – opvolgrapport 2011
NICE Respiratory tract 2008{National Institute for Health and Clinical Excellence, 2008 #10}	National Institute for Health and Clinical Excellence – Respiratory Tract Infections – antibiotic prescribing – 2008 (reaffirmed 2012)

Table 172: Selected guidelines and their abbreviations as used in this report

10.1.2.2 Grades of recommendation

Grades of recommendation and levels of evidence as defined in each guideline, can be found in table Table 173 toTable 175.

BAPCOC 2012		
Grades of recommendation:	1	Strong recommendation
	2	Weak recommendation
Levels of evidence	A	High degree of evidence; RCTs without limitations or strong, compelling evidence from observational studies

	B	Medium level of evidence; RCTs with limitations or strong evidence from observational studies
	C	(very) low degree of evidence; observational studies or case studies

Table 173: Grades of recommendation and level of evidence of BAPCOC 2012 guideline

DM acute cough 2011	
Level 1	For level 1 the condition is that at least two independently executed trials with converging results exist. Trials must be of the following type: • Good quality RCTs • An independent blind comparison of a diagnostic test with a reference test of good quality (patients from a target group undergo both the new diagnostic test and the reference test) • A prospective cohort study of good quality with a follow up of 80% or more For this level of evidence, a systematic review or meta-analysis of those types of articles with a high degree of consistency is also sufficient. Conclusions from those type of studies are formulated with "*it is proven that*"
Level 2	For level 2 the condition is that at least two independently executed trials with converging results exist. Trials must be of the following types: • Moderate quality RCTs • An independent blind comparison or a diagnostic test with a reference test of moderate quality (a fraction of the target group has been tested, or the reference test was not performed on every patient) • A (retrospective) cohort study of moderate quality or patient-control study For this level of evidence a systematic review or meta-analysis of those types of articles with a high degree of consistency is also sufficient. Conclusions from those type of studies are formulated with "*it is probably that*"
Level 3	When there are no comparative studies of good quality, we speak of the third level of evidence: • There are no RCTs of good quality • There is only one study of moderate quality and there are no meta-analyses of moderate quality available

	• The results from RCTs or meta-analyses conflict Opinions of at least two experts, recommendations or conclusions after surveying the available evidence and reaching a consensus in the working group are also comprised in this level. Conclusions are formulated with "*there are indications that"* or *"the working group considers that"*

Table 174: Grades of recommendation and Level of evidence of DM acute cough 2011 guideline

NICE respiratory tract 2008		
Levels of evidence	1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
	1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
	1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
	2++	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
	2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
	2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
	3	Non-analytic studies, eg case reports, case series
	4	Expert opinion

Table 175: Grades of recommendation and level of evidence of NICE respiratory tract 2008 guideline

10.1.2.3 Agree II score

Information about the Agree II score can be found in the section "Methodology".

A summary of the assessment by the literature group of the individual items of the domain score for each guideline can be found Table 176 The total domain score is also reported in this table.

Rigour of development item	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Total**	**Domain score**
DM acute cough 2011	7	2	3	4	2	7	6	7	**38**	**68%**
NICE respiratory tract 2008	7	7	7	6	5	7	5	5	**49**	**88%**

Table 176: AGREE score of selected guidelines on item "Rigour of development", see 2.1.2.6 for a description of the items.

10.1.2.4 Included populations – interventions – main outcomes

Table 177 to Table 179 , the populations, interventions and main outcomes considered in the selected guidelines are represented.

BAPCOC 2012	
Population	Ambulant care patients
Interventions	Antibiotic treatment (indication, choice, dose, duration)
Outcomes	Not specified

Table 177: Included population, intervention and main outcome of guideline

DM acute cough 2011	
Population	Patients of 12 years and older with primary symptoms being acute cough with or without purulent sputum
Interventions	Diagnosis, antibiotic prescription, other medications
Outcomes	not specified

Table 178: Included population, intervention and main outcomes of guideline.

NICE respiratory tract 2008	
Population	Adults and children (3 months and older) in whom immediate antibiotic prescribing is not indicated
Interventions	Assessment, antibiotic management strategies (delayed treatment, no treatment), advice
Outcomes	• the presence, duration and severity of symptoms such as fever, pain and malaise • the risk of complications from not prescribing antibiotics • adverse events from prescribing antibiotics (for example, diarrhoea, vomiting, rashes, abdominal pain) • the level of antibiotic prescribing, including antibiotic prescriptions consumed or collected • resource use (including reconsultation rates and rates of referral to secondary care) • patient satisfaction and health-related quality of life.

Table 179: included population, intervention and main outcomes of guideline

10.1.2.5 Members of development group – target audience

Members of the development group that produced the guidelines, and the target audience for whom the guidelines are intended, can be found in Table 180 to Table 182.

BAPCOC 2012	
Development group	General practitioners, microbiologists, pneumologists, infectiologists, paediatricians, pharmacists

Target audience	Physicians working in ambulant care

Table 180: Members of the development group and target audience of the BAPCOC 2012 guideline

DM acute cough 2011	
Development group	Unspecified
Target audience	General practitioners

Table 181: Members of the development group and target audience of the DM acute cough 2011 guideline

NICE respiratory tract 2008	
Development group	General practitioners, pediatricians, pharmacists, microbiologists, patient representative, consultant in respiratory medicine
Target audience	Primary care and community settings. These will include general practices, community pharmacies, NHS walk-in centres and primary medical and nursing care provided in emergency departments.

Table 182: Members of the development group and target audience of the NICE respiratory tract 2008 guideline.

10.1.3 Definition

10.1.3.1 Summary

Because the problem is looked at from various angles (cough, RTI) no guideline gives an actual definition for the term “bronchitis”.

10.1.3.2 BAPCOC 2012

The guideline doesn’t define this term.

10.1.3.3 DM acute cough 2011

The guideline doesn’t define this term, and never speaks of bronchitis outright.
Acute cough is defined as cough that lasts for less than three weeks.

(The focus of this guideline is on the exclusion of diagnoses that might mean immediate danger to the life of the patient, and then on the treatment of suspected respiratory infection).

10.1.3.4 NICE respiratory tract 2008

Respiratory tract infection (RTI) is defined as any infectious disease of the upper or lower respiratory tract. Lower respiratory tract infections (LRTIs) include acute bronchitis, bronchiolitis, pneumonia and tracheitis.

10.1.4 Indications for antibiotic treatment

10.1.4.1 Summary

BAPCOC 2012, DM acute cough 2011 and Nice respiratory tract 2008 agree that antibiotics are not indicated or should not be prescribed. DM acute cough 2011 and NICE respiratory tract 2008 mention some cases in which an antibiotic can still be indicated, such as compromised immunity or being severely unwell.

10.1.4.2 BAPCOC 2012

Children with acute bronchitis: antibiotics are not indicated, only symptomatic treatment (Grade 1C)

10.1.4.3 DM acute cough 2011

In the case of respiratory tract infections with acute (productive) cough, with the exclusion of pneumonia, an antibiotic will not influence (the duration of) the productive cough or the impairments regarding work or other activities.
For ten patients after 7 to 11 days, 8 will be better clinically regardless of the antibiotic. Less than one extra patient improves due to the antibiotic, at a cost of as many patients with side effects from the antibiotic (level 1).
The possible advantages of an antibiotic do not compensate the disadvantages. Antibiotics can only be justified in the case of compromised immunity (level 3)

Despite no clinical study to support this evidence, antibiotics are indicated for risk patients, for example patients with diminished immunity (like in the case of poorly controlled diabetes mellitus or bedridden patients.

10.1.4.4 NICE respiratory tract 2008

A no antibiotic prescribing strategy or a delayed antibiotic prescribing strategy should be agreed for patients with the following conditions:
[…]

- *acute cough/acute bronchitis*

However, antibiotics may still be beneficial for a subgroup of patients who present with an RTI in primary care settings and who are likely to be at risk of developing complications.

An immediate antibiotic prescription and/or further appropriate investigation and management should only be offered to patients (both adults and children) in the following situations:

- *if the patient is systemically very unwell*
- *if the patient has symptoms and signs suggestive of serious illness and/or complications (particularly pneumonia, mastoiditis, peritonsillar abscess, peritonsillar cellulitis, intraorbital and intracranial complications)*
- *if the patient is at high risk of serious complications because of pre-existing comorbidity. This includes patients with significant heart, lung, renal, liver or neuromuscular disease, immunosuppression, cystic fibrosis, and young children who were born prematurely*

10.1.5 Choice of antibiotic, dose and duration

10.1.5.1 Summary

Only the DM acute cough 2008 guideline mentions amoxicillin as a first choice when antibiotic is prescribed in a high risk patient.

10.1.5.2 BAPCOC 2012

Since the guideline doesn't recommend use of antibiotics and recommends transferring children with a heightened risk or severe illness, no antibiotic recommendation is made.

10.1.5.3 DM acute cough 2011

In the case of high risk patients, amoxicillin is the preferred antibiotic.

10.1.5.4 NICE respiratory tract 2008

No information found in the guideline.

10.1.6 Non-antibiotic treatment

10.1.6.1 Summary

The DM acute cough 2012 guidelines states that there is little evidence for prescribing β2 agonists for acute cough and that those can give a lot of side effects (in 1 to 2 out of 3 patients).
It also states that cough medicine usually doesn't work, with the exception of dextromethorphan and guaifenesin, which can be prescribed in the case of bothersome nocturnal coughing. However, this statement applies to adults.

10.1.6.2 BAPCOC 2012

Since the guideline only reports on antibiotics, no information on non-antibiotic treatment is to be found in the guideline.

10.1.6.3 DM acute cough 2011

Cough Medicine
Patients often use cough medicine on their own initiative and doctors also prescribe them quite often. However there is little evidence that this medication is effective.
The effectiveness of antitussives with codeine and derivatives has not been proven.
Dextromethorphan does diminish coughing.
Guaifenesin, an expectorant, fluidifies sputum and lessens the coughing frequency and intensity.
Mucolytics, antihistaminics, combinations of antihistaminics with decongestants can't be recommended for the symptomatic treatment of coughing. They are not effective, not available or they are combinations. It is unclear of any OTC-medication is effective for the treatment of cough. On top of that there is little evidence for or against their effectiveness. If symptomatic treatment is wanted, dextromethorphan (30 mg) or guaifenesin (480 mg/30ml) can be prescribed, especially in the case of bothersome nocturnal coughing. Important side effects from those OTC drugs have not been described.

β2 agonists for acute cough
When a respiratory infection is suspected a lot of patient will show symptoms of obstruction on top of coughing. However there is little evidence that routinely prescribing a β2-agonist is effective in the treatment of acute cough. A possible positive effect in the case of airway obstruction isn't underpinned by sufficient evidence. On top of that the use of β2-agonists must be weighed against the side effects in one to two out of three patients.

10.1.6.4 NICE respiratory tract 2008

No information found in the guideline.

10.1.7 Referrals

10.1.7.1 Summary

Two out of three guidelines give recommendations for when to refer a child to the hospital. Those include worsening condition, psychosocial environment in which care is possibly not guaranteed, underlying conditions, very young age, insufficient fluid or food intake.

10.1.7.2 BAPCOC 2012

Children with heightened risk or severely ill presentation should be hospitalized immediately (Grade 1C).

Children with heightened risk are:

- *Severe underlying condition: chronic respiratory illness, cystic fibrosis, immune deficiency, serious psychomotor retardation, metabolic illness, malignancy, pulmonary hypertension due to congenital heart defect*
- *Younger than 3 months*
- *Younger than 1 year and the child drinks less than half of his usual quantity*
- *Insufficient fluid intake and vomiting*
- *Exhaustion (drowsiness, hypotonia)*
- *Infant with respiratory frequency >70/min*
- *Child with respiratory frequency >50/min*
- *Adequate care can not be guaranteed given the social situation*
- *Oxygen saturation ≤92%*

10.1.7.3 DM acute cough 2011

Sudden worsening of the subjective or objective situation, or changes in the psychosocial context, can form a reason to have the patient hospitalized.

10.1.7.4 NICE respiratory tract 2008

No information found in the guideline.

10.2 Evidence tables and conclusions

10.2.1 Antibiotics versus placebo or no treatment for acute bronchitis/ cough

10.2.1.1 Clinical evidence profile

Systematic review: Smith 2014{Smith Susan, 2014 #203} " antibiotics for acute bronchitis (review)"
Inclusion criteria: Randomised controlled trials (RCTs) comparing any antibiotic therapy with placebo or no treatment in acute bronchitis or acute productive cough, in patients without underlying pulmonary disease.
Search strategy: "We searched CENTRAL 2013, Issue 12, MEDLINE (1966 to January week 1, 2014), EMBASE (1974 to January 2014) and LILACS (1982 to January 2014).
Assessment of quality of included trials: Assessment according to the "Risk of Bias" guidelines

Other methodological remarks:

- Of the 13 studies selected only 2 recruited only children (Little 2005 and King 1996). King 1996 is always pooled with other studies but Little 2005 is sometimes analysed on its own and thus reported here.
- The SR defines the link between cough and bronchitis in the following terms: "*Acute bronchitis is a clinical diagnosis for an acute cough, which may or may not be productive of mucus or sputum*."

Table 183

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Smith 2014 {Smith Susan, 2014 #203} SR + MA	Antibiotics vs no treatment	N = 1 n = 426	**Mean number of days of cough**	Mean number of days on AB: 11.56 Mean number of days on no treatment: 11.45 Mean difference: 0.11 (-1.00 ; 1.23) NS
		N = 1 n = 374	**Mean number of days of feeling ill**	Mean number of days on AB: 8.12 Mean number of days on no treatment: 8.98 Mean difference: -0.86 (-1.97; 0.25)

				NS
		N = 1 n = 374	**Mean number of days of impaired activities**	Mean number of days on AB: 7.61 Mean number of days on no treatment: 8.18 Mean difference: -0.57 (-1.75 , 0.61) NS
		N = 1 n = 334	**Number of patients with adverse effects**	With AB: 34 / 187 With no treatment: 28/147 RR: 0.95 (0.61 , 1.50) NS

Table 184

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
Little 2005{Little, 2005 #270} RCT Open label	426	Inclusion criteria: aged 3 or more with uncomplicated LRTI for less than 21 days with cough as main symptom and at least 1 of sputum, chest pain, dyspnoea and wheeze	10 days ab course, 3 weeks symptom diary	Amoxicillin 250 mg 3 times per day (125 mg if less than 10 years) for 10 days or erythromycin 250 mg four times per day if penicillin allergic	Randomisation: low risk of bias Allocation concealment: Low risk of bias Blinding: High risk (open label)

Table 185

Author's conclusions: No offer or a delayed offer of antibiotics for acute uncomplicated lower respiratory tract infection is acceptable, associated with little difference in symptom resolution, and is likely to considerably reduce antibiotic use and beliefs in the effectiveness of antibiotics..

10.2.1.2 Summary and conclusions

Antibiotics versus placebo or no treatment for bronchitis / cough			
Bibliography: Smith 2014{Smith Susan, 2014 #203}			
Outcomes	**N° of participants (studies) Follow up**	**Results (95%CI)**	**Quality of the evidence (GRADE)**
Mean number of days of cough	426 (1)	Mean difference in days of cough: 0.11 (-1.00, 1.23) NS	⊕⊕⊕⊖: **MODERATE** Study quality: -1 (open label, no ITT) Consistency: NA Directness: ok Imprecision: ok
Mean number of days of feeling ill	374 (1)	Mean difference in days of feeling ill: -0.86 (-1.97,0.25) NS	⊕⊕⊕⊖: **MODERATE** Study quality: -1 (open label, no ITT) Consistency: NA Directness: ok Imprecision: ok
Mean number of days of impaired activities	374 (1)	Mean difference in days of impaired activities: -0.57 (-1.75,0.61) NS	⊕⊕⊕⊖: **MODERATE** Study quality: -1 (open label, no ITT) Consistency: NA Directness: ok Imprecision: ok
Number of patients with adverse effect	334 (1)	RR: 0.95 (0.61 – 1.50) NS	⊕⊕⊕⊖: **MODERATE** Study quality: -1 (open label, no ITT) Consistency: NA Directness: ok Imprecision: ok

Table 186

The systematic review and meta-analysis by Smith{Smith Susan, 2014 #203} reports one open label RCT with children (Little 2005{Little, 2005 #270}) where a 10 day course of antibiotics (amoxicillin 750 mg/day in 3 doses per day; 375 mg/day if under 10 years; erythromycin 1000 mg/day in four doses per day in case of allergy) was compared with no treatment.

In children with acute cough, a treatment with antibiotics (amoxicillin or erythromycin) compared to no treatment **did not** result in a statistically significant difference in mean number of days of cough.
GRADE: MODERATE quality of evidence

In children with acute cough, a treatment with antibiotics (amoxicillin or erythromycin) compared to no treatment **did not** result in a statistically significant difference in mean number of days of feeling ill.
GRADE: MODERATE quality of evidence

In children with acute cough, a treatment with antibiotics (amoxicillin or erythromycin) compared to no treatment **did not** result in a statistically significant difference in mean number of days of impaired activities.
GRADE: MODERATE quality of evidence

In children with acute cough, a treatment with antibiotics compared to no treatment **did not** result in a statistically significant difference in the number of patients with adverse effects.
GRADE: MODERATE quality of evidence

10.2.2 Antibiotic A versus antibiotic B for acute bronchitis

10.2.2.1 Clinical evidence profile

Systematic review: Wark 2015{Wark, 2015 #205} “Bronchitis (acute)” Inclusion criteria: Study design criteria for inclusion in this systematic overview were systematic reviews and double-blinded RCTs published in English, containing more than 20 people. We excluded all studies described as 'open', 'open label', not blinded, or single-blinded. There was no minimum length of follow-up and studies were not excluded based on loss to followup, but people had to receive a minimum of 3 days of treatment. We included people of any age or sex with acute bronchitis. We excluded trials conducted in those who had chronic respiratory disease or other acute respiratory diseases. BMJ Clinical Evidence does not necessarily report every study found (e.g., every systematic review). Search strategy: BMJ Clinical Evidence search and appraisal date May 2015. Databases used to identify studies for this systematic overview include: Medline 1966 to May 2015, Embase 1980 to May 2015, The Cochrane Database of Systematic Reviews 2015, issue 5 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. Assessment of quality of included trials: Grade evaluation Other methodological remarks: BMJ Clinical Evidence does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant, and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors.

Table 187

Remarks:

Only one study with children was found but one of the antibiotics used in the comparison is not on the market in Belgium.

10.2.2.2 Summary and conclusions

The Clinical Evidence review bij Wark{Wark, 2015 #205} searched for RCTs about antibiotics versus placebo or other treatments. Only one study was found in children but the antibiotics used in the comparison are not on the market in Belgium.

10.2.3 Delayed AB versus immediate AB or no AB for acute bronchitis

10.2.3.1 Clinical evidence profile

Systematic review: Spurling 2013{Spurling Geoffrey, 2013 #204} "Delayed antibiotics for respiratory infections" Inclusion criteria: "Randomised controlled trials (RCTs) involving participants of all ages defined as having an ARTI, where delayed antibiotics were compared to antibiotics used immediately or no antibiotics." Search strategy: "We searched CENTRAL (The Cochrane Library 2013, Issue 2), which includes the Acute Respiratory Infection Group's Specialised Register; Ovid MEDLINE (January 1966 to February Week 3 2013); Ovid MEDLINE In-Process & Other Non-Indexed Citations (28 February 2013); EMBASE (1990 to 2013 Week 08); Science Citation Index - Web of Science (2007 to May 2012) and EBSCO CINAHL (1982 to 28 February 2013)." Assessment of quality of included trials: GRADE Other methodological remarks: Meta-analysis was not possible for most outcomes due to high heterogeneity. Bronchitis is equated with coughing for a number of outcomes.

Table 188

Author's conclusions: The only study about immediate versus delayed antibiotics for the outcomes relating to cough or the common cold (Arroll 2002{Arroll, 2002 #271}) found no difference between the two prescribing strategies for the clinical outcomes of fever, cough, pain and malaise. Population was both adults and children.

10.2.3.2 Summary and conclusions

In this systematic review by Spurling et al.{Spurling Geoffrey, 2013 #204} only one study was found comparing immediate versus delayed antibiotics for outcomes relating to cough (Arroll 2002{Arroll, 2002 #271}). However population in this study was both adults and children, with no subgroup analysis. The study found no difference between the two prescribing strategies for the clinical outcomes of fever, cough, pain or malaise.

11 Bronchiolitis

11.1 Guidelines

11.1.1 Method of reporting of the recommendations and notes

Formal recommendations, that are supplied with grades of recommendations or levels of evidence, are written in **bold**.

Text taken directly from the guidelines, that is not graded but provides supplemental information or a clarification of the formal recommendations, is written in *italics*.

Comments by the bibliography group are written in plain text.

11.1.2 General information on selected guidelines

11.1.2.1 Selected guidelines

The selected guidelines and their abbreviations as used in this report can be found inTable 189.

Abbreviation	Guideline
BAPCOC 2012{BAPCOC, 2012 #3}	BAPCOC - Belgische gids voor anti-infectieuze behandeling in de ambulante praktijk; editie 2012/ Guide Belge des traitements anti-infectieux en pratique ambulatoire; édition 2012
NICE bronchiolitis 2015{National Collaborating Centre for Women's and Children's Health, 2015 #9}	National Institute for Health and Care Excellence – Bronchiolitis: diagnosis and management of bronchiolitis in children - 2015

Table 189: Selected guidelines and their abbreviations as used in this report.

11.1.2.2 Grades of recommendation

Grades of recommendation and levels of evidence as defined in each guideline, can be found in table Table 190 to Table 191.

BAPCOC 2012		
Grades of recommendation:	1	Strong recommendation
	2	Weak recommendation
Levels of evidence	A	High degree of evidence; RCTs without limitations or strong, compelling evidence from observational studies

	B	Medium level of evidence; RCTs with limitations or strong evidence from observational studies
	C	(very) low degree of evidence; observational studies or case studies

Table 190 Grades of recommendation and Level of evidence of BAPCOC 2012 guideline.

The quality of evidence is assessed by using the GRADE approach, but where GRADE allocates labels or symbols to represent the strength of a recommendation, NICE does not do this. Instead, the concept of strength is reflected in the wording of the recommendation (see section 9.3.3 in the NICE guidelines manual 2012)

NICE bronchiolitis 2015		
Recommendations that must be used	There is a legal duty to apply the recommendation / intervention	Use "must" or "must not" Use the passive voice: "intervention x must be used"
Recommendations that should be used	The intervention will do more good than harm and will be cost-effective	Use direct instructions Prefer " (do not) offer, refer, advise, discuss" to "should"
Recommendations that could be used	The intervention will do more good than harm for most patients and will be cost-effective Other options may be similarly cost-effective Some patients may opt for a less effective but cheaper intervention Results of the intervention are more likely to vary	Use direct instructions Prefer "(do not) consider" to "could" Other options depending on phrasing: "think about, assess".

Table 191: Grades of recommendation and Level of evidence of NICE CKD 2014 guideline.

11.1.2.3 Agree II score

Information about the Agree II score can be found in the section "Methodology".

A summary of the assessment by the literature group of the individual items of the domain score for each guideline can be found in Table 192. The total domain score is also reported in this table.

Rigour of development item	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Total**	**Domain score**

NICE bronchiolitis 2015	6	3	6	4	5	7	4	1	**36**	**64%**

Table 192: AGREE score of selected guidelines on item "Rigour of development", see 1.1.2.6 for a description of the items.

11.1.2.4 Included populations – interventions – main outcomes

In Table 193 to Table 194, the populations, interventions and main outcomes considered in the selected guidelines are represented.

BAPCOC 2012	
Population	Ambulant care patients
Interventions	Antibiotic treatment (indication, choice, dose, duration)
Outcomes	Not specified

Table 193: Included population, intervention and main outcomes of the guideline

NICE bronchiolitis 2015	
Population	Children with bronchiolitis
Interventions	Capillary blood gas testing, fluids and nutritional support, SpO2 monitoring, chest radiography, chest physiotherapy, antibiotic treatment, inhaled bronchodilator therapy, systemic corticosteroid therapy, combination of the latter two, heliox, montelukast, oxygen supplementation
Outcomes	- relative risks and odds ratios for progressing to severe bronchiolitis - referral rate to secondary care - admission to hospital - duration of oxygen supplementation - change in O2 saturation - length of hospital stay - need for high flow, continuous positive airway pressure (CPAP) or mechanical ventilation - antibiotics administration - change in disease severity score - oral feed toleration

Table 194: Included population, intervention and main outcomes of guideline

11.1.2.5 Members of development group – target audience

Members of the development group that produced the guidelines, and the target audience for whom the guidelines are intended, can be found in **Fout! Verwijzingsbron niet gevonden.** to Table 196.

BAPCOC 2012	
Development group	General practitioners, microbiologists, pneumologists, infectiologists, paediatricians, pharmacists

Target audience	Physicians working in ambulant care

Table 195: Members of the development group and target audience of the guideline

NICE bronchiolitis 2015	
Development group	Multi-professional and lay working group: pediatricians, pediatric nurses, a pediatric specialist pharmacist, a GP, 2 patient/carer members
Target audience	All those who work in or use the National Health Service (NHS) in England and Wales (all healthcare professionals as well as families and carers of children with bronchiolitis).

Table 196: Members of the development group and target audience of the guideline

11.1.3 Definition

11.1.3.1 Summary

The term bronchiolitis isn't clearly defined but both guidelines give diagnostic criteria's for bronchiolitis.

11.1.3.2 BAPCOC 2012

Bronchiolitis is an affliction seen in young children (frequent between 3 and 6 months) associated with breathing difficulties, poor drinking, irritability, wheezing and/or crepitation and apnea in very young children. Bronchiolitis is most commonly caused by the RSV virus.

11.1.3.3 NICE bronchiolitis 2015

The guideline gives diagnostic criteria's for the term, but doesn't define it.

11.1.4 Indications for antibiotic treatment

11.1.4.1 Summary

Both guidelines agree that antibiotics should not be used in children with bronchiolitis.

11.1.4.2 BAPCOC 2012

There is no indication for antibiotic treatment and there is no evidence that antiviral treatments are efficient (GRADE 1A).

11.1.4.3 NICE bronchiolitis 2015

Do not use any of the following to treat bronchiolitis in children:

- *Antibiotics*
- *[…]*

Mentioned further in the report:

The Committee was conscious of the fact that children can sometimes present with bronchiolitis and associated pneumonia. In such cases antibiotic therapy might be effective, and indeed essential, and such cases should not be overlooked. The Committee agreed that there might be a need to give antibiotic treatment to some children with a significant deterioration due to such complications. Antibiotic treatment might be effective, and indeed essential, and such cases should not be overlooked. Antibiotic treatment might occasionally be justified in a sick child where the diagnosis of bronchiolitis was in doubt.

11.1.5 Choice of antibiotic, dose and duration

11.1.5.1 Summary

Since both guidelines state that antibiotics are not indicated for bronchiolitis, they do not recommend a specific one.

11.1.5.2 BAPCOC 2012

Since antibiotics are not indicated, the guideline doesn't make a recommendation.

11.1.5.3 NICE bronchiolitis 2015

No information found in the guideline.

11.1.6 Non-antibiotic treatment

11.1.6.1 Summary

The NICE bronchiolitis 2015 guideline recommends against using any of the following: hypertonic saline, nebulized adrenaline, salbutamol, montelukast, ipratropium bromide, systemic of inhaled corticosteroids, a combination of systemic corticosteroids and nebulized adrenaline.

11.1.6.2 BAPCOC 2012

Since the guideline only reports on antibiotics, no information on non-antibiotic treatment is to be found in the guideline.

11.1.6.3 NICE bronchiolitis 2015

Do not use any of the following to treat bronchiolitis in children:

- **Hypertonic saline**
- **Adrenaline (nebulised)**
- **Salbutamol**
- **Montelukast**
- **Ipratropium bromide**
- **Systemic or inhaled corticosteroids**
- **A combination of systemic corticosteroids and nebulised adrenaline**

11.1.7 Referrals

11.1.7.1 Summary

According to the NICE bronchiolitis 2015 guideline, warning signs for referral to the hospital include respiratory rate over 60 breaths/min and (risk of) dehydration. More severe signs (apnea, cyanosis, severe respiratory distress) than this can warrant a referral to emergency hospital care.
Secondary care can also be indicated in case of comorbidities, young or prematurely born infants, or uncertainty about the quality of care the patient would receive.

11.1.7.2 BAPCOC 2012

No information found in the guideline.

11.1.7.3 NICE bronchiolitis 2015

Immediately refer children with bronchiolitis for emergency hospital care (usually by 999 ambulance) if they have any of the following:

- *apnea (observed or reported)*
- *child looks seriously unwell to a healthcare professional*
- *severe respiratory distress, for example grunting, marked chest recession, or a respiratory rate of over 70 breaths/minute*
- *central cyanosis*
- *persistent oxygen saturation of less than 92% when breathing air.*

Consider referring children with bronchiolitis to hospital if they have any of the following:

- *a respiratory rate of over 60 breaths/minute*
- *difficulty with breastfeeding or inadequate oral fluid intake (50-75% of usual volume, taking account of risk factors [see recommendation 16] and using clinical judgement)*
- *clinical dehydration*

When deciding whether to refer a child with bronchiolitis to secondary care, take account of the following risk factors for more severe bronchiolitis:

- *chronic lung disease (including bronchopulmonary dysplasia)*
- *hemodynamically significant congenital heart disease*
- *age in young infants (under 3 months)*
- *premature birth, particularly under 32 weeks*
- *neuromuscular disorders*
- *immunodeficiency.*

When deciding whether to refer a child to secondary care, take into account factors that might affect a carer's ability to look after a child with bronchiolitis, for example:

- *social circumstances*
- *the skill and confidence of the carer in looking after a child with bronchiolitis at home*
- *confidence in being able to spot red flag symptoms (see recommendation 14)*
- *distance to healthcare in case of deterioration.*

11.2 Evidence tables and conclusions

11.2.1 Antibiotics versus placebo or no treatment for bronchiolitis in children under 2 years of age

11.2.1.1 Clinical evidence profile

Systematic review: Farley 2014{Farley, 2014 #268} "Antibiotics for bronchiolitis in children under two years of age"
Inclusion criteria:
Single or double-blind randomised controlled trials (RCTs) comparing antibiotics to placebo or control to treat bronchiolitis
Children under the age of two years diagnosed with bronchiolitis using clinical criteria, such as respiratory distress preceded by coryzal symptoms, with or without fever.
Oral, intravenous, intramuscular or inhaled antibiotics versus placebo.
Search strategy:
"We searched the Cochrane Central Register of Controlled Trials (CENTRAL 2014, Issue 6), which includes the Cochrane Acute Respiratory Infection Group's Specialised Register, and the Database of Abstracts of Reviews of Effects, MEDLINE (1966 to June 2014), EMBASE (1990 to June 2014) and Current Contents (2001 to June 2014)."
Assessment of quality of included trials: yes
Other methodological remarks:

Table 197

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Farley 2014{Farley, 2014 #268}	**Antibiotics versus placebo or no treatment**	N=3 n=350 (McCallum 2013, Pinto 2012, Kneyber 2008)	**Days of supplementary oxygen**	MD -0.20 (-0.72 to 0.33) NS

		N=1 n=104 (Mazumder 2009)	**Wheeze (day 1)**	Crude AR: 61/61 vs 43/43 OR Not estimable
		N=1 n=104 (Mazumder 2009)	**Wheeze (day 3)**	Crude AR: 18/61 vs 26/43 **OR 0.27 (0.12 to 0.62)** **SS** **(less wheeze on day 3 with AB)**
		N=1 n=104 (Mazumder 2009)	**Wheeze (day 5)**	Crude AR: 13/61 vs 2/43 **OR 5.55 (1.18 to 26.05)** **SS** **(more wheeze on day 5 with AB)**
		N=1 n=295 (Kabir 2009)	**Wheeze (day 7)**	Crude AR: 17/198 vs 4/97 OR 2.18 (0.71 to 6.68) NS
		N=1 n=104 (Mazumder 2009)	**Oxygen saturation <96% (day 1)**	Crude AR: 33/61 vs 23/43 OR 1.02 (0.47 to 2.24) NS
		N=1 n=104 (Mazumder 2009)	**Oxygen saturation <96% (day 3)**	Crude AR: 15/61 vs 5/43 OR 2.48 (0.83 to 7.44) NS
		N=1 n=104 (Mazumder 2009)	**Oxygen saturation <96% (day 5)**	Crude AR: 5/61 vs 2/43 OR 1.83 (0.43 to 9.91) NS
		N=1 n=295 (Kabir 2009)	**Fever**	Crude AR: 11/198 vs 4/97 OR 1.37 (0.42 to 4.41) NS

		N=2 n=123 (Field 1966, Kneyber 2008)	**Duration of symptoms**	MD 0.32 (-1.14 to 1.78) NS
		N=5 n=543 (Field 1966, Kabir 2009, Kneyber 2008, Mazumder 2009, Tahan 2007)	**Deaths**	Crude AR: 0/331 vs 0/212 OR Not estimable

Table 198

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
Field 1966{Field, 1966 #240}	52	Infants Inclusion criteria Coryza Paroxysmal cough Expiratory wheeze Increased respiratory rate Exclusion criteria Not reported.	Not reported	125 mg of ampicillin or placebo six-hourly.	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Unclear risk (Risk unclear) BLINDING Low risk INCOMPLETE OUTCOME DATA High risk (No intention-to-treat analysis but withdrawal rates were acceptable) SELECTIVE REPORTING Low risk OTHER BIAS Unclear risk (Funding sources do not

					appear to be identified. Beechams Research Laboratories supplied both the ampicillin and the placebo)
Kabir 2009{Kabir, 2009 #199}	295	Children under 2 years of age with clinical suspected bronchiolitis: Hospitalised due to preceding or existing runny nose, cough, breathing difficulty, chest in-drawing and rhonchi on auscultation	7 days	IV ampicillin (parenteral ampicillin 50 mg/kg/6-hourly + supportive care), oral erythromycin (oral erythromycin 10 mg/kg 6-hourly + supportive care), control AB for 7 days	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Unclear risk (Not described) BLINDING High risk (Seems unlikely, not described) INCOMPLETE OUTCOME DATA Low SELECTIVE REPORTING High risk OTHER BIAS Low risk
Kneyber 2008{Kneyber, 2008 #241}	71	Hospitalised infants younger than 24 months with clinically confirmed viral lower respiratory tract infection Inclusion criteria Aged less than 24 months Virologically confirmed diagnosis of RSV LRTD Definition of RSV First attack of dyspnoea and one or more symptoms compatible with lower respiratory tract infection including: Body temperature > 37.5°C Coughing Wheezing Crackles on pulmonary auscultation RSV was confirmed using direct	Not found	Oral Azithromycin 10 mg/kg/day, once daily for 3 days Or placebo	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk BLINDING Low risk INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk OTHER BIAS Unclear risk (Funding sources do not appear to be identified)

		immunofluorescent assay (DIFA) using FITC labelled monoclonal antibodies or enzyme-linked immunosorbent assay (EIA).			
Mazumder 2009{Mazumder, 2009 #269}	126	Children aged 1 month to 2 years clinical bronchiolitis (runny nose followed by wheeze, cough, breathing difficulty perceived by caregiver, chest in-drawing and rhonchi on auscultation)	7 days	Supportive management, supportive management plus IV ampicillin, supportive management plus oral erythromycin (30-50 mg/ kg/ day every 6 hours)	RANDOM SEQUENCE GENERATION High risk (Odds and evens) ALLOCATION CONCEALMENT Unclear risk (Not discussed) BLINDING Unclear risk (Not specified) INCOMPLETE OUTCOME DATA Unclear risk (Not specified) SELECTIVE REPORTING Unclear risk (Unsure) OTHER BIAS Unclear risk (Funding sources do not appear to be identified)
McCallum 2013{McCallum, 2013 #201}	97	Children aged <18months, admitted with a clinical diagnosis of bronchiolitis (according to standardised hospital protocols; 18 months, with cough and coryza, wheezing +/- crackles, respiratory distress with both tachypnoea (respiratory rate > 50 breaths/ minute) and retractions).	6 months	A single large dose (30 mg/kg) of azithromycin within 24 hours of hospitalisation	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk BLINDING Low risk INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk OTHER BIAS Low risk
Pinto 2012{Pinto, 2012 #198}	185	Children < 12 months of age hospitalised with acute viral bronchiolitis	Until discharge from hospital	Oral azithromycin (10 mg/kg/d)for 7 days	RANDOM SEQUENCE GENERATION Unclear risk (Infants were randomised (simple/unrestricted randomisation) to receive either a

					daily oral dose of azithromycin or an equivalent volume of placebo) ALLOCATION CONCEALMENT Unclear risk (Not described) BLINDING Unclear risk (The patients were infants. A blinded study team member supervised the intervention. A standardised form was used to collect clinical information on the patients included in the trial. Whether or not the outcome assessors were blind to the intervention was not described) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk OTHER BIAS Low risk
Tahan 2007{Tahan, 2007 #243}	30	Infants less than or equal to 7 months with Inclusion criteria First episode of wheezing requiring hospitalisation Clinical diagnosis of bronchiolitis Definition of bronchiolitis Based on clinical findings including: Wheezing or wheezing with crackles Respiratory distress with retractions	6 months	Clarithromycin 15 mg/kg/day, once daily for 3 weeks Vs placebo	RANDOM SEQUENCE GENERATION Unclear risk ("... infants were randomised by a single study nurse..." "Simple randomisation was used") ALLOCATION CONCEALMENT Unclear risk (Allocation after enrolment by study nurse) BLINDING Low risk INCOMPLETE OUTCOME DATA Unclear risk (30 patients were

					randomised, however 9 were later excluded as they received corticosteroid therapy) SELECTIVE REPORTING Unclear risk (Unsure if trial was registered) OTHER BIAS Unclear risk (Unsure if there were any conflicts of interest; funding sources do not appear to be identified)

Table 199

11.2.1.2 Summary and conclusions

Antibiotics versus placebo or no treatment for bronchiolitis in children under two years of age			
Bibliography: Farley 2014{Farley, 2014 #268}			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Deaths	543 (5 studies)	Crude AR: 0/331 vs 0/212 OR Not estimable	⊕⊕⊕⊖: **MODERATE** Study quality: -1 (3 RCTs with methodological flaws (incl inadequate randomization, no blinding) Consistency: ok Directness: ok Imprecision: na
Days of supplementary oxygen	350 (3 studies)	MD -0.20 (-0.72 to 0.33) NS	⊕⊕⊕⊕**:HIGH** Study quality:ok Consistency: ok Directness: ok Imprecision: ok
Wheeze (day 1)	104 (1 study)	Crude AR: 61/61 vs 43/43 OR Not estimable	⊕⊕⊖⊖: **LOW** Study quality:-2 (inadequate rando, unclear allocation concealment, unclear methodology) Consistency: na Directness: ok Imprecision: na
Wheeze (day 3)	104 (1 study)	**OR 0.27 (0.12 to 0.62)** **SS** **(less wheeze on day 3 with AB)**	⊕⊕⊖⊖: **LOW** Study quality: -2 (inadequate rando, unclear allocation concealment, unclear methodology) Consistency: na Directness: ok Imprecision: ok
Wheeze (day 5)	104 (1 study)	**OR 5.55 (1.18 to 26.05)** **SS** **(more wheeze on day 5 with AB)**	⊕⊕⊖⊖: **LOW** Study quality: -2 (inadequate rando, unclear allocation concealment, unclear methodology) Consistency: na Directness: ok Imprecision: ok
Wheeze (day 7)	295 (1 study)	OR 2.18 (0.71 to 6.68) NS	⊕⊕⊕⊖: **MODERATE** Study quality:-1 (no blinding) Consistency: na Directness: ok Imprecision: ok
Oxygen saturation <96% (day 1)	104 (1 study)	OR 1.02 (0.47 to 2.24) NS	⊕⊖⊖⊖: **VERY LOW** Study quality: -2 (inadequate rando, unclear allocation concealment, unclear methodology) Consistency: na Directness: ok Imprecision: 1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)

Oxygen saturation <96% (day 3)	104 (1 study)	OR 2.48 (0.83 to 7.44) NS	⊕⊕⊖⊖: **LOW** Study quality: -2 (inadequate rando, unclear allocation concealment, unclear methodology; only one study) Consistency: na Directness: ok Imprecision: ok
Oxygen saturation <96% (day 5)	104 (1 study)	OR 1.83 (0.43 to 9.91) NS	⊕⊖⊖⊖: **VERY LOW** Study quality: -2 (inadequate rando, unclear allocation concealment, unclear methodology; only one study) Consistency: na Directness: ok Imprecision: 1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Fever	295 (1 study)	OR 1.37 (0.42 to 4.41) NS	⊕⊕⊖⊖: **LOW** Study quality:-1 (no blinding) Consistency: na Directness: ok Imprecision:-1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Duration of symptoms	123 (2 studies)	MD 0.32 (-1.14 to 1.78) NS	⊕⊕⊕⊕**:HIGH** Study quality:ok Consistency: ok Directness: ok Imprecision: ok

Table 200

In this meta-analysis, RCTs were sought that compared a treatment with an antibiotic with placebo or no treatment for bronchiolitis in children under the age of two years.

7 RCTs were found. Infants up to two years of age were included.

In six trials, bronchiolitis was diagnosed clinically. One trial included only children with a virologically confirmed diagnosis of RSV infection.

The oral antibiotics used in the trials were ampicillin, erythromycin, azithromcyin and clarithromycin.

In children *with bronchiolitis*, a treatment with antibiotics, compared to placebo, **did** result in a statistically significant **decrease** in *wheeze on day 3.*
GRADE: LOW quality of evidence

In children *with bronchiolitis*, a treatment with antibiotics, compared to placebo, **did** result in a statistically significant **increase** in *wheeze on day 5.*
GRADE: LOW quality of evidence

In children *with bronchiolitis*, a treatment with antibiotics, compared to placebo, **did not** result in a statistically significant difference in *days of supplementary oxygen*, and *duration of symptoms*.
GRADE: HIGH quality of evidence

In children *with bronchiolitis*, a treatment with antibiotics, compared to placebo, **did not** result in a statistically significant difference in *deaths* and *wheeze on day 7*.
GRADE: MODERATE quality of evidence

In children *with bronchiolitis*, a treatment with antibiotics, compared to placebo, **did not** result in a statistically significant difference in *wheeze on day1, oxygen saturation <96% on day 3,* or *fever.*
GRADE: LOW quality of evidence

In children *with bronchiolitis*, a treatment with antibiotics, compared to placebo, **did not** result in a statistically significant difference in *oxygen saturation <96% on day 1 and day 5.*
GRADE: VERY LOW quality of evidence

11.2.2 Azithromycin versus placebo or no treatment for bronchiolitis in children under two years of age

11.2.2.1 Clinical evidence profile

Systematic review: Farley 2014{Farley, 2014 #268} "Antibiotics for bronchiolitis in children under two years of age" Inclusion criteria: Single or double-blind randomised controlled trials (RCTs) comparing antibiotics to placebo or control to treat bronchiolitis Children under the age of two years diagnosed with bronchiolitis using clinical criteria, such as respiratory distress preceded by coryzal symptoms, with or without fever. Oral, intravenous, intramuscular or inhaled antibiotics versus placebo. Search strategy: "We searched the Cochrane Central Register of Controlled Trials (CENTRAL 2014, Issue 6), which includes the Cochrane Acute Respiratory Infection Group's Specialised Register, and the Database of Abstracts of Reviews of Effects, MEDLINE (1966 to June 2014), EMBASE (1990 to June 2014) and Current Contents (2001 to June 2014)." Assessment of quality of included trials: yes Other methodological remarks:

Table 201

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Farley 2014{Farley, 2014 #268	**Azithromycin vs placebo**	N=3 n=350 (Kneyber 2008, McCallum 2013, Pinto 2012)	**Length of hospital stay**	MD -0.58 (-1.18 to 0.02) NS

Table 202

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
Kneyber 2008{Kneyber, 2008 #241}	71	Hospitalised infants younger than 24 months with clinically confirmed viral lower respiratory tract infection Inclusion criteria Aged less than 24 months Virologically confirmed diagnosis of RSV LRTD Definition of RSV First attack of dyspnoea and one or more symptoms compatible with lower respiratory tract infection including: Body temperature > 37.5°C Coughing Wheezing Crackles on pulmonary auscultation RSV was confirmed using direct immunofluorescent assay (DIFA) using FITC labelled monoclonal antibodies or enzyme-linked immunosorbent assay (EIA).	Not found	Oral Azithromycin 10 mg/kg/day, once daily for 3 days Or placebo	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk BLINDING Low risk INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk OTHER BIAS Unclear risk (Funding sources do not appear to be identified)
McCallum 2013{McCallum, 2013 #201}	97	Children aged <18months, admittedwith a clinical diagnosis of bronchiolitis (according to standardised hospital protocols; 18 months, with cough and coryza, wheezing +/- crackles, respiratory distress with both tachypnoea (respiratory rate > 50 breaths/ minute) and retractions).	6 months	A single large dose (30 mg/kg) of azithromycin within 24 hours of hospitalisation	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk BLINDING Low risk INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk

					OTHER BIAS Low risk
Pinto 2012{Pinto, 2012 #198}	185	Children < 12 months of age hospitalised with acute viral bronchiolitis	Until discharge from hospital	Oral azithromycin (10 mg/kg/d)for 7 days	RANDOM SEQUENCE GENERATION Unclear risk (Infants were randomised (simple/unrestricted randomisation) to receive either a daily oral dose of azithromycin or an equivalent volume of placebo) ALLOCATION CONCEALMENT Unclear risk (Not described) BLINDING Unclear risk (The patients were infants. A blinded study team member supervised the intervention. A standardised form was used to collect clinical information on the patients included in the trial. Whether or not the outcome assessors were blind to the intervention was not described) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk OTHER BIAS Low risk

Table 203

« Three-weekly doses of azithromycin for indigenous infants hospitalized with bronchiolitis: a multicentre, randomized, placebo-controlled trial »

Study details	n/Population	Comparison	Outcomes		Methodological
Ref McCallum 2015{McCallum, 2015 #200} Design: RCT (DB; PG) Duration of follow-up: 6 months	n= 219 Mean age: 5.7 months (azithromycin) 5.6 months (placebo) Inclusion aged ≤24 months and hospitalized with a standardized clinical diagnosis of bronchiolitis (age-adjusted tachypnea with wheeze or crackles),had parent-ascribed Indigenous ethnicity (Australian Aboriginal, Torres	Azithromycin (30 mg/kg), once a week, for 3 weeks Vs Placebo	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Lost-to follow-up: 3 % Drop-out and Exclusions: unclear • Described: yes • Balanced across groups: yes ITT: no (“Data were analyzed according to the group the child was allocated
			Hospital length of stay (PO)	Azithromycin: median 54 hours Placebo: median 54 hours Group difference 0h (-6 to 8h) NS; p 0.8	
			Duration of oxygen supplementation subgroup analysis in those who needed oxygen supplementation (PO)	Azithromycin: 40h Placebo: 65h Group difference 5h (-8 to 11h) NS; p 0.7	
			Day 21-symptoms/signs presence of cough, wheeze, abnormal auscultatory chest signs and suppurative otitis media.	Azithromycin: 23/100 Placebo: absolute 35/110 Risk difference: -8% (-20% to 3%) NS; p 0.2	
			Respiratory rehospitalisations within 6 months post-discharge	Azithromycin: 31/106 Placebo: 25/113 OR 1.5 (0.8 to 3.0) NS en p 0.2	
			Safety		

	Strait Islander, Maori, and/or Pacific Islander), were consented within 24h of hospitalization and had caregivers with a mobilephone <u>Exclusion</u> severe disease (admitted to the intensive care unit); underlying chronic lung or congenital heart disease, contraindications to macrolides (e.g. hypersensitivity or liver dysfunction,), diarrhoea (>2 two watery stools above the normal daily pattern), received macrolides within last seven-days, or clinical and radiographic features of a primary pneumonia.		**Adverse events**	Azithromycin: 2 (vomiting, diarrhoea) Placebo: 1 (wheezing and rash) No statistical analysis	to. Only available data were analyzed.") SELECTIVE REPORTING: no Sponsor: The authors declare that they have no conflicts of Interest relevant to this article to disclose. This study was funded by National Health And Medical Research Council (NHMRC) grants

Table 204

11.2.2.2 Summary and conclusions

Azithromycin versus placebo or no treatment for bronchiolitis in children under two years of age			
Bibliography: Farley 2014{Farley, 2014 #268}			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Length of hospital stay	350 (3 studies)	MD -0.58 (-1.18 to 0.02) NS	⨁⨁⨁⨁: **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok

Table 205

In this meta-analysis, RCTs were sought that compared a treatment with azithromycin with placebo or no treatment for bronchiolitis in children under the age of two years.

3 RCTs were found. The children in these studies were infants up to two years of age.

Azithromycin was used in a dose of 10 mg/kg/day for 3 days in one study, for 7 days in one study, and in a single large dose of 30 mg/kg in a third study.

In children *with bronchiolitis*, a treatment with azithromycin, compared to placebo, **did not** result in a statistically significant difference in *length of hospital stay.*
GRADE: HIGH quality of evidence

Azithromycin versus placebo for bronchiolitis in children under two years of age
Bibliography: Farley 2014{Farley, 2014 #268}

Table 206

This RCT compared a treatment with azithromycin with placebo or no treatment for bronchiolitis in Australian Indigenous children under the age of two years.

Azithromycin was given in a dose of 30 mg/kg once a week for 3 weeks.

In this population of high-risk infants, no statistically significant difference was seen with antibiotics versus placebo in length of hospital stay, duration of oxygen supplementation, symptoms and signs on day 21, or respiratory rehospitalisations within 6 months.

11.2.3 Erythromycin versus placebo or no treatment for bronchiolitis in children under two years of age

11.2.3.1 Clinical evidence profile

Systematic review: Farley 2014{Farley, 2014 #268} "Antibiotics for bronchiolitis in children under two years of age" Inclusion criteria: Single or double-blind randomised controlled trials (RCTs) comparing antibiotics to placebo or control to treat bronchiolitis Children under the age of two years diagnosed with bronchiolitis using clinical criteria, such as respiratory distress preceded by coryzal symptoms, with or without fever. Oral, intravenous, intramuscular or inhaled antibiotics versus placebo. Search strategy: "We searched the Cochrane Central Register of Controlled Trials (CENTRAL 2014, Issue 6), which includes the Cochrane Acute Respiratory Infection Group's Specialised Register, and the Database of Abstracts of Reviews of Effects, MEDLINE (1966 to June 2014), EMBASE (1990 to June 2014) and Current Contents (2001 to June 2014)." Assessment of quality of included trials: yes Other methodological remarks:

Table 207

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Farley 2014{Farley, 2014 #268}	**Erythromycin vs placebo**	N=1 n=196 (Kabir 2009)	**Length of hospital stay**	**MD 0.70 (0.22 to 1.18)** **SS** **(greater length of hospital stay with erythromycin)**

Table 208

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
Kabir 2009{Kabir, 2009 #199}	295	Children under 2 years of age with clinical suspected bronchiolitis:	7 days	IV ampicillin (parenteral ampicillin 50 mg/kg/6-hourly	RANDOM SEQUENCE GENERATION Low risk

		Hospitalised due to preceding or existing runny nose, cough, breathing difficulty, chest in-drawing and rhonchi on auscultation		+ supportive care), oral erythromycin (oral erythromycin 10 mg/kg 6-hourly + supportive care), control AB for 7 days	ALLOCATION CONCEALMENT Unclear risk (Not described) BLINDING High risk (Seems unlikely, not described) INCOMPLETE OUTCOME DATA Low SELECTIVE REPORTING High risk OTHER BIAS Low risk

Table 209

11.2.3.2 Summary and conclusions

Erythromycin versus placebo or no treatment for bronchiolitis in children under two years of age			
Bibliography: Farley 2014{Farley, 2014 #268}			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Length of hospital stay	196 (1 study)	**MD 0.70 (0.22 to 1.18)** **SS** **(greater length of hospital stay with erythromycin)**	⨁⨁⨁⊖: **MODERATE** Study quality: -1 (no blinding, high risk of selective reporting) Consistency: na Directness: ok Imprecision: ok

Table 210

In this meta-analysis, RCTs were sought that compared a treatment with erythromycin with placebo or no treatment for bronchiolitis in children under the age of two years.

1 RCT was found. The children in these studies were infants up to two years of age.

Erythromycin was used in a dose of 40 mg/kg/day in four doses a day for 7 days.

In children *with bronchiolitis*, a treatment with erythromycin, compared to placebo, **did** result in a statistically significant **increase** in *length of hospital stay.*
GRADE: MODERATE quality of evidence

12 Community acquired pneumonia

12.1 Guidelines

12.1.1 Method of reporting of the recommendations and notes

Formal recommendations, that are supplied with grades of recommendations or levels of evidence, are written in **bold**.

Text taken directly from the guidelines, that is not graded but provides supplemental information or a clarification of the formal recommendations, is written in *italics*.

Comments by the bibliography group are written in plain text.

12.1.2 General information on selected guidelines

12.1.2.1 Selected guidelines

The selected guidelines and their abbreviations as used in this report can be found in Table 211.

Abbreviation	Guideline
BAPCOC 2012{BAPCOC, 2012 #3}	BAPCOC - Belgische gids voor anti-infectieuze behandeling in de ambulante praktijk; editie 2012/ Guide Belge des traitements anti-infectieux en pratique ambulatoire; édition 2012
IDSA CAP 2011{Bradley, 2011 #4}	Infectious Diseases Society of America – The management of community-acquired pneumonia in infants and children older than 3 months of age – 2011
BTS CAP 2011{Harris, 2011 #1}	British Thoracic Society guidelines for the management of community acquired pneumonia in children: update 2011

Table 211: Selected guidelines and their abbreviations as used in this report.

12.1.2.2 Grades of recommendation

Grades of recommendation and levels of evidence as defined in each guideline, can be found in table Table 212, Table 213 and Figure 5.

BAPCOC 2012		
Grades of recommendation:	1	Strong recommendation
	2	Weak recommendation
Levels of evidence	A	High degree of evidence; RCTs without limitations or strong, compelling evidence

		from observational studies
	B	Medium level of evidence; RCTs with limitations or strong evidence from observational studies
	C	(very) low degree of evidence; observational studies or case studies

Table 212: Grades of recommendation and levels of evidence from the BAPCOC 2012 guideline

IDSA CAP 2011

Strength of Recommendations and Quality of Evidence

Strength of recommendation and quality of evidence	Clarity of balance between desirable and undesirable effects	Methodologic quality of supporting evidence (examples)	Implications
Strong recommendation			
High-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Consistent evidence from well-performed RCTs[a] or exceptionally strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances; further research is unlikely to change our confidence in the estimate of effect.
Moderate-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or exceptionally strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances; further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence for ≥1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence	Recommendation may change when higher quality evidence becomes available; further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low-quality evidence (rarely applicable)	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence for ≥1 critical outcome from unsystematic clinical observations or very indirect evidence	Recommendation may change when higher quality evidence becomes available; any estimate of effect for ≥1 critical outcome is very uncertain.
Weak recommendation			
High-quality evidence	Desirable effects closely balanced with undesirable effects	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies	The best action may differ depending on circumstances or patients or societal values; further research is unlikely to change our confidence in the estimate of effect.
Moderate-quality evidence	Desirable effects closely balanced with undesirable effects	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or exceptionally strong evidence from unbiased observational studies	Alternative approaches are likely to be better for some patients under some circumstances; further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low-quality evidence	Uncertainty in the estimates of desirable effects, harms, and burden; desirable effects, harms, and burden may be closely balanced	Evidence for ≥1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence	Other alternatives may be equally reasonable; further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low-quality evidence	Major uncertainty in estimates of desirable effects, harms, and burden; desirable effects may or may not be balanced with undesirable effects may be closely balanced	Evidence for ≥1 critical outcome from unsystematic clinical observations or 2very indirect evidence	Other alternatives may be equally reasonable; any estimate of effect, for at ≥1 critical outcome, is very uncertain.

Figure 5: Grades of recommendation and Level of Evidence from the IDSA CAP 2011 guideline

BTS CAP 2011:

Each statement is first given an evidence level (Ia to IVb) by the authors of each chapter. Then, at the end of each chapter when evidence statements were collated, a summative evidence level was attached to each statement depending on the level of evidence underpinning that statement. Finally, each recommendation was graded (A to D) based upon a considered judgement of the body of evidence.

BTS CAP 2011		
Evidence level	**Definition**	**Guideline statement grade**
Ia	A good recent systematic review of studies designed to answer the question of interest	A+
Ib	One or more rigorous studies designed to answer the question, but not formally combined	A -
II	One or more prospective clinical studies which illuminate, but do not rigorously answer, the question.	B+
III	One or more retrospective clinical studies which illuminate, but do not rigorously answer, the question	B-
IVa	Formal combination of expert views	C
IVb	Other information	D

Table 213: Grades of recommendation and Level of evidence of BTS CAP 2011 guideline

12.1.2.3 Agree II score

Information about the Agree II score can be found in the section “Methodology”.

A summary of the assessment by the literature group of the individual items of the domain score for each guideline can be found in Table 214. The total domain score is also reported in this table.

Rigour of development item	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Total**	**Domain score**
IDSA CAP 2011	3	2	2	6	3	7	3	1	**27**	**48%**
BTS CAP 2011	7	5	4	1	3	6	3	5	**34**	**61%**

Table 214: AGREE score of selected guidelines on item “Rigor of development”, see 1.1.2.6 for a description of the items.

12.1.2.4 Included populations – interventions – main outcomes

In Table 215 to Table 217, the populations, interventions and main outcomes considered in the selected guidelines are represented.

BAPCOC 2012	
Population	Ambulant care patients
Interventions	Antibiotic treatment (indication, choice, dose, duration)
Outcomes	Not specified

Table 215: Included population, intervention and main outcome of guideline

IDSA CAP 2011	
Population	Otherwise healthy infants and children with CAP in both inpatient and outpatient settings (so exclusion of neonates and young infants under 3 months, immunocompromised children, children receiving home mechanical ventilation, and children with chronic conditions or underlying lung disease)
Interventions	Site-of-care management decision, diagnostic testing, anti-infective treatment, adjunctive surgical and non-anti-infective therapy for pediatric CAP, unresponsive child, discharge, prevention
Outcomes	Not specified

Table 216: Included population, intervention and main outcomes of guideline

BTS CAP 2011	
Population	Infants and children, but not neonates, infants with respiratory syncytial virus bronchiolitis or children with upper respiratory tract infection, mild fever and wheeze
Interventions	investigations, severity assessment, general management, antiobiotic management, complications, follow up
Outcomes	not specified

Table 217: Included population, intervention and main outcomes of guideline

12.1.2.5 Members of development group – target audience

Members of the development group that produced the guidelines, and the target audience for whom the guidelines are intended, can be found in Table 219 to Table 220.

BAPCOC 2012	
Development group	General practitioners, microbiologists, pneumologists, infectiologists, paediatricians, pharmacists
Target audience	Physicians working in ambulant care

Table 218: Members of the development group and target audience of the guideline

IDSA CAP 2011	
Development group	Panel participants were representatives from the following collaborating organizations: AAP, American college of Emergency physicians, American Thoracic Society-Pediatric Section, Society for hospital Medicine, Society of Critical Care Medicine and American Pediatric Surgical Association, with expert consultants in diagnostic microbiology and interventional radiology.
Target audience	Primary care and subspecialty providers responsible for the management of otherwise healthy infants with CAP both in- and outpatients.

Table 219: Members of the development group and target audience of the guideline

BTS CAP 2011	
Development group	2 pediatricians with a special interest in respiratory disease, a pediatrician with a special interest in pediatric infectious diseases, a general pediatrician with a special interest in ambulatory pediatrics, a general practitioner with an interest in childhood infection and a pediatric pharmacist.
Target audience	Not defined

Table 220: Members of the development group and target audience of the guideline

12.1.3 Definition

12.1.3.1 Summary

Two out of three guidelines define the term "Community Acquired Pneumonia". The IDSA CAP 2011 guideline and the BTS CAP 2011 guideline use the exact same definition, namely "the signs and symptoms of pneumonia in a previously healthy child caused by an infection that has been acquired outside of the hospital".

12.1.3.2 BAPCOC 2012

The guideline doesn't define this term.

12.1.3.3 IDSA CAP 2011

Community Acquired Pneumonia is defined as the presence of signs and symptoms of pneumonia in a previously healthy child caused by an infection that has been acquired outside of the hospital.

12.1.3.4 BTS CAP 2011

CAP can be clinically defined as the presence of signs and symptoms of pneumonia in a previously healthy child due to an infection which has been acquired outside hospital.

12.1.4 Indications for antibiotic treatment

12.1.4.1 Summary

The BAPCOC 2012 and BTS CAP 2011 guideline both recommend that all children who have a clinical diagnosis of pneumonia receive antibiotic (strong recommendation for BAPCOC 2012 but with low evidence, expert opinion for BTS CAP 2011). BTS CAP 2011 makes an exception to this rule for children under 2 years for whom a viral pathogen is more common (expert opinion).

IDSA CAP 2011 recommends amoxicillin in cases where a bacterial pathogen is suspected (the guideline recommends testing to track viral pathogens first, see also "choice of antibiotic" section below). Levels of evidence are unclear because they apply to the choice of antibiotic, except for the statement advising against the use of antibiotics in children of preschool age (that one is a strong recommendation with high quality evidence).

12.1.4.2 BAPCOC 2012

Children with a community acquired pneumonia (CAP) without heightened risk or who aren't severely ill: treatment at home with antibiotics (Grade 1C).

12.1.4.3 IDSA CAP 2011

For children in outpatient settings:

Antimicrobial therapy is not routinely required for preschool-aged children with CAP, because viral pathogens are responsible for the great majority of clinical disease. (strong recommendation; high-quality evidence)

The guideline's first recommendations are about diagnosis of CAP and include testing children for influenza virus and other viruses. In case of a suspected bacterial pathogen, the guideline immediately recommends amoxicillin for the following populations:
- *previously healthy, appropriately immunized infants and preschool children with mild to moderate CAP suspected to be of bacterial origin*
- *previously healthy, appropriately immunized school-aged children and adolescents with mild to moderate CAP suspected to be of bacterial origin*
Levels of evidence apply to the antibiotic recommended for those populations.

12.1.4.4 BTS CAP 2011

All children with a clear clinical diagnosis of pneumonia should receive antibiotics as bacterial and viral pneumonia cannot reliably be distinguished from each other. [C]

Children aged <2 years presenting with mild symptoms of lower respiratory tract infection do not usually have pneumonia and need not to be treated with antibiotics but should be reviewed if symptoms persist. A history of conjugate pneumococcal vaccination gives greater confidence to this decision. [C]

12.1.5 Choice of antibiotic, dose and duration

12.1.5.1 Summary

All three guidelines recommend amoxicillin as first choice, although BAPCOC 2012 at higher doses (75-100 mg/kg/day in 3 to 4 doses) than IDSA CAP 2011 (90 mg/kg/d in 2 doses, or 75 mg/kg/d in 3 doses). The BTS CAP 2011 doesn't recommend a dosage.
Alternatives are co-amoxiclav or macrolides, azithromycin and clarithromycin are mentioned by both BAPCOC 2012 and BTS CAP 2011. IDSA CAP 2011 keeps macrolide antibiotics for atypical pathogens only.
IDSA CAP 2011 is the only guideline to also recommend anti-influenza therapy in case of a CAP consistent with viral infections during high circulation of the virus.

12.1.5.2 BAPCOC 2012

First choice (grade 1C):
- amoxicilline: 75-100 mg/kg/day in 3 to 4 doses during 5-7 days
Children older than 5 years in good physical condition and with clear interstitial infiltrates on thorax radio-imaging (high risk of atypical pneumonia):
- azithromycine: 10 mg/kg/day in 1 dose during 3 days; or 10 mg/kg/day in 1 dose on the first day, then 5 mg/kg/day in 1 dose during 4 days
- clarithromycine: 15 mg/kg/day in 2 doses during 5-7 days

Alternative in case of non-IgE-mediated penicillin allergy (Grade 1C)
- cefuroxime axetil: 30-50 mg/kg/day in 3 doses during 5-7 days

Alternative in case of IgE-mediated penicillin allergy (grade 1C):
The child needs to be hospitalized for intravenous antibiotic therapy

If there is no improvement after 48 hours with amoxicillin and there are no signs of pleural effusion at auscultation or with throrax radio-imaging: (Grade 1C)
Add azithromycin or clarithromycin to amoxicillin

12.1.5.3 IDSA CAP 2011

- Amoxicillin should be used as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate CAP suspected to be of bacterial origin. Amoxicillin provides appropriate coverage for Streptococcus pneumoniae, the most prominent invasive bacterial pathogen. Table 5 lists preferred agents and alternative agents for children allergic to amoxicillin (strong recommendation; moderate-quality evidence).

Amoxicillin should be used as first-line therapy for previously healthy appropriately immunized school-aged children and adolescents with mild to moderate CAP for S. pneumoniae, the most prominent invasive bacterial pathogen. Atypical bacterial pathogens (eg, M. pneumoniae), and less common lower respiratory tract bacterial pathogens, as discussed in the Evidence Summary, should also be considered in management decisions. (strong recommendation; moderate quality evidence).

Macrolide antibiotics should be prescribed for treatment of children (primarily school-aged children and adolescents) evaluated in an outpatient setting with findings compatible with CAP caused by atypical pathogens. Laboratory testing for M. pneumoniae should be performed if available in a clinically relevant time frame. Table 5 lists preferred and alternative agents for atypical pathogens. (weak recommendation; moderate-quality evidence)

Influenza antiviral therapy should be administered as soon as possible to children with moderate to severe CAP consistent with influenza virus infection during widespread local circulation of influenza viruses, particularly for those with clinically worsening disease documented at the time of an outpatient visit. Because early antiviral treatment has been shown to provide maximal benefit, treatment should not be delayed until confirmation of positive influenza test results. Negative results of influenza diagnostic tests, especially rapid antigen tests, do not conclusively exclude influenza disease. Treatment after 48 hours of symptomatic infection may still provide clinical benefit to those with more severe disease. (strong recommendation; moderate-quality evidence)

Selection of Antimicrobial Therapy for Specific Pathogens

Pathogen	Parenteral therapy	Oral therapy (step-down therapy or mild infection)
Streptococcus pneumoniae with MICs for penicillin ≤2.0 μg/mL	Preferred: ampicillin (150–200 mg/kg/day every 6 hours) or penicillin (200 000–250 000 U/kg/day every 4–6 h); Alternatives: ceftriaxone (50–100 mg/kg/day every 12–24 hours) (preferred for parenteral outpatient therapy) or cefotaxime (150 mg/kg/day every 8 hours); may also be effective: clindamycin (40 mg/kg/day every 6–8 hours) or vancomycin (40–60 mg/kg/day every 6–8 hours)	Preferred: amoxicillin (90 mg/kg/day in 2 doses or 45 mg/kg/day in 3 doses); Alternatives: second- or third-generation cephalosporin (cefpodoxime, cefuroxime, cefprozil); oral levofloxacin, if susceptible (16–20 mg/kg/day in 2 doses for children 6 months to 5 years old and 8–10 mg/kg/day once daily for children 5 to 16 years old; maximum daily dose, 750 mg) or oral linezolid (30 mg/kg/day in 3 doses for children <12 years old and 20 mg/kg/day in 2 doses for children ≥12 years old)
S. pneumoniae resistant to penicillin, with MICs ≥4.0 μg/mL	Preferred: ceftriaxone (100 mg/kg/day every 12–24 hours); Alternatives: ampicillin (300–400 mg/kg/day every 6 hours), levofloxacin (16–20 mg/kg/day every 12 hours for children 6 months to 5 years old and 8–10 mg/kg/day once daily for children 5–16 years old; maximum daily dose, 750 mg), or linezolid (30 mg/kg/day every 8 hours for children <12 years old and 20 mg/kg/day every 12 hours for children ≥12 years old); may also be effective: clindamycin[a] (40 mg/kg/day every 6–8 hours) or vancomycin (40–60 mg/kg/day every 6–8 hours)	Preferred: oral levofloxacin (16–20 mg/kg/day in 2 doses for children 6 months to 5 years and 8–10 mg/kg/day once daily for children 5–16 years, maximum daily dose, 750 mg), if susceptible, or oral linezolid (30 mg/kg/day in 3 doses for children <12 years and 20 mg/kg/day in 2 doses for children ≥12 years); Alternative: oral clindamycin[a] (30–40 mg/kg/day in 3 doses)
Group A *Streptococcus*	Preferred: intravenous penicillin (100 000–250 000 U/kg/day every 4–6 hours) or ampicillin (200 mg/kg/day every 6 hours); Alternatives: ceftriaxone (50–100 mg/kg/day every 12–24 hours) or cefotaxime (150 mg/kg/day every 8 hours); may also be effective: clindamycin, if susceptible (40 mg/kg/day every 6–8 hours) or vancomycin[b] (40–60 mg/kg/day every 6–8 hours)	Preferred: amoxicillin (50–75 mg/kg/day in 2 doses), or penicillin V (50–75 mg/kg/day in 3 or 4 doses); Alternative: oral clindamycin[a] (40 mg/kg/day in 3 doses)
Stapyhylococcus aureus, methicillin susceptible (combination therapy not well studied)	Preferred: cefazolin (150 mg/kg/day every 8 hours) or semisynthetic penicillin, eg oxacillin (150–200 mg/kg/day every 6–8 hours); Alternatives: clindamycin[a] (40 mg/kg/day every 6–8 hours) or >vancomycin (40–60 mg/kg/day every 6–8 hours)	Preferred: oral cephalexin (75–100 mg/kg/day in 3 or 4 doses); Alternative: oral clindamycin[a] (30–40 mg/kg/day in 3 or 4 doses)
S. aureus, methicillin resistant, susceptible to clindamycin (combination therapy not well-studied)	Preferred: vancomycin (40–60 mg/kg/day every 6–8 hours or dosing to achieve an AUC/MIC ratio of >400) or clindamycin (40 mg/kg/day every 6–8 hours); Alternatives: linezolid (30 mg/kg/day every 8 hours for children <12 years old and 20 mg/kg/day every 12 hours for children ≥12 years old)	Preferred: oral clindamycin (30–40 mg/kg/day in 3 or 4 doses); Alternatives: oral linezolid (30 mg/kg/day in 3 doses for children <12 years and 20 mg/kg/day in 2 doses for children ≥12 years)
S. aureus, methicillin resistant, resistant to clindamycin (combination therapy not well studied)	Preferred: vancomycin (40–60 mg/kg/day every 6-8 hours or dosing to achieve an AUC/MIC ratio of >400); Alternatives: linezolid (30 mg/kg/day every 8 hours for children <12 years old and 20 mg/kg/day every 12 hours for children ≥12 years old)	Preferred: oral linezolid (30 mg/kg/day in 3 doses for children <12 years and 20 mg/kg/day in 2 doses for children ≥12 years old); Alternatives: none; entire treatment course with parenteral therapy may be required

Figure 6: Antibiotic recommendations for specific pathogens from the IDSA CAP 2011 guideline.

Pathogen	Parenteral therapy	Oral therapy (step-down therapy or mild infection)
Haemophilus influenza, typeable (A-F) or nontypeable	Preferred: intravenous ampicillin (150-200 mg/kg/day every 6 hours) if β-lactamase negative, ceftriaxone (50–100 mg/kg/day every 12-24 hours) if β-lactamase producing, or cefotaxime (150 mg/kg/day every 8 hours); Alternatives: intravenous ciprofloxacin (30 mg/kg/day every 12 hours) or intravenous levofloxacin (16-20 mg/kg/day every 12 hours for children 6 months to 5 years old and 8-10 mg/kg/day once daily for children 5 to 16 years old; maximum daily dose, 750 mg)	Preferred: amoxicillin (75-100 mg/kg/day in 3 doses) if β-lactamase negative) or amoxicillin clavulanate (amoxicillin component, 45 mg/kg/day in 3 doses or 90 mg/kg/day in 2 doses) if β-lactamase producing; Alternatives: cefdinir, cefixime, cefpodoxime, or ceftibuten
Mycoplasma pneumoniae	Preferred: intravenous azithromycin (10 mg/kg on days 1 and 2 of therapy; transition to oral therapy if possible); Alternatives: intravenous erythromycin lactobionate (20 mg/kg/day every 6 hours) or levofloxacin (16-20 mg/kg/day every 12 hours; maximum daily dose, 750 mg)	Preferred: azithromycin (10 mg/kg on day 1, followed by 5 mg/kg/day once daily on days 2–5); Alternatives: clarithromycin (15 mg/kg/day in 2 doses) or oral erythromycin (40 mg/kg/day in 4 doses); for children >7 years old, doxycycline (2–4 mg/kg/day in 2 doses; for adolescents with skeletal maturity, levofloxacin (500 mg once daily) or moxifloxacin (400 mg once daily)
Chlamydia trachomatis or *Chlamydophila pneumoniae*	Preferred: intravenous azithromycin (10 mg/kg on days 1 and 2 of therapy; transition to oral therapy if possible); Alternatives: intravenous erythromycin lactobionate (20 mg/kg/day every 6 hours) or levofloxacin (16-20 mg/kg/day in 2 doses for children 6 months to 5 years old and 8-10 mg/kg/day once daily for children 5 to 16 years old; maximum daily dose, 750 mg)	Preferred: azithromycin (10 mg/kg on day 1, followed by 5 mg/kg/day once daily days 2–5); Alternatives: clarithromycin (15 mg/kg/day in 2 doses) or oral erythromycin (40 mg/kg/day in 4 doses); for children >7 years old, doxycycline (2-4 mg/kg/day in 2 doses); for adolescents with skeletal maturity, levofloxacin (500 mg once daily) or moxifloxacin (400 mg once daily)

Doses for oral therapy should not exceed adult doses.

Abbreviations: AUC, area under the time vs. serum concentration curve; MIC, minimum inhibitory concentration.

[a] Clindamycin resistance appears to be increasing in certain geographic areas among *S. pneumoniae* and *S. aureus* infections.

[b] For β-lactam–allergic children.

Figure 7: (cont.) Antibiotic recommendations for specific pathogens from the IDSA CAP 2011 guideline .

12.1.5.4 BTS CAP 2011

- **Amoxicillin is recommended as first choice for oral antibiotic therapy in all children because it is effective against the majority of pathogens which cause CAP in this group, is well tolerated and cheap. Alternatives are co-amoxiclav, cefaclor, erythromycin, azithromycin and clarithromycin. [B]**
- **Macrolide antibiotics may be added at any age if there is no response to first-line empirical therapy. [D]**
- **Macrolide antibiotics should be used if either mycoplasma or chlamydia pneumonia is suspected or in very severe disease. [D]**
- **In pneumonia associated with influenza, co-amoxiclav is recommended. [D]**
- **Antibiotics administered orally are safe and effective for children presenting with even severe CAP and are recommended. [A+]**
- **Intravenous antibiotics should be used in the treatment of pneumonia in children when the child is unable to tolerate oral fluids or absorb oral antibiotics (eg, because of vomiting) or presents with signs of septicaemia or complicated pneumonia. [D]**

12.1.6 Non-antibiotic treatment

12.1.6.1 Summary

The IDSA CAP 2011 guidelines talks about the treatment options for pleural effusions. They should not routinely be drained but need antibiotic therapy in any case (strong recommendation, moderate LoE).
The BTS CAP 2011 guideline mentions several other options: oxygen is recommended if oxygen saturation falls ≤92%, nasogastric tubes are not recommended (weak recommendation) and neither is chest physiotherapy (strong recommendation).

12.1.6.2 BAPCOC 2012

Since the guideline only reports on antibiotics, no information on non-antibiotic treatment is to be found in the guideline.

12.1.6.3 IDSA CAP 2011

The guideline also mentions the possibility of adjunctive surgical therapies for pleural effusions.

Small, uncomplicated parapneumonic effusions should not routinely be drained and can be treated with antibiotic therapy alone. (strong recommendation; moderate-quality evidence).
Moderate parapneumonic effusions associated with respiratory distress, large parapneumonic effusions or documented purulent effusion should be drained. (strong recommendation; moderate-quality evidence)

12.1.6.4 BTS CAP 2011

Patients whose oxygen saturation is ≤92% while breathing air should be treated with oxygen given by nasal cannulae, high flow delivery device, head box or face mask to maintain oxygen saturation >92%. [B]

Nasogastric tubes may compromise breathing and should therefore be avoided in severely ill children and especially in infants with small nasal passages. If use cannot be avoided, the smallest tube should be passed down the smallest nostril. [D]

Chest physiotherapy is not beneficial and should not be performed in children with pneumonia. [A-]

12.1.7 Referrals

12.1.7.1 Summary

All three guidelines mention referral to a hospital in case of respiratory distress or hypoxemia, with ≤92% oxygen saturation as threshold.
The BTS CAP 2011 recommends hospitalization in case of pneumonia complicated by effusion. Both BAPCOC 2012 and IDSA CAP 2011 recommend hospitalization also for certain ages (younger than 3-6 months), for underlying diseases or in cases where adequate care cannot be guaranteed at home.

12.1.7.2 BAPCOC 2012

Children with heightened risk or severely ill presentation should be hospitalized immediately (Grade 1C).

Children with heightened risk are:

- *Severe underlying condition: chronic respiratory illness, cystic fibrosis, immune deficiency, serious psychomotor retardation, metabolic illness, malignancy, pulmonary hypertension due to congenital heart defect*
- *Younger than 3 months*
- *Younger than 1 year and the child drinks less than half of his usual quantity*
- *Insufficient fluid intake and vomiting*
- *Exhaustion (drowsiness, hypotonia)*
- *Infant with respiratory frequency >70/min*
- *Child with respiratory frequency >50/min*
- *Adequate care can not be guaranteed given the social situation*
- *Oxygen saturation ≤92%*

12.1.7.3 IDSA CAP 2011

A child requires hospitalization in the following cases:

- **Children and infants who have moderate to severe CAP, as defined by several factors, including respiratory distress and hypoxemia (sustained saturation of peripheral oxygen [SpO2], 90 % at sea level) (Table 3) should be hospitalized for management, including skilled pediatric nursing care. (strong recommendation; high-quality evidence)**
- **Infants less than 3–6 months of age with suspected bacterial CAP are likely to benefit from hospitalization. (strong recommendation; low-quality evidence)**
- **Children and infants with suspected or documented CAP caused by a pathogen with increased virulence, such as community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA) should be hospitalized. (strong recommendation; low quality evidence)**
- **Children and infants for whom there is concern about careful observation at home or who are unable to comply with therapy or unable to be followed up should be hospitalized. (strong recommendation; low-quality evidence)**

12.1.7.4 BTS CAP 2011

- **Children who have oxygen saturations <92% should be referred to hospital for assessment and management. [B+]**
- **Auscultation revealing absent breath sounds with a dull percussion note should raise the possibility of a pneumonia complicated by effusion and should trigger a referral to hospital. [B-]**

12.2 Evidence tables and conclusions

12.2.1 Antibiotics versus placebo or no treatment for CAP in children

12.2.1.1 AB vs placebo or no treatment in pneumonia with wheeze in children

12.2.1.1.1 Clinical evidence profile

Meta-analysis: Lassi 2014{Lassi, 2014 #219} "Antibiotic therapy versus no antibiotic therapy for children aged two to 59 months with WHO-defined non-severe pneumonia and wheeze"
Inclusion criteria:
RCTs
Children aged two to 59 months with a cough or difficulty in breathing or rapid breathing (as per WHO-classified non-severe pneumonia) and wheeze
Any antibiotic therapy compared with no other medical treatment or placebo
Search strategy:
"We searched CENTRAL (2014, Issue 1), MEDLINE (1946 to March week 3, 2014), EMBASE (January 2010 to March 2014), CINAHL (1981 to March 2014), LILACS (1982 to March 2014), Networked Digital Library of Theses and Dissertations (23 July 2013) and Web of Science (1985 to March 2014)."
Assessment of quality of included trials: not applicable

Table 221

Conclusion authors: "We performed a search for clinical trials published until March 2014 that evaluated this question. We were unable to identify any studies that were conducted on our review question."

12.2.1.1.2 Summary and conclusions

Antibiotic therapy vs placebo or no treatment for pneumonia with wheeze in children
Bibliography: Lassi 2014{Lassi, 2014 #219}

Table 222

In this systematic review, a search was performed for RCTs where any antibiotic was compared to placebo or no treatment for non-severe pneumonia and wheeze in children aged 2-59 months.

No studies that met the inclusion criteria were found.

12.2.1.2 AB vs placebo or no treatment in Mycoplasma pneumoniae infection

12.2.1.2.1 Clinical evidence profile

Meta-analysis: Gardiner 2015{Gardiner, 2015 #223} "Antibiotics for community-acquired lower respiratory tract infections secondary to Mycoplasma pneumoniae in children" Inclusion criteria: Randomised controlled trials (RCTs) comparing antibiotics from the macrolide, tetracycline or quinolone class (i.e. antibiotics that are efficacious for Mycoplasma) versus placebo, or antibiotics from any other class (i.e. medications that are not efficacious for mycoplasma). children under 18 years of age with community- acquired LRTI secondary to M. pneumoniae (diagnosed via antibody titre, culture or PCR) Exclusion criteria: Children with underlying chronic cardiorespiratory illnesses, such as cystic fibrosis, bronchiectasis, immunodeficiency, chronic neonatal lung disease and symptomatic congenital heart disease. Children with non-community-acquired LRTI. Search strategy: "For this 2014 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2014, Issue 3) (accessed 8 July 2014) limited to year published 2011 to 2014, which contains the Acute Respiratory Infection Group's Specialised Register, MEDLINE (1 January 2012 to June week 4, 2014) and EMBASE (1 January 2012 to July 2014). Previously we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2012, Issue 2) (accessed 13 March 2012), which contains the Acute Respiratory Infection Group's Specialised Register, MEDLINE (1966 to February Week 5, 2012) and EMBASE (1980 to March 2012)." Assessment of quality of included trials: yes Other methodological remarks:

Table 223

This meta-analysis found only one RCT for this comparison. This RCT did not distinguish between upper and lower respiratory tract infection. Therefore we did not report this trial.

12.2.1.2.2 Summary and conclusions

AB vs placebo or no treatment for community-acquired lower respiratory tract infections secondary to Mycoplasma pneumoniae in children
Bibliography: Gardiner 2015{Gardiner, 2015 #223}

Table 224

In this meta-analysis, RCTs comparing antibiotics versus placebo or no treatment for CAP secondary to Mycoplasma pneumoniae in children were searched.

This meta-analysis found only one RCT for this comparison. This RCT did not distinguish between upper and lower respiratory tract infection. Therefore we did not report this trial.

12.2.2 Antibiotic A versus antibiotic B for CAP in children

12.2.2.1 Azithromycin vs erythromycin

12.2.2.1.1 Clinical evidence profile

Meta-analysis: Lodha 2013{Lodha, 2013 #218} "Antibiotics for community-acquired pneumonia in children" Inclusion criteria: "Randomised controlled trials (RCTs) comparing antibiotics for CAP in children. We considered only those studies using the case definition of pneumonia (as given by the WHO) or radiologically confirmed pneumonia in this review We included children under 18 years of age with CAP treated in a hospital or community setting. We excluded studies describing pneumonia post-hospitalisation in immunocompromised patients (for example, following surgical procedures) or patients with underlying illnesses like congenital heart disease or those in an immune deficient state. We compared any intervention with antibiotics (administered by intravenous route, intramuscular route or orally) with another antibiotic for the treatment of CAP" Search strategy: "For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 10, part of The Cochrane Library, www.thecochranelibrary.com (accessed 7 November 2012); MEDLINE (September 2009 to October week 4, 2012); EMBASE (September 2009 to November 2012); CINAHL (2009 to November 2012); Web of Science (2009 to November 2012) and LILACS (2009 to November 2012)." Assessment of quality of included trials: yes Other methodological remarks:

Table 225

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Lodha 2013{Lodha, 2013 #218}	**Azithromycin vs erythromycin**	N=3 n=363 (Harris 1998, Kogan 2003,	**Cure rate** The definition of clinical cure is symptomatic and involves clinical recovery by the end of treatment	Crude AR 179/230 vs 100/133 OR 1.22 [0.50, 2.94] NS

		Roord 1996)		
		N=3 n=392 (Harris 1998, Roord 1996, Wubbel 1999)	**Failure rate** The definition of treatment failure is the presence of any of the following: development of chest indrawing, convulsions, drowsiness or inability to drink at any time, respiratory rate above the age-specific cut-off point on completion of treatment, or oxygen saturation of less than 90% (measured by pulse oximetry) after completion of the treatment. Loss to follow-up or withdrawal from the study at any time after recruitment indicated failure in the analysis	Crude AR 6/236 vs 6/156 OR 0.73 [0.18, 2.89] NS
		N=2 n=153 (Roord 1996, Wubbel 1999)	**Side effects** (not specified)	Crude AR 17/84 vs 14/69 OR 0.92 [0.18, 4.73] NS

Table 226

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
Harris 1998{Harris, 1998 #306} Multicentre, USA	219	Children aged 6 months to 16 years with clinical or radiological evidence of pneumonia	15-19 days	PO azithromycin (10 mg/kg/day 1 followed by 5 mg/kg/day for 4 days) or amoxycillin clavulanic acid	RANDOM SEQUENCE GENERATION Unclear risk (Sequence generation not mentioned) ALLOCATION CONCEALMENT

				(40 mg/kg/day) for 10 days or erythromycin (40 mg/kg/day) for 10 days	Low risk BLINDING OF PARTICIPANTS AND PERSONNEL Low risk BLINDING OF OUTCOME ASSESSMENT Low risk SELECTIVE REPORTING Unclear risk (No details) INCOMPLETE OUTCOME DATA (Unclear risk (Intention-to-treat analysis not performed and no details of excluded patients) OTHER BIAS Unclear risk (Funded by Pfizer Inc., New York)
Kogan 2003{Kogan, 2003 #309} Chile	59	Children aged 1 month to 14 years with non-severe atypical pneumonia	14 days	azithromycin 10 mg/kg/day for 3 days, or erythromycin 50 mg/kg/day for 14 days.	RANDOM SEQUENCE GENERATION Unclear risk (Information on sequence generation not mentioned) ALLOCATION CONCEALMENT High risk (Allocated by investigators) BLINDING OF PARTICIPANTS AND PERSONNE High risk (Open-label study) BLINDING OF OUTCOME ASSESSMENT High risk (Open-label study) SELECTIVE REPORTING Low risk INCOMPLETE OUTCOME DATA Low risk OTHER BIAS Unclear risk (Source of funding not

					mentioned)
Roord 1996{Roord, 1996 #307} The Nederlands	85	Children aged 2 months to 16 years with non-severe pneumonia (acute LRTI)	25-30 days	Azithromycin 10 mg/kg/day for 3 days or erythromycin 40 mg/kg/day for 10 days	RANDOM SEQUENCE GENERATION Unclear risk (Information not provided) ALLOCATION CONCEALMENT Unclear risk (Open-label randomised controlled trial. Block randomisation. No mention about allocation concealment) BLINDING OF PARTICIPANTS AND PERSONNEL High risk (Open-label study) BLINDING OF OUTCOME ASSESSMENT High risk (Open-label study) SELECTIVE REPORTING Low risk INCOMPLETE OUTCOME DATA Low risk OTHER BIAS Unclear risk (Funded by Pfizer – BV)
Wubbel 1999{Wubbel, 1999 #308} USA	174	Children aged between 6 months a 16 years with pneumonia	10-37 days	PO azithromycin (10 mg/kg on day 1 followed by 5 mg/kg/day for next 4 days) or coamoxyclavulanic acid 40 mg/kg/day for 10 days in children under 5 years of age; and erythromycin 40 mg/kg/day for 10 days in children over 5 years	RANDOM SEQUENCE GENERATION Unclear risk (Details not mentioned) ALLOCATION CONCEALMENT Unclear risk (Allocation concealment not clearly described) BLINDING OF PARTICIPANTS AND PERSONNEL High risk (Unblinded study) BLINDING OF OUTCOME ASSESSMENT High risk (Unblinded study) SELECTIVE REPORTING

					Low risk INCOMPLETE OUTCOME DATA Low risk OTHER BIAS Unclear risk (Funded by Pfizer Inc).

Table 227

12.2.2.1.2 Summary and conclusions

Azithromycin vs erythromycin for CAP in children			
Bibliography: Lodha 2013{Lodha, 2013 #218}			
Outcomes	**N° of participants (studies) Follow up**	**Results (95%CI)**	**Quality of the evidence (GRADE)**
Cure rate	363 (3 studies)	OR 1.22 [0.50, 2.94] NS	⊕⊕⊖⊖: **LOW** Study quality: -1(open-label; unclear rando) Consistency: ok Directness: ok Imprecision:-1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Failure rate	392 (3 studies)	OR 0.73 [0.18, 2.89] NS	⊕⊕⊖⊖: **LOW** Study quality: -1(open-label; unclear rando) Consistency: ok Directness: ok Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Side effects (not specified)	153 (2 studies)	OR 0.92 [0.18, 4.73] NS	⊕⊕⊖⊖: **LOW** Study quality: -1(open-label; unclear rando, 2/2 studies funded by Pfizer) Consistency: ok Directness: ok Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)

Table 228

In this meta-analysis, a treatment with oral azithromycin was compared to oral erythromycin for CAP in children.

The children in the studies were 1 month to 16 years old and were followed for 14 to30 days. The studies took place in the Netherlands, the US and Chile.

The diagnosis of pneumonia in the studies was based on either clinical or radiological signs.

Azithromycin was given in a dose of 10 mg/kg/day for 3 days (2 studies) or 10 mg/kg/day for 1 day, followed by 5 mg/kg/day for 4 days (2 studies).

Erythromycin was given in a dose of 40 mg/kg/day for 10 days in three studies, and in a dose of 50 mg/kg/day for 14 days in one study.

In children *with community-acquired pneumonia*, a treatment with azithromycin for 3-4 days, compared to erythromycin for 10-14 days, **did not** result in a statistically significant difference in *cure rate, failure rate, or side effects*.
GRADE: LOW quality of evidence

12.2.2.2 Clarithromycin vs erythromycin

12.2.2.2.1 Clinical evidence profile

Meta-analysis: Lodha 2013{Lodha, 2013 #218} "Antibiotics for community-acquired pneumonia in children"
Inclusion criteria:
"Randomised controlled trials (RCTs) comparing antibiotics for CAP in children. We considered only those studies using the case definition of pneumonia (as given by the WHO) or radiologically confirmed pneumonia in this review
We included children under 18 years of age with CAP treated in a hospital or community setting. We excluded studies describing pneumonia post-hospitalisation in immunocompromised patients (for example, following surgical procedures) or patients with underlying illnesses like congenital heart disease or those in an immune deficient state.
We compared any intervention with antibiotics (administered by intravenous route, intramuscular route or orally) with another antibiotic for the treatment of CAP"
Search strategy:
"For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 10, part of The Cochrane Library, www.thecochranelibrary.com (accessed 7 November 2012); MEDLINE (September 2009 to October week 4, 2012); EMBASE (September 2009 to November 2012); CINAHL (2009 to November 2012); Web of Science (2009 to November 2012) and LILACS (2009 to November 2012)."
Assessment of quality of included trials: yes
Other methodological remarks:

Table 229

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Lodha 2013{Lodha, 2013 #218}	**Clarithromycin vs erythromycin**	N=1 n=234 (Block 1995)	**Cure rate** The definition of clinical cure is symptomatic and involves clinical recovery by the end of treatment	Crude AR 104/124 vs 84/110 OR 1.61 [0.84, 3.08] NS
		N=1 n=234 (Block 1995)	**Clinical success rate** (not defined)	Crude AR 121/124 vs 105/110 OR 1.92 [0.45, 8.23] NS

		N=1 n=234 (Block 1995)	**Failure rate** The definition of treatment failure is the presence of any of the following: development of chest indrawing, convulsions, drowsiness or inability to drink at any time, respiratory rate above the age-specific cut-off point on completion of treatment, or oxygen saturation of less than 90% (measured by pulse oximetry) after completion of the treatment. Loss to follow-up or withdrawal from the study at any time after recruitment indicated failure in the analysis	Crude AR 3/124 vs 5/110 OR 0.52 [0.12, 2.23] NS
		N=1 n=226 (Block 1995)	**Relapse rate** defined as children declared 'cured', but developing recurrence of disease at follow-up in a defined period.	Crude AR 1/121 vs 5/105 OR 0.17 [0.02, 1.45] NS
		N=1 n=260	**Adverse events** (not specified)	Crude AR OR 1.07 [0.60, 1.90] NS

Table 230

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
Block 1995{Block, 1995 #310} Multicenter, USA	234	Children between 3 to 16 years of age with radiographically confirmed pneumonia	unclear	PO clarithromycin (15 mg/kg/day) for 10 days or erythromycin 40 mg/kg/day for 10 days	RANDOM SEQUENCE GENERATION Unclear risk (Patients were randomly allocated) ALLOCATION CONCEALMENT

					Unclear risk (Not mentioned clearly. Open-label study. Study drugs were dispensed and compliance was monitored by third party) BLINDING OF PARTICIPANTS AND PERSONNEL High risk (Unblinded study) BLINDING OF OUTCOME ASSESSMENT Low risk SELECTIVE REPORTING Low risk INCOMPLETE OUTCOME DATA Low risk OTHER BIAS Unclear risk (Funded by Abbott Laboratories and role of funding agency not clear)

Table 231

12.2.2.2.2 Summary and conclusions

Clarithromycin vs erythromycin for CAP in children			
Bibliography: Lodha 2013{Lodha, 2013 #218}			
Outcomes	**N° of participants (studies) Follow up**	**Results (95%CI)**	**Quality of the evidence (GRADE)**
Cure rate	234 (1 study)	OR 1.61 [0.84, 3.08] NS	⊕⊕⊕⊖: **MODERATE** Study quality: -1 (unclear rando and allocation, open label) Consistency: na Directness: ok Imprecision: ok
Clinical success rate	234 (1 study)	OR 1.92 [0.45, 8.23] NS	⊕⊕⊖⊖: **LOW** Study quality: -1 (unclear rando and allocation, open label) Consistency: na Directness: ok Imprecision:-1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Failure rate .	234 (1 study)	OR 0.52 [0.12, 2.23] NS	⊕⊕⊖⊖: **LOW** Study quality: -1 (unclear rando and allocation, open label) Consistency: na Directness: ok Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Relapse rate	226 (1 study)	OR 0.17 [0.02, 1.45] NS	⊕⊕⊖⊖: **LOW** Study quality: -1 (unclear rando and allocation, open label) Consistency: na Directness: ok Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Adverse effects (not specified)	260 (1 study)	OR 1.07 [0.60, 1.90] NS	⊕⊕⊕⊖: **MODERATE** Study quality: -1 (unclear rando and allocation, open label) Consistency: na Directness: ok Imprecision: ok

Table 232

In this meta-analysis, a treatment with oral clarithromycin was compared to oral erythromycin for CAP in children.

Only one study was found. It took place in the US. The children were 3 to 16 years old.

The pneumonia was confirmed radiologically.

Clarithromycin was given in a dose of 15 mg/kg/day for 10 days. Erythromycin was given in a dose of 40 mg/kg/day for 10 days.

In children *with community-acquired pneumonia*, a treatment with clarithromycin for 10 days, compared to erythromycin for 10 days, **did not** result in a statistically significant difference in *cure rate, or adverse effects.*
GRADE: MODERATE quality of evidence

In children *with community-acquired pneumonia*, a treatment with clarithromycin for 10 days, compared to erythromycin for 10 days, **did not** result in a statistically significant difference in *clinical success rate, failure rate, or relapse rate.*
GRADE: LOW quality of evidence

12.2.2.3 Azithromycin vs amoxicillin+clavulanate

12.2.2.3.1 Clinical evidence profile

Meta-analysis: Laopaiboon 2015{Laopaiboon, 2015 #224} "Azithromycin for acute lower respiratory tract infections" Inclusion criteria: Randomised controlled trials (RCTs) and quasi-RCTs. Participants of any age or gender, with clinical evidence of acute LRTI such as acute bronchitis, pneumonia and acute exacerbations of chronic bronchitis. Azithromycin of any dose or regimen compared to amoxycillin or amoxycillin/clavulanic acid (amoxyclav). Search strategy: For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL 2014, Issue 10) (accessed 7 November 2014), which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE (June 2011 to October week 5, 2014) and EMBASE (June 2011 to November 2014). Previously we searched CENTRAL (2011, Issue 3), MEDLINE (July 2007 to July week 4, 2011) and Embase.com (July 2007 to August 2011). Assessment of quality of included trials: yes Other methodological remarks: A subgroup analysis in children was done for the outcome "clinical failure". These RCT's were all done in children with pneumonia and they were all given amoxicillin+clavulanate. All the RCTs of this SR for acute bronchitis included adults only. We did not report these.

Table 233

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Laopaiboon 2015{Laopaiboon, 2015 #224}	**azithromycin vs amoxicillin+clavulanate**	N=3 n=384 (Ferwerda 2001, Harris 1998, Wubbel 1999)	SUBGROUP ANALYSIS: pediatric studies **Clinical failure** persistence or deterioration of symptoms, death or relapse assessed at about 10 to 14 days after therapy started	Crude AR: 17/219 vs 13/165 RR 0.93 [0.45, 1.94] NS

Table 234

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
Ferwerda 2001{Ferwerda, 2001 #315} The Netherlands	118	participants aged 3 months to 12 years with community-acquired lower respiratory tract infection	30 days	1. Azithromycin suspension 10 mg/kg/day single dose for 3 days 2. Co-amoxyclav suspension 45/11.25 mg/kg/day 3 times a day for 10 days	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk BLINDING Low risk INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Unclear risk (The study protocol is not available) OTHER BIAS Low risk
Harris 1998{Harris, 1998 #306} Multicentre, USA	195	Participants with community-acquired pneumonia at 23 centres in the US, aged 6 months to 16 years.	6 weeks	1. Azithromycin oral suspension 10 mg/kg (maximum 500 mg) once on day 1, followed by 5 mg/kg (maximum 250 mg) once daily on days 2 to 5 2. Conventional therapy, 3 times daily for 10 days (amoxycillin/clavulanic acid 40 mg/ kg/day for participants aged 6 months to 5 years, and erythromycin estolate 40 mg/kg/ day for	RANDOM SEQUENCE GENERATION Unclear risk (The study did not report how randomisation was done. Quote: “Patients were randomized 2:1 to receive either azithromycin. ...”) ALLOCATION CONCEALMENT High risk (No concealment information was available. Quote: “Patients were randomized 2:1 to receive either azithromycin....”) BLINDING Low risk

				children aged 5 to 16 years)	INCOMPLETE OUTCOME DATA Low SELECTIVE reporting Unclear risk (The study protocol is not available) OTHER BIAS Low risk
Wubbel 1999{Wubbel, 1999 #308} USA	88	aged 6months to 16 years, CAP	37 days	1. Azithromycin oral suspension 10 mg/kg (maximum 500 mg) once on day 1, followed by 5 mg/kg (maximum 250 mg) once daily for 4 days 2. Conventional therapy, 3 times daily for 10 days (amoxycillin/clavulanic acid 40 mg/ kg/day for participants aged 6 months to 5 years, and erythromycin estolate 40 mg/kg/ day for children aged 5 to 16 years)	RANDOM SEQUENCE GENERATION Unclear risk (No information about how the list of randomised therapy assignments was generated) ALLOCATION CONCEALMENT Unclear risk (No information was available) BLINDING High risk (Unblinded treatment) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Unclear risk (The study protocol is not available) OTHER bias Low risk

Table 235

12.2.2.3.2 Summary and conclusions

Azithromycin vs amoxicillin+clavulanate for pneumonia in children			
Bibliography: Laopaiboon 2015{Laopaiboon, 2015 #224			
Outcomes	**N° of participants (studies) Follow up**	**Results (95%CI)**	**Quality of the evidence (GRADE)**
Clinical failure **SUBGROUP: pediatric studies**	384 (3 studies)	RR 0.93 [0.45, 1.94] NS	⨁⊖⊖⊖: **VERY LOW** Study quality: -1 (unclear rando and allocation, no blinding in 1 study) Consistency: ok Directness: -1 (low dose) Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)

Table 236

In this meta-analysis, a treatment with oral azithromycin was compared to oral amoxicillin+clavulanate for CAP.

The diagnosis of pneumonia in the studies was based on either clinical or radiological signs.

A subgroup analysis of pediatric studies was made. The children in these studies were 3 months to 16 years old. The follow-up ranged from 30 days to 6 weeks.

The studies took place in the Netherlands and the US.

Azithromycin was given in a dose 10 mg/kg/day once daily for 3 days in one study, and in a dose of 10 mg/kg once on day 1, followed by 5 mg/kg once daily for 4 days in two studies.

Amoxicillin+clavulanate was given in a dose of 40-45 mg/kg/day (amoxicillin portion), in three doses, for 10 days, which is a lower dose than usually recommended in Belgium (75 mg/kg/day).

In children *with community-acquired pneumonia*, a treatment with azithromycin, compared to amoxicillin+clavulanate for 10 days, **did not** result in a statistically significant difference in *clinical failure.*
GRADE: VERY LOW quality of evidence

12.2.2.4 Azithromycin vs amoxicillin

12.2.2.4.1 Clinical evidence profile

Meta-analysis: Lodha 2013{Lodha, 2013 #218} "Antibiotics for community-acquired pneumonia in children" Inclusion criteria: "Randomised controlled trials (RCTs) comparing antibiotics for CAP in children. We considered only those studies using the case definition of pneumonia (as given by the WHO) or radiologically confirmed pneumonia in this review We included children under 18 years of age with CAP treated in a hospital or community setting. We excluded studies describing pneumonia post-hospitalisation in immunocompromised patients (for example, following surgical procedures) or patients with underlying illnesses like congenital heart disease or those in an immune deficient state. We compared any intervention with antibiotics (administered by intravenous route, intramuscular route or orally) with another antibiotic for the treatment of CAP" Search strategy: "For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 10, part of The Cochrane Library, www.thecochranelibrary.com (accessed 7 November 2012); MEDLINE (September 2009 to October week 4, 2012); EMBASE (September 2009 to November 2012); CINAHL (2009 to November 2012); Web of Science (2009 to November 2012) and LILACS (2009 to November 2012)." Assessment of quality of included trials: yes Other methodological remarks:

Table 237

We did not report the results for the comparison azithromycin vs amoxicillin as the sample size was too small (<40 participants per arm).

12.2.2.4.2 Summary and conclusions

Azithromycin vs amoxicillin for CAP in children
Bibliography: Lodha 2013{Lodha, 2013 #218}

Table 238

In this systematic review, a search was performed for RCTs where a treatment with azithromycin was compared to amoxicillin for CAP in children.

We did not report the results as the sample size was too small (<40 participants per arm).

12.2.2.5 Amoxicillin+clavulanate vs amoxicillin

12.2.2.5.1 Clinical evidence profile

Meta-analysis: Lodha 2013{Lodha, 2013 #218}"Antibiotics for community-acquired pneumonia in children"
Inclusion criteria:
"Randomised controlled trials (RCTs) comparing antibiotics for CAP in children. We considered only those studies using the case definition of pneumonia (as given by the WHO) or radiologically confirmed pneumonia in this review
We included children under 18 years of age with CAP treated in a hospital or community setting. We excluded studies describing pneumonia post-hospitalisation in immunocompromised patients (for example, following surgical procedures) or patients with underlying illnesses like congenital heart disease or those in an immune deficient state.
We compared any intervention with antibiotics (administered by intravenous route, intramuscular route or orally) with another antibiotic for the treatment of CAP"
Search strategy:
"For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 10, part of The Cochrane Library, www.thecochranelibrary.com (accessed 7 November 2012); MEDLINE (September 2009 to October week 4, 2012); EMBASE (September 2009 to November 2012); CINAHL (2009 to November 2012); Web of Science (2009 to November 2012) and LILACS (2009 to November 2012)."
Assessment of quality of included trials: yes
Other methodological remarks:

Table 239

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Lodha 2013{Lodha, 2013 #218}	**Amoxicillin/ clavulanate vs amoxicillin**	N=1 n=100 (Jibril 1989)	**Poor or no response** (not defined)	Crude AR 1/50 vs 10/50 **OR 0.08 [0.01, 0.67]** **SS**
		N=1 n=100 (Jibril 1989)	**Cure rate** The definition of clinical cure is symptomatic and involves clinical recovery by the end	Crude AR 47/50 vs 30/50 **OR 10.44 [2.85, 38.21]** **SS**

			of treatment	
		N=1 n=100 (Jibril 1989)	**Complications** (not specified)	Crude AR 2/50 vs 0/50 OR 5.21 [0.24, 111.24] NS
		N=1 n=100 (Jibril 1989)	**Side effects** (not specified)	Crude AR 2/50 vs 0/50 OR 5.21 [0.24, 111.24] NS

Table 240

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
Jibril 1989{Jibril, 1989 #312}	100	Children aged 2 years to 12 years age, with non-severe pneumonia	Not reported	Amoxycillin and co-amoxyclavulanic acid (250 mg + 62.5 mg or 500 + 125 mg tds) with amoxycillin (250 mg or 500 mg tds) for 10 days	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Unclear risk (Not mentioned) BLINDING OF PARTICIPANTS AND PERSONNEL High risk (Unblinded study) BLINDING OF OUTCOME ASSESSMENT High risk (Unblinded study) SELECTIVE REPORTING Unclear risk (No selective reporting) INCOMPLETE OUTCOME DATA Unclear risk (Incomplete data adequately addressed) OTHER BIAS

					Unclear risk (Source of funding not mentioned)

Table 241

12.2.2.5.2 Summary and conclusions

Amoxicillin/clavulanate vs amoxicillin for CAP in children			
Bibliography: Lodha 2013{Lodha, 2013 #218}			
Outcomes	**N° of participants (studies) Follow up**	**Results (95%CI)**	**Quality of the evidence (GRADE)**
Poor or no response	100 (1 study)	**OR 0.08 [0.01, 0.67]** **SS** **(less cases of poor or no response with amoxicillin/clavulanate)**	⨁⨁⨀⨀: **LOW** Study quality: -1 (unclear allocation, open label) Consistency: na Directness: -1 (dose) Imprecision: ok
Cure rate	100 (1 study)	**OR 10.44 [2.85, 38.21]** **SS** **(increased cure rate with amoxicillin/clavulanate)**	⨁⨀⨀⨀: **VERY LOW** Study quality: -1 (unclear allocation, open label) Consistency: na Directness: -1 (dose) Imprecision:-1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Complications .	100 (1 study)	OR 5.21 [0.24, 111.24] NS	⨁⨀⨀⨀: **VERY LOW** Study quality: -1 (unclear allocation, open label) Consistency: na Directness: -1 (dose) Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Side effects (not specified)	100 (1 study)	OR 5.21 [0.24, 111.24] NS	⨁⨀⨀⨀: **VERY LOW** Study quality: -1 (unclear allocation, open label) Consistency: na Directness: -1 (dose) Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)

Table 242

In this meta-analysis, a treatment with oral amoxicillin+clavulanate was compared to oral amoxicillin alone for CAP in children.

Only one study was found. The children were 2 to 12 years old.

WHO-defined non-severe pneumonia was diagnosed clinically.

Amoxicillin+clavulanate was given in a dose of 250+62.5 mg/day or 500+125 mg/day in three doses for 10 days.

Amoxicillin was given in a dose of 250 or 500 mg/day in three doses for 10 days.

As adjustment of dose according to weight was limited to two options, it is possible that these doses were sub-or supratherapeutic.

In children *with community-acquired non-severe pneumonia*, a treatment with amoxicillin+clavulanate for 10 days, compared to amoxicillin for 10 days, **did** result in a statistically significant **decrease** in *poor or no response.*
GRADE: LOW quality of evidence

In children *with community-acquired non-severe pneumonia*, a treatment with amoxicillin+clavulanate for 10 days, compared to amoxicillin for 10 days, **did** result in a statistically significant **increase** in *cure rate.*
GRADE: VERY LOW quality of evidence

In children *with community-acquired non-severe pneumonia*, a treatment with amoxicillin+clavulanate for 10 days, compared to amoxicillin for 10 days, **did not** result in a statistically significant difference in *complications,* or *side effects.*
GRADE: VERY LOW quality of evidence

12.2.2.6 Co-trimoxazole vs amoxicillin

12.2.2.6.1 Clinical evidence profile

Meta-analysis: Lodha 2013{Lodha, 2013 #218}"Antibiotics for community-acquired pneumonia in children"
Inclusion criteria:
"Randomised controlled trials (RCTs) comparing antibiotics for CAP in children. We considered only those studies using the case definition of pneumonia (as given by the WHO) or radiologically confirmed pneumonia in this review
We included children under 18 years of age with CAP treated in a hospital or community setting. We excluded studies describing pneumonia post-hospitalisation in immunocompromised patients (for example, following surgical procedures) or patients with underlying illnesses like congenital heart disease or those in an immune deficient state.
We compared any intervention with antibiotics (administered by intravenous route, intramuscular route or orally) with another antibiotic for the treatment of CAP"
Search strategy:
"For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 10, part of The Cochrane Library, www.thecochranelibrary.com (accessed 7 November 2012); MEDLINE (September 2009 to October week 4, 2012); EMBASE (September 2009 to November 2012); CINAHL (2009 to November 2012); Web of Science (2009 to November 2012) and LILACS (2009 to November 2012)."
Assessment of quality of included trials: yes
Other methodological remarks:

Table 243

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Lodha 2013{Lodha, 2013 #218}	**Cotrimoxazole vs amoxicillin**	N=3 n=1787 (Awasthi 2008, CATCHUP 2002, Straus 1998)	**Failure rate in non-severe pneumonia** The definition of treatment failure is the presence of any of the following: development of chest indrawing, convulsions, drowsiness or inability to drink at any time, respiratory rate above the age-specific cut-off point on completion of treatment, or oxygen saturation of less than 90% (measured by	Crude AR 166/948 vs 1362/839 OR 1.18 [0.91, 1.51] NS

			pulse oximetry) after completion of the treatment. Loss to follow-up or withdrawal from the study at any time after recruitment indicated failure in the analysis	
		N=2 n=2050 (CATCHUP 2002, Straus 1998)	**Death rate**	Crude AR 2/1132 vs 0/918 OR 2.08 [0.22, 20.06] NS
		N=2 n=1732 (Awasthi 2008, CATCHUP 2002)	**Cure rate** The definition of clinical cure is symptomatic and involves clinical recovery by the end of treatment	Crude AR 720/872 vs 724/860 OR 1.03 [0.56, 1.89] NS

Table 244

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
Awasthi 2008{Awasthi, 2008 #311}	37	Children of either sex, between 2 months to 59 months with WHO-defined non-severe pneumonia	15 days	Eligible children were randomised to receive oral dispersible scored amoxycillin (125 mg per tablet) given thrice a day (tds) for 3 days or co-trimoxazole (20 mg trimethoprim per tablet) given twice a day (bd) for 5 days. Doses of amoxycillin were between 31 to 51	RANDOM SEQUENCE GENERATION Low risk Allocation concealmen Low risk BLINDING OF PARTICIPANTS AND PERSONNEL Unclear risk (Open-label randomised controlled trial) BLINDING OF OUTCOME ASSESSMENT High risk (Open-label randomised

				mg/kg/day and trimethoprim 7 to 11 mg/kg/day	controlled trial) SELECTIVE REPORTING Low risk INCOMPLETE OUTCOME DATA Low risk OTHER BIAS Low risk
CATCHUP 2002{CATCHUP Authors, 2002 #313}	1459	Children 2 to 59 months with non-severe pneumonia	7 days	PO amoxycillin 25 mg/kg/day for 5 days or co-trimoxazole 20/4 mg/kg/day for 5 days	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk BLINDING OF PARTICIPANTS AND PERSONNEL Low risk BLINDING OF OUTCOME ASSESSMENT Low risk SELECTIVE REPORTING Low risk INCOMPLETE OUTCOME DATA Low risk OTHER BIAS Low risk
Straus 1998{Straus, 1998 #314}	595	Children aged 2 months to 59 months with non-severe pneumonia	Not found	PO co-trimoxazole 20 mg/kg/day for 5 days or amoxycillin 45 mg/kg/day for 5 days	RANDOM SEQUENCE GENERATION Unclear risk (Sequence generation not mentioned) ALLOCATION CONCEALMENT Unclear risk (Drug allotment was concealed from participants. Details not clear) BLINDING OF PARTICIPANTS AND PERSONNEL High risk (Open-label study. Details

					not included) BLINDING OF OUTCOME ASSESSMENT High risk (Open-label study. Details not included) SELECTIVE REPORTING Low risk INCOMPLETE OUTCOME DATA Low risk OTHER BIAS Unclear risk (Source of funding not mentioned)

Table 245

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Rajesh 2013{Rajesh, 2013 #216} Design: RCT OL, PG Duration of follow-up: 5 days	n= 204 Age: 2 m to 1 y: 34.80% 1 y to 3 y: 40.20% 3to 5 y: 25% <u>Inclusion</u> All children in the age group of 2 months to 5 years, with WHO defined features of non-severe pneumonia, attending outpatient department of a large tertiary care hospital <u>Exclusion</u> WHO signs of very severe pneumonia, history of having received antibiotics for any illness anywhere 48 h before coming. Previous history of wheezing including	amoxicillin (40 mg/kg/day in 3 divided doses) Vs Cotrimoxazole (8 mg/kg/day of trimethoprim in 2 divided doses)	Efficacy		RANDO: Unclear ("Patients were randomly assigned into study and control group by using standard randomization procedure") ALLOCATION CONC: Unclear (not stated) BLINDING : Participants: unclear Personnel: unclear Assessors: unclear Remarks on blinding method: (not reported; probably not done) FOLLOW-UP: Not described ITT: Not stated SELECTIVE REPORTING: no Other important methodological remarks Methodological information very sparse
			Clinical cure Defined as: respiratory rate of less than 50 per min between 2 months to 1 year of age and less than 40 per min between 1 yr to 5 yr of age and absence of any of clinical signs of treatment failure given below.	Amoxicillin: 91/99 Cotrimoxazole: 64/105 **SS** **P: 0.0001** **More clinical cure with amoxicillin**	
			Treatment failure • Occurrence of any signs of WHO defined severe pneumonia • Increase in respiratory rate more than 10 breaths per min above base line and • Respiratory rate more than 70 per min for children 2 months to 1 year of age or more than 60 per min for children between 1 year and 5 year of age.	Amoxicillin: 8/99 Cotrimoxazole: 41/105 **SS** **P: 0.0001** **Less treatment failure with amoxicillin**	
			Safety		
			Not reported		

	asthma or children who have been prescribed corticosteroids along with bronchodilators, children with congenital heart disease, Immunodeficiency (congenital or acquired) including suspected or confirmed HIV infection, any chronic illness including chronic infections like tuberculosis, malignancy, acute/chronic organ disorder, known allergy/hypersensitivity to penicillin/Sulpha.				Sponsor: Indian Council of Medical Research SRF Project

Table 246

12.2.2.6.2 Summary and conclusions

Cotrimoxazole vs amoxicillin for CAP in children			
Bibliography: Lodha 2013{Lodha, 2013 #218}			
Outcomes	**N° of participants (studies) Follow up**	**Results (95%CI)**	**Quality of the evidence (GRADE)**
Failure rate in non-severe pneumonia	1787 (3 studies)	OR 1.18 [0.91, 1.51] NS	⊕⊕⊖⊖: **LOW** Study quality: -1 (open-label; unclear rando and allocation concealment) Consistency: ok Directness: -1(low dose) Imprecision: ok
Death rate	2050 (2 studies)	OR 2.08 [0.22, 20.06] NS	⊕⊖⊖⊖:**VERY LOW** Study quality: -1 (open label) Consistency: ok Directness: -1(low dose) Imprecision:-1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Cure rate	1732 (2 studies)	OR 1.03 [0.56, 1.89] NS	⊕⊕⊖⊖: **LOW** Study quality: -1 (open-label; unclear rando and allocation concealment) Consistency: ok Directness: -1(low dose) Imprecision: ok

Table 247

In this meta-analysis, a treatment with oral cotrimoxazole was compared to oral amoxicillin for CAP in children.

The children in the studies were aged 2 to 59 months. All had WHO-defined non-severe pneumonia.

The diagnosis of pneumonia was based on clinical signs.

The trimethoprim portion of cotrimoxazole was given in a dose ranging from 7-20 mg/kg/day for 5 days, which is a lower dose than usually recommended in Belgium.

Amoxicillin was given in a dose ranging from 25-50 mg/kg/day for 3-5 days, which is a lower dose than usually recommended in Belgium (75-100mg/kg/day).

In children *with non-severe community-acquired pneumonia*, a treatment with cotrimoxazole for 5 days, compared to amoxicillin for 3-5 days, **did not** result in a statistically significant difference in *failure rate* or *cure rate.*
GRADE: LOW quality of evidence

In children *with non-severe community-acquired pneumonia*, a treatment with cotrimoxazole for 5 days, compared to amoxicillin for 3-5 days, **did not** result in a statistically significant difference in *death rate.*
GRADE: VERY LOW quality of evidence

An additional RCT (Rajesh 2013{Rajesh, 2013 #216}), published after the end date of the search of this meta-analysis, was found.

It included 204 children aged 2 months to 5 years. Amoxicillin was given in a dose of 40 mg/kg/day in three doses (lower dose than usually recommended in Belgium), cotrimoxazole was given in a dose of 8 mg/kg/day (trimethoprim portion) in two doses.

In this study, there was a statistically significant **increase** in *clinical cure* and a statistically significant **decrease** in *treatment failure* with amoxicillin, compared to cotrimoxazole.

However, as it was an open-label trial with very poor reporting (unclear randomization, allocation concealment, follow-up, no confidence intervals calculated), our confidence in those results are severely limited.

12.2.3 Antibiotic A versus antibiotic B for Mycoplasma pneumonia

12.2.3.1 Clinical evidence profile

Meta-analysis: Gardiner 2015{Gardiner, 2015 #223} "Antibiotics for community-acquired lower respiratory tract infections secondary to Mycoplasma pneumoniae in children" Inclusion criteria: Randomised controlled trials (RCTs) comparing antibiotics from the macrolide, tetracycline or quinolone class (i.e. antibiotics that are efficacious for Mycoplasma) versus placebo, or antibiotics from any other class (i.e. medications that are not efficacious for mycoplasma). children under 18 years of age with community- acquired LRTI secondary to M. pneumoniae (diagnosed via antibody titre, culture or PCR) Exclusion criteria: Children with underlying chronic cardiorespiratory illnesses, such as cystic fibrosis, bronchiectasis, immunodeficiency, chronic neonatal lung disease and symptomatic congenital heart disease. Children with non-community-acquired LRTI. Search strategy: "For this 2014 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2014, Issue 3) (accessed 8 July 2014) limited to year published 2011 to 2014, which contains the Acute Respiratory Infection Group's Specialised Register, MEDLINE (1 January 2012 to June week 4, 2014) and EMBASE (1 January 2012 to July 2014). Previously we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2012, Issue 2) (accessed 13 March 2012), which contains the Acute Respiratory Infection Group's Specialised Register, MEDLINE (1966 to February Week 5, 2012) and EMBASE (1980 to March 2012)." Assessment of quality of included trials: yes Other methodological remarks:

Table 248

Author's conclusions:

"There is insufficient evidence to draw any specific conclusions about the efficacy of antibiotics for this condition in children (although one trial suggests macrolides may be efficacious in some children with LRTI secondary to Mycoplasma). The use of antibiotics has to be balanced with possible adverse events. There is still a need for high quality, double-blinded RCTs to assess the efficacy and safety of antibiotics for LRTI secondary to M. pneumoniae in children"

Remarks:

“This review failed to find any randomised controlled trials (RCTs) that specifically looked at the effectiveness of antibiotics for lower respiratory tract infection (LRTI) secondary to M. pneumoniae.”

“From the other studies, in the subgroup of children with LRTI secondary to M. pneumoniae the intervention was a macrolide antibiotic versus a non-macrolide antibiotic, usually amoxycillin-clavulanate. This subgroup identified only 38 children with M. pneumoniae infection and there were insufficient data to analyse the efficacy of macrolide antibiotics in this group. Adverse events were common: reported in 11% to 67% of children. The majority of adverse events related to the gastrointestinal tract (diarrhoea, vomiting, abdominal pain, nausea, anorexia) and where reported were more common in younger children (under five years of age).” (difference between groups not reported)

12.2.3.2 Summary and conclusions

Antibiotics from the macrolide, tetracycline or quinolone class vs antibiotics from any other class for community-acquired lower respiratory tract infections secondary to Mycoplasma pneumoniae in children
Bibliography: Gardiner 2015{Gardiner, 2015 #223}

Table 249

In this meta-analysis, RCTs comparing antibiotics from the macrolide, tetracycline or quinolone class (i.e. antibiotics that are efficacious for Mycoplasma) versus placebo, or antibiotics from any other class (i.e. medications that are not efficacious for mycoplasma), were searched.

It failed to find any randomised controlled trials (RCTs) that specifically looked at the effectiveness of antibiotics for lower respiratory tract infection (LRTI) secondary to M. pneumoniae.

12.2.4 Shorter versus longer duration of same antibiotic for CAP in children

12.2.4.1 3 days vs 5 days amoxicillin

12.2.4.1.1 Clinical evidence profile

Meta-analysis: Haider 2008{Haider Batool, 2008 #221} "Short-course versus long-course antibiotic therapy for non-severe community-acquired pneumonia in children aged 2 months to 59 months"
Inclusion criteria:
RCTs evaluating the efficacy of short-course versus long-course therapy using the same antibiotic for non-severe CAP in children.
children aged 2 months to 59 months with nonsevere CAP.
We excluded studies including children with severe or very severe CAP (defined on the basis of chest in-drawing, inability to drink, convulsions, abnormal sleepiness or difficulty waking), any chronic illness, or those who had received antibiotics in the past 48 hours.
Search strategy:
"We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2010, Issue 3) which contains the Cochrane Acute Respiratory Infections Group's Specialised Register and the Database of Abstracts of Reviews of Effects, MEDLINE (OVID) (January 1966 to August Week 4, 2010), EMBASE (Embase.com) (1974 to August 2010) and LILACS (1982 to August 2010)."
Assessment of quality of included trials: yes
Other methodological remarks:

Table 250

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Haider 2008{Haider Batool, 2008 #221	**3 days vs 5 days amoxicillin**	N=2 n=4012 (Agarwal 2004, MASCOT 2002)	**Clinical cure** Return of respiratory rate to the normal age-specific range	Crude AR: 1783/2013 vs 1794/1999 RR: 0.99 (0.97 to 1.01) NS

		N=2 n=4012 (Agarwal 2004, MASCOT 2002)	**Treatment failure** development of chest in-drawing, convulsions, drowsiness, or inability to drink at any time; respiratory rate above the age-specific cut-off on completion of treatment; or oxygen saturation, measured by pulse oximetry, of less than 90% after completion of the treatment; loss to follow up or withdrawal from the study.	Crude AR: 230/2013 vs 205/1999 RR: 1.11 (0.94 to 1.33) NS
		N=2 n=3577 (Agarwal 2004, MASCOT 2002)	**Relapse rate** development of any sign of CAP within seven days after fast breathing had returned to normal.	Crude AR: 44/1783 vs 42/1794 RR: 1.05 (0.69 to 1.60) NS

Table 251

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
Agarwal 2004{Agarwal, 2004 #316}	2188	Children aged 2 to 59 months; clinically diagnosed pneumonia	14 days	dispersible tablets of amoxicillin (125 mg) for the first 3 days. Amoxicillin was given 3 times daily dissolved in 5 ml of water. Effective dose per kilogram body weight varied from 31 to 54 mg/kg/day. For the next 2 days participants received either amoxicillin or placebo	Adequate sequence generation? Yes Allocation concealment? Yes Blinding? Unclear (Quote: “Double blind”) Incomplete outcome data addressed? Yes Free of selective reporting? Yes Free of other bias? Yes
MASCOT 2002{MASCOT	2000	Children aged 2 to 59 months with clinically diagnosed pneumonia	14 days	15 mg/kg oral amoxicillin every 8 hours for 3 days. In	Adequate sequence generation? Yes

Authors, 2002 #317}				the next 2 days, children were given either active medicine or placebo	Allocation concealment? Yes Blinding? Yes Incomplete outcome data addressed? Yes Free of selective reporting? Yes Free of other bias? Yes

Table 252

Author's conclusions:

"The evidence of this review suggests that a short course (three days) of antibiotic therapy is as effective as a longer treatment (five days) for non-severe CAP in children under five years of age. However, there is a need for more well-designed RCTs to support our review findings"

12.2.4.1.2 Summary and conclusions

3 days vs 5 days amoxicillin for non-severe CAP in children aged 2 -59 months			
Bibliography: Haider 2008{Haider Batool, 2008 #221}			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Clinical cure	4012 (2 studies)	RR: 0.99 (0.97 to 1.01) NS	⊕⊕⊕⊖: **MODERATE** Study quality: ok Consistency: ok Directness: -1 (low dose) Imprecision: ok
Treatment failure	4012 (2 studies)	RR: 1.11 (0.94 to 1.33) NS	⊕⊕⊕⊖: **MODERATE** Study quality: ok Consistency: ok Directness: -1 (low dose) Imprecision: ok
Relapse rate	3577 (2 studies)	RR: 1.05 (0.69 to 1.60) NS	⊕⊕⊕⊖: **MODERATE** Study quality: ok Consistency: ok Directness: -1 (low dose) Imprecision: ok

Table 253

In this meta-analysis, a treatment with oral amoxicillin for 3 days was compared with 5 days of treatment with amoxicillin in children with non-severe CAP.

The children included in the studies were aged between 2 and 59 months.

The diagnosis of pneumonia in the studies was based on clinical signs.

The dose of amoxicillin was 31-54 mg/kg/day. This dose is lower than what is usually recommended in Belgium.

In children *with non-severe CAP*, a treatment with 3 days of amoxicillin, compared to 5 days, **did not** result in a statistically significant difference in *clinical cure, treatment failure* or *relapse rate*.
GRADE: MODERATE quality of evidence

12.2.4.2 5 days amoxicillin vs 10 days amoxicillin

12.2.4.2.1 Clinical evidence profile

"Short-course antibiotic treatment for community-acquired alveolar pneumonia in ambulatory children: a double-blind, randomized, placebo-controlled trial"

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Greenberg 2014{Greenberg, 2014 #222} Design: RCT DB; PG Duration of follow-up: 30 days	n= 140 (5 days= 56 10 days= 72 3 days:=12) Mean age: 27 months <u>Inclusion</u> age 6–59 months; radiologically confirmed community-acquired alveolar pneumonia; temperature ≥38.5°C; peripheral white blood cell count ≥15,000/mm3; status permitting outpatient treatment.	Amoxicillin (80 mg/kg/d; divided into 3 daily doses) for 5 days Vs Amoxicillin (80 mg/kg/d; divided into 3 daily doses) for 10 days (we did not report third arm (3 days of treatment), see "Other important	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Lost-to follow-up: 0% Drop-out and Exclusions: 19 % • Described: yes • Balanced across groups: yes ITT: No ("evaluable subjects" did not comprise all randomized subjects)
			Treatment failure within 30 days(PO) Need for a rescue treatment or hospitalisation	5 days: 0/42 10 days: 0/56	
			Duration of fever and symptoms	"similar between groups" No numerical data See Figure 8 and Figure 9below	
			Safety		
			Adverse events not assessed		

	Exclusion Any of the following: (1) antimicrobial drug received within ≤14 days; (2) need of parenteral treatment (ie, impaired perfusion, hypotension, oliguria, lactic acidosis, impaired consciousness, presence of pleural effusion, vomiting); (3) oxygen saturation <94%; (4) known impaired immunity; (5) ≥2 pneumonia episodes in last year; (6) chronic illness (ie, cystic fibrosis or cerebral palsy) potentially influencing current illness (however, asthma was not considered per se as an exclusion criterion); (7) presence of an	methodological remarks")		SELECTIVE REPORTING: Yes (No numerical data for secondary outcomes) Other important methodological remarks "We aimed initially at comparing 3- to 10-day treatment courses (Stage 1). Overall, 25 children were enrolled: 12 in the 3-day arm and 13 in the 10-day arm . Seven participants dropped out from the study: 2 in the 3-day arm and 5 in the 10-day arm. One child in the 10-day arm had to be hospitalized due to treatment failure before day 3 of the treatment randomization. Four patients had treatment failure between days 4 and 10. All belonged to the 3-day arm. Following observed failure in Stage 1, the study was temporarily stopped and the analysis performed showed that all failures occurred within the 3-day arm. Stage 1 was discontinued and replaced by

	additional infection necessitating a longer or different antibiotic treatment; (8) unavailability for follow up; (9) known β-lactam hypersensitivity and (10) known allergy to soy milk.			Stage 2. In Stage 2, 115 children were enrolled: 56 in the 5-day regimens and 59 in the 10-day regimens" "All analyses were performed after a "run-in period" of 3 days in Stage 1 and 5 days in Stage 2. Thus, study failures were calculated only after 3 days of treatment in Stage 1 and 5 days of treatment in Stage 2." Sponsor: "The authors have no funding or conflicts of interest to disclose"

Table 254

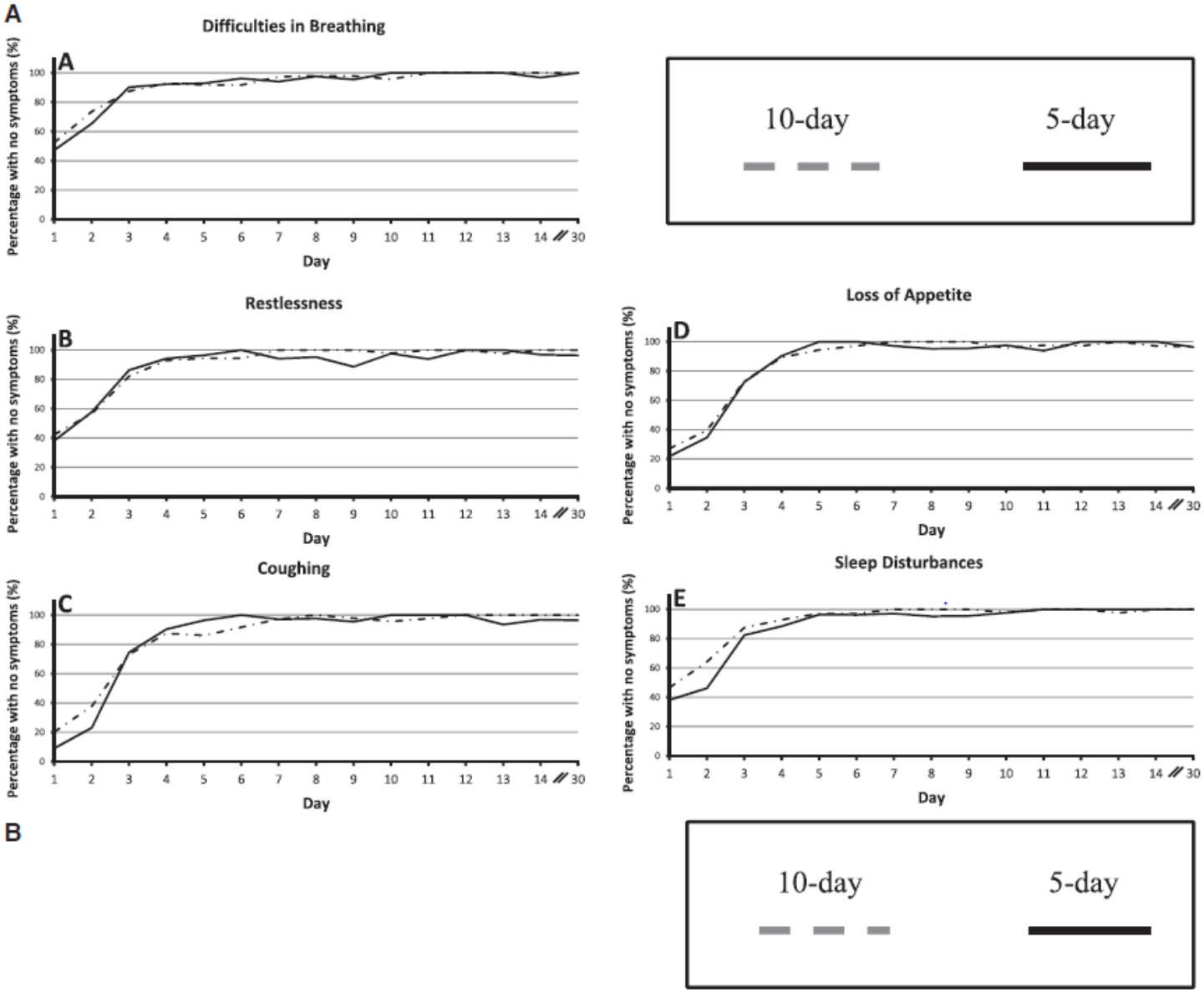

A
Difficulties in Breathing
A
Percentage with no symptoms (%)
Day
10-day
5-day
Restlessness
B
Loss of Appetite
D
Coughing
C
Sleep Disturbances
E
B

Figure 8: results of clinical outcomes in Greenberg 2014

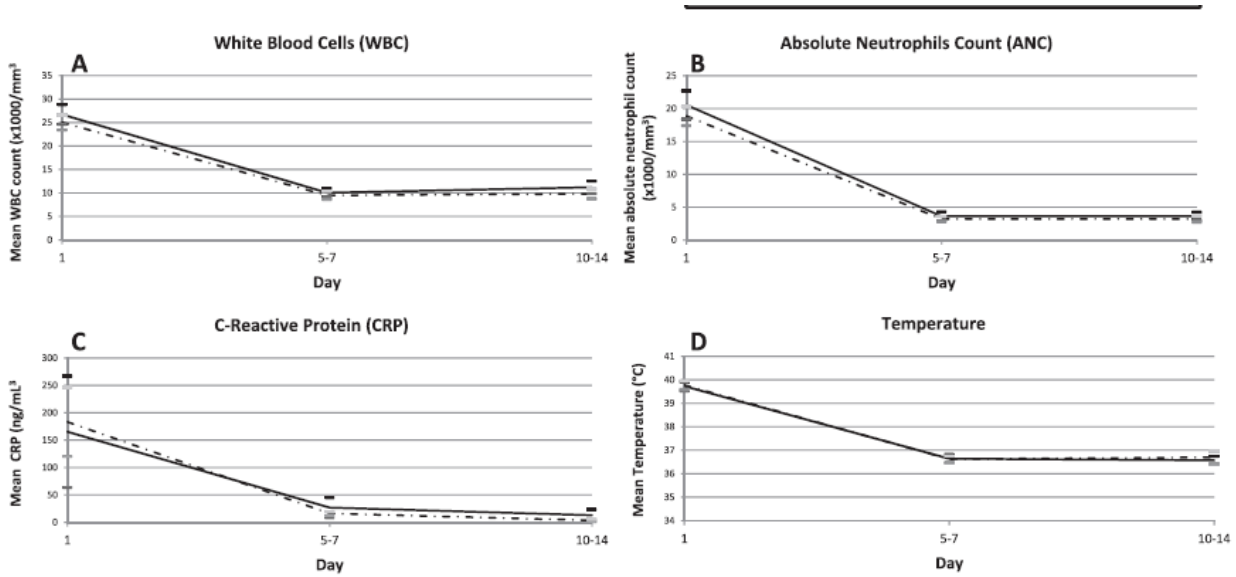


FIGURE 3. A) Comparison of clinical symptoms from day 1 to day 30 between the 5-day and the 10-day treatment groups. The number of children tested for the 10-day treatment group was 59 and for the 5-day treatment groups 55; B). Comparison of selected laboratory parameters and temperature measurements from day 1 to day 30 between the 5-day and the 10-day treatment groups. Number of children tested at each visit for the 10-day and 5-day—WBC and ANC: days 5–7, 56 and 42 and days 10–14, 42 and 32; CRP: days 5–7, 52 and 41 and days 10–14: 37 and 32 and temperature: days 5–7, 44 and 32 and days 10–14, 25 and 29, respectively.

Figure 9 Results of laboratory outcomes in Greenberg 2014

12.2.4.2.2 Summary and conclusions

5 days versus 10 days amoxicillin for CAP in children			
Bibliography: Greenberg 2014{Greenberg, 2014 #222}			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Treatment failure within 30 days(PO)	98 (1 study)	0 vs 0	⨁⨁⨁⨀: **MODERATE** Study quality: -1 (no ITT, high attrition) Consistency: na Directness: ok Imprecision: na

Table 255

In this trial, a treatment with 5 days of oral amoxicillin was compared with a 10-day treatment for CAP in children.

The children were aged 6 to 59 months and were followed for 30 days.

The diagnosis of pneumonia was radiologically confirmed.

Amoxicillin was given in a dose of 80 mg/kg/day in 3 doses.

The analyses of this trial were not performed according to the intention-to-treat principle, and there was a rather high attrition rate (19%). Therefore our confidence in the results is limited.

In children *with CAP*, a treatment with amoxicillin for 5 days, compared to 10 days, **did not** result in a difference in *treatment failure within 30 days*.
GRADE: MODERATE

12.2.4.3 3 days vs 5 days co-trimoxazole

12.2.4.3.1 Clinical evidence profile

Meta-analysis: Haider 2008{Haider Batool, 2008 #221} "Short-course versus long-course antibiotic therapy for non-severe community-acquired pneumonia in children aged 2 months to 59 months"
Inclusion criteria:
RCTs evaluating the efficacy of short-course versus long-course therapy using the same antibiotic for non-severe CAP in children.
children aged 2 months to 59 months with nonsevere CAP.
We excluded studies including children with severe or very severe CAP (defined on the basis of chest in-drawing, inability to drink, convulsions, abnormal sleepiness or difficulty waking), any chronic illness, or those who had received antibiotics in the past 48 hours.
Search strategy:
"We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2010, Issue 3) which contains the Cochrane Acute Respiratory Infections Group's Specialised Register and the Database of Abstracts of Reviews of Effects, MEDLINE (OVID) (January 1966 to August Week 4, 2010), EMBASE (Embase.com) (1974 to August 2010) and LILACS (1982 to August 2010)."
Assessment of quality of included trials: yes

Table 256

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Haider 2008{Haider Batool, 2008 #221}	**3 days vs 5 days cotrimoxazole**	N=1 n=1589 (Kartasasmita 2002)	**Clinical cure** Return of respiratory rate to the normal age-specific range	Crude AR 799/879 vs 790/872 RR 1.00 (0.97 to 1.03) NS
		N=1 n=1589 (Kartasasmita 2002)	**Treatment failure** development of chest in-drawing, convulsions, drowsiness, or inability to drink at any time; respiratory rate above the age-specific cut-off on completion of treatment; or oxygen saturation, measured by pulse oximetry, of less than 90%	Crude AR 80/879 vs 82/872 RR 0.97 (0.72 to 1.30) NS

			after completion of the treatment; loss to follow up or withdrawal from the study.	
		N=2 n=1892 (Kartasasmita 2002, Lupison 1999)	**Relapse rate** development of any sign of CAP within seven days after fast breathing had returned to normal.	Crude AR 66/952 vs 58/940 RR 1.12 (0.80 to 1.58) NS

Table 257

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
Kartasasmita 2002{Kartasasmita, 2004 #327}	2022	Children aged 2 to 59 months with non-severe CAP	Not found	oral cotrimoxazole either for 3 days or for 5 days. Effective dose per kilogram body weight varied from 30 to 45 mg/kg/day	Adequate sequence generation? Unclear (Quote: “Randomised” Comment: insufficient information to permit judgement) Allocation concealment? Unclear (Insufficient information to permit judgement) Blinding? Unclear (Quote: “double-blind” Comment: insufficient information to permit judgement) Incomplete outcome data addressed? Unclear (Insufficient information to permit judgement) Free of selective reporting? Unclear (Insufficient information to permit judgement)

					Free of other bias? Unclear (Insufficient information to permit judgement)
Lupison 1999{Lupison, 1999 #326}	Not found	Children of 2 to 59 months	Not found	Children > 12 month old were given cotrimoxazole 80 mg twice daily and children 2 to 12 months old were given cotrimoxazole 40 mg twice daily	Adequate sequence generation? Yes Allocation concealment? Yes Blinding? Yes Incomplete outcome data addressed? Yes Free of selective reporting? Yes Free of other bias? Yes

Table 258

Author's conclusions:

"The evidence of this review suggests that a short course (three days) of antibiotic therapy is as effective as a longer treatment (five days) for non-severe CAP in children under five years of age. However, there is a need for more well-designed RCTs to support our review findings"

12.2.4.3.2 Summary and conclusions

3 days vs 5 days cotrimoxazole for non-severe CAP in children aged 2 -59 months			
Bibliography: Haider 2008{Haider Batool, 2008 #221}			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Clinical cure	1589 (1 study)	RR 1.00 (0.97 to 1.03) NS	⨁⨁⨁⊖: **MODERATE** Study quality: -1 (unclear rando, aloocation concealment) Consistency: na Directness: ok Imprecision: ok
Treatment failure	1589 (1 study)	RR 0.97 (0.72 to 1.30) NS	⨁⨁⨁⊖: **MODERATE** Study quality: -1 (unclear rando, aloocation concealment) Consistency: na Directness: ok Imprecision: ok
Relapse rate	1892 (2 studies)	RR 1.12 (0.80 to 1.58) NS	⨁⨁⨁⊖: **MODERATE** Study quality: -1 (unclear rando, aloocation concealment) Consistency: ok Directness: ok Imprecision: ok

Table 259

In this meta-analysis, a treatment with oral cotrimoxazole for 3 days was compared with 5 days of treatment with cotrimoxazole in children with non-severe CAP.

The children included in the studies were aged between 2 and 59 months.

It is not clear how the diagnosis of pneumonia was established.

The dose of cotrimoxazole was 30-45 mg/kg/day in one study and 80 mg/day for children 2-12 months and 160 mg/day for children >12 months in another study.

In children *with non-severe CAP*, a treatment with 3 days of cotrimoxazole, compared to 5days, **did not** result in a statistically significant difference in *clinical cure, treatment failure* or *relapse rate*.
GRADE: MODERATE quality of evidence

12.2.5 Different dose regimens of same antibiotic for CAP

12.2.5.1 Double dose co-trimoxazole vs standard dose

12.2.5.1.1 Clinical evidence profile

Systematic review: Lassi 2014{Lassi, 2014 #220} "Systematic review on antibiotic therapy for pneumonia in children between 2 and 59 months of age" Inclusion criteria: "RCTs that assessed the route, dose, combination and duration of antibiotics in the management of WHO defined non-severe/severe/very severe CAP. Only those studies that used standard WHO definition and/or classification for CAP9 were included, irrespective of language or publication status. Study participants included children of 2–59 months of age with CAP. The review included studies that compared any intervention that either examined a single drug or a combination; or a different dose, duration and route of the same drug. We included studies that analysed outcomes including clinical cure rate (ie, symptomatic and clinical recovery by end of treatment), treatment failure (ie, developing worsening clinical signs at any point in time; a respiratory rate (RR) exceeding age-specific cut-off and/or <90% oxygen saturation on pulse oximetry after completion of treatment), relapse rate (developing disease recurrence after being declared 'cured'), change in antibiotic required and mortality rate. We grouped and analysed the outcomes according to very severe, severe and non-severe pneumonia. " Search strategy: "The electronic search was last performed on 15 March 2013 on Medline, Cochrane Library, Pubmed, Google Scholar with the following search terms: (('Pneumonia' OR 'very severe pneumonia' OR 'severe pneumonia' OR 'non-severe pneumonia' OR 'acute respiratory illness' OR 'Community acquired pneumonia') AND ('child*' OR 'infant' OR 'preschool*' OR 'schoolchild' OR 'school age' OR 'preschool' OR 'kid*' OR 'toddler*') AND ('treatment' OR 'anti-infective agent' OR 'anti-bacterial agents' OR 'antibiotic' OR 'management')). The bibliographies of all relevant RCTs and reviews were cross-checked, and clinical trial registries were browsed for any on-going trials." Assessment of quality of included trials: yes, in supplementary material Other methodological remarks: no meta-analysis for this comparison

Table 260

Ref	Comparison	N/n	Outcomes	Result (95% CI)

Lassi 2014{Lassi, 2014 #220}	Cotrimoxazole 8/40 mg/kg/day vs 16/80 mg/kg/day	N=1 n=1143 randomized, 1134 analysed	**Treatment failure** *ie, developing worsening clinical signs at any point in time; a respiratory rate (RR) exceeding age-specific cut-off and/or <90% oxygen saturation on pulse oximetry after completion of treatment*	Crude AR: 112/578 vs 188/556 RR 1.10 (0.87 to 1.37) NS

Table 261

Study ID/ Year/ Country	Type of study	Participants	Study location	Intervened by	Case definition	Recovery from disease	Antibiotic therapy		Outcome
							Group 1	Group 2	
Rasmussen 2005 [40] (COMET) Pakistan	RCT	1143 Children 2–59 months WHO defined pneumonia	October 1995 and July 1996 Pakistan	4 mg trimethoprim plus 20 mg sulfamethoxazole/kg of body weight vs. 8 mg trimethoprim plus 40 mg sulfamethoxazole/kg of body weight orally BID for 5 days	Included: Children 2–59 months with cough and difficult or tachypnea according to standard WHO acute respiratory infection (ARI) algorithm Excluded: Children with severe pneumonia, very severe disease, stridor, acute non-pulmonary or underlying chronic illness, history of Cotrimoxazole allergy, use of antimicrobials in the past 48 hours, or refusal of participation	Treatment failure	4 mg trimethoprim + 20 mg sulfamethoxazole/kg of body weight BID for 5 days (n= 578)	8 mg trimethoprim plus 40 mg sulfamethoxazole/kg of body weight orally twice-daily for 5 days (n= 556)	Cure rate Treatment failure

Ref: Rasmussen 2005{Rasmussen, 2005 #325}

Study ID	Sequence generation		Allocation concealment		Blinding		Incomplete Data assessment		Free of selective reporting	Free of other bias
	Quote	Comment	Quote	Comment	Quote	Comment	Attrition (%) and reasons	Exclusion (%) and reasons		
Rasmussen 2005 [40] (COMET) Pakistan	"A randomization scheme for 200 patients was generated for each site using a computer program that allocated patients to uneven blocks of two, four and six patients"	Yes	The randomization list with unique identi-fication numbers was kept by the company preparing the Cotrimoxazole and a health professional who randomly allocated the drugs but who was not involved in study implementation. Drug assignment was concealed from parents and study personnel. The code was broken after primary analysis of the data.	Yes	A randomization scheme for 200 patients was generated for each site using a computer program that allocated patients to uneven blocks of two, four and six patients	Yes	Standard Dose: 583-5= 578 (0.86%) 560- Received the double dose of Cotrimoxazole. In standard 5 children were removed -4 enrolled incorrectly , 1 received bottle with two codes and drug strengths And 4 from double dose group due to improper enrollment. 16 were lost to follow up in both groups	1134/1143 patients, excluding 8 who were incorrectly enrolled and 1 who did not received the allocated intervention. After excluding these 9 cases of protocol violation,	Free of selective reporting	Funded by a local pharmaceutical company: Glaxo–Well come Pakistan

Figure 10 Details and quality of studies, as assessed by Lassi 2014

12.2.5.1.2 Summary and conclusions

Double dose cotrimoxazole versus standard dose for non-severe CAP in children between 2 and 59 months of age			
Bibliography: Lassi 2014{Lassi, 2014 #220}			
Outcomes	**N° of participants (studies) Follow up**	**Results (95%CI)**	**Quality of the evidence (GRADE)**
Treatment failure	1134 (1 study)	RR 1.10 (0.87 to 1.37) NS	⨁⨁⨁⨁: **HIGH** Study quality:ok Consistency: na Directness: ok Imprecision: ok

Table 262

In this systematic review, a dose of 16/80 mg/kg/day of cotrimoxazole was compared to a standard dose of 8/40 mg/kg/day. Both doses were given in two daily doses, for 5 days.

Only one study was found. The children were 2 to 59 months old.

The diagnosis of pneumonia was based on clinical signs.

In children *with community-acquired pneumonia*, a treatment with cotrimoxazole in a dose of 16/80 mg/kg/day for 5 days, 8/40 mg/kg/day for 5 days, **did not** result in a statistically significant difference in *treatment failure.*
GRADE: HIGH quality of evidence

12.2.5.2 2x/day vs 3x/day amoxicillin

12.2.5.2.1 Clinical evidence profile

Systematic review: Lassi 2014{Lassi, 2014 #220} "Systematic review on antibiotic therapy for pneumonia in children between 2 and 59 months of age"
Inclusion criteria:
"RCTs that assessed the route, dose, combination and duration of antibiotics in the management of WHO defined non-severe/severe/very severe CAP. Only those studies that used standard WHO definition and/or classification for CAP were included, irrespective of language or publication status. Study participants included children of 2–59 months of age with CAP. The review included studies that compared any intervention that either examined a single drug or a combination; or a different dose, duration and route of the same drug. We included studies that analysed outcomes including clinical cure rate (ie, symptomatic and clinical recovery by end of treatment), treatment failure (ie, developing worsening clinical signs at any point in time; a respiratory rate (RR) exceeding age-specific cut-off and/or <90% oxygen saturation on pulse oximetry after completion of treatment), relapse rate (developing disease recurrence after being declared 'cured'), change in antibiotic required and mortality rate. We grouped and analysed the outcomes according to very severe, severe and non-severe pneumonia. "
Search strategy:
"The electronic search was last performed on 15 March 2013 on Medline, Cochrane Library, Pubmed, Google Scholar with the following search terms: (('Pneumonia' OR 'very severe pneumonia' OR 'severe pneumonia' OR 'non-severe pneumonia' OR 'acute respiratory illness' OR 'Community acquired pneumonia') AND ('child*' OR 'infant' OR 'preschool*' OR 'schoolchild' OR 'school age' OR 'preschool' OR 'kid*' OR 'toddler*') AND ('treatment' OR 'anti-infective agent' OR 'anti-bacterial agents' OR 'antibiotic' OR 'management')). The bibliographies of all relevant RCTs and reviews were cross-checked, and clinical trial registries were browsed for any on-going trials."
Assessment of quality of included trials: yes, in supplementary material
Other methodological remarks: no meta-analysis for this comparison

Table 263

The systematic review found 2 RCT's with very small sample sizes (<40 participants per arm). We do not report the results.

Study details	n/Population	Comparison	Outcomes		Methodological
Ref	n= 820	amoxicillin (50	Efficacy		RANDO:
Vilas-Boas		mg/kg/day)	**Treatment failure up to**	3x/day: 94/412	Adequate

2014{Vilas-Boas, 2014 #215} Design: RCT DB; PG Duration of follow-up: 4 weeks	Median age:26 months <u>Inclusion</u> Potentially eligible cases were identified by paediatricians based on the report of respiratory complaints and the detection of lower respiratory findings plus presence of pulmonary infiltrate/consolidation on the chest radiograph (CXR) (frontal and lateral views) taken on admission. <u>Exclusion</u> Lower-chest indrawing Danger signs Chronic debilitating diseases Severe malnutrition Other concurrent infection	given orally 3x/day for 10 days Vs amoxicillin (50 mg/kg/day) given orally 2x/day for 10 days	**48 h of treatment(PO)** any of the following: • development of danger signs • persistence of fever • persistence of tachypnoea • development of serious adverse reactions • withdrawal from the trial • death	2x/day: 94/408 Risk Difference(%): 0.2 (-5.5 to 6.0) NS	ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Lost-to follow-up: 3.4 % Drop-out and Exclusions: 9 % • Described: yes • Balanced across groups: 36/412 (3 doses) vs 39/408 (2 doses) ITT: Yes (“The primary analysis was intention to treat and involved all patients who were randomly assigned. Participants excluded after randomization because they were found not to meet eligibility criteria (protocol violators), those who had the intervention stopped and those who were lost to follow-up “)were excluded from the secondary per-protocol analyses and were assumed to
			Cumulative treatment failure up to 5 days after enrolment any of the following: • development of danger signs • persistence of fever • persistence of tachypnoea • persistence of cough • development of serious adverse • reactions • recurrence of fever • withdrawal from the trial • death • previously defined as treatment • failure (at 48 h or 5 days)	3x/day: 107/412 2x/day: 133/408 Risk Difference(%): 1.7 (-4.3 to 7.8) NS	

	HIV-infected mother Hospitalization during the previous 7 days Amoxicillin or similar antibiotic use during the last 48 h Amoxicillin allergy History of aspiration		**Cumulative treatment failure up to 14 days after enrolment** any of the following: • development of danger signs • persistence of fever • persistence of tachypnoea • persistence of cough • development of serious adverse • reactions • recurrence of fever • withdrawal from the trial • death • previously defined as treatment • failure (at 48 h or 5 days)	3x/day: 174/412 2x/day: 160/408 Risk Difference(%): -3.0 (-9.7 to 3.7) NS	have treatment failure in the intention-to-treat analysis") SELECTIVE REPORTING: no Sponsor: grant from the Bahia State Agency for Research Funding (FAPESB)
			Safety		

			Adverse reactions	3x/day: 23/376 (abdominal pain (n=1) diarrhoea (n=27) and urticaria (n=1)) 2x/day: 28/369 (diarrhoea (n=27) and urticaria (n=1)) NS; p=0.5	

Table 264

12.2.5.2.2 Summary and conclusions

3x/day vs 2x/day amoxicillin for non-severe CAP in children between 2 and 59 months of age
Bibliography: Lassi 2014{Lassi, 2014 #220}

Table 265

In this systematic review, twice daily amoxicillin was compared to three times daily amoxicillin in children between 2 and 59 months of age with non-severe CAP.

The systematic review found 2 RCT's with very small sample sizes (<40 participants per arm). They did not perform a meta-analysis. We do not report the results.

3x/day vs 2x/day amoxicillin+clavulanate for non-severe CAP in children between 2 and 59 months of age			
Bibliography: Vilas-Boas 2014{Vilas-Boas, 2014 #215}			
Outcomes	**N° of participants (studies) Follow up**	**Results (95%CI)**	**Quality of the evidence (GRADE)**
Treatment failure up to 48 h of treatment	820 (1 study)	Risk Difference(%): 0.2 (-5.5 to 6.0) NS	⨁⨁⨁⨁: **HIGH** Study quality: ok Consistency: na Directness: ok Imprecision: ok
Cumulative treatment failure up to 5 days after enrolment	820 (1 study)	Risk Difference(%): 1.7 (-4.3 to 7.8) NS	⨁⨁⨁⨁: **HIGH** Study quality: ok Consistency: na Directness: ok Imprecision: ok
Cumulative treatment failure up to 14 days after enrolment	820 (1 study)	Risk Difference(%): -3.0 (-9.7 to 3.7) NS	⨁⨁⨁⨁: **HIGH** Study quality: ok Consistency: na Directness: ok Imprecision: ok
Adverse reactions	820 (1 study)	3x/day: 23/376 (abdominal pain (n=1) diarrhoea (n=27) and urticaria (n=1)) 2x/day: 28/369 (diarrhoea (n=27) and urticaria (n=1)) NS; p=0.5	Insufficient data

Table 266

We found one additional RCT, published after the final search date of the systematic review, that compared twice daily amoxicillin to three times daily amoxicillin in children between 2 and 59 months of age with non-severe CAP.

The clinical diagnosis of pneumonia was confirmed radiologically.

In children *with community-acquired pneumonia*, a treatment with twice daily amoxicillin, compared with three times daily, **did not** result in a statistically significant difference in *treatment failure up to 48 h of treatment, up to 5 days after enrolment,* or *up to 14 days after enrolment*.
GRADE: HIGH quality of evidence

In children *with community-acquired pneumonia*, a treatment with twice daily amoxicillin, compared with three times daily, **did not** result in a statistically significant difference in *adverse reactions.*
GRADE: Insufficient data to GRADE

12.2.5.3 2x/day vs 3x/day amoxicillin-clavulanate

12.2.5.3.1 Clinical evidence profile

Systematic review: Lassi 2014{Lassi, 2014 #220} "Systematic review on antibiotic therapy for pneumonia in children between 2 and 59 months of age"
Inclusion criteria:
"RCTs that assessed the route, dose, combination and duration of antibiotics in the management of WHO defined non-severe/severe/very severe CAP. Only those studies that used standard WHO definition and/or classification for CAP9 were included, irrespective of language or publication status. Study participants included children of 2–59 months of age with CAP. The review included studies that compared any intervention that either examined a single drug or a combination; or a different dose, duration and route of the same drug. We included studies that analysed outcomes including clinical cure rate (ie, symptomatic and clinical recovery by end of treatment), treatment failure (ie, developing worsening clinical signs at any point in time; a respiratory rate (RR) exceeding age-specific cut-off and/or <90% oxygen saturation on pulse oximetry after completion of treatment), relapse rate (developing disease recurrence after being declared 'cured'), change in antibiotic required and mortality rate. We grouped and analysed the outcomes according to very severe, severe and non-severe pneumonia. "
Search strategy:
"The electronic search was last performed on 15 March 2013 on Medline, Cochrane Library, Pubmed, Google Scholar with the following search terms: (('Pneumonia' OR 'very severe pneumonia' OR 'severe pneumonia' OR 'non-severe pneumonia' OR 'acute respiratory illness' OR 'Community acquired pneumonia') AND ('child*' OR 'infant' OR 'preschool*' OR 'schoolchild' OR 'school age' OR 'preschool' OR 'kid*' OR 'toddler*') AND ('treatment' OR 'anti-infective agent' OR 'anti-bacterial agents' OR 'antibiotic' OR 'management')). The bibliographies of all relevant RCTs and reviews were cross-checked, and clinical trial registries were browsed for any on-going trials."
Assessment of quality of included trials: yes, in supplementary material
Other methodological remarks: no meta-analysis for this comparison

Table 267

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Lassi 2014{Lassi, 2014 #220}	Amoxicillin+clavulanate 3x/day vs 2x/day	N=1 n=437	**Clinical cure rate** *symptomatic and clinical recovery by end of treatment*	Risk difference: 3.2% (-4.36 to 10.80) NS

Table 268

Study ID/ Year/ Country	Type of study	Participants	Study location	Intervened by	Case definition	Recovery from disease	Antibiotic therapy		Outcome
							Group 1	Group 2	
Cook 1996 [43] UK	Quasi RCT	437 pts aged 2mo to 12 yrs	437 pts from 26 centers across UK	Amoxicillin/ clavulanate BID Vs Amoxicillin / clavulanate TID	Pts with mild to moderate symptoms of ALRI. As evidenced by at least 2 of the following symptoms: high grade fever >38C, abrupt onset <72 hrs, productive cough, sudden deterioration within 72 hours in mild resp. illness, shortness of breath, respiratory crepititions or wheeze.	Clinical Cure Clinical failure relapse	Amoxicillin/clavulanate BID group n=221	Amoxicillin/ clavulanate TID group N=216	Clinical cure Clinical failure

Study ID	Sequence generation		Allocation concealment		Blinding		Incomplete Data assessment		Free of selective reporting	Free of other bias
	Quote	Comment	Quote	Comment	Quote	Comment	Attrition (%) and reasons	Exclusion (%) and reasons		
Cook [43] 1996	"The study was observer blind. Pts were randomized to treatment for seven days with amoxicillin/clavulanate 25/3.6 mg/kg/day bid or amoxicillin/ clavulanate tid as fixed dose based on 20/5mg/kg/day"	Yes	Not mentioned	Unclear	Not mentioned	Unclear	64/221= 29% attrition in BID group (39 withdrew, 6 developed adverse event, 19 patients had infection other than pneumonia) 79/216= 36% attrition in the TID group. (45 withdrew, 13 developed adverse event and 21 had illness other than pneumonia	143/447= 32% Reasons mentioned under attrition	Free of selective reporting	

Figure 11 Details and quality of studies, as assessed by Lassi 2014

Ref: Cook 1996{Cook, 1996 #324}

12.2.5.3.2 Summary and conclusions

3x/day vs 2x/day amoxicillin+clavulanate for non-severe CAP in children between 2 and 59 months of age			
Bibliography: Lassi 2014{Lassi, 2014 #220}			
Outcomes	**N° of participants (studies) Follow up**	**Results (95%CI)**	**Quality of the evidence (GRADE)**
Clinical cure rate	437 (1 study)	Risk difference: 3.2% (-4.36 to 10.80) NS	⊕⊕⊖⊖: **LOW** Study quality: -2(unclear allocation concealment, unclear blinding, >20% attrition and unequal in groups) Consistency: na Directness: ok Imprecision: ok

Table 269

In this systematic review, twice daily amoxicillin+clavulanate was compared with three times daily amoxicillin+clavulanate in children between 2 and 59 months with non-severe CAP.

Only one study was found.

The diagnosis of pneumonia was based on clinical signs.

In children *with community-acquired pneumonia*, a treatment with twice daily amoxicillin+ clavulanate, compared with three times daily, **did not** result in a statistically significant difference in *clinical cure rate.*
GRADE: LOW quality of evidence

12.2.6 Different modes of administration of antibiotics for CAP in children

12.2.6.1 Oral versus parenteral AB for severe and non-severe pneumonia

12.2.6.1.1 Clinical evidence profile

Meta-analysis: Lodha 2013{Lodha, 2013 #218}"Antibiotics for community-acquired pneumonia in children"
Inclusion criteria:
"Randomised controlled trials (RCTs) comparing antibiotics for CAP in children. We considered only those studies using the case definition of pneumonia (as given by the WHO) or radiologically confirmed pneumonia in this review
We included children under 18 years of age with CAP treated in a hospital or community setting. We excluded studies describing pneumonia post-hospitalisation in immunocompromised patients (for example, following surgical procedures) or patients with underlying illnesses like congenital heart disease or those in an immune deficient state.
We compared any intervention with antibiotics (administered by intravenous route, intramuscular route or orally) with another antibiotic for the treatment of CAP"
Search strategy:
"For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 10, part of The Cochrane Library, www.thecochranelibrary.com (accessed 7 November 2012); MEDLINE (September 2009 to October week 4, 2012); EMBASE (September 2009 to November 2012); CINAHL (2009 to November 2012); Web of Science (2009 to November 2012) and LILACS (2009 to November 2012)."
Assessment of quality of included trials: yes
Other methodological remarks:

Table 270

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Lodha 2013{Lodha, 2013 #218}	**Oral vs parenteral antibiotics**	N=3 n=3942 (Addo-Yobo 2004, Atkinson 2007, Hazir 2008)	**Failure rates on day 3** The definition of treatment failure is the presence of any of the following: development of chest indrawing, convulsions, drowsiness or inability to drink at any time, respiratory rate above the age-specific cut-off point on	Crude AR 247/1982 vs 255/1960 OR 0.95 [0.78, 1.15] NS

			completion of treatment, or oxygen saturation of less than 90% (measured by pulse oximetry) after completion of the treatment. Loss to follow-up or withdrawal from the study at any time after recruitment indicated failure in the analysis	
		N=6 n=4331 (Addo-Yobo 2004, Atkinson 2007, Campbell 1988, Hazir 2008, Sidal 1994, Tsarouhas 1998)	**Failure rates on day 6**	Crude AR 291/2174 vs 319/2157 OR 0.84 [0.56, 1.24] NS
		N=3 n=3870 (Addo-Yobo 2004, Campbell 1988, Hazir 2008)	**Failure rates in children below 5 years of age**	Crude AR 279/1948 vs 297/1922 OR 0.91 [0.76, 1.09] NS
		N=4 n=4112 (Addo-Yobo 2004, Atkinson 2007, Hazir 2008, Tsarouhas 1998)	**Failure rates in children receiving oral amoxicillin or injectable antibiotics**	Crude AR 284/2026 vs 300/2050 OR 0.92 [0.77, 1.10] NS

		N=2 n=219 (Campbell 1988, Sidal 1994)	**Failure rate in children receiving cotrimoxazole or injectable penicillin**	Crude AR 7/112 vs 19/107 OR 0.31 [0.03, 3.29] NS
		N=3 n=458 (Campbell 1988, Sidal 1994, Tsarouhas 1998)	**Hospitalisations** (in outpatient studies only): defined as the need for hospitalisation in children who were getting treatment or in an ambulatory (outpatient) setting.	Crude AR 7/192 vs 7/266 OR 1.13 [0.38, 3.34] NS
		N=2 n=2076 (Atkinson 2007, Hazir 2008)	**Relapse rates** defined as children declared 'cured', but developing recurrence of disease at follow-up in a defined period.	Crude AR 31/1048 vs 33/1028 OR 1.28 [0.34, 4.82] NS
		N=3 n=3942 (Addo-Yobo 2004, Atkinson 2007, Hazir 2008)	**Death rates**	Crude AR 1/1970 vs 11/1972 **OR 0.15 [0.03, 0.87]** **SS**
		N=2 n=334 (Atkinson 2007, Sidal 1994)	**Cure rate** The definition of clinical cure is symptomatic and involves clinical recovery by the end of treatment	Crude AR 167/172 vs 141/162 **OR 5.05 [1.19, 21.33]** **SS**

Table 271

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
Addo-Yobo 2004{Addo-Yobo, 2004 #318}	1702	Children 3 to 59 months with clinical diagnosis of severe pneumonia	14 days	Daily IM penicillin 200,000 IU/kg or PO amoxycillin 45 mg/kg/day	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk BLINDING OF PARTICIPANTS AND PERSONNEL High risk (Open-label study) BLINDING OF OUTCOME ASSESSMENT High risk (Open-label study) SELECTIVE REPORTING Low risk INCOMPLETE OUTCOME DATA Low risk OTHER BIAS Low risk
Atkinson 2007{Atkinson, 2007 #319}	203	Children admitted with radiologically confirmed pneumonia	Not found	Oral amoxycillin (doses for 6 months to 12 years of age 8 mg/kg/dose 3 times a day above 12 years of age 500 mg 3 times a day) or IV benzyl penicillin (doses 25 mg/kg/ dose 4 times a day)	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk BLINDING OF PARTICIPANTS AND PERSONNEL High risk (Open-label study) BLINDING OF OUTCOME ASSESSMENT High risk (Open-label study) SELECTIVE REPORTING Unclear risk (While the authors mention the primary outcome as “the time from randomisation until the temperature was less than 38

					degree celsius for 24 continuous hours and oxygen requirement had ceased", they calculated the sample size based on the proportion meeting the primary outcome measure at any time. The authors have not reported on these proportions in the results) INCOMPLETE OUTCOME DATA Low risk OTHER BIAS Low risk
Campbell 1988{Campbell, 1988 #320}	131	Children 1 month to 4 years of age with clinically diagnosed non-severe pneumonia	Not found	Daily co-trimoxazole PO for 5 days or single-dose procaine penicillin with daily PO ampicillin	RANDOM SEQUENCE GENERATION Unclear risk (Sequence generation and randomisation not clear) ALLOCATION CONCEALMENT High risk (Eligible children were allocated sequentially to 2 treatment groups by study physician) BLINDING OF PARTICIPANTS AND PERSONNEL High risk (Open-label study) BLINDING OF OUTCOME ASSESSMENT High risk (Open-label study) SELECTIVE REPORTING Unclear risk (Data not recorded clearly) INCOMPLETE OUTCOME DATA Unclear risk (Data not recorded clearly) OTHER BIAS

					Unclear risk (Source of funding not mentioned)
Hazir 2008{Hazir, 2008 #321}	2037	Children aged 3 to 59 months with clinically diagnosed WHO-defined severe pneumonia	Not found	Oral amoxycillin syrup (80 to 90 mg/kg per day in 2 doses) and sent home (ambulatory group), or to receive intravenous ampicillin (100 mg/kg per day in 4 doses) for 48 hours as an inpatient (hospitalised group)	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk BLINDING OF PARTICIPANTS AND PERSONNEL High risk (Open-label study) BLINDING OF OUTCOME ASSESSMENT Unclear risk (Open-label study) SELECTIVE REPORTING Low risk INCOMPLETE OUTCOME DATA Low risk OTHER BIAS Low risk
Sidal 1994{Sidal, 1994 #322}	88	Children aged 3 months to 14 years with non-severe pneumonia (including moderate pneumonia)	10 days	PO co-trimoxazole (40 mg/kg/day) for 10 days or IM procaine penicillin (50,000 IU/ kg/day) for 10 days	RANDOM SEQUENCE GENERATION Unclear risk (Information not provided) ALLOCATION CONCEALMENT High risk (No details of randomisation or ALLOCATION CONCEALMENT) BLINDING OF PARTICIPANTS AND PERSONNEL High risk (Open-label study) BLINDING OF OUTCOME ASSESSMENT High risk (Open-label study) SELECTIVE REPORTING Low risk

					INCOMPLETE OUTCOME DATA Low risk OTHER BIAS Unclear risk (Source of funding not mentioned)
Tsarouhas 1998{Tsarouhas, 1998 #323}	Not found	Children aged 6 months to 18 years with radiologically confirmed pneumonia	Not found	PO amoxycillin (50 mg/kg/day) or procaine penicillin IM (50,000 IU/kg/day)	RANDOM SEQUENCE GENERATION Unclear risk (Sequence generation not mentioned) ALLOCATION CONCEALMENT Low risk BLINDING OF PARTICIPANTS AND PERSONNEL High risk (Open-label study) BLINDING OF OUTCOME ASSESSMENT High risk (Open-label study) SELECTIVE REPORTING Low risk INCOMPLETE OUTCOME DATA Low risk OTHER BIAS Unclear risk (Source of funding not mentioned)

Table 272

Remarks:

Very high dose of IM penicillin versus relatively low dose oral of amoxicillin in one study (Addo Yobo 2004)

Very low dose of oral amoxicillin in one study (Atkinson 2007)

12.2.6.1.2 Summary and conclusions

Oral vs parenteral antibiotics for treatment of pneumonia in children			
Bibliography: Lodha 2013{Lodha, 2013 #218}			
Outcomes	**N° of participants (studies) Follow up**	**Results (95%CI)**	**Quality of the evidence (GRADE)**
Failure rates on day 3	3942 (3 studies)	OR 0.95 [0.78, 1.15] NS	⊕⊕⊖⊖: **LOW** Study quality: -1 (open-label) Consistency: ok Directness: -1 (injectable AB not usually recommended in Be) Imprecision: ok
Failure rates on day 6	4331 (6 studies)	OR 0.84 [0.56, 1.24] NS	⊕⊕⊖⊖: **LOW** Study quality: -1 (open-label) Consistency: ok Directness: -1 (injectable AB not usually recommended in Be) Imprecision: ok
Failure rates in children below 5 years of age	3870 (3 studies)	OR 0.91 [0.76, 1.09] NS	⊕⊕⊖⊖: **LOW** Study quality: -1 (open-label) Consistency: ok Directness: -1 (injectable AB not usually recommended in Be) Imprecision: ok
Failure rates in children receiving oral amoxicillin or injectable antibiotics	4112 (4 studies)	OR 0.92 [0.77, 1.10] NS	⊕⊕⊖⊖: **LOW** Study quality: -1 (open-label) Consistency: ok Directness: -1 (injectable AB not usually recommended in Be) Imprecision: ok
Failure rate in children receiving cotrimoxazole or injectable penicillin	219 (2 studies)	OR 0.31 [0.03, 3.29] NS	⊕⊖⊖⊖: **VERY LOW** Study quality: -1 (open-label) Consistency: -1 (I^2=82%) Directness: -1 (injectable AB not usually recommended in Be) Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Hospitalisations	458 (3 studies)	OR 1.13 [0.38, 3.34] NS	⊕⊖⊖⊖: **VERY LOW** Study quality: -1 (open-label) Consistency: ok Directness: -1 (injectable AB not usually recommended in Be) Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Relapse rates	2076 (2 studies)	OR 1.28 [0.34, 4.82] NS	⊕⊕⊖⊖: **LOW** Study quality: -1 (open-label) Consistency: ok Directness: ok Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)

Death rates	3942 (3 studies)	**OR 0.15 [0.03, 0.87]** **SS** **(fewer deaths with oral treatment)**	⊕⊕⊖⊖: **LOW** Study quality: -1 (open-label) Consistency: ok Directness: -1 (injectable AB not usually recommended in Be) Imprecision: ok
Cure rate	334 (2 studies)	**OR 5.05 [1.19, 21.33]** **SS** **(higher cure rate with oral treatment)**	⊕⊕⊖⊖: **LOW** Study quality: -1 (open-label) Consistency: ok Directness: -1 (injectable AB not usually recommended in Be) Imprecision: ok

Table 273

In this meta-analysis, a treatment with oral antibiotics was compared to a treatment with parenteral antibiotics (either IM or IV) for CAP in children.

The children in these studies were 1 month to 18 years old.

The diagnosis of pneumonia was based on clinical signs only in 4 studies, and was radiologically confirmed in two. Both studies that included WHO-defined severe and non-severe pneumonia were included in the meta-analysis.

The oral antibiotics used in the studies were amoxicillin or co-trimoxazole.

The parenteral antibiotics used in the studies were IM procaine penicillin, IV benzyl penicillin, or IV ampicillin. IM penicillin is not usually recommended in Belgium.

In children *with community-acquired pneumonia*, a treatment with oral antibiotics, compared to parenteral antibiotics (IM or IV), **did** result in a statistically significant **decrease** in *death rates.*
GRADE: LOW quality of evidence

In children *with community-acquired pneumonia*, a treatment with oral antibiotics, compared to parenteral antibiotics (IM or IV), **did** result in a statistically significant **increase** in *cure rates.*
GRADE: LOW quality of evidence

In children *with community-acquired pneumonia*, a treatment with oral antibiotics, compared to parenteral antibiotics (IM or IV), **did not** result in a statistically significant difference in *failure rates on day 3 or day 6, or relapse rates.*
GRADE: LOW quality of evidence

In children *with community-acquired pneumonia*, a treatment with oral antibiotics, compared to parenteral antibiotics (IM or IV), **did not** result in a statistically significant difference in *hospitalisations.*
GRADE: VERY LOW quality of evidence

In children younger than 5 years, *with community-acquired pneumonia*, a treatment with oral antibiotics, compared to parenteral antibiotics (IM or IV), **did not** result in a statistically significant difference in *failure rates.*

GRADE: LOW quality of evidence

In children *with community-acquired pneumonia*, a treatment with oral amoxicillin, compared to injectable antibiotics, **did not** result in a statistically significant difference in *failure rates.*
GRADE: LOW quality of evidence

In children *with community-acquired pneumonia*, a treatment with oral co-trimoxazole, compared to injectable penicillin, **did not** result in a statistically significant difference in *failure rates.*
GRADE: VERY LOW quality of evidence

13 Urinary tract infections

13.1 Guidelines

13.1.1 Method of reporting of the recommendations and notes

Formal recommendations, that are supplied with grades of recommendations or levels of evidence, are written in **bold**.

Text taken directly from the guidelines, that is not graded but provides supplemental information or a clarification of the formal recommendations, is written in *italics*.

Comments by the bibliography group are written in plain text.

13.1.2 General information on selected guidelines

13.1.2.1 Selected guidelines

The selected guidelines and their abbreviations as used in this report can be found in Table 274.

Abbreviation	Guideline
AAP UTI 2011{Subcommittee on Urinary Tract Infection, 2011 #19}	AAP – American Academy of Pediatrics : Urinary Tract Infection: Clinical Practice Guideline for the Diagnosis and Management of the Initial UTI in Febrile Infants and Children 2 to 24 Months - 2011
BAPCOC 2012{BAPCOC, 2012 #3}	BAPCOC - Belgische gids voor anti-infectieuze behandeling in de ambulante praktijk; editie 2012/ Guide Belge des traitements anti-infectieux en pratique ambulatoire; édition 2012
NHG UWI 2013{NHG - Dutch College of General Practitioners, 2013 #12}	NHG - Dutch College of General Practitioners: Urineweginfecties (M05) - 2013

Table 274: Selected guidelines and their abbreviations as used in this report.

13.1.2.2 Grades of recommendation

Grades of recommendation and levels of evidence as defined in each guideline, can be found inTable 275 to Table 276, Figure 12 and Figure 13.

13.1.2.2.1 AAP UTI 2011

Evidence Quality	Preponderance of Benefit or Harm	Balance of Benefit and Harm
A. Well designed RCTs or diagnostic studies on relevant population	Strong Recommendation	Option
B. RCTs or diagnostic studies with minor limitations;overwhelmingly consistent evidence from observational studies	Recommendation	
C. Observational studies (case-control and cohort design)		
D. Expert opinion, case reports, reasoning from first principles	Option	No Rec
X. Exceptional situations where validating studies cannot be performed and there is a clear preponderance of benefit or harm	Strong Recommendation / Recommendation	

Figure 12: AAP evidence strength table

TABLE Guideline Definitions for Evidence-Based Statements

Statement	Definition	Implication
Strong recommendation	A strong recommendation in favor of a particular action is made when the anticipated benefits of the recommended intervention clearly exceed the harms (as a strong recommendation against an action is made when the anticipated harms clearly exceed the benefits) and the quality of the supporting evidence is excellent. In some clearly identified circumstances, strong recommendations may be made when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Recommendation	A recommendation in favor of a particular action is made when the anticipated benefits exceed the harms but the quality of evidence is not as strong. Again, in some clearly identified circumstances, recommendations may be made when high-quality evidence is impossible to obtain but the anticipated benefits outweigh the harms.	Clinicians would be prudent to follow a recommendation, but should remain alert to new information and sensitive to patient preferences.
Option	Options define courses that may be taken when either the quality of evidence is suspect or carefully performed studies have shown little clear advantage to one approach over another.	Clinicians should consider the option in their decision-making, and patient preference may have a substantial role.
No recommendation	No recommendation indicates that there is a lack of pertinent published evidence and that the anticipated balance of benefits and harms is presently unclear.	Clinicians should be alert to new published evidence that clarifies the balance of benefit versus harm.

Figure 13 AAP Guideline definitions for Evidence-based statements

13.1.2.2.2 BAPCOC 2012

BAPCOC 2012		
Grades of recommendation:	1	Strong recommendation
	2	Weak recommendation
Levels of evidence	A	High degree of evidence; RCTs without limitations or strong, compelling evidence from observational studies
	B	Medium level of evidence; RCTs with limitations or strong evidence from observational studies
	C	(very) low degree of evidence; observational studies or case studies

Table 275 Guideline definitions for Evidence-based statements

13.1.2.2.3 NHG UWI 2013

The NHG guidelines do not explicitly attribute grades of recommendation or levels of evidence to their recommendations. In their manual they mention that they do perform a GRADE- evaluation of the included evidence on which the recommendations are based. They also express the grade of recommendation in the wording of the recommendation itself (i.e. strongly or weakly recommended) (see https://www.nhg.org/sites/default/files/content/nhg_org/uploads/handleiding_standaarden_2015.pdf)

However the guideline on UTI 2013 was formulated before the manual. It is therefore not clear if those grades of recommendation are applied in this guideline.

NHG UWI 2013		
Grades of recommendation:	Strong; Expressed in the wording of the recommendation	/
	Weak; Expressed in the wording of the recommendation	This often means there is not enough evidence to recommend a specific option and that medical professionals, together with their patient, make a choice from different options.
Levels of evidence	High	The true effect lies close to the estimated effect
	Moderate	The true effect probably lies close to the estimated effect, but the possibility exists that it differs substantially from it.
	Low	The true effect can differ substantially from the estimated effect.
	Very Low	The true effect probably differs substantially from the estimated effect.

Table 276 Guideline definitions for Evidence-based statements

13.1.2.3 Agree II score

Information about the Agree II score can be found in the section “Methodology”.

A summary of the assessment by the literature group of the individual items of the domain score for each guideline can be found in Table 277. The total domain score is also reported in this table.

Rigour of development item	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Total**	**Domain score**
NHG Urineweginfecties 2013	5	2	3	2	4	1	7	2	**26**	**46%**
AAP UTI 2011	7	7	5	7	7	7	5	4	**49**	**88%**

Table 277: AGREE score of selected guidelines on item “Rigour of development”, see 1.1.2.6 for a description of the items.

13.1.2.4 Included populations – interventions – main outcomes

In Table 278 to Table 280, the populations, interventions and main outcomes considered in the selected guidelines are represented.

AAP Urinary Tract Infection 2011	
Population	Febrile infants and children 2 to 24 months with initial urinary tract infection
Interventions	Diagnosis, urinalysis, management, antibiotic use
Outcomes	Primary outcome: episodes of pyelonephritis or febrile UTI diagnosed on the basis of the presence of fever and bacterial growth in urine cultures Secondary outcome: an episode of any type of UTI, including cystitis, nonfebrile UTI, and asymptomatic bacteriuria in addition to the cases of pyelonephritis or febrile UTI

Table 278 : Included population, intervention and main outcomes of the NHG UWI 2013 guideline.

BAPCOC 2012	
Population	Ambulant care patients (adults and children)
Interventions	Antibiotic treatment (indication, choice, dose, duration)
Outcomes	Not specified

Table 279: Included population, intervention and main outcomes of the BAPCOC 2012 guideline

NHG Urineweginfecties 2013	
Population	Adults and children with urinary tract infections
Interventions	Diagnosis, clinical examination, examination of urine, antibiotic use
Outcomes	Not defined

Table 280: Included population, intervention and main outcomes of the NHG UWI 2013 guideline.

13.1.2.5 Members of development group – target audience

Members of the development group that produced the guidelines, and the target audience for whom the guidelines are intended, can be found in Table 281 to Table 283.

AAP UTI 2011	
Development group	General practitioners
Target audience	Clinicians who treat infants and young children

Table 281: Members of the development group and target audience of the NHG UWI 2013 guideline

BAPCOC 2012	
Development group	General practitioners, microbiologists, pneumologists, infectiologists, paediatricians, pharmacists
Target audience	Physicians working in ambulant care

Table 282: Members of the development group and target audience of the BAPCOC 2012 guideline

NHG UWI 2013	
Development group	General practitioners, specialist (infectious disease specialist), researchers
Target audience	general practitioners

Table 283: Members of the development group and target audience of the NHG UWI 2013 guideline

13.1.3 Definition

13.1.3.1 Summary

Two out of three guidelines define what is understood by urinary tract infection. The AAP UTI 2011 defines it as pyuria and bacteriuria, the NHG UWI 2013 as bacteriuria with clinical symptoms. The amount of colony-forming units /ml is different between both.

13.1.3.2 AAP UTI 2011

Diagnosis (of a UTI) is made on the basis of the presence of both pyuria and at least 50 000 colonies / ml of a single uropathogenic organism in an appropriately collected specimen of urine.

13.1.3.3 BAPCOC 2012

The guideline doesn't define this term.

13.1.3.4 NHG UWI 2013

Urinary tract infection: bacteriuria with clinical symptoms. One speaks of bacteriuria in case of a positive nitrite-test, a dipslide of at least 10^4 colony forming units per milliliter or a culture with at least 10^5 cfu/ml.

13.1.4 Diagnosis

13.1.4.1 Summary

For the two guidelines that mention diagnostic criteria a urine sample is crucial. The NHG UTI 2013 mentions it is necessary for children under 12.
The criteria for the AAP UTI 2011 guideline is both a urinalysis that suggest infection and a culture, proving the presence of at least 50.000 cfu/ml. The urine for culture should be obtained through catherization or SPA.
For the diagnosis of children under 12 years old the NHG UTI 2013 guideline recommends a culture. The urine should be obtained through clean catch or through catherization if clean catch is impossible. Urine from a urine bag cannot prove a UTI, but a negative test on a urine bag sample can exclude UTI.

13.1.4.2 AAP UTI 2011

To establish the diagnosis of UTI, clinicians should require both urinalysis results that suggest infection (pyuria and/or bacteriuria) and the presence of at least 50 000 colony-forming units

(CFUs) per mL of a uropathogen cultured from a urine specimen obtained through catheterization or SPA (evidence quality: C; recommendation).

If a clinician assesses a febrile infant with no apparent source for the fever as not being so ill as to require immediate antimicrobial therapy, then the clinician should assess the likelihood of UTI.

If a febrile infant is not in a low-risk group, two options (evidence quality: A; strong Recommendation):

- **Option 1 is to obtain a urine specimen through catheterization or SPA for culture and urinalysis.**
- **Option 2 is to obtain a urine specimen through the most convenient means and to perform a urinalysis. If the urinalysis results suggest a UTI (positive leukocyte esterase test results or nitrite test or microscopic analysis results positive for leukocytes or bacteria), then a urine specimen should be obtained through catheterization or SPA and cultured; if urinalysis of fresh (<1 hour since void) urine yields negative leukocyte esterase and nitrite test results, then it is reasonable to monitor the clinical course without initiating antimicrobial therapy, recognizing that negative urinalysis results do not rule out a UTI with certainty.**

13.1.4.3 BAPCOC 2012

No information found in the guideline.

13.1.4.4 NHG UWI

A positive culture is required for the diagnosis with children under 12 years old.

Collection a sample in children who are not toilet trained:
Preferably, urine is collected by means of a clean catch. The urine bag is a method that gives more opportunity for contamination. A positive nitrite or leukotest of urine from a urine bag still requires investigation of clean "clean catch" urine to confirm the diagnosis of urinary tract infection. If a clean catch fails, catheterization (by a pediatrician) is indicated.

Instructions for catching urine in children who are not toilet trained (clean catch)

- *Give the child plenty to drink. Children under 2 years will generally urinate within 20 to 30 minutes.*
- *Spread the labia or pull back the foreskin and wash the vulva or penis thoroughly with plenty of water (no soap) by rinsing with the shower or by pressing wetted cotton balls (do not rub).*
- *Let the child lie with bare genitals on a changing cushion or walk around naked and catch midstream urine in a clean container.*
- *If this proves impossible, use a urine bag and check every 10 minutes if there is urine production.*
- *Don't leave the urine bag on more than 1 hour, because after this time period the risk of contamination is high. Although urine from a urine bag cannot be used to reliably demonstrate a urinary tract infection, it is useful to exclude a urinary tract infection*

13.1.5 Indications for antibiotic treatment

13.1.5.1 Summary

The AAP UTI 2011 guideline recommends assessing the likelihood of UTI unless an infant is so ill as to require immediate antimicrobial therapy. In case of a low likelihood, follow-up monitoring is sufficient. Antibiotic treatment should only be started after a positive culture.
BAPCOC 2012 recommends a quick empirical treatment rather than a delayed treatment based on culture.
NHG UTI 2013 recommends always treating a proven UTI with antibiotics, but requires a positive culture for children under 12 years old before a diagnostic of UTI can be made.

13.1.5.2 AAP UTI 2011

If a clinician assesses a febrile infant with no apparent source for the fever as not being so ill as to require immediate antimicrobial therapy, then the clinician should assess the likelihood of UTI

If the clinician determines the febrile infant to have a low likelihood of UTI (see text), then clinical follow-up monitoring without testing is sufficient (evidence quality: A; strong recommendation).

If the clinician determines that the febrile infant is not in a low-risk group (see below), then there are 2 choices (evidence quality: A; strong recommendation). […] (see diagnosis) **if urinalysis of fresh (<1 hour since void) urine yields negative leukocyte esterase and nitrite test results, then it is reasonable to monitor the clinical course without initiating antimicrobial therapy, recognizing that negative urinalysis results do not rule out a UTI with certainty.**

13.1.5.3 BAPCOC 2012

A quick empirical treatment leads to less renal sequellae than a delayed aetiological treatment based and culture and antibiogram (Grade 1B).

13.1.5.4 NHG UWI 2013

Note: A positive culture is required for the diagnosis with children under 12 years old (see diagnosis). Dipslide tests are accepted (see definition).

Always treat proven UTI in young children with antibiotics for these infections can quickly lead to kidney damage.

13.1.6 Choice of antibiotic, dose and duration

13.1.6.1 Summary

Since the AAP UTI 2011 diagnoses UTI only based on culture, treatment of UTI should be based on the sensitivity testing of the cultured uropathogen.
BAPCOC 2012 and NHG UTI 2013 guidelines recommend nitrofurantoin as first choice. Second choice differs between the two, BAPCOC 2012 chooses trimethoprim, NHG UTI 2013 amoxicillin + clavulanate.

NHG UTI 2013 makes recommendations specifically for infections with tissue invasion, first choice is amoxicillin + clavulanate, second choice in that case is cotrimoxazol.

13.1.6.2 AAP UTI 2011

When initiating treatment, the clinician should base the choice of route of administration on practical considerations. Initiating treatment orally or parenterally is equally efficacious.
The clinician should base the choice of agent on local antimicrobial sensitivity patterns (if available) and should adjust the choice according to sensitivity testing of the isolated uropathogen (evidence quality: A; strong recommendation).

The clinician should choose 7 to 14 days as the duration of antimicrobial therapy (evidence quality: B; recommendation).

13.1.6.3 BAPCOC 2012

Urinary tract infections in the child (GRADE 1C):
- nitrofurantoïne
5-7 mg/kg per day in 4 doses during 3 days (magistral preparation or compounding)
- trimethoprim
From 6 weeks to 5 months old: 6-8 mg/kg per day in 2 doses during 3d (magistral preparation or compounding)
From 6 months to 5 year old: 100 mg per day in 2 doses during 3d (magistral preparation or compounding)
From 6 to 12 years old: 200 mg per day in 2 doses during 3d (magistral preparation or compounding)

13.1.6.4 NHG UWI 2013

Cystitis:

- *First choice: a treatment with nitrofurantoin for 5 days (5 to 6 mg/kg bodyweight in 4 doses, maximum 400mg/day)*
- *Second choice: a treatment with amoxicillin/clavulanate potassium (30/7,5 mg/kg bodyweight in 3 doses, maximum 3g/750 mg/day)*

In case of signs of tissue invasion:

- *First choice: a treatment with amoxicillin/clavulanate potassium for 10 days (50/12,5 mg/kg bodyweight in 3 doses; maximum 3g/750 mg/day)*
- *Second choice (and in case of penicillin hypersensitivity): a treatment with cotrimoxazol for 10 days (6/30 mg/kg bodyweight in 2 doses; maximum 320/1600 per day)*

13.1.7 Non-antibiotic treatment

13.1.7.1 Summary

Only the NHG UWI 2013 guideline gives additional information on non-antibiotic treatment. It recommends to give advice on how pelvic floor muscles work and to explain again how a child best urinates (position on the toilet, no pressure on the belly), to make sure to void the bladder completely.

13.1.7.2 AAP UTI 2011

The guideline doesn't give information on other treatments than antibiotics.

13.1.7.3 BAPCOC 2012

Since the guideline only reports on antibiotics, no information on non-antibiotic treatment is to be found in the guideline.

13.1.7.4 NHG UWI 2013

Give the parents of toilet-trained children older than 5 years explanation about how pelvic floor muscles work, and explain that those need to be relaxed for a complete voiding of bladder and bowels.
If there are indications for abnormal urination pattern, give the following advice:
Let the child sit calmly and relaxed on the toilet. Make sure that the upper legs are resting horizontally on the toilet pot and that the feet are reaching the ground or a small stool. Pay attention that the child isn't exerting pressure during urinating. The belly should be stay relaxed; this can be done by whistling, blowing or humming. If the child refrains from urinating for too long, there are more chances that they would wet themselves or would not be able to void the bladder properly.
Try to make sure the child urinates six to seven times a day, for which the child needs to drink seven times a day at least.

Cranberry supplements are only mentioned for adult women.

13.1.8 Referrals

13.1.8.1 Summary

If urine samples should be obtained through catherization (as recommended by AAP UTI 2011 and NHG UTI 2013 guideline when clean catch fails), NHG UTI 2013 recommends that the child is referred to a paediactrician.
BAPCOC 2012 recommends seeking the advice of a specialist, with a possible exception in the case of a first infection in girls older than 5 years. Recurrent infections warrant a referral to a specialist.
NHG UTI 2013 recommends referral for neonates (<1 month), very ill children, or those who do not improve after 48h, in case of a palpable mass in the abdomen, in case of recurrences under 6 weeks, or a non-E.Coli infection.

13.1.8.2 AAP UTI 2011

The guideline mentions renal and bladder ultrasonography for febrile infants with UTI and further evaluation in case of recurrence of UTI's, implying a referral to other practitioners (pediatricians, radiologists etc.). However no outright mention of when to refer a patient is made.

13.1.8.3 BAPCOC 2012

The advice of a specialist is indicated for UTI in a child, but according to some experts an exception can be made for a first UTI in girls older than 5 years.
In case of recurrence, further clinical and microbiological investigation is necessary. For prophylaxis of recurrent UTI's in children referral to a specialist is indicated.

13.1.8.4 NHG UWI 2013

Refer immediately to a pediatrician:

- *children younger than 1 month with fever and children from 1 to 3 months with fever without focus)*
- *children with (suspected) a urinary tract infection who are seriously ill and / or vomiting*
- *children who do not improve within 48 hours of antimicrobial therapy*

Refer immediately for diagnosis to a pediatrician:

- *Children who are not toilet trained and in whom a clean catch fails, with a positive nitrite or leukotest in a puddle of urine from a pouch (catheterization indicated)*
- *If during the infection there is a diminished flow or palpable mass in the abdomen.*

Referral to a pediatrician within six weeks after the infection is indicated in the case of:

- *A urinary tract infection twice, at least once with fever*
- *a urinary tract infection three times, without fever*
- *urinary tract infection with a pathogen other than E. coli.*

13.2 Cystitis: Evidence tables and conclusions

13.2.1 Antibiotics versus placebo or no treatment

13.2.1.1 Antibiotics versus placebo or no treatment for lower urinary tract infection

13.2.1.1.1 Clinical evidence profile

Meta-analysis: Cochrane Fitzgerald 2012a{Fitzgerald, 2012 #114} "Antbiotics for treating lower urinary tract infection in children"
Inclusion criteria: All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) in which antibiotic therapy was used to treat lower UTI in children. Children aged zero to 18 years with bacteriologically proven UTI (at least one culture of a known urinary pathogen (bacterial culture > 10^5 cfu/mL) in a child with first time or recurrent UTI and who had at least one localised symptom of UTI (such as dysuria or frequency) treated with antibiotics in primary and community health care settings or an outpatient department were included.
Exclusion:
Children hospitalised for a condition not related to UTI. Children with bacteriologically proven UTI and symptoms or signs of systemic illness (including fever, loin pain, toxicity). Children with covert bacteriuria (non-symptomatic). Children with pre-existing renal abnormalities or known underlying renal conditions (including high grade (3-4) VUR, nephrotic syndrome and neurogenic bladder). Children receiving prophylactic antibiotics for UTI. Children receiving antibiotics for any other condition. Immunosuppressed children.
Search strategy: We searched the Cochrane Renal Group's Specialised Register (May 2012) through contact with the Trials' Search Co-ordinator using search terms relevant to this review.
The Cochrane Renal Group's Specialised Register contains studies identified from:
1. Quarterly searches of the Cochrane Central Register of
Controlled Trials CENTRAL;
2. Weekly searches of MEDLINE OVID SP;
3. Handsearching of renal-related journals & the proceedings
of major renal conferences;
4. Searching of the current year of EMBASE OVID SP;
5. Weekly current awareness alerts for selected renal-journals;
6. Searches of the International Clinical Trials Register
(ICTRP) Search Portal & ClinicalTrials.gov
Assessment of quality of included trials:

Table 284

Remarks: no RCTs found for this comparison.

13.2.1.1.2 Summary and conclusions

In this meta-analysis, a search was conducted for RCTs and quasi-RCTs where antibiotic therapy was compared to placebo or no therapy in children with lower urinary tract infection.

There were no RCTs or quasi-RCTs that met the inclusion criteria.

13.2.1.2 Antibiotics versus placebo or no treatment for covert bacteriuria

13.2.1.2.1 Clinical evidence profile

Meta-analysis: Fitzgerald 2012b{Fitzgerald, 2012 #115} "Interventions for covert bacteriuria in children"
Inclusion criteria: All RCTs and quasi-RCTs (studies where allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods). in which any intervention was used to treat covert bacteriuria in children were included. Children aged up to and including 18 years with covert bacteriuria who were treated in any healthcare or community setting were included. In this review, covert bacteriuria was defined as at least one culture of a known urinary pathogen (of at least 10^5 cfu/mL) in a child who had no known associated urinary symptoms at the time of diagnosis. Children who had urine collected by suprapubic aspiration, catheter, bag, pad or clean-catch methods and follow-up urine culture were included.
Exclusion: Children with symptoms of UTI or signs of systemic illness (pyelonephritis). Children with urinary symptoms, such as dysfunctional voiding, vulvovaginitis or balanitis. Children with pre-existing uropathies or known underlying kidney disease, such as vesicoureteric reflux (VUR), nephrotic syndrome, neurogenic bladder. Children receiving prophylactic antibiotics. Children receiving antibiotics for any other condition. Immunosuppressed children.
Search strategy: Cochrane Register of Controlled Trials (CENTRAL) was last searched Issue 12, 2011 using a strategy developed for this review with input from the Trials Search Coordinator. • EMBASE (OvidSP) Last searched March 15, 2010 for records added since the latest contribution to CENTRAL by the UK Cochrane Centre, using a strategy developed with input from the Trials Search Coordinator plus the strategy used by the UK Cochrane Centre for identification of RCTs. Reference lists of nephrology textbooks, review articles and relevant studies. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.
Assessment of quality of included trials: yes

Table 285

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Fitzgerald 2012b{Fitzgerald, 2012 #115}	Antbiotics versus no treatment	N= 1 n=205 (NCBRG 1981)	**Cystitis (lower UTI)**	Crude AR: 7/105 vs 4/100 RR= 1.67 [0.50, 5.52] NS

		N=2 n=247 (NCBRG 1981, Savage 1975)	**Pyelonephritis**	RR= 0.55 [0.15, 1.97] NS
		N=2 n=355 (COBSG 1978, Savage 1975)	**Renal growth** *(Any parenchymal damage on dimercaptosuccinic acid (DMSA) kidney scan or intravenous pyelogram (IVP) four to six months following treatment, measured by kidney growth)*	MD= 0.62 [-0.43, 1.68] NS

Table 286

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
COBSG 1978{COBSG, 1978 #180}	248 randomised, 208 analysed	Age 5 to 12 years, all participants were female	Follow-up: 4 years	Antibiotic therapy (Initially 7 or 14 day courses were given, but longer courses (3 to 12 months) of low dose maintenance therapy were given to girls with recurrent bacteriuria. Antibiotics were prescribed depending on the drug sensitivity of the organism; usually co-trimoxazole, but also ampicillin, nitrofurantoin, nalidixic acid and pivmecillinam.) vs no treatment	RANDOM SEQUENCE GENERATION Unclear risk (Not reported) ALLOCATION CONCEALMENT Unclear risk (Not reported) BLINDING Low risk INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk
NCBRG	211	Age 4 to 18 years, all particicpants	Follow-	Two year courses of	RANDOM SEQUENCE GENERATION

1981{NCBRG, 1981 #181}	randomised, 199 analysed	were female	up: 2 years and 5 years	antibiotics were prescribed depending on the drug sensitivity of the organism. Antibiotics included co-trimoxazole (4 mg/kg trimethoprim daily for three weeks followed by sulphadimidine 40 to 50 mg/kg), nalidixic acid 40 mg/kg/day (reducing to 20 to 30 mg/kg/day after 3 weeks), ampicillin 40 mg/kg/day (reducing to 20 to 30 mg/kg/day) and nitrofurantoin 5 to 8 mg/kg (reducing to 2 to 3 mg/kg). Therapy was changed if resistant organisms emerged or side effects developed Vs no treatment	Unclear risk (Not reported) ALLOCATION CONCEALMENT Low risk BLINDING Unclear risk (Not reported) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk
Savage 1975{Savage, 1975 #182}	63 randomised, 42 analysed	Age: 5 to 7 years 10 months, all participants were female	Follow-up 6 months	Girls with normal IVP and MCUGs received 3 months' treatment and a further 3 months treatment following their first relapse; later relapses received 6 months treatment. Antibiotic treatments were prescribed on the drug sensitivity of the organism and included ampicillin (250 mg four times daily for	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Unclear risk (Not reported) BLINDING Low risk INCOMPLETE OUTCOME DATA Unclear risk (Loss to follow-up was reported but discrepancies exist between reporting in the text and tables. It appears that two children (3%)were lost to follow-up soon

				2 weeks with no prophylaxis); nitrofurantoin (8 mg/kg/day 2 weeks followed by half this dose prophylactically for the next 10 weeks); or trimethoprim 40 mg + sulphamethoxazole 200 mg three times daily for 2 weeks followed by 10 weeks prophylaxis with 20 to 40 mg trimethoprim and 100 to 200 mg sulphamethoxazole twice daily. Vs no treatment	after treatment and by the 2 year assessment, 13 (4/ 9 control/treatment) (21%) children were lost to follow-up) SELECTIVE REPORTING Low risk

Table 287

Author's conclusions: The included studies do not provide sufficient detail about the harms and benefits of treating covert bacteriuria to enable forming reliable conclusions. It appears that antibiotic treatment for covert bacteriuria is not likely to offer long-term benefit to children. Although it is possible to eliminate urinary infections with antibiotics, this does not appear to be an effective course of action in children.

13.2.1.2.2 Summary and conclusions

Antibiotics versus no treatment for covert bacteriuria in children			
Bibliography: Fitzgerald 2012b{Fitzgerald, 2012 #115}			
Outcomes	**N° of participants (studies) Follow up**	**Results (95%CI)**	**Quality of the evidence (GRADE)**
Cystitis (lower UTI)	205 (1 study)	RR= 1.67 [0.50, 5.52] NS	⊕⊖⊖⊖: **VERY LOW** As assessed by Cochrane group
Pyelonephritis	247 (2 studies)	RR= 0.55 [0.15, 1.97] NS	⊕⊖⊖⊖: **VERY LOW** As assessed by Cochrane group
Renal growth *(as a marker for parenchymal damage)*	355 (2 studies)	MD= 0.62 [-0.43, 1.68] NS	⊕⊖⊖⊖: **VERY LOW** As assessed by Cochrane group

Table 288

In this meta-analysis, a treatment with antibiotics was compared to no treatment in children with covert bacteriuria (defined as at least one culture of a known urinary pathogen (of at least 10^5 cfu/mL) in a child who had no known associated urinary symptoms at the time of diagnosis).

The children in these trials were aged 4 to 18 and all female. The follow-up was 6 months to 5 years. They had no pre-existing uropathies or underlying kidney disease.

The antibiotic treatment was prescribed depending on the drug sensitivity and included co-trimoxazole, ampicillin, nitrofurantoin, nalidixic acid, pivmecillinam and sulphadimidine. The duration of treatment ranged from 2 weeks to 2 years.

There were few trials that studied hard endpoints in this population. All had some methodological problems (small sample sizes, unclear blinding and allocation concealment). Furthermore, there was significant heterogeneity between groups, possibly due to differences in antibiotic regimen. These problems severely limit our confidence in the results.

In girls *with covert bacteriuria*, a treatment with antibiotics for, compared to no treatment, **did not** result in a statistically significant difference in *cystitis*, *pyelonephritis*, *or renal growth.*
GRADE: VERY LOW quality of evidence

13.2.2 Antibiotic A versus antibiotic B

13.2.2.1 Trimethoprim (10d) vs trimethoprim+sulfamethoxazole (10d)

13.2.2.1.1 Clinical evidence profile

Meta-analysis: Cochrane Fitzgerald 2012a{Fitzgerald, 2012 #114} "Antbiotics for treating lower urinary tract infection in children"
Inclusion criteria: All randomised controlled trials (RCTs) and quasi-RCTs (RCTs
in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) in which antibiotic therapy was used to treat lower UTI in children. Children aged zero to 18 years with bacteriologically proven UTI (at least one culture of a known urinary pathogen (bacterial culture > 10^5 cfu/mL) in a child with first time or recurrent UTI and who had at least one localised symptom of UTI (such as dysuria or frequency) treated with antibiotics in primary and community health care settings or an outpatient department were included.
Exclusion:
Children hospitalised for a condition not related to UTI. Children with bacteriologically proven UTI and symptoms or signs of systemic illness (including fever, loin pain, toxicity). Children with covert bacteriuria (non-symptomatic). Children with pre-existing renal abnormalities or known underlying renal conditions (including high grade (3-4) VUR, nephrotic syndrome and neurogenic bladder). Children receiving prophylactic antibiotics for UTI. Children receiving antibiotics for any other condition. Immunosuppressed children.
Search strategy: We searched the Cochrane Renal Group's Specialised Register (May 2012) through contact with the Trials' Search Co-ordinator using search terms relevant to this review.
The Cochrane Renal Group's Specialised Register contains studies identified from:
1. Quarterly searches of the Cochrane Central Register of Controlled Trials CENTRAL;
2. Weekly searches of MEDLINE OVID SP;
3. Handsearching of renal-related journals & the proceedings of major renal conferences;
4. Searching of the current year of EMBASE OVID SP;
5. Weekly current awareness alerts for selected renal-journals;
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal & ClinicalTrials.gov
Assessment of quality of included trials: yes

Table 289

Ref	Comparison	N/n	Outcomes	Result (95% CI)

Cochrane Fitzgerald 2012a{Fitzgerald, 2012 #114}	**Trimethoprim (10d) versus trimethoprim+sulfamethoxazole (10d)**	N=1 n= 59 (Ahmed 2001)	**Persistent symptoms** *(at completion of treatment)*	Crude AR: 2/30 vs 0/29 RR: 4.84 [0.24, 96.66] NS
		N=1 n= 59 (Ahmed 2001)	**Recurrence**	Crude AR: 1/30 vs 0/29 RR: 2.90 [0.12, 68.50] NS

Table 290

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
Ahmed 2001{Ahmed, 2001 #177}	125 randomised, 59 analysed	Children aged between 6 months and 12 years	16-19 days following treatment	10-day TMP (monotherapy; 10 mg/kg/d) in 2 doses versus 10-day TMP (8 mg/kg/d) + (SMX 40 mg/kg/d) in 2 doses	RANDOM SEQUENCE GENERATION Unclear risk (Not reported) ALLOCATION CONCEALMENT Unclear risk (Not reported) BLINDING Low risk INCOMPLETE OUTCOME DATA High risk (Less than half the randomised patients were analysed, no reason for losses to follow-up given) SELECTIVE REPORTING Low risk

Table 291

Author's conclusions: This review adds to the evidence that short-course therapy is an appropriate therapy for children with lowerUTI.While 10 days of therapy was significantly more effective than single-dose therapy, there were no differences in either this review or Michael 2003 between short and longer duration antibiotic therapy. Single-dose therapy is not recommended in children with UTI; 10-day treatment was significantly more effective in eliminating bacteriuria.

No comparisons showed any differences between groups for persisting symptoms, recurrence, or re-infection following treatment, however this is due to a paucity of RCTs rather than demonstrating equivalence. This review did not provide incontrovertible evidence about the optimal duration of antibiotic therapy or which antibiotic should be used.

13.2.2.1.2 Summary and conclusions

Trimethoprim (10d) versus trimethoprim+sulfamethoxazole (10d) for lower urinary tract infection			
Bibliography: Cochrane Fitzgerald 2012a{Fitzgerald, 2012 #114}			
Outcomes	**N° of participants (studies) Follow up**	**Results (RR(95%CI))**	**Quality of the evidence (GRADE)**
Persistent symptoms	59 (1 study)	RR: 4.84 [0.24, 96.66] NS	⨁⊖⊖⊖: **VERY LOW** As assessed by Cochrane group
Recurrence	59 (1 study)	RR: 2.90 [0.12, 68.50] NS	⨁⊖⊖⊖: **VERY LOW** As assessed by Cochrane group

Table 292

In this meta-analysis, a treatment with trimethoprim was compared to a treatment with trimethoprim and sulfamethoxazole, in children with a lower urinary tract infection.

The children were aged between 6 months and 12 years. The follow-up was 16-19 days after treatment.

The treatment duration for both arms was 10 days. The dose of trimethoprim in monotherapy was 10 mg/kg/day in 2 doses, while in the combination treatment the dose was 8 mg/kg/day of trimethoprim and 40 mg/kg/day of sulfamethoxazole, in 2 doses.

The meta-analysis found only one small trial that studied this comparison, and it had serious methodological flaws (unclear randomisation and allocation, no intention-to-treat analysis, loss to follow-up >10%). This severely limits our confidence in the results.

In children *with lower urinary tract infection*, a treatment with trimethoprim for 10 days, compared with trimethoprim and sulfamethoxazole for 10 days, **did not** result in a statistically significant difference in *persistent symptoms,* or *recurrence*.
GRADE: VERY LOW quality of evidence

13.2.2.2 Cefadroxil (10d) vs ampicillin (10d)

13.2.2.2.1 Clinical evidence profile

Meta-analysis: Cochrane Fitzgerald 2012a{Fitzgerald, 2012 #114} "Antbiotics for treating lower urinary tract infection in children" Inclusion criteria: All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) in which antibiotic therapy was used to treat lower UTI in children. Children aged zero to 18 years with bacteriologically proven UTI (at least one culture of a known urinary pathogen (bacterial culture > 10^5 cfu/mL) in a child with first time or recurrent UTI and who had at least one localised symptom of UTI (such as dysuria or frequency) treated with antibiotics in primary and community health care settings or an outpatient department were included. Exclusion: Children hospitalised for a condition not related to UTI. Children with bacteriologically proven UTI and symptoms or signs of systemic illness (including fever, loin pain, toxicity). Children with covert bacteriuria (non-symptomatic). Children with pre-existing renal abnormalities or known underlying renal conditions (including high grade (3-4) VUR, nephrotic syndrome and neurogenic bladder). Children receiving prophylactic antibiotics for UTI. Children receiving antibiotics for any other condition. Immunosuppressed children. Search strategy: We searched the Cochrane Renal Group's Specialised Register (May 2012) through contact with the Trials' Search Co-ordinator using search terms relevant to this review. The Cochrane Renal Group's Specialised Register contains studies identified from: 1. Quarterly searches of the Cochrane Central Register of Controlled Trials CENTRAL; 2. Weekly searches of MEDLINE OVID SP; 3. Handsearching of renal-related journals & the proceedings of major renal conferences; 4. Searching of the current year of EMBASE OVID SP; 5. Weekly current awareness alerts for selected renal-journals; 6. Searches of the International Clinical Trials Register (ICTRP) Search Portal & ClinicalTrials.gov Assessment of quality of included trials: yes

Table 293

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Cochrane Fitzgerald 2012a{Fitzgerald, 2012 #114}	**Cefadroxil (10d) versus ampicillin (10 d)**	N=1 n=32 (Malaka-Zafirui 1984)	**Persistent symptoms** *(at completion of treatment)*	Crude Ar: 0/16 vs 1/16 RR: 0.33 [0.01, 7.62] NS

Table 294

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
Malaka-Zafirui 1984{Malaka-Zafiriu, 1984 #173}	32	Children aged 8 months to 11.1 years	10 days following treatment	Cefadroxil 25 mg/kg once daily for 10 days versus Ampicillin 50 mg/kg/d in 4 divided doses for 10 days	RANDOM SEQUENCE GENERATION Unclear risk (Not reported) ALLOCATION CONCEALMENT Unclear risk (Not reported) BLINDING Unclear risk (Not reported) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk

Table 295

Author's conclusions: This review adds to the evidence that short-course therapy is an appropriate therapy for children with lowerUTI.While 10 days of therapy was significantly more effective than single-dose therapy, there were no differences in either this review or Michael 2003 between short and longer duration antibiotic therapy. Single-dose therapy is not recommended in children with UTI; 10-day treatment was significantly more effective in eliminating bacteriuria.

No comparisons showed any differences between groups for persisting symptoms, recurrence, or re-infection following treatment, however this is due to a paucity of RCTs rather than demonstrating equivalence. This review did not provide incontrovertible evidence about the optimal duration of antibiotic therapy or which antibiotic should be used.

13.2.2.2.2 Summary and conclusions

Cefadroxil (10d) versus ampicillin (10d) for lower urinary tract infection			
Bibliography: Cochrane Fitzgerald 2012a{Fitzgerald, 2012 #114}			
Outcomes	**N° of participants (studies) Follow up**	**Results (RR(95%CI))**	**Quality of the evidence (GRADE)**
Persistent symptoms	32 (1 study)	RR: 0.33 [0.01, 7.62] NS	⨁⊖⊖⊖: **VERY LOW** As assessed by Cochrane group

Table 296

In this meta-analysis, a treatment with cefadroxil was compared to a treatment with ampicillin, in children with a lower urinary tract infection.

The children were aged between 8 months and 11 years. The follow-up was 10 days after treatment.

The treatment duration for both arms was 10 days. The dose of cefadroxil was 25mg/kg/day in one dose. Ampicillin was given in a dose of 50mg/kg/day in 4 divided doses. In Belgium, the usually recommended posology of cefadroxil is 30 mg/kg/day in 2 to 3 doses (according to BAPCOC).

The meta-analysis found only one small trial that studied this comparison, and it had serious methodological flaws (unclear randomisation, allocation, and blinding). This severely limits our confidence in the results.

In children *with lower urinary tract infection*, a treatment with cefadroxil for 10 days, compared with ampicillin for 10 days, **did not** result in a statistically significant difference in *persistent symptoms.*
GRADE: VERY LOW quality of evidence

13.2.3 Duration of antibiotic treatment

13.2.3.1 Single-dose versus conventional 10d treatment

13.2.3.1.1 Clinical evidence profile

Meta-analysis: Cochrane Fitzgerald 2012a{Fitzgerald, 2012 #114} "Antbiotics for treating lower urinary tract infection in children"
Inclusion criteria: All randomised controlled trials (RCTs) and quasi-RCTs (RCTs
in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) in which antibiotic therapy was used to treat lower UTI in children. Children aged zero to 18 years with bacteriologically proven UTI (at least one culture of a known urinary pathogen (bacterial culture > 10^5 cfu/mL) in a child with first time or recurrent UTI and who had at least one localised symptom of UTI (such as dysuria or frequency) treated with antibiotics in primary and community health care settings or an outpatient department were included.
Exclusion:
Children hospitalised for a condition not related to UTI. Children with bacteriologically proven UTI and symptoms or signs of systemic illness (including fever, loin pain, toxicity). Children with covert bacteriuria (non-symptomatic). Children with pre-existing renal abnormalities or known underlying renal conditions (including high grade (3-4) VUR, nephrotic syndrome and neurogenic bladder). Children receiving prophylactic antibiotics for UTI. Children receiving antibiotics for any other condition. Immunosuppressed children.
Search strategy: We searched the Cochrane Renal Group's Specialised Register (May 2012) through contact with the Trials' Search Co-ordinator using search terms relevant to this review.
The Cochrane Renal Group's Specialised Register contains studies identified from:
1. Quarterly searches of the Cochrane Central Register of
Controlled Trials CENTRAL;
2. Weekly searches of MEDLINE OVID SP;
3. Handsearching of renal-related journals & the proceedings
of major renal conferences;
4. Searching of the current year of EMBASE OVID SP;
5. Weekly current awareness alerts for selected renal-journals;
6. Searches of the International Clinical Trials Register
(ICTRP) Search Portal & ClinicalTrials.gov
Assessment of quality of included trials:

Table 297

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Cochrane Fitzgerald 2012a{Fitzgerald, 2012 #114}	**Single dose versus conventional 10 day**	N=1 n= 30 (Fine 1985)	**Persistent symptoms** *(at completion of treatment)*	Crude AR: 1/16 vs 3/14 RR: 0.29 [0.03, 2.50] NS
		N=2 n= 79 (Shapiro 1981, Wallen 1983)	**Recurrence**	Crude AR: 9/41 vs 6/38 1.38 [0.55, 3.50] NS

Table 298

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
Fine 1985{Fine, 1985 #168}	34 randomised, 31 analysed	Female adolescents aged 12 to 18 years	5 days following treatment	Single-dose amoxicillin 3.0 g vs 10-day amoxicillin 250 mg, 3 times/day	RANDOM SEQUENCE GENERATION Unclear risk (Not reported) ALLOCATION CONCEALMENT Unclear risk (Not reported) BLINDING Unclear risk (Not reported) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk
Shapiro 1981{Shapiro, 1981 #175}	37 randomised, 35 analysed	Girls aged 2 to 18 years	3 months after treatment	Single-dose amoxicillin 50 mg/kg (to a maximum of 2.5 g) vs 10-day amoxicillin 40	RANDOM SEQUENCE GENERATION Unclear risk (Not reported) ALLOCATION CONCEALMENT Unclear risk (Not reported) BLINDING

				mg/kg/d in 3 divided doses (to a maximum of 500 mg/ dose)	Low risk INCOMPLETE OUTCOME DATA Unclear risk (Two children were excluded from analyses because the second urine culture was negative) SELECTIVE REPORTING Low risk
Wallen 1983{Wallen, 1983 #176}	54 randomised, 49 analysed	Girls aged 1 year to 12 years	40 days after treatment	Single-dose intramuscular amikacin sulfate 7.5 mg/kg (to a maximum of 240 mg) vs 10-day sulfisoxazole 150 mg/kg/day in 4 divided doses	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Unclear risk (Not reported) BLINDING Unclear risk (Not reported) INCOMPLETE OUTCOME DATA High risk (At the 2-4 day follow-up, 6 girls were lost to follow-up. By the 30-40 day follow-up, 10 girls were lost to follow-up) SELECTIVE REPORTING Low risk

Table 299

Author's conclusions: This review adds to the evidence that short-course therapy is an appropriate therapy for children with lowerUTI.While 10 days of therapy was significantly more effective than single-dose therapy, there were no differences in either this review or Michael 2003 between short and longer duration antibiotic therapy. Single-dose therapy is not recommended in children with UTI; 10-day treatment was significantly more effective in eliminating bacteriuria.

No comparisons showed any differences between groups for persisting symptoms, recurrence, or re-infection following treatment, however this is due to a paucity of RCTs rather than demonstrating equivalence. This review did not provide incontrovertible evidence about the optimal duration of antibiotic therapy or which antibiotic should be used.

13.2.3.1.2 Summary and conclusions

Single dose versus conventional 10 day treatment for lower urinary tract infection			
Bibliography: Cochrane Fitzgerald 2012a{Fitzgerald, 2012 #114}			
Outcomes	**N° of participants (studies) Follow up**	**Results (RR(95%CI))**	**Quality of the evidence (GRADE)**
Persistent symptoms	30 (1 study)	RR: 0.33 [0.01, 7.62] NS	⨁⊖⊖⊖: **VERY LOW** As assessed by Cochrane group
Recurrence	79 (2 studies)	1.38 [0.55, 3.50] NS	⨁⊖⊖⊖: **VERY LOW** As assessed by Cochrane group

Table 300

In this meta-analysis, a treatment with a single dose of an antibiotic was compared to a conventional 10 day course, in children with a lower urinary tract infection.

The children were aged between 1 year and 18 years. They were all female. The follow-up was varied between 5 days and 3 months after treatment.

2 trials compared a single dose of amoxicillin (in a maximum dose of 2.5 to 3g) to a 10 day course of amoxicillin (750-1500 mg/day in 3 doses). One study compared a single dose of intramuscular amikacin sulfate to a 10 day course of sulfisoxazole.

The meta-analysis found only small trials that studied this comparison, and these studies had methodological flaws (unclear randomisation, allocation, and blinding, no intention-to-treat analysis). This severely limits our confidence in the results.

The authors of the Cochrane review did not recommend a single dose treatment for UTI in children, as it was significantly less effective at eliminating bacteriuria than a 10-day course. However, we did not report this outcome as we focused on clinical outcomes.

In children *with lower urinary tract infection*, a treatment with a single dose of an antibiotic, compared with a conventional 10 day course, **did not** result in a statistically significant difference in *persistent symptoms.*
GRADE: VERY LOW quality of evidence

13.2.3.2 Single dose versus short course (3-7d)

13.2.3.2.1 Clinical evidence profile

Meta-analysis: Cochrane Fitzgerald 2012a{Fitzgerald, 2012 #114} "Antbiotics for treating lower urinary tract infection in children"
Inclusion criteria: All randomised controlled trials (RCTs) and quasi-RCTs (RCTs
in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) in which antibiotic therapy was used to treat lower UTI in children. Children aged zero to 18 years with bacteriologically proven UTI (at least one culture of a known urinary pathogen (bacterial culture > 10^5 cfu/mL) in a child with first time or recurrent UTI and who had at least one localised symptom of UTI (such as dysuria or frequency) treated with antibiotics in primary and community health care settings or an outpatient department were included.
Exclusion:
Children hospitalised for a condition not related to UTI. Children with bacteriologically proven UTI and symptoms or signs of systemic illness (including fever, loin pain, toxicity). Children with covert bacteriuria (non-symptomatic). Children with pre-existing renal abnormalities or known underlying renal conditions (including high grade (3-4) VUR, nephrotic syndrome and neurogenic bladder). Children receiving prophylactic antibiotics for UTI. Children receiving antibiotics for any other condition. Immunosuppressed children.
Search strategy: We searched the Cochrane Renal Group's Specialised Register (May 2012) through contact with the Trials' Search Co-ordinator using search terms relevant to this review.
The Cochrane Renal Group's Specialised Register contains studies identified from:
1. Quarterly searches of the Cochrane Central Register of
Controlled Trials CENTRAL;
2. Weekly searches of MEDLINE OVID SP;
3. Handsearching of renal-related journals & the proceedings
of major renal conferences;
4. Searching of the current year of EMBASE OVID SP;
5. Weekly current awareness alerts for selected renal-journals;
6. Searches of the International Clinical Trials Register
(ICTRP) Search Portal & ClinicalTrials.gov
Assessment of quality of included trials:

Table 301

Ref	Comparison	N/n	Outcomes	Result (95% CI)

Cochrane Fitzgerald 2012a{Fitzgerald, 2012 #114}	**Single dose versus short course (3-7 days)**	N=2 n=145 (Grimwood 1988, Lidefelt 1991)	**Recurrence** *(at completion of treatment)*	Crude AR: 11/75 vs 7/70 RR: 1.50 [0.43, 5.26] NS
		N=1 n= 45 (Grimwood 1988)	**Re-infection**	Crude AR: 1/25 vs 5/20 RR: 0.16 [0.02, 1.26] NS

Table 302

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by
Grimwood 1988{Grimwood, 1988 #169}	45	Children aged 2 weeks to 12 years	unclear	Single intramuscular gentamicin injection 3 mg/kg vs 7-day course of appropriate antibiotic depending on culture sensitivity in standard doses (included TMP-SMX, amoxicillin, cephlosporins)	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Unclear risk (Not reported) BLINDING Unclear risk (Not reported) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk
Lidefelt 1991{Lidefelt, 1991 #172}	100	Children aged less than 3 years to 12 years	unclear	Single-dose TMP 6 mg/kg vs 5-day TMP 3 mg/kg/12 h	RANDOM SEQUENCE GENERATION Unclear risk (Not reported) ALLOCATION CONCEALMENT Unclear risk (Not reported) BLINDING Unclear risk (Not reported) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING

					Low risk

Table 303

Author's conclusions: This review adds to the evidence that short-course therapy is an appropriate therapy for children with lowerUTI.While 10 days of therapy was significantly more effective than single-dose therapy, there were no differences in either this review or Michael 2003 between short and longer duration antibiotic therapy. Single-dose therapy is not recommended in children with UTI; 10-day treatment was significantly more effective in eliminating bacteriuria.

No comparisons showed any differences between groups for persisting symptoms, recurrence, or re-infection following treatment, however this is due to a paucity of RCTs rather than demonstrating equivalence. This review did not provide incontrovertible evidence about the optimal duration of antibiotic therapy or which antibiotic should be used.

13.2.3.2.2 Summary and conclusions

Single dose versus short course (3-7 days) for lower urinary tract infection			
Bibliography: Cochrane Fitzgerald 2012a{Fitzgerald, 2012 #114}			
Outcomes	**N° of participants (studies) Follow up**	**Results (RR(95%CI))**	**Quality of the evidence (GRADE)**
Recurrence	145 (2 studies)	RR: 1.50 [0.43, 5.26] NS	⨁⊖⊖⊖: **VERY LOW** As assessed by Cochrane group
Re-infection	45 (1 study)	RR: 0.16 [0.02, 1.26] NS	⨁⊖⊖⊖: **VERY LOW** As assessed by Cochrane group

Table 304

In this meta-analysis, a treatment with a single dose of an antibiotic was compared to a short course of 3-5 days, in children with a lower urinary tract infection.

The children were aged between 2 weeks and 12 years.

One trial compared a single dose of trimethoprim (6 mg/kg) with a 5-day course of trimethoprim (6 mg/kg/day in 2 doses), the other trial compared a single intramuscular injection of gentamicin with a 7 day course of an antibiotic depending on culture sensitivity.

The meta-analysis found only two small trials that studied this comparison, and these studies had methodological flaws (unclear allocation concealment and blinding). This severely limits our confidence in the results.

The authors of the Cochrane review did not recommend a single dose treatment for UTI in children, as it was significantly less effective at eliminating bacteriuria than a 10-day course. However, we did not report this outcome as we focused on clinical outcomes.

In children *with lower urinary tract infection*, a treatment with a single dose of an antibiotic, compared with a short course of 3-5 days, **did not** result in a statistically significant difference in *recurrence* or *re-infection.*
GRADE: VERY LOW quality of evidence

13.2.3.3 Short course (3-7d) versus long course (10-14d)

13.2.3.3.1 Clinical evidence profile

Meta-analysis: Cochrane Fitzgerald 2012a{Fitzgerald, 2012 #114} "Antbiotics for treating lower urinary tract infection in children"
Inclusion criteria: All randomised controlled trials (RCTs) and quasi-RCTs (RCTs
in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) in which antibiotic therapy was used to treat lower UTI in children. Children aged zero to 18 years with bacteriologically proven UTI (at least one culture of a known urinary pathogen (bacterial culture > 10^5 cfu/mL) in a child with first time or recurrent UTI and who had at least one localised symptom of UTI (such as dysuria or frequency) treated with antibiotics in primary and community health care settings or an outpatient department were included.
Exclusion:
Children hospitalised for a condition not related to UTI. Children with bacteriologically proven UTI and symptoms or signs of systemic illness (including fever, loin pain, toxicity). Children with covert bacteriuria (non-symptomatic). Children with pre-existing renal abnormalities or known underlying renal conditions (including high grade (3-4) VUR, nephrotic syndrome and neurogenic bladder). Children receiving prophylactic antibiotics for UTI. Children receiving antibiotics for any other condition. Immunosuppressed children.
Search strategy: We searched the Cochrane Renal Group's Specialised Register (May 2012) through contact with the Trials' Search Co-ordinator using search terms relevant to this review.
The Cochrane Renal Group's Specialised Register contains studies identified from:
1. Quarterly searches of the Cochrane Central Register of
Controlled Trials CENTRAL;
2. Weekly searches of MEDLINE OVID SP;
3. Handsearching of renal-related journals & the proceedings
of major renal conferences;
4. Searching of the current year of EMBASE OVID SP;
5. Weekly current awareness alerts for selected renal-journals;
6. Searches of the International Clinical Trials Register
(ICTRP) Search Portal & ClinicalTrials.gov
Assessment of quality of included trials: yes

Table 305

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Cochrane Fitzgerald 2012a{Fitzgerald, 2012 #114}	**Short course (3-7 days) versus long course (10 -14 days**	N=4 n=328 (CSG 1991, Helin 1984, Khan 1981, Mitnik 1985)	**Recurrence**	Crude AR: 25/163 vs 21/165 RR: 1.25 [0.74, 2.13] NS
		N=2 n=211 (CSG 1991, Helin 1984)	**Re-infection**	Crude AR: 14/109 vs 15/102 RR: 0.88 [0.44, 1.74] NS

Table 306

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
CSG 1991{CSG, 1991 #167}	359 randomised, 264 analysed; 168 included in this review	Children aged 1 to 15 years with, all female	10 days following treatment	Pivmecillinam, 20-40 mg/kg/d in 2 doses for 3 days vs Sulfamethizole, 40-80 mg/kg/d in 2 doses for 10 days	RANDOM SEQUENCE GENERATION Unclear risk (To ensure an equal number of patients in each group, a block randomisation method was used. Randomisation was in blocks of 6 within each of the 10 participating departments. No details about the way the block randomisation was performed were reported) ALLOCATION CONCEALMENT Low risk BLINDING Unclear risk (Not reported) INCOMPLETE OUTCOME DATA

					Unclear risk (36 children did not fulfil inclusion criteria (26 bacteriuria not significant, 10 provided bag sample); treatment was discontinued in 6 children before scheduled; 32 children did not have urine cultures completed within 10 days from treatment; 2 children were not evaluated for other reasons; 19 boys were excluded because of the small number and because they were not evenly distributed between groups. The side effects of the 95 children who were not analysed were included as they received treatment) SELECTIVE REPORTING Low risk
Helin 1984{Helin, 1984 #170}	43	Children aged under 15 years	Follow-up 8 months	3-day cephalexin 25-50 mg/kg/d in 2 doses vs 10-day nitrofurantoin 3-4 mg/kg/d in 2 or 3 doses	RANDOM SEQUENCE GENERATION Unclear risk (Not reported) ALLOCATION CONCEALMENT Unclear risk (Not reported) BLINDING Unclear risk (Not reported) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk

Khan 1981{Khan, 1981 #171}	54	Children aged six months to 15 years	>2 months following treatment	3-day treatment vs 10-day treatment (Antimicrobial agents were 'chosen at random' for both groups and included ampicillin, sulfisoxazole and cephalexin in conventional doses given orally 4 times/day)	RANDOM SEQUENCE GENERATION Unclear risk (Alternation) ALLOCATION CONCEALMENT Unclear risk (Not reported) BLINDING Unclear risk (Not reported) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk
Mitnik 1985{Mitnik, 1985 #178}	98	Children aged 2 years to 14 years	2-3 months	3-day antibiotics vs 5-day antibiotics vs 10-day antibiotics (Children were administered a first generation cephalosporin, nitrofurantoin or TMPSMX depending on the sensitivity of the organism cultured)	RANDOM SEQUENCE GENERATION Unclear risk (Not reported) ALLOCATION CONCEALMENT Unclear risk (Not reported) BLINDING Unclear risk (Not reported) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk

Table 307

Author's conclusions: This review adds to the evidence that short-course therapy is an appropriate therapy for children with lowerUTI.While 10 days of therapy was significantly more effective than single-dose therapy, there were no differences in either this review or Michael 2003 between short and longer duration antibiotic therapy. Single-dose therapy is not recommended in children with UTI; 10-day treatment was significantly more effective in eliminating bacteriuria.

No comparisons showed any differences between groups for persisting symptoms, recurrence, or re-infection following treatment, however this is due to a paucity of RCTs rather than demonstrating equivalence. This review did not provide incontrovertible evidence about the optimal duration of antibiotic therapy or which antibiotic should be used.

13.2.3.3.2 Summary and conclusions

Short course (3-7 days) versus long course (10 -14 days) treatment for lower urinary tract infection			
Bibliography: Cochrane Fitzgerald 2012a{Fitzgerald, 2012 #114}			
Outcomes	**N° of participants (studies) Follow up**	**Results (RR(95%CI))**	**Quality of the evidence (GRADE)**
Recurrence	328 (4 studies)	RR: 1.25 [0.74, 2.13] NS	⨁⊖⊖⊖: **VERY LOW** As assessed by Cochrane group
Re-infection	211 (2 studies)	RR: 0.88 [0.44, 1.74] NS	⨁⊖⊖⊖: **VERY LOW** As assessed by Cochrane group

Table 308

In this meta-analysis, a treatment with a short course (3-7 days) of an antibiotic was compared to a long course of 10-14 days, in children with a lower urinary tract infection.

The children were aged between 6 months and 15 years. The follow-up ranged between 10 days and 8 months after treatment.

The studies were clinically heterogenous, as the treatment given differed a lot between studies. The antibiotics given in the trials were not necessarily the same in both arms, and included ampicillin, sulfisoxazole, cephalexin, nitrofurantoin, pivmecillinam and sulfamethizole. Sulfisoxazole, pivmecillinam and sulfamethizole are not available in Belgium.

The studies included in this meta-analysis had methodological flaws (unclear randomisation, allocation concealment and blinding). This limits our confidence in the results.

In children *with lower urinary tract infection*, a treatment with a short course (3-7 days) of an antibiotic, compared with a long course of 10-14 days, **did not** result in a statistically significant difference in *recurrence* or *re-infection.*
GRADE: VERY LOW quality of evidence

13.3 Pyelonephritis: Evidence tables and conclusions

13.3.1 Antibiotics versus placebo or no treatment

13.3.1.1 Clinical evidence profile

Antibiotic therapy versus placebo or no treatment for pyelonephritis in children

Meta-analysis: Strohmeier 2014{Strohmeier, 2014 #111} "Antibiotics for acute pyelonephritis in children"
Inclusion criteria:
"All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) in which antibiotics were used in the treatment of children (birth to 18 years) with acute pyelonephritis were included.
Where studies included both children with acute pyelonephritis and those with cystitis, these were included if data for participants with acute pyelonephritis could be extracted separately; otherwise, these studies were excluded."
Search strategy:
"For the 2014 update, we searched the Cochrane Renal Group's Specialised Register through contact with the Trials' Search Coordinator using search terms relevant to this review. The Cochrane Renal Group's Specialised Register contains studies identified from the following sources.
1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP Antibiotics
3. Handsearching of renal-related journals and the proceedings of major renal conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected renal journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov."
Assessment of quality of included trials: yes

Table 309

This systematic review found no RCTs or quasi-RCTs that studied this comparison.

13.3.1.2 Summary and conclusions

In this meta-analysis, a search was conducted for RCTs and quasi-RCTs where antibiotic therapy was compared to placebo or no therapy in children with pyelonephritis.

There were no RCTs or quasi-RCTs that met the inclusion criteria.

13.3.2 Mode of administration of antibiotics

13.3.2.1 Oral versus IV followed by oral (11 days) therapy

13.3.2.1.1 Clinical evidence profile

Meta-analysis: Strohmeier 2014{Strohmeier, 2014 #111} "Antibiotics for acute pyelonephritis in children"
Inclusion criteria:
"All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) in which antibiotics were used in the treatment of children (birth to 18 years) with acute pyelonephritis were included.
Where studies included both children with acute pyelonephritis and those with cystitis, these were included if data for participants with acute pyelonephritis could be extracted separately; otherwise, these studies were excluded."
"Children with previously diagnosed urinary tract abnormalities including VUR or previous UTI could be included."
Search strategy:
"For the 2014 update, we searched the Cochrane Renal Group's Specialised Register through contact with the Trials' Search Coordinator using search terms relevant to this review. The Cochrane Renal Group's Specialised Register contains studies identified from the following sources.
1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP Antibiotics
3. Handsearching of renal-related journals and the proceedings of major renal conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected renal journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov."
Assessment of quality of included trials:

Table 310

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Strohmeier 2014{Strohmeier, 2014 #111}	**Oral versus IV followed by oral (11 days) therapy**	N=2 n=808 (Hoberman 1999, Montini 2007)	Time to fever resolution	MD: 2.05 [-0.84, 4.94] NS

		N=2 n=542 (Montini 2007, Neuhaus 2008)	Number with persistent UTI at 72 hours	Crude AR: 1/266 vs 1/276 RR: 1.10 [0.07, 17.41] NS
		N=1 n=287 (Hoberman 1999)	Recurrent symptomatic UTI within 6 months	Crude AR:7/140 vs 11/147 RR: 0.67 [0.27, 1.67] NS
		N=4 n=943 (Hoberman 1999, Montini 2007, Neuhaus 2008, Bocquet 2012)	Persistent kidney damage at 6-12 months (all included patients with acute pyelonephritis)	Crude AR: 88/470 vs 106/473 RR: 0.82 [0.59, 1.12] NS
		N=4 n=681 (Hoberman 1999, Montini 2007, Neuhaus 2008, Bocquet 2012)	Persistent kidney damage at 6-12 months (patients with kidney parenchymal damage on initial DMSA)	Crude AR: 88/350 vs 106/331 RR: 0.79 [0.61, 1.03] NS

Table 311

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of

					review
Bocquet 2012{Bocquet, 2012 #183}	171	Children aged 1 month to 36 months;	follow-up: 6 to 8 months	Oral cefixime: 8 mg/kg single dose, then oral 4 mg/kg/dose twice daily for 10 days vs IV ceftriaxone: 50 mg/kg daily for 4 days and Oral cefixime: 4 mg/kg/dose twice daily for 6 days (days 5 to 10)	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Unclear risk (No information provided) BLINDING OF PARTICIPANTS AND PERSONNEL High risk (No blinding. Clinical management could be influenced by lack of blinding) BLINDING OF OUTCOME ASSESSMENT Low risk INCOMPLETE OUTCOME DATA High risk (18.5%(27/146) excluded for reasons other than no APN on acute DMSA) SELECTIVE REPORTING High risk (No report on bacteriologic resolution of UTI) OTHER BIAS Low risk
Hoberman 1999{Hoberman, 1999 #184}	306	Children aged 1 month to 2 years	follow-up: 7 months	Oral cefixime: 16 mg/kg on day 1 then 4 mg/kg/dose, 2 doses/d for 13 days vs IV cefotaxime: 50 mg/kg/dose, 4 doses/d for 3 days or till afebrile for 24 hours and Oral cefixime: 16 mg/kg following IV cefotaxime for 1 day then 4	RANDOM SEQUENCE GENERATION Unclear risk ("Subjects were randomized at each site based on age and duration of fever") ALLOCATION CONCEALMENT Unclear risk (No information provided) BLINDING OF PARTICIPANTS AND PERSONNEL High risk (No blinding. Clinical

				mg/kg/dose, 2 doses/d for 13 days	management could be influenced by lack of blinding) BLINDING OF OUTCOME ASSESSMENT Low risk INCOMPLETE OUTCOME DATA High risk (34/306 (11%) no follow-up DMSA scans) SELECTIVE REPORTING High risk (No information on adverse effects) OTHER BIAS High risk (Supported by Lederle/Wyeth-Ayerst Laboratories and by NIH grants)
Montini 2007{Montini, 2007 #186}	502	Children aged 1 month to < 7 years	follow-up: 12 months	Oral amox/clav: 50 mg/kg/d in three doses for 10 days vs IV ceftriaxone: 50 mg/kg/d till resolution of fever and Oral amox/clav: 50 mg/kg/d to complete 10 day course	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk BLINDING OF PARTICIPANTS AND PERSONNEL High risk (No blinding. Lack of blinding could influence clinical assessment. “Could not blind group assignment because of the different routes of administration of the drug”) BLINDING OF OUTCOME ASSESSMENT Low risk INCOMPLETE OUTCOME DATA High risk (Loss to follow-up was 20.3% and could influence results)

					SELECTIVE REPORTING Low risk OTHER BIAS Low risk
Neuhaus 2008{Neuhaus, 2008 #187}	152	Children aged 6 months to 16 years	follow-up: 6 months	Oral ceftibuten: 9 mg/kg once daily for 14 days vs IV ceftriaxone: 50 mg/kg once daily for 3 days and Oral ceftibuten: 9 mg/kg once daily for 11 days	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk BLINDING OF PARTICIPANTS AND PERSONNEL High risk (No blinding. Lack of blinding could influence patient management) BLINDING OF OUTCOME ASSESSMENT Low risk INCOMPLETE OUTCOME DATA High risk (67/219 (30%) excluded from analysis as had no FU DMSA. This could influence results) SELECTIVE REPORTING High risk (No report of adverse effects) OTHER BIAS High risk (Financial support from the Essex Company)

Table 312

Author's conclusions:

The following implications for practice in the treatment of children with acute pyelonephritis have been identified:

• Oral antibiotics (cefixime, ceftibuten or amoxicillin/ clavulanic acid) given alone for 10 to 14 days are as effective as sequential IV therapy given for three days followed by oral therapy for a total duration of 10 to 14 days suggesting that children with acute pyelonephritis can be treated effectively with oral antibiotics.

• Studies comparing oral therapy alone with IV then oral antibiotics or IV then oral with IV therapy involved children greater than one month of age and were biased towards children who were less sick and so findings cannot be extrapolated to children less than one month of age or who are severely ill. The studies were also not stratified according to the grade of VUR so it remains unclear whether results differ according to the presence or absence of dilating VUR (grades III-V).

Remarks:

Children with previously diagnosed urinary tract abnormalities including VUR or previous UTI could be included, and this might have an impact on the effectiveness of oral therapy.

13.3.2.1.2 Summary and conclusions

Oral versus IV followed by oral (11 days) antibiotic therapy for pyelonephritis in children			
Bibliography: Cochrane Strohmeier 2014{Strohmeier, 2014 #111}			
Outcomes	**N° of participants (studies) Follow up**	**Results (95%CI)**	**Quality of the evidence (GRADE)**
Time to fever resolution	808 (2 studies)	MD: 2.05 [-0.84, 4.94] NS	⊕⊕⊕⊖: **MODERATE** As assessed by Cochrane group
Number with persistent UTI at 72 hours	542 (2 studies)	RR: 1.10 [0.07, 17.41] NS	⊕⊕⊖⊖: **LOW** Study quality: -1 (no blinding, incomplete outcome data) Consistency: na Directness: ok Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Recurrent symptomatic UTI within 6 months	287 (1 study)	RR: 0.67 [0.27, 1.67] NS	⊕⊕⊖⊖: **LOW** Study quality:-1 (unclear rando, allocation concealment, no blinding, 11% no followup) Consistency: na Directness: ok Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Persistent kidney damage at 6-12 months (all included patients with acute pyelonephritis)	943 (4 studies)	RR: 0.82 [0.59, 1.12] NS	⊕⊕⊕⊖: **MODERATE** As assessed by Cochrane group
Persistent kidney damage at 6-12 months (patients with kidney parenchymal damage on initial DMSA)	681 (4 studies)	RR: 0.79 [0.61, 1.03] NS	⊕⊕⊕⊖: **MODERATE** As assessed by Cochrane group

Table 313

In this meta-analysis, a treatment with oral antibiotics was compared to IV antibiotics followed by oral antibiotic therapy for pyelonephritis in children.

The children in the studies were aged 1 month to 16 years, and were followed for 6 to 12 months.

The oral antibiotics used in these trials include amoxicillin+clavulanate, cefixime, and ceftibuten. These last two antibiotics are not available in Belgium.

In children *with pyelonephritis*, a treatment with oral antibiotics, compared to IV treatment followed by oral treatment, **did not** result in a statistically significant difference in t*ime to fever resolution,* or *persistent kidney damage at 6-12 months.*
GRADE: MODERATE quality of evidence

In children *with pyelonephritis*, a treatment with oral antibiotics, compared to IV treatment followed by oral treatment, **did not** result in a statistically significant difference *in number with persistent UTI at 72 hours*, or *recurrent symptomatic UTI within 6 months.*
GRADE: LOW quality of evidence

13.3.2.2 Single dose parenteral therapy and oral therapy versus oral therapy alone

13.3.2.2.1 Clinical evidence profile

Meta-analysis: Strohmeier 2014{Strohmeier, 2014 #111} "Antibiotics for acute pyelonephritis in children"
Inclusion criteria:
"All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) in which antibiotics were used in the treatment of children (birth to 18 years) with acute pyelonephritis were included.
Where studies included both children with acute pyelonephritis and those with cystitis, these were included if data for participants with acute pyelonephritis could be extracted separately; otherwise, these studies were excluded."
"Children with previously diagnosed urinary tract abnormalities including VUR or previous UTI could be included."
Search strategy:
"For the 2014 update, we searched the Cochrane Renal Group's Specialised Register through contact with the Trials' Search Coordinator using search terms relevant to this review. The Cochrane Renal Group's Specialised Register contains studies identified from the following sources.
1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP Antibiotics
3. Handsearching of renal-related journals and the proceedings of major renal conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected renal journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov."
Assessment of quality of included trials:

Table 314

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Strohmeier 2014{Strohmeier, 2014 #111}	**Single dose parenteral therapy and oral therapy versus oral therapy alone**	N=1 n=69 (Baker 2001)	Treatment failure after 48 hours of therapy	Crude AR: 4/34 vs 5/35 RR: 0.82 [0.24, 2.81] NS

	Ceftriaxone/TMP+SMX TMP+SMX	N=1 n=69 (Baker 2001)	Recurrent UTI within 1 month	Crude AR: 0/34 vs 0/35 RR: Not estimable
		N=1 n=69 (Baker 2001)	Total adverse events	Crude AR: 4/34 vs 3/35 RR: 1.37 [0.33, 5.68] NS
		N=1 n=69 (Baker 2001)	Gastrointestinal adverse events	Crude AR: 3/34 vs 3/35 RR: 1.03 [0.22, 4.75] NS

Table 315

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by
Baker 2001{Baker, 2001 #188}	69	Children 6 months to 12 years	follow-up: 1 month	IM ceftriaxone: 50 mg/kg, single dose and Oral TMP/SMX: 5 mg/kg/d twice daily for 10 days vs Oral TMP/SMX: 5 mg/kg/d twice daily for 10 days	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk BLINDING OF PARTICIPANTS AND PERSONNEL High risk (No placebo injections so participants aware of assignment. "Physicians caring for the patients were unaware of study group assignment") BLINDING OF OUTCOME ASSESSMENT Low risk INCOMPLETE OUTCOME DATA

					Low risk SELECTIVE REPORTING Low risk OTHER BIAS High risk (Study grant from Roche Pharmaceuticals, Denver, Colorado)

Table 316

13.3.2.2.2 Summary and conclusions

Single dose IM ceftriaxone and oral therapy versus oral therapy alone for pyelonephritis in children			
Bibliography: Cochrane Strohmeier 2014{Strohmeier, 2014 #111}			
Outcomes	**N° of participants (studies) Follow up**	**Results (95%CI)**	**Quality of the evidence (GRADE)**
Treatment failure after 48 hours of therapy	69 (1 study)	RR: 0.82 [0.24, 2.81] NS	⊕⊕⊖⊖: **LOW** Study quality: -1 (no placebo, small sample size) Consistency: na Directness: ok Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Recurrent UTI within 1 month	69 (1 study)	Crude AR: 0/34 vs 0/35 RR: Not estimable	Insufficient data
Total adverse events	69 (1 study)	RR: 1.37 [0.33, 5.68] NS	⊕⊕⊖⊖: **LOW** Study quality: -1 (no placebo, small sample size) Consistency: na Directness: ok Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Gastrointestinal adverse events	69 (1 study)	RR: 1.03 [0.22, 4.75] NS	⊕⊕⊖⊖: **LOW** Study quality: -1 (no placebo, small sample size) Consistency: na Directness: ok Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)

Table 317

In this meta-analysis, a treatment with a single dose of parenteral antibiotics (intramuscular ceftriaxone), followed by oral antibiotics (trimethoprim-sulfamethoxazole) was compared to oral antibiotic therapy alone (trimethoprim-sulfamethoxazole) for pyelonephritis in children.

The children were aged 6 months to 12 years, and were followed for 1 month.

For the single intramuscular injection with ceftriaxone, a dose of 50 mg/kg was used. A dose of 10 mg/kg/day in two doses was used for the trimethoprim portion of the trimethoprim-sulfamethoxazole. The duration of both treatment arms was 10 days.

This systematic review found only one small trial with methodological flaws that studied this comparison. This severely limits our confidence in the results.

In children *with pyelonephritis*, a treatment with a single dose of intramuscular ceftriaxone, followed by oral trimethoprim-sulfamethoxazole for 10 days, compared to only oral trimethoprim-

sulfamethoxazole for 10 days, **did not** result in a statistically significant difference *in treatment failure after 48 hours of therapy, total adverse events, or gastrointestinal adverse events.*
GRADE: LOW quality of evidence

There is insufficient data to conclude whether in children *with pyelonephritis*, a treatment with a single dose of intramuscular ceftriaxone, followed by oral trimethoprim-sulfamethoxazole for 10 days, compared to only oral trimethoprim-sulfamethoxazole for 10 days results in a statistically significant difference *in recurrent UTI within 1 month.*
GRADE: Insufficient data

13.3.2.3 Single dose of parenteral antibiotic versus 7-10 days oral therapy

13.3.2.3.1 Clinical evidence profile

Meta-analysis: Strohmeier 2014{Strohmeier, 2014 #111} "Antibiotics for acute pyelonephritis in children"
Inclusion criteria:
"All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) in which antibiotics were used in the treatment of children (birth to 18 years) with acute pyelonephritis were included.
Where studies included both children with acute pyelonephritis and those with cystitis, these were included if data for participants with acute pyelonephritis could be extracted separately; otherwise, these studies were excluded."
"Children with previously diagnosed urinary tract abnormalities including VUR or previous UTI could be included."
Search strategy:
"For the 2014 update, we searched the Cochrane Renal Group's Specialised Register through contact with the Trials' Search Coordinator using search terms relevant to this review. The Cochrane Renal Group's Specialised Register contains studies identified from the following sources.
1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP Antibiotics
3. Handsearching of renal-related journals and the proceedings of major renal conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected renal journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov."
Assessment of quality of included trials: yes

Table 318

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Strohmeier 2014{Strohmeier, 2014 #111}	**Single dose of parenteral antibiotic**	N=2 n=35 (Repetto 1984,	UTI relapse or reinfection within 6 weeks	Crude AR: 1/18 vs 3/17 RR: 0.24 [0.03, 1.97] NS

	versus 7-10 days oral therapy	Grimwood 1988)		

Table 319

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
Repetto 1984{Repetto, 1984 #189}	37	Children aged 1 month to 14 years	follow-up: 6 weeks	IV cefotaxime: 50 mg/kg single dose vs Appropriate oral antibiotic for 10 days: TMP/SMX (14), nalidixic acid (2) nitrofurantoin (2), cephalexin (1), gentamicin (1)	RANDOM SEQUENCE GENERATION Unclear risk (No information provided. ”Patients..were treated randomly with either...). Not stratified for APN) ALLOCATION CONCEALMENT Unclear risk (No information provided) BLINDING OF PARTICIPANTS AND PERSONNEL High risk (No blinding. Lack of blinding could influence clinical management) BLINDING OF OUTCOME ASSESSMENT High risk (No blinding. Primary outcomes were clinical and laboratory based. Clinical outcomes could be influenced by lack of blinding) INCOMPLETE OUTCOME DATA

					Low risk SELECTIVE REPORTING High risk (No clinical outcomes reported) OTHER BIAS Unclear risk (No information provided)
Grimwood 1988{Grimwood, 1988 #185}	69	Mean age (range): 4.9 years (range 2 weeks to 12 years)	follow-up: 6 weeks	IV gentamicin: 3 mg/kg single dose vs 7 days of antibiotic according to sensitivity: TMP/SMX (16); amoxicillin (11); cephalosporins (3)	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Unclear risk (No information provided) BLINDING OF PARTICIPANTS AND PERSONNEL High risk (No blinding. Lack of blinding could influence clinical management) BLINDING OF OUTCOME ASSESSMENT Low risk INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING High risk (No results provided on clinical resolution or adverse events) OTHER BIAS Low risk

Table 320

Author's conclusions:

The following implications for practice in the treatment of children with acute pyelonephritis have been identified:

• Oral antibiotics (cefixime, ceftibuten or amoxicillin/ clavulanic acid) given alone for 10 to 14 days are as effective as sequential IV therapy given for three days followed by oral therapy for a total duration of 10 to 14 days suggesting that children with acute pyelonephritis can be treated effectively with oral antibiotics.

• Studies comparing oral therapy alone with IV then oral antibiotics or IV then oral with IV therapy involved children greater than one month of age and were biased towards children who were less sick and so findings cannot be extrapolated to children less than one month of age or who are severely ill. The studies were also not stratified according to the grade of VUR so it remains unclear whether results differ according to the presence or absence of dilating VUR (grades III-V).

13.3.2.3.2 Summary and conclusions

Single dose of IV antibiotic versus 7-10 days oral therapy for pyelonephritis in children			
Bibliography: Cochrane Strohmeier 2014{Strohmeier, 2014 #111}			
Outcomes	**N° of participants (studies) Follow up**	**Results (95%CI)**	**Quality of the evidence (GRADE)**
UTI relapse or reinfection within 6 weeks	35 (2 studies)	RR: 0.24 [0.03, 1.97] NS	⊕⊕⊖⊖: **LOW** Study quality: -1 (no blinding, unclear allocation concealment, unclear rando in 1 study) Consistency: na (no events in one trial) Directness: ok Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)

Table 321

In this meta-analysis, a treatment with a single dose of an IV antibiotic was compared to 7-10 days oral antibiotic therapy for pyelonephritis in children.

The children were aged 2 weeks to 14 years, and were followed for 6 weeks.

The antibiotics used for the single dose of IV treatment were cefotaxime and gentamicin.

The antibiotics used for the oral treatment were chosen according to the sensitivity and included trimethoprim-sulfamethoxazole, nalidixic acid, nitrofurantoin, gentamicin, amoxicllin, cephalexin, and other cephalosporins (not specified).

This systematic review found two very small trials with methodological flaws that studied this comparison. This severely limits our confidence in the results.

In children *with pyelonephritis*, a treatment with a single dose of an IV antibiotic, compared to 7-10 days oral therapy, **did not** result in a statistically significant difference *in UTI relapse or reinfection within 6 weeks.*
GRADE: LOW quality of evidence

13.4 Prophylaxis in recurrent UTI: Evidence tables and conclusions

13.4.1 Antibiotic prophylaxis versus placebo or no treatment

13.4.1.1 Antibiotic prophylaxis versus placebo or no treatment in children at risk of recurrent urinary tract infection

13.4.1.1.1 Clinical evidence profile

Meta-analysis: Williams 2011{Williams, 2011 #109} "Long-term antibiotics for preventing recurrent urinary tract infection in children"
Inclusion criteria: "All randomised controlled trials (RCTs) and quasi-RCTs of antibiotic treatment versus placebo/no treatment for the prevention of recurrent UTI. All RCTs and quasi-RCTs that compared antibiotics with placebo/no treatment or compared two or more antibiotics administered daily for a period of at least two months for the prevention of recurrent UTI, were included. Children less than 18 years of age who were at risk of recurrence were included. Studies were included if the majority of participants (> 50%) did not have a predisposing cause such as a renal tract abnormality, or a major neurological, urological or muscular disease."
Search strategy: "For the current update we searched the Cochrane Renal Group's specialised register (November 2010) and MEDLINE/EMBASE (November 2010). Please refer to The Cochrane Renal Review Group's Module in The Cochrane Library for the complete list of nephrology conference proceedings searched (RenalGroup 2011). Relevant studies were obtained from the following sources (see Appendix 1 - Electronic search strategies)
1. The Cochrane Renal Group Specialised Register (January 2001).
2. Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library Issue 1, 2001.
3. MEDLINE (1966 - January 2001).
4. EMBASE (1980 - January 2001).
5. Reference lists of relevant articles, reviews and studies.
6. Pharmaceutical industry representatives.
7. Known authors in the field.
There were no language restrictions."
Assessment of quality of included trials: yes

Table 322

Ref	Comparison	N/n	Outcomes	Result (95% CI)

Williams 2011{Williams, 2011 #109}	**Antibiotic treatment versus placebo/no treatment**	N=4 n=1024 (Smellie 1978, Savage 1975, Montini 2008, PRIVENT study 2009)	**Recurrence of symptomatic UTI (all studies)**	Crude AR: 58/553 vs 81/471 RR 0.75 [0.36, 1.53] NS
		N=3 n=491 (Smellie 1978, Montini 2008, PRIVENT study 2009)	**Recurrence of symptomatic UTI (Children without VUR)**	Crude AR: 20/273 vs 30/218 RR 0.56 [0.15, 2.12] NS
		N=2 n=914 (Montini 2008, PRIVENT study 2009)	**All adverse events**	Crude AR: 19/499 vs 10/415 RR 2.31 [0.03, 170.67] NS
		N=1 n=576 (PRIVENT study 2009)	**Discontinuation of treatment due to adverse events**	Crude AR: 4/288 vs 10/288 RR 0.4 [0.13, 1.26] NS

Table 323

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
Montini 2008{Montini, 2008 #192}	338	Age: 2 months to 7 years VUR: 19	Follow-up: 12 months	Cotrimoxazole 15 mg/kg/d Duration: 12 months Vs Co-amoxiclav 15 mg/kg/d	ADEQUATE SEQUENCE GENERATION Yes ALLOCATION CONCEALMENT? Yes

				Duration: 12 months Vs No prophylaxis (no placebo)	BLINDING? No (Open label) INCOMPLETE OUTCOME DATA ADDRESSED? Yes FREE OF SELECTIVE REPORTING? Yes FREE OF OTHER BIAS? Yes
PRIVENT study 2009{Craig, 2009 #193}	576	birth to 18 years VUR: 85	12 months	TMP 2 mg/kg/d vs SMX 10 mg/kg/d vs Colour and taste matched placebo in the same volume	ADEQUATE SEQUENCE GENERATION? Yes ALLOCATION CONCEALMENT? Yes BLINDING? Yes INCOMPLETE OUTCOME DATA ADDRESSED? Yes FREE OF SELECTIVE REPORTING? Yes FREE OF OTHER BIAS? Yes
Savage 1975{Savage, 1975 #194}	63	Age: 5 years to 7 years 10 months All female VUR:19	Follow-up: to 6 months	Antibiotic treatment according to sensitivities: nitrofurantoin 4 mg/kg/d for 10 weeks after 2 weeks acute treatment, or cotrimoxazole 20 to 40 mg TMP; 100 to 200 mg SMX twice daily for 10 weeks after 2 weeks acute treatment	ADEQUATE SEQUENCE GENERATION? Unclear (States randomised but no details) ALLOCATION CONCEALMENT? Unclear (States allocated by random numbers except for those with history of past UTI) BLINDING? Unclear (Not stated and unclear

				vs No treatment for 10 weeks after 2 weeks of acute treatment with ampicillin	from report) INCOMPLETE OUTCOME DATA ADDRESSED? Yes FREE OF SELECTIVE REPORTING? Yes FREE OF OTHER BIAS? Unclear (Many methodology details missing)
Smellie 1978{Smellie, 1978 #195}	47	Age: 2 to 12 years VUR: None	Follow-up: to 1 year	Low dose cotrimoxazole SMX 10 mg/kg/d for: 6 to 12 months TMP 2 mg/kg/d for: 6 to 12 months vs Nitrofurantoin 1 to 2 mg/kg/d for 6 to 12 months vs No treatment	ADEQUATE SEQUENCE GENERATION? Unclear (States randomised, no details given) ALLOCATION CONCEALMENT? Unclear (Treatment allocation know to clinician, possibly manipulatable more children with a history of priorUTIs received prophylaxis) BLINDING? No (Clinicians aware of treatment group, likely parents also aware) INCOMPLETE OUTCOME DATA ADDRESSED? Yes FREE OF SELECTIVE REPORTING? Yes FREE OF OTHER BIAS? Unclear (Many methods details are not detailed)

Table 324

Authors' conclusions: "Long-term antibiotics appear to reduce the risk of repeat symptomatic UTI in susceptible children but the benefit is small and must be considered together with the increased risk of microbial resistance."

13.4.1.1.2 Summary and conclusions

Antibiotic prophylaxis versus placebo/no treatment in children at risk of recurrent urinary tract infection			
Bibliography: Williams 2011{Williams, 2011 #109}			
Outcomes	**N° of participants (studies) Follow up**	**Results (RR(95%CI))**	**Quality of the evidence (GRADE)**
Recurrence of symptomatic UTI (Children with and without VUR)	1024 (4 studies)	RR 0.75 [0.36, 1.53] NS	⊕⊕⊖⊖: **LOW** Study quality: -1 (unclear rando, unclear allocation concealment, open label) Consistency: ok Directness: ok Imprecision:-1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Recurrence of symptomatic UTI (Children without VUR)	491 (3 studies)	RR 0.56 [0.15, 2.12] NS	⊕⊕⊖⊖: **LOW** Study quality: -1 (unclear allocation concealment, open label) Consistency: ok Directness: ok Imprecision: 1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
All adverse events	914 (2 studies)	RR 2.31 [0.03, 170.67] NS	⊕⊖⊖⊖: **VERY LOW** Study quality: -1 (open label) Consistency: -1 (I^2=88%) Directness: ok Imprecision: 1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)
Discontinuation of treatment due to adverse events	576 (1 study)	RR 0.4 [0.13, 1.26] NS	⊕⊕⊕⊖: **MODERATE** Study quality: ok Consistency: na Directness: ok Imprecision: 1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)

Table 325

In this meta-analysis, a prophylactic antibiotic treatment was compared to placebo or no treatment in children at risk of recurrent urinary tract infection.

Children from birth to 18 years of age were included in the trials and were followed during 6 to 12 months.

The antibiotics used in the trials were trimethoprim+ sulfamethoxazole, amoxicillin+ clavulanate, trimethoprim, sulfamethoxazole or nitrofurantoin. These were given daily for a duration ranging from 10 weeks to 12 months.

For the results of prophylactic antibiotic treatment versus no treatment in children with vesico-ureteric reflux, we refer to a more recent meta-analysis, which is described in the next section (see 13.4.1.2)

In children *at risk of recurrent urinary tract infection,with or without vesico-ureteric reflux*, a prophylactic treatment with antibiotics for at least 10 weeks, compared to placebo or no treatment , **did not** result in a statistically significant difference in *recurrence of symptomatic urinary tract infection*.
GRADE: LOW quality of evidence

In children *at risk of recurrent urinary tract infection, without vesico-ureteric reflux*, a prophylactic treatment with antibiotics for at least 10 weeks, compared to placebo or no treatment , **did not** result in a statistically significant difference in *recurrence of symptomatic urinary tract infection*.
GRADE: LOW quality of evidence

In children *at risk of recurrent urinary tract infection,with or without vesico-ureteric reflux*, a prophylactic treatment with antibiotics for at least 10 weeks, compared to placebo or no treatment , **did not** result in a statistically significant difference in *adverse events*.
GRADE: VERY LOW quality of evidence

In children *at risk of recurrent urinary tract infection,with or without vesico-ureteric reflux*, a prophylactic treatment with antibiotics for at least 10 weeks, compared to placebo or no treatment , **did not** result in a statistically significant difference in *discontinuation of treatment due to adverse events.*
GRADE: MODERATE quality of evidence

13.4.1.2 Antibiotic prophylaxis versus placebo or no treatment in VUR

13.4.1.2.1 Clinical evidence profile

Meta-analysis: Wang 2015{Wang, 2015 #110} "Efficacy of antibiotic prophylaxis in children with vesicoureteral reflux: systematic review and meta-analysis"
Inclusion criteria: "Inclusion criteria consisted of age 18 years or younger and history of VUR treated with CAP. Study patients were compared to individuals 18 years or younger with VUR undergoing no treatment or treatment with placebo (controls). We chose to include only RCTs that described the number of patients treated as well as the fraction in whom treatment was successful. No study was excluded based on method of analysis, definition of success, language of publication, perceived quality or susceptibility to bias. In cases of ambiguity or where study reporting made evaluation difficult we attempted to err on the side of inclusiveness."
Search strategy:
"We searched MEDLINE, EMBASE, Cochrane Controlled Trials Register, www.clinicaltrials.gov and Google Scholar electronic databases for studies published between January 2010 and May 2014 in any language based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.17 We additionally evaluated all studies previously included in systematic reviews of this topic.16 This date range was chosen to provide a contemporary selection of series. We used the search terms "vesicoureteral reflux," "vesicoureteric reflux," "vesico-ureteral reflux" and "vesico-ureteric reflux" (see Appendix).
Reference lists of included studies were manually screened for any additional series. We also manually searched for unpublished abstracts presented at relevant scientific meetings, including meetings of the American Urological Association, Society for Pediatric Urology, American Academy of Pediatrics Section on Urology, Pediatric Academic Societies, World Congress of Endourology, Société Internationale d'Urologie, International Pediatric Nephrology Association and the European Association of Urology."
Assessment of quality of included trials: yes

Table 326

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Wang 2015{Wang, 2015 #110}	**Antibiotics versus placebo or no treatment**	N=8 n=1594 (RIVUR 2014, Swedish Reflux trial 2011,	**Febrile or symptomatic UTI**	107/803 vs 176/791 **OR: 0.63 (0.42 to 0.96)** **SS**

		PRIVENT 2009, Montini 2008, Roussey-Kesler 2008, Garin 2006, Pennesi 2008; Craig 2002)		
		N=7 n=1342 (RIVUR 2014, Swedish Reflux trial 2011, PRIVENT 2009, Montini 2008, Garin 2006, Pennesi 2008; Craig 2002)	**New renal scarring**	25/710 (3,5%) vs 33/632 (5,2%) OR not reported NS
		N=3 n=963 (RIVUR 2014, PRIVENT 2009, Garin 2006)	**Adverse events**	155/479 (32,4%) vs 170/484 (35,1%) OR not reported NS

Table 327

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors SR:
RIVUR 2014{Hoberman, 2014 #106}	607	Age 2-72 months % female: 92	2 years	Trimethoprim-sulfamethoxazole vs placebo	see figure below
Swedish Reflux trial	137	Age 12-24 months	2 years	Trimethoprim,	

2011{Brandstrom, 2011 #107}		% female 93		nitrofurantoin, cefadroxil vs no treatment	
PRIVENT 2009{Craig, 2009 #193}	243	Age 0-18 years % female 62	1 year	Trimethoprim-sulfamethoxazole vs placebo	
Montini 2008{Montini, 2008 #192}	128	Age 2-84 months % female not reported	1 year	Trimethoprim-sulfamethoxazole, amoxicillin/clavulanate vs no treatment	
Roussey-Kesler 2008{De Cunto, 2008 #329}	225	Age 1-36 months % female 69	1.5 years	Trimethoprim-sulfamethoxazole vs no treatment	
Garin 2006{Garin, 2006 #331}	113	Age 3 months -12 years % female 81	1 year	Trimethoprim-sulfamethoxazole, nitrofurantoin vs no treatment	
Pennesi 2008{Pennesi, 2008 #330}	100	Age 0-30 months % female 52	2 years	Trimethoprim-sulfamethoxazole vs no treatment	
Craig 2002{Craig, 2002 #332}	41	Age 0-3 months % female 37	3 years	Trimethoprim-sulfamethoxazole vs placebo	

Table 328

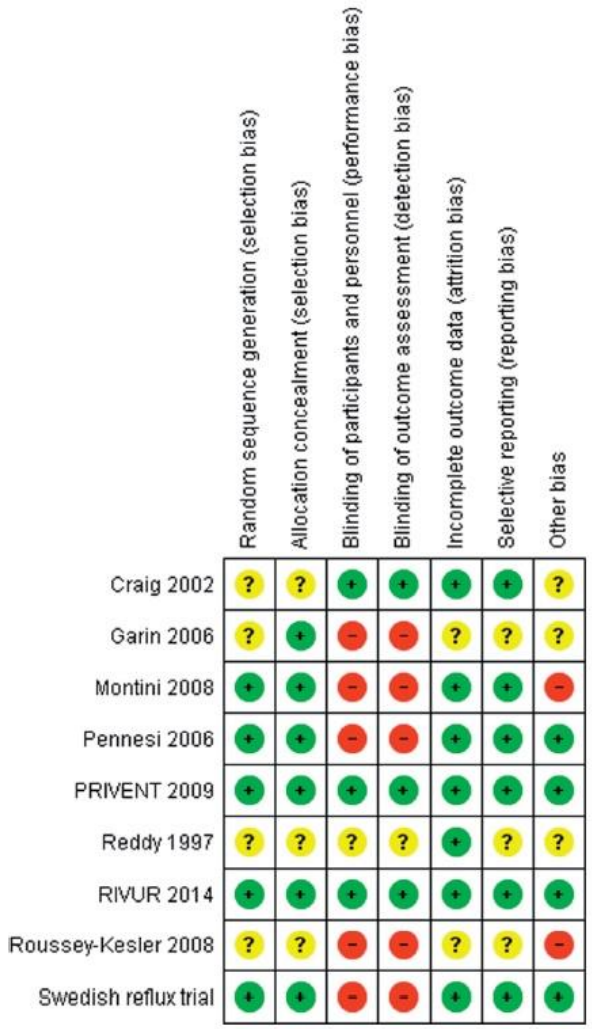


Figure 1. Risk of bias detail. Green circles represent positive risk of bias. Red circles indicate negative risk of bias. Yellow circles signify unknown risk of bias.

Figure 14 Quality of studies, as assessed by Wang 2015

Author's conclusions:

"Compared to no treatment or placebo, CAP significantly reduced the risk of febrile and symptomatic urinary tract infections in children with VUR, although it increased the risk of infection due to antibiotic resistant bacteria. The protective effect of CAP was more prominent in studies deemed to have a low risk of bias. CAP did not significantly impact the rate of new renal scarring or reported treatment related adverse events."

Remarks:

Generally prophylaxis is not given after a certain age, e.g. when continence is reached; if the proportion of older children is important this might perhaps bias the results. (Children up to 12 years of age were included in Garin 2006).

Cotrimoxazole versus placebo in VUR

Study details	n/Population	Comparison	Outcomes		Methodological
Hari 2015{Hari, 2015 #113} Design: RCT (DB, PG) Duration of follow-up: 12 months	n= 93 Mean age: AB group: 5.7±3.2y Placebo group: 4.8±3.1y 31% male <u>Inclusion</u> Children of either sex aged <12 years who were diagnosed with VUR on micturating cystourethrogram following a febrile UTI at a tertiary care	trimethoprim–sulfamethoxazole (2 mg/kg/day of trimethoprim + 10 mg/kg/day of sulfamethoxazole) for 12 months Vs placebo for 12 months			RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Lost-to follow-up: 9% Drop-out and Exclusions: 5% • Described: yes • Balanced across groups: no: 7 patients lost to follow-up in antibiotic group to 1 in placebo group
			Proportion of patients developing symptomatic UTI within 12 months (PO)	AR: 10/47 (21.3%) vs 3/46 (6.5%) **Risk difference: −14,8 (−28 to −1)** **P= 0,03** **SS in favour of antibiotics**	
			UTI with bacteria resistant to TMP-SMX	AR: 13/47 (61.9%) vs 12/46 (44.4%) Risk difference:−17.5 (−45.4 to 10.5) P= 0.2 NS	
			Antibiotic administration for concomitant infections	AR: 16/47 (34.0%) vs 11/46 (23.9%) Risk difference: 10.1 (−28.4 to 8.1) P= 0.3 NS	
			Worsening of scarring on renal scintigraphy	AR: 4/47 (10.8%) vs 3/46 (7.0%) Risk difference: −3.8 (−16.4 to 8.7) P= 0.6 NS	

	hospital. <u>Exclusion</u> *Children aged < 1 year *grade V VUR or VUR secondary to urinary tract obstruction, including posterior urethral valves, neurogenic bladder and primary megaureter *Children with a history of voiding dysfunction or drug sensitivity to sulphonamides or with an estimated glomerular filtration rate (eGFR) of <30 ml/min/1.73 m2		Adverse events	AR: 12/47 (25.5%) vs 11/47 (23.4%) No statistical analysis	ITT: Yes SELECTIVE REPORTING: no Sponsor: The study was funded by the Indian Council of Medical Research.

Table 329

<u>Author's conclusions:</u>

"Compared to no treatment, continuous antibiotic prophylaxis significantly reduced the risk of febrile and symptomatic urinary tract infections in children with vesicoureteral reflux, although it increased the risk of infection due to antibiotic resistant bacteria. Continuous antibiotic prophylaxis did not significantly impact the occurrence of new renal scarring or reported adverse events."

13.4.1.2.2 Summary and conclusions

Prophylactic treatment with antibiotics versus placebo or no treatment in children with VUR			
Bibliography: Wang 2015{Wang, 2015 #110}			
Outcomes	**N° of participants (studies) Follow up**	**Results (OR(95%CI))**	**Quality of the evidence (GRADE)**
Febrile or symptomatic UTI	1594 (8 studies)	**OR: 0.63 (0.42 to 0.96)** **SS** **(fewer UTIs with profylactic antibiotics)**	⨁⨁⨀⨀: **LOW** Study quality:-1 (no blinding in 5 studies) Consistency: -1 (previous MA (same studies without RIVUR trial) showed NS result) Directness: ok Imprecision: ok
New renal scarring	1342 (7 studies)	25/710 (3,5%) vs 33/632 (5,2%) OR not reported NS	⨁⨁⨁⨀: **MODERATE** Study quality: -1 (no blinding in 4 studies) Consistency: ok Directness: ok Imprecision: na
Adverse events	963 (3 studies)	155/479 (32,4%) vs 170/484 (35,1%) OR not reported NS	⨁⨁⨁⨁:**HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: na

Table 330

In this meta-analysis, a prophylactic treatment with antibiotics was compared to placebo or no treatment in children with vesico-ureteric reflux.

The children in the included studies were 0 months to 18 years old. The follow-up ranged from 1 to 3 years.

The antibiotics used in the studies were trimethoprim+ sulfamethoxazole, nitrofurantoin, trimethoprim, cefadroxil, and amoxicillin+ clavulanate. They were administered continuously for 1 to 3 years.

In children *with vesico-ureteric reflux*, a prophylactic treatment with antibiotics for, compared to placebo or no treatment, **did** result in a statistically significant **decrease** in *febrile or symptomatic UTI*.
GRADE: LOW quality of evidence

In children *with vesico-ureteric reflux*, a prophylactic treatment with antibiotics for, compared to placebo or no treatment, **did not** result in a statistically significant difference in *new renal scarring.*
GRADE: MODERATE quality of evidence

In children *with vesico-ureteric reflux*, a prophylactic treatment with antibiotics for, compared to placebo or no treatment, **did not** result in a statistically significant difference in *adverse events.*
GRADE: HIGH quality of evidence

One small RCT (Hari 2015{Hari, 2015 #113}), comparing prophylactic treatment with cotrimoxazole for 12 months with placebo in 93 children with VUR, was published after the final search date of the meta-analysis. It confirmed the results of the meta-analysis: a statistically significant **reduction** in the *proportion of patients developing symptomatic UTI*, and **no difference** in *renal scarring*.

13.4.2 Antibiotics A versus antibiotic B

13.4.2.1 Nitrofurantoin versus cotrimoxazole in children at risk of recurrent urinary tract infection

13.4.2.1.1 Clinical evidence profile

Meta-analysis: Williams 2011{Williams, 2011 #109} "Long-term antibiotics for preventing recurrent urinary tract infection in children" Inclusion criteria: "All randomised controlled trials (RCTs) and quasi-RCTs of antibiotic treatment versus placebo/no treatment for the prevention of recurrent UTI. All RCTs and quasi-RCTs that compared antibiotics with placebo/no treatment or compared two or more antibiotics administered daily for a period of at least two months for the prevention of recurrent UTI, were included. Children less than 18 years of age who were at risk of recurrence were included. Studies were included if the majority of participants (> 50%) did not have a predisposing cause such as a renal tract abnormality, or a major neurological, urological or muscular disease." Search strategy: "For the current update we searched the Cochrane Renal Group's specialised register (November 2010) and MEDLINE/EMBASE (November 2010). Please refer to The Cochrane Renal Review Group's Module in The Cochrane Library for the complete list of nephrology conference proceedings searched (RenalGroup 2011). Relevant studies were obtained from the following sources (see Appendix 1 - Electronic search strategies) 1. The Cochrane Renal Group Specialised Register (January 2001). 2. Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library Issue 1, 2001. 3. MEDLINE (1966 - January 2001). 4. EMBASE (1980 - January 2001). 5. Reference lists of relevant articles, reviews and studies. 6. Pharmaceutical industry representatives. 7. Known authors in the field. There were no language restrictions." Assessment of quality of included trials: yes

Table 331

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Williams 2011{Williams, 2011 #109}	Nitrofurantoin versus cotrimoxazole	N=1 n=132 (Falakaflaki 2007)	**Recurrence of symptomatic UTI**	Crude AR: 17/66 vs 30/66 **RR 0.57 [0.35, 0.92]** **SS**

Table 332

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
Falakaflaki 2007{Falakaflaki, 2007 #196}	132	Age: 3 months to 12 years VUR: 56	Unstated	TMP/SMX 2 mg/kg/d for 6 months vs Nitrofurantoin 1 to 2mg/kg/d for 6 months	ADEQUATE SEQUENCE GENERATION? Unclear (No details reported) ALLOCATION CONCEALMENT? Unclear (Study states randomised only, no details about allocation concealment) BLINDING? Unclear (Not stated) INCOMPLETE OUTCOME DATA ADDRESSED? Unclear (No withdrawals or loss to follow up stated, unsure of completeness of reporting) FREE OF SELECTIVE REPORTING? Yes FREE OF OTHER BIAS? Unclear (Many details not reported, difficult to determine)

Table 333

Authors' conclusions: "Long-term antibiotics appear to reduce the risk of repeat symptomatic UTI in susceptible children but the benefit is small and must be considered together with the increased risk of microbial resistance."

13.4.2.1.2 Summary and conclusions

Prophylactic nitrofurantoin versus cotrimoxazole in children at risk for recurrent urinary tract infection			
Bibliography: Williams 2011{Williams, 2011 #109}			
Outcomes	**N° of participants (studies) Follow up**	**Results (RR(95%CI))**	**Quality of the evidence (GRADE)**
Recurrence of symptomatic UTI	132 (1 study)	**RR 0.57 [0.35, 0.92]** **SS** **(lower recurrence of symptomatic UTI with nitrofurantoin)**	⊕⊕⊖⊖: **LOW** Study quality: -2 (unclear rando, allocation concealment, blinding, possible incomplete outcome data) Consistency: na Directness: ok Imprecision: ok

Table 334

In this meta-analysis, a prophylactic antibiotic treatment with nitrofurantoin was compared to cotrimoxazole in children at risk of recurrent urinary tract infection.

The included children were 3 months to 12 years old.

The duration of both treatments was 6 months. Trimethoprim+ sulfamethoxazole was given in a dose of 2 mg/kg/day, and nitrofurantoin in a dose of 1-2mg/kg/day.

As this review only found one small study with serious methodological flaws (unclear or no reporting of method of randomisation, allocation concealment, blinding, loss to follow-up or withdrawals), our confidence in the results is severely limited.

In children *at risk of recurrent urinary tract infection, with or without vesico-ureteric reflux*, a prophylactic treatment with nitrofurantoin for 6 months, compared to trimethoprim+ sulfamethoxazole , **did** result in a statistically significant **decrease** in *recurrence of symptomatic urinary tract infection*.
GRADE: LOW quality of evidence

13.4.2.2 Cotrimoxazole vs cephadroxil in children at risk of recurrent urinary tract infection

13.4.2.2.1 Clinical evidence profile

Meta-analysis: Williams 2011{Williams, 2011 #109} "Long-term antibiotics for preventing recurrent urinary tract infection in children" Inclusion criteria: "All randomised controlled trials (RCTs) and quasi-RCTs of antibiotic treatment versus placebo/no treatment for the prevention of recurrent UTI. All RCTs and quasi-RCTs that compared antibiotics with placebo/no treatment or compared two or more antibiotics administered daily for a period of at least two months for the prevention of recurrent UTI, were included. Children less than 18 years of age who were at risk of recurrence were included. Studies were included if the majority of participants (> 50%) did not have a predisposing cause such as a renal tract abnormality, or a major neurological, urological or muscular disease." Search strategy: "For the current update we searched the Cochrane Renal Group's specialised register (November 2010) and MEDLINE/EMBASE (November 2010). Please refer to The Cochrane Renal Review Group's Module in The Cochrane Library for the complete list of nephrology conference proceedings searched (RenalGroup 2011). Relevant studies were obtained from the following sources (see Appendix 1 - Electronic search strategies) 1. The Cochrane Renal Group Specialised Register (January 2001). 2. Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library Issue 1, 2001. 3. MEDLINE (1966 - January 2001). 4. EMBASE (1980 - January 2001). 5. Reference lists of relevant articles, reviews and studies. 6. Pharmaceutical industry representatives. 7. Known authors in the field. There were no language restrictions." Assessment of quality of included trials: yes

Table 335

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Williams 2011{Williams, 2011 #109}	**Cotrimoxazole versus cephadroxil**	N=1 n=46 (Belet 2004)	**Recurrence of symptomatic UTI**	Crude AR: 3/21 vs 2/25 RR 1.79 [0.33, 9.70] NS

Table 336

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
Belet 2004{Belet, 2004 #190}	80	VUR: none	Follow-up: 6 months	TMP/SMX for 3 months vs cephadroxil for 3 months vs cefprozil for 3 months	ADEQUATE SEQUENCE GENERATION? Unclear (No details of how sequence was generated, states randomised by draw lots) ALLOCATION CONCEALMENT? Unclear (No details on whether allocation was concealed) BLINDING? No (Stated that patients/parents were not blind to treatment type) INCOMPLETE OUTCOME DATA ADDRESSED? Yes FREE OF SELECTIVE REPORTING? Yes FREE OF OTHER BIAS? Unclear (Nephrology patients and no gender distribution given, uncertain how representative these children are (selection bias))

Table 337

Authors' conclusions: "Long-term antibiotics appear to reduce the risk of repeat symptomatic UTI in susceptible children but the benefit is small and must be considered together with the increased risk of microbial resistance."

13.4.2.2.2 Summary and conclusions

Prophylactic cotrimoxazole versus cephadroxil in children at risk for recurrent urinary tract infection			
Bibliography: Williams 2011{Williams, 2011 #109}			
Outcomes	**N° of participants (studies) Follow up**	**Results (RR(95%CI))**	**Quality of the evidence (GRADE)**
Recurrence of symptomatic UTI	46 (1 study)	RR 1.79 [0.33, 9.70] NS	⨁⊖⊖⊖: **VERY LOW** Study quality: -2 (unclear rando, allocation concealment, no blinding) Consistency: na Directness: ok Imprecision: -1 (95%-CI crosses both the point of appreciable harm AND the point of appreciable benefit)

Table 338

In this meta-analysis, a prophylactic antibiotic treatment with cephadroxil was compared to cotrimoxazole in children at risk of recurrent urinary tract infection.

None of the included children had vesico-ureteric reflux. They were followed for 6 months.

The duration of both treatments was 3 months.

As this review only found one very small study with serious methodological flaws (unclear or no reporting of method of randomisation, no blinding), our confidence in the results is severely limited.

In children *at risk of recurrent urinary tract infection, without vesico-ureteric reflux*, a prophylactic treatment with cotrimoxazole for 3 months, compared to cephadroxil for 3 months, **did not** result in a statistically significant difference in *recurrence of symptomatic urinary tract infection*.
GRADE: VERY LOW quality of evidence

13.4.2.3 Nitrofurantoin versus trimethoprim in children at risk of recurrent urinary tract infection

13.4.2.3.1 Clinical evidence profile

Meta-analysis: Williams 2011{Williams, 2011 #109} "Long-term antibiotics for preventing recurrent urinary tract infection in children" Inclusion criteria: "All randomised controlled trials (RCTs) and quasi-RCTs of antibiotic treatment versus placebo/no treatment for the prevention of recurrent UTI. All RCTs and quasi-RCTs that compared antibiotics with placebo/no treatment or compared two or more antibiotics administered daily for a period of at least two months for the prevention of recurrent UTI, were included. Children less than 18 years of age who were at risk of recurrence were included. Studies were included if the majority of participants (> 50%) did not have a predisposing cause such as a renal tract abnormality, or a major neurological, urological or muscular disease." Search strategy: "For the current update we searched the Cochrane Renal Group's specialised register (November 2010) and MEDLINE/EMBASE (November 2010). Please refer to The Cochrane Renal Review Group's Module in The Cochrane Library for the complete list of nephrology conference proceedings searched (RenalGroup 2011). Relevant studies were obtained from the following sources (see Appendix 1 - Electronic search strategies) 1. The Cochrane Renal Group Specialised Register (January 2001). 2. Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library Issue 1, 2001. 3. MEDLINE (1966 - January 2001). 4. EMBASE (1980 - January 2001). 5. Reference lists of relevant articles, reviews and studies. 6. Pharmaceutical industry representatives. 7. Known authors in the field. There were no language restrictions." Assessment of quality of included trials: yes

Table 339

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Williams 2011{Williams, 2011 #109}	**Nitrofurantoin versus trimethoprim**	N=1 n=120 (Brendstrup 1990)	**Adverse events**	Crude Ar: 37/60 vs 17/60 **RR 2.18 [1.39, 3.41]** **SS** *(nausea, vomiting or stomach ache)*

Table 340

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
Brendstrup 1990{Brendstrup, 1990 #191}	130	1-14 years old (mean 7.5) VUR: 30	Follow-up: 6 months	Nitrofurantoin 1 to 1.5 mg/kg for 6 months vs TMP 2 to 3 mg/kg for 6 months	ADEQUATE SEQUENCE GENERATION? Unclear (Does not state how sequence was generated "randomised by the local hospital") ALLOCATION CONCEALMENT? Yes BLINDING? Yes INCOMPLETE OUTCOME DATA ADDRESSED? Yes FREE OF SELECTIVE REPORTING? No (Primary outcome is positive culture rather than symptomatic UTI) FREE OF OTHER BIAS? Unclear (Some uncertainty in methods because of insufficient reporting)

Table 341

Authors' conclusions: "Long-term antibiotics appear to reduce the risk of repeat symptomatic UTI in susceptible children but the benefit is small and must be considered together with the increased risk of microbial resistance."

13.4.2.3.2 Summary and conclusions

Prophylactic nitrofurantoin versus trimethoprim in children at risk for recurrent urinary tract infection			
Bibliography: Williams 2011{Williams, 2011 #109}			
Outcomes	**N° of participants (studies) Follow up**	**Results (RR(95%CI))**	**Quality of the evidence (GRADE)**
Adverse events	120 (1 study)	**RR 2.18 [1.39, 3.41]** **SS** **(more adverse events with nitrofurantoin)** *(nausea, vomiting or stomach ache)*	⊕⊕⊖⊖: **LOW** Study quality: -2 (only one study, unclear rando, selective reporting) Consistency: na Directness: ok Imprecision: ok

Table 342

In this meta-analysis, a prophylactic antibiotic treatment with nitrofurantoin was compared to trimethoprim in children at risk of recurrent urinary tract infection.

The children were 1-14 years old. They were followed for 6 months.

The duration of both treatments was 6 months. Nitrofurantoin was given in a dose of 1-1.5 mg/kg/day and trimethoprim in a dose of 3 mg/kg/day.

As this review only found one small study with methodological flaws (unclear method of randomisation, selective reporting), our confidence in the results is limited.

In children *at risk of recurrent urinary tract infection, with or without vesico-ureteric reflux*, a prophylactic treatment with nitrofurantoin for 6 months, compared to trimethoprim for 6 months, **did** result in a statistically significant increase in *adverse effects*.
GRADE: LOW quality of evidence

13.4.3 Duration of prophylactic antibiotic treatment in children at risk of recurrent UTI

13.4.3.1 Clinical evidence profile

Systematic review: Larcombe 2013{Larcombe, 2015 #112} "Urinary tract infection in children: recurrent infections"
Inclusion criteria:
Study design criteria for inclusion in this review were systematic reviews and RCTs published in English, at least single-blinded, and containing 20 or more individuals (10 in each arm), of whom more than 80% were followed up.
Studies comparing different durations of prophylactic antibiotics
Search strategy:
"BMJ Clinical Evidence search and appraisal December 2013. Databases used to identify studies for this systematic review included: Medline 1966 to December 2013, Embase 1980 to December 2013, The Cochrane Database of Systematic Reviews 2013, issue 11 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database."

Table 343

Results:
No systematic reviews or RCTs were found that met the inclusion criteria of this review.

13.4.3.2 Summary and conclusions

In this meta-analysis, a search was conducted for RCTs and quasi-RCTs where different durations of prophylactic antibiotic therapy were compared in children at risk for recurrent UTI.

There were no RCTs or quasi-RCTs that met the inclusion criteria.

14 Acute gastroenteritis

14.1 Guidelines

14.1.1 Method of reporting of the recommendations and notes

Formal recommendations, that are supplied with grades of recommendations or levels of evidence, are written in **bold**.

Text taken directly from the guidelines, that is not graded but provides supplemental information or a clarification of the formal recommendations, is written in *italics*.

Comments by the bibliography group are written in plain text.

14.1.2 General information on selected guidelines

14.1.2.1 Selected guidelines

The selected guidelines and their abbreviations as used in this report can be found inTable 344.

Abbreviation	Guideline
BAPCOC 2012{BAPCOC, 2012 #3}	BAPCOC - Belgische gids voor anti-infectieuze behandeling in de ambulante praktijk; editie 2012/ Guide Belge des traitements anti-infectieux en pratique ambulatoire; édition 2012
DM acute GE 2010{Van Winckel, 2010 #21}	Domus Medica - Acute gastro-enteritis; 2010
ESPGHAN-ESPID AGE 2014{Guarino, 2014 #328}	ESPGHAN/ESPID - Evidence-based guidelines for the management of acute gastro-enteritis in children in Europe; 2014
NHG acute diarrhea 2014{NHG - Dutch College of General Practitioners, 2014 #15}	Nederlands Huisartsen Genootschap “NHG-standaard acute diarree” 2014

Table 344: Selected guidelines and their abbreviations as used in this report.

14.1.2.2 Grades of recommendation

Grades of recommendation and levels of evidence as defined in each guideline, can be found in Table 345, Table 346, Figure 12, and Figure 13.

BAPCOC 2012		
Grades of	1	Strong recommendation

recommendation:	2	Weak recommendation
Levels of evidence	A	High degree of evidence; RCTs without limitations or strong, compelling evidence from observational studies
	B	Medium level of evidence; RCTs with limitations or strong evidence from observational studies
	C	(very) low degree of evidence; observational studies or case studies

Table 345 Grades of recommendation and Level of evidence

DM Acute GE 2010				
Grades of recommendation		**Advantages, disadvantages and risks**	**Methodological quality of the studies**	**Implications**
1A	Strong recommendation, high level of evidence	Advantages clearly outweigh the disadvantages or risks	RCTs without limitations or cogent evidence from observational studies	Strong recommendation, can be applied to most patients in most circumstances
1B	Strong recommendation, moderate level of evidence	Advantages clearly outweigh the disadvantages or risks	RCTs with limitations or strong evidence from observational studies	Strong recommendations, can be applied to most patients in most circumstances
1C	Strong recommendation (very) low level of evidence	Advantages clearly outweigh the disadvantages or risks	Observational studies or case reports	Strong recommendation, but are prone to change should new evidence arise
2A	Weak recommendation, strong level of evidence	Advantages and disadvantages are balanced	RCTs without limitations or cogent evidence from observational studies	Weak recommendation, the best course of action can differ based on circumstances, patients or societal values
2B	Weak recommendation, moderate levels of evidence	Advantages and disadvantages are balanced	RCTs with limitations or strong evidence from observational studies	Weak recommendation, the best course of action can differ based on circumstances, patients or societal values
2C	Weak recommendation, (very) low levels of evidence	Uncertainty about advantages or disadvantages – they could be balanced	Observational studies or case reports, or RCTs with major limitations	Very weak recommendation, alternatives can be just as valid

Table 346: Grades of recommendation and Level of evidence of DM Acute GE 2010 guideline.

ESPGHAN/ESPID AGE 2014

TABLE 1. Strength of evidence and grade of recommendations in support of the recommendations formulated in the 2008 ESPGHAN/ESPID guidelines for the management of AGE in children in Europe

Strength of evidence	
I	Strong evidence from ≥1 systematic review(s) of well-designed RCTs
II	Strong evidence from ≥1 properly designed RCT(s) of appropriate size
III	Evidence from well-designed trials without randomization, single group pre–post, cohort, time series, or matched case–control studies
IV	Evidence from well-designed trials, nonexperimental studies from >1 center or research group
Va	Opinion of respected authorities
Vb	Clinical evidence, descriptive studies, or reports of expert committees
Grade of recommendation	
A	Supported by level I evidence, highly recommended
B	Supported by level II evidence, recommended
C	Supported by level III evidence, recommended
D	Supported by level IV and level V evidence; the consensus route would have to be adopted

AGE = acute gastroenteritis; ESPGHAN = European Society for Pediatric Gastroenterology, Hepatology, and Nutrition; ESPID = European Society for Pediatric Infectious Diseases; RCT = randomized controlled trial.

Figure 15: ESPGHAN/ESPIC AGE 2014 strength of evidence and grades of recommendations

TABLE 2. GRADE system

Quality of evidence	
High quality	Further research is unlikely to change our confidence in the estimate of effect
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality	Further research is extremely likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality	Any estimate of effect is extremely uncertain
Grade of recommendation	
Strong	When the desirable effects of an intervention clearly outweigh the undesirable effects, or they clearly do not
Weak	When the tradeoffs are less certain (either because of the low quality of evidence or because the evidence suggests that desirable and undesirable effects are closely balanced)

GRADE = Grading of Recommendations, Assessment, Development, and Evaluations.

Figure 16: GRADE system as used in the ESPGHAN/ESPID AGE 2014 guideline

The **NHG guidelines** do not explicitly attribute grades of recommendation or levels of evidence to their recommendations. They do perform a GRADE- evaluation of the included evidence on which the recommendations are based. They also express the grade of recommendation in the wording of the recommendation itself (i.e. strongly or weakly recommended). (see https://www.nhg.org/sites/default/files/content/nhg_org/uploads/handleiding_standaarden_2015.pdf)

14.1.2.3 Agree II score

Information about the Agree II score can be found in the section “Methodology”.

A summary of the assessment by the literature group of the individual items of the domain score for each guideline can be found in Table 347.The total domain score is also reported in this table.

Rigour of development item	7	8	9	10	11	12	13	14	Total	Domain score
DM acute GE 2010	7	7	3	3	7	6	4	2	**39**	**70%**
ESPGHAN/ESPID AGE 2014	6	6	6	4	1	3	4	6	**36**	**64%**
NHG Acute diarrhea 2014	6	3	2	2	3	4	7	2	**29**	**52%**

Table 347: AGREE score of selected guidelines on item “Rigour of development”, see 1.1.2.6 for a description of the items.

14.1.2.4 Included populations – interventions – main outcomes

In Table 348 to Table 351, the populations, interventions and main outcomes considered in the selected guidelines are represented.

BAPCOC 2012	
Population	Ambulant care patients (adults and children)
Interventions	Antibiotic treatment (indication, choice, dose, duration)
Outcomes	Not specified

Table 348: Included population, intervention and main outcomes of guideline.

DM acute GE 2010	
Population	Adults and children with acute diarrhea (traveler's diarrhea excluded, immunodepressed patients excluded)
Interventions	Diagnosis, clinical examination, sanitary advice, ORS, antibiotics, rotavirus vaccination
Outcomes	Not specified

Table 349: Included population, intervention and main outcomes of guideline.

ESPGHAN/ESPID AGE 2014	
Population	The aim was children >5 years but in some cases data may include individuals up to age 18.
Interventions	Definition, epidemiology, risk factors, clinical evaluation, diagnostic, hospital management, treatment
Outcomes	Not specified

Table 350: included population, intervention and main outcomes of guideline.

NHG Acute Diarrhea 2014	
Population	Adults and children with acute diarrhea (from any origin)
Interventions	Diagnosis, sanitary advice, medication (ORS, loperamide, antibiotics)
Outcomes	Not specified

Table 351 : Included population, intervention and main outcomes of guideline.

14.1.2.5 Members of development group – target audience

Members of the development group that produced the guidelines, and the target audience for whom the guidelines are intended, can be found in Table 352 to Table 355.

BAPCOC 2012	
Development group	General practitioners, microbiologists, pneumologists, infectiologists, paediatricians, pharmacists
Target audience	Physicians working in ambulant care

Table 352: Members of the development group and target audience of the BAPCOC 2012 guideline

DM acute GE 2010	
Development group	General practitioners and pediatricians

Target audience	General practitioners, pediatricians and emergency doctors

Table 353: Members of the development group and target audience of the DM acute GE 2010 guideline

ESPGHAN/ESPID AGE 2014	
Development group	Pediatricians with a special interest in gastroenterology and infectious diseases
Target audience	Practitioners

Table 354: Members of the development group and target audience of the ESPGHAN/ESPID AGE 2014 guideline.

NHG Acute Diarrhea 2014	
Development group	General practitioners, microbiologists, scientific collaborators
Target audience	General practitioners

Table 355: members of the development group and target audience of the NHG acute diarrhea guideline 2014

14.1.3 Definition

14.1.3.1 Summary

Three out of four guidelines define acute gastro-enteritis as a sudden-onset condition with a decrease in consistency, and increase in the frequency, of stools.
Two guidelines specify a frequency of >3 times in 24 hours. Duration is limited to <14 days by one guideline, <7 days by another. One guideline mentions infectious origins.

14.1.3.2 BAPCOC 2012

No definition given.

14.1.3.3 DM acute GE 2010

Acute gastro-enteritis is defined as an acutely occurring diarrhea, frequent (at least 3 times a day during more than 24 hours) and/or loose stools, from infectious origins.

14.1.3.4 ESPGHAN/ESPID AGE 2014

Acute gastroenteritis is generally defined as a decrease in the consistency of stools (loose or liquid) and/or an increase in the frequency of evacuations (typically >3 in 24 hours), with or without fever or vomiting; however, a change in stool consistency versus previous stool consistency is more indicative of diarrhea than stool number, particularly in the first months of life. Acute diarrhea typically lasts <7 days and not >14 days.

14.1.3.5 NHG acute diarrhea 2014

Acute diarrhea is the sudden onset of a deviation from the usual defecation pattern, for less than 14 days; the frequency and the quantity of stool have increased and the stool contains more water than usual.

14.1.4 Indications for antibiotic treatment

14.1.4.1 Summary

All four guidelines agree that antibiotic treatment is not needed routinely or generally useless, but they differ on the approach needed to treat specific bacterial agents.

The BAPCOC 2012 guideline only recommends antibiotics in case of dysentery syndrome and for high risk patients (weak recommendation, low LoE).

Two guidelines recommend different courses of action depending on the identified pathogen.

Pathogen	**ESPGHAN/ ESPID AGE 2014**		**NHG acute diarrhea2014 (no LoE)**	
	Recommendation	Strength of rec./LoE	Recommendation	Strength of rec./LoE
Shigella	Yes	STRONG, Mod.	Only severe cases	/
Salmonella	No in general	STRONG, Mod.	No in general	/
	Yes for high risk patients	STRONG, Low.	Yes for high risk groups	/
Campylo-bacter	Only for dysenteric syndrome	STRONG, Mod.	Only severe cases or immunocompromised patients	/
E.Coli	No	WEAK, Very Low.	EHEC/STEC: No ETEC: Only severe cases	/
Yersinia	/	/	Only in case of complications or immunocompromised patient	/

Table 356

14.1.4.2 BAPCOC 2012

There is no evidence that an antibiotic treatment has a positive influence on the natural evolution of acute gastro-enteritis. Acute gastro-enteritis is caused by bacterial pathogens in a small percentage of cases (10-20%).

Antibiotic treatment is recommended (by consensus) for high risk patients (patients with implants or heart valve disease and in case of a dysentery syndrome (diarrhea with fever, bloody stools and/ or an important degradation of the general condition) (GRADE 2C)

14.1.4.3 DM acute GE 2010

Prescription of antibiotics in ambulatory care for acute gastro-enteritis in adults or children is generally useless. Acute gastro-enteritis is usually self-limiting and is caused by a bacterial agent in only 10 to 20% of cases. Even if there is a known bacterial origin, the benefit of antibiotics is limited.

Pathogen	*Position of guideline on antibiotic use*
Shigella	*Rare in Belgium. Some evidence that duration of symptoms can be shortened with*

	antibiotic use.
Campylobacter	*Some evidence that duration of symptoms can be shortened with antibiotic use.*
Traveller's diarrhea	*Outside of the scope of the guideline. Some evidence that duration of symptoms can be shortened with antibiotic use.*
Salmonella	*In case of mild diarrhea there is evidence that antibiotics do not positively influence the course of illness.* *More patients treated with antibiotics become carriers post-infection.* *Significantly more patients who were treated with antibiotics still had abdominal complaints 3 months after the infection compared to patients who didn't receive antibiotics.*

Table 357: position of DM acute GE 2010 guideline on antibiotic use with certain bacterial pathogens

14.1.4.4 ESPGHAN/ESPID AGE 2014

Antibiotic therapy for acute bacterial gastroenteritis is not needed routinely but only for specific pathogens or in defined clinical settings (Va, D) (strong recommendation, low-quality evidence).

In children with watery diarrhea, antibiotic therapy is not recommended unless the patient has recently traveled or may have been exposed to cholera (Vb, D) (strong recommendation, moderate-quality evidence).
Bloody diarrhea with low or no fever is typical of STEC (enterohemorrhagic E coli), but can be mild shigellosis or salmonellosis. Antibiotics are not recommended unless epidemiology suggests shigellosis (Vb, D) (weak recommendation, low-quality evidence).

Shigella gastroenteritis
Antibiotic therapy is recommended for culture-proven or suspected Shigella gastroenteritis (II, B) (strong recommendation, moderate-quality evidence).

Salmonella gastroenteritis
Antibiotic therapy is not effective on symptoms and does not prevent complications. It is associated with a prolonged fecal excretion of Salmonella. Therefore, antibiotics should not be used in an otherwise healthy child with Salmonella gastroenteritis (I, A) (strong recommendation, moderate quality evidence).
Antibiotics are suggested in high-risk children to reduce the risk of bacteremia and extraintestinal infections (Vb, D) (strong recommendation, low-quality evidence). These include neonates and young infants (<3 months) and children with underlying immune deficiency, anatomical or functional asplenia, corticosteroid or immunosuppressive therapy, IBD, or achlorhydria (Vb, D) (weak recommendation, low-quality evidence).

Campylobacter gastroenteritis
Antibiotic therapy for Campylobacter gastroenteritis is recommended mainly for the dysenteric form and to reduce transmission in day-care centers and institutions. It reduces symptoms if instituted in the early stage of the disease (within 3 days after onset) (I, A) (strong recommendation, moderate-quality evidence).

Diarrheagenic E. Coli

Antibiotics should not be routinely given for AGE due to E coli. The treatment is nonspecific and administration of antibiotics could have adverse effect (Vb, D) (weak recommendation, very low-quality evidence).
Antibiotic therapy for Shiga toxin-producing E coli is not recommended (Vb, D) (strong recommendation, low-quality evidence).
Antibiotic therapy for enterotoxigenic E coli is recommended (II, B) (strong recommendation, moderate-quality evidence).

Other causes
Antibiotic therapy is recommended for Vibrio cholera gastroenteritis (II, B) (strong recommendation, moderate-quality evidence).

14.1.4.5 NHG acute diarrhea 2014

The use of antimicrobial drugs to treat acute infectious diarrhea without additional symptoms is advised against, because this type of diarrhea usually has a favourable outcome in healthy individuals and thus antibiotics have no added value. On top of that some of those drugs can have side effects and in some cases (like salmonella-infections) even heighten the chances that the patient might become a carrier.
Only in the case of general ill condition (prolonged or high fever and bloody stools), or in immunocompromised patients should the general practitioner consider prescribing an antibiotic on top of rehydration salts.

Pathogen	*Antibiotic treatment*
campylobacter spp.	*No treatment except in case of severe infection or in immonucompromised patients; then treat as soon as possible*
salmonella spp. (non-typhi)	*No treatment except in case of severe infection, endovascular stent or in immonucompromised patients; Antibiotics can cause a prolonged carrier-state, heighten the risk of relapse and of development of resistance*
Shigela spp.	*No treatment, except with severe infections*
Yersinia spp.	*No treatment except in case of complications such as joint complaints, erythema nodosum or with an immunocompromised patient*
EHEC/STEC	*Antibiotics and anti-diarrheal medication is contra-indicated; antibiotics are ineffective.* *Follow up on the patient, if necessary consult secondary healthcare providers and refer in case of suspicion of a hemolytic-uremic syndrom*
ETEC	*No treatment except in the case of a severe infection*

Table 358

14.1.5 Choice of antibiotic, dose and duration

14.1.5.1 Summary

The BAPCOC 2012 guideline only gives a specific recommendation in case of dysentery syndrome. DM acute GE 2010 only gives recommendations for adults.

Pathogen	**BAPCOC 2012**	**ESPGHAN/ ESPID AGE 2014**	**NHG acute diarrhea2014 (no LoE)**
	Recommendation for 1st choice	Recommendation for 1st choice	Recommendation for 1st choice
Shigella	No specific AB recommended SoR/LoE: /	**Azithromycin** Day 1: 12 mg /kg/d Day 2-5: 50 mg /kg/d SoR/LoE: STRONG, mod	**Ciprofloxacine** 30 mg/kg/d in 2 doses /d max 1500 mg/d /
Salmo-nella	No specific AB recommended SoR/LoE: /	**Ceftriaxone** 50-10mg /kg/d SoR/LoE: /	**Ciprofloxacine** 30 mg/kg/d in 2 doses /d max 1500 mg/d /
Campylo-bacter	**Quinolone** during 3 days then according to antibiogram Cave AB resistance (in that case: **azithromycine**) SoR/LoE: STRONG, (very) weak	**Azithromycine** 10 mg /kg/d during 3 days OR Single dose: 30 mg/kg Cave resistance SoR/LoE: WEAK, low	**Azithromycine** 10 mg/kg/d in 1 dosis/d during 3 d max 500 mg/d SoR/LoE: /
STEC	No specific AB recommended SoR/LoE: /	AB therapy is not recommended SoR/LoE: : /	**Cotrimoxazol**: 30/6 mg/kg/d in 2 doses max 1600/320 mg/d SoR/LoE: /
ETEC	No specific AB recommended SoR/LoE: /	**Azithromycine** 10mg / kg /d during 3 days SoR/LoE: /	No SoR/LoE: /
Yersinia	No specific AB recommended /	/ /	**Ciprofloxacine** 30 mg/kg/d in 2 doses /d max 1500 mg/d /

Table 359

14.1.5.2 BAPCOC 2012

Only with dysentery-syndrome in risk patients does the guideline make a recommendation, which does not differ between adults and children:

Dysentery syndrome in risk patients
A quinolone during 3 days then aetiological treatment according to culture and antibiogram. (Grade 1C).

14.1.5.3 DM acute GE 2010

The guideline only gives recommendations for choice of antibiotics for adults.

14.1.5.4 ESPGHAN/ESPID AGE 2014

The choice of the antimicrobial agent depends on the local prevalence of the 3 pathogens (Shigella spp, Campylobacter spp, and Salmonella enterica) and the resistance patterns (Va, B) (strong recommendation, moderate-quality evidence).

In children with watery diarrhea, antibiotic therapy is not recommended unless the patient has recently traveled or may have been exposed to cholera (Vb, D) (strong recommendation, moderate-quality evidence).

Bloody diarrhea with low or no fever is typical of STEC (enterohemorrhagic E coli), but can be mild shigellosis or salmonellosis. Antibiotics are not recommended unless epidemiology suggests shigellosis (Vb, D) (weak recommendation, low-quality evidence).

Sepsis workup and antibiotics should be considered according to local protocols

Shigella gastroenteritis

The first-line treatment for shigellosis is azithromycin for 5 days (II, B) (strong recommendation, moderate-quality evidence).

Campylobacter gastroenteritis

The drug of choice is azithromycin, but antibiotic choice should be based on local resistance pattern (III, C) (weak recommendation, low-quality evidence).

TABLE 7. Antibiotic therapy of bacterial gastroenteritis

Pathogen	Indication for antibiotic therapy	Drug of choice*	Alternative agents
Shigella spp	Proven or suspected shigellosis	Oral: azithromycin (12 mg/kg on day 1, followed by 6 mg/kg for 4 days); parenteral, IV, IM: ceftriaxone (50 mg/kg for 2–5 days)†	Cefixime (8 mg · kg^{-1} · day^{-1}); ciprofloxacin‡ PO (20–30 mg · kg^{-1} · day^{-1}). For a known susceptible strain: TMP/SMX† (8 mg · kg^{-1} · day^{-1} of TMP) or ampicillin (100 mg · kg^{-1} · day^{-1}) or nalidixic acid (55 mg · kg^{-1} · day^{-1})
Salmonella spp (nontyphoidal)	Antibiotic therapy is indicated only in high-risk children§ to reduce the risk of bacteremia and extraintestinal focal infections	Ceftriaxone (50–100 mg · kg^{-1} · day^{-1})	Azithromycin (10 mg · kg^{-1} · day^{-1}); ciprofloxacin‡ PO (20–30 mg · kg^{-1} · day^{-1}); for a known susceptible strain, TMP/SMX§ (8 mg · kg^{-1} · day^{-1} of TMP).
Campylobacter spp	Antibiotic therapy is recommended mainly for the dysenteric *Campylobacter* gastroenteritis and most efficacious when started within 3 days after onset of the disease	Azithromycin (10 mg · kg^{-1} · day^{-1} for 3 days, or a single dose of 30 mg/kg)	Doxycycline (>8 years) or ciprofloxacin (>17 years), when susceptible)
Shiga toxin-producing *Escherichia coli*	Antibiotic therapy is not recommended	—	—
Enterotoxigenic; *Escherichia coli*	Antibiotic therapy is recommended, mainly for traveler's diarrhea	Azithromycin (10 mg · kg^{-1} · day^{-1} for 3 days)	Cefixime (8 mg · kg^{-1} · day^{-1} for 5 days); TMP/SMX§ (8 mg · kg^{-1} · day^{-1} of TMP); ciprofloxacin§ PO (20–30 mg · kg^{-1} · day^{-1}); rifaximin (>12 years, 600 mg/day, for 3 days)
Vibrio cholerae	Antibiotic therapy is recommended for confirmed or suspected case by travel history	Azithromycin (10 mg · kg^{-1} · day^{-1} for 3 days, or a single 20 mg/kg dose)	Doxycycline (>8 years), Ciprofloxacin (>17 years), or TMP/SMX§ (when susceptible)
Clostridium difficile	Antibiotic therapy is recommended for moderate and severe cases	Metronidazole (30 mg · kg^{-1} · day^{-1} for 10 days)	Vancomycin PO (40 mg · kg^{-1} · day^{-1})

PO = per os.
* Depends on local antibiotic susceptibility profile, which should be monitored.
† TMP/SMX, trimethoprim–sulfamethoxazole.
‡ Ciprofloxacin is usually not recommended in the pediatric age group, but it can be used in children <17 years when an alternative is not feasible.
§ See text.

Figure 17: ESPGHAN/ESPID AGE 2014 indication, choice, duration and alternative agents for antibiotic therapy depending on pathogen

14.1.5.5 NHG acute diarrhea 2014

No difference is made in the recommendations between adult patients and children except for the dosage of the recommended antibiotics.

- *No treatment of non-pathogenic protozoa*
- *In case of an unknown pathogen, the general practitioner (eventually after a consultation with a microbiologist or an infectious disease specialist) can prescribe azithromycine 1 tablet 500 mg in 1 dose/day, during 3 days.*
- *If the results of the faecal findings are known, the general practitioner can prescribe an antibiotic in accordance of the results and the antibiotic resistance (see table). These recommendations are based on the guidelines of the SWAB.*

Antibiotic treatment of acute infectious diarrhea with a bacterial pathogen (dosages for children reproduced by literature group from "kinderformularium" (www.kinderformularium.nl))

Pathogen	*Antibiotic treatment*	*Antibiotics (1st, 2nd, 3rd*	*Contra-indications/*

		choice)	*interactions*
campylobacter spp.	*No treatment except in case of severe infection or in immonucompromised patients; then treat as soon as possible*	*Azithromycine* Children 1 month to 18 years: 10 mg/kg/day in 1 dosis/d during 3 days Max 500mg/day	*Be mindful of possible QT-prolongation and heightened digoxine levels.*
salmonella spp. (non-typhi)	*No treatment except in case of severe infection, endovascular stent or in immonucompromised patients; Antibiotics can cause a prolonged carrier-state, heighten the risk of relapse and of development of resistance*	1. *Ciprofloxacine* Children 1 month to 18 years: 30 mg/kg/d in 2 doses/d during 7 days, max: 1.500mg/day 2. *Cotrimoxazol* Children 1 month to 18 years: 30/6 mg/kg/d in 2 doses, max: 1.600/320 mg/day In case of endovascular stent or immuno-compromised patients: treatment during 14 days	*Cotrimoxazol and ciprofloxacine:* *half dosage if eGFR < 30 ml/min* *Cotrimoxazol: do not combine with methotrexate (toxicity) or coumarin derivatives (severe disturbance of anticoagulation level)*
Shigela spp.	*No treatment, except with severe infections*	1. *Ciprofloxacine* Children 1 month to 18 years: 30 mg/kg/d in 2 doses/d during 7 days, max: 1.500mg/day 2. *Azithromycine* Children 1 month to 18 years: 10 mg/kg/day in 1 dose/d during 3 days, max 500 mg/day 3. *Cotrimoxazol* Children 1 month to 18 years: 30/6 mg/kg/day in 2 doses, max: 1.600/320 mg/day	*Cotrimoxazol and ciprofloxacine:* *half dosage if eGFR < 30 ml/min* *Cotrimoxazol: do not combine with methotrexate (toxicity) or coumarin derivatives (severe disturbance of anticoagulation level)* *Azitromycine:* *Be mindful of possible QT-prolongation and heightened digoxine levels.*
Yersinia spp.	*No treatment except in case of complications such as joint complaints, erythema nodosum or with an immunocompromised patient*	1. *Ciprofloxacine* Children 1 month to 18 years: 30 mg/kg/d in 2 doses/d during 7 days, max: 1.500mg/day 2. *Cotrimoxazol*	*Cotrimoxazol en ciprofloxacine:* *half dosage if eGFR < 30 ml/min* *Cotrimoxazol: do not combine with*

		Children 1 month to 18 years: 30/6 mg/kg/day in 2 doses, max: 1.600/320 mg/day	*methotrexate (toxicity) or coumarin derivatives (severe disturbance of anticoagulation level)*
EHEC/STEC	*Antibiotics and anti-diarrheal medication is contra-indicated; antibiotics are ineffective.* *Follow up on the patient, if necessary consult secondary healthcare providers and refer in case of suspicion of a hemolytic-uremic syndrom*	1. *Cotrimoxazol* Children 1 month to 18 years: 30/6 mg/kg/day in 2 doses, max: 1.600/320 mg/dag 2. *Ciprofloxacine* Children 1 month to 18 years: 30 mg/kg/d in 2 doses/d during 7 days max: 1.500mg/dag	
ETEC	*No treatment except in the case of a severe infection*		*Cotrimoxazol en ciprofloxacine: half dosage if eGFR < 30 ml/min* *Cotrimoxazol: do not combine with methotrexate (toxicity) or coumarin derivatives (severe disturbance of anticoagulation level)*

Table 360

Another table exists for the treatment of a diarrhea caused by protozoa with anti-protozoal drugs. This falls outside of the scope of this literature review.

14.1.6 Non-antibiotic treatment

14.1.6.1 Probiotics

14.1.6.1.1 Summary

Three out of four guidelines mention probiotics. NHG acute diarrhea 2014 does not recommend them in any circumstances. DM acute GE 2010 speaks of a product-specific, limited positive effect (L. acidophilus and S. Boulardii strains are mentioned), especially if given early in the course of the illness. However probiotics do not lessen the risk for dehydration. ESPGHAN/ESPID guideline AGE 2014 says there is an effect in reducing duration and intensity of acute gastro-enteritis, (strong recommendation with moderate evidence), and they mention the strains L. Rhamnosus and S. Boulardii (strong recommendation with low evidence).

14.1.6.1.2 BAPCOC 2014

No information found in the guideline

14.1.6.1.3 DM acute GE 2010

There are two probiotic products registered as drugs (as opposed to food supplements) *in Belgium. They contain Lactobacillus acidophilus (Lacteol ®) or Saccharomyces boulardii (Enterol®). There are also a lot of other products available as food supplements, which are thus not registered as drugs.*

Several meta-analyses have been published on the use of probiotics in children with acute gastro-enteritis. The results point to a limited positive effect, that seems to be product-specific (the use of L. acidophilus and S. boulardii is the most substantiated) and dose-dependent (>1010-1011 CFU). It also seems to be more pronounced with watery diarrhea or viral gastro-enteritis and clearer when started early in the course of the diarrhea. The use of probiotics results in a lesser risk of continued diarrhea after three days and a somewhat less long diarrhea (0.5 – 1 day shorter in general). However, though a positive effect is possible, it has not been shown that the use of probiotics lessens the risk of dehydration or the risk of hospitalization. The limited positive effect must be weighed against the cost, the rare risk of bacterial translocation or the chance that parents would pay more attention to their child taking the medication rather than take in enough fluids and food. Standard usage of probiotics in diarrhea is thus not recommended.

Treatment with S. boulardii however has a demonstrated effect on Clostridium difficile-diarrhea or diarrhea due to antibiotic use.

Probiotics have been administered for prolonged periods of time to prevent diarrhea, without convincing effect. Side effects are very seldom, however sepsis with probiotics has been described in immunodepressed patients.

14.1.6.1.4 ESPGHAN/ESPID AGE 2014

Active treatment with probiotics, in adjunct to ORS, is effective in reducing the duration and intensity of symptoms of gastroenteritis. Selected probiotics can be used in children with AGE (I, A) (strong recommendation, moderate-quality evidence).

New evidence has confirmed that probiotics are effective in reducing the duration of symptoms in children with AGE (I, A) (strong recommendation, moderate-quality evidence).

The use of the following probiotics should be considered in the management of children with AGE as an adjunct to rehydration therapy: L rhamnosus GG and S boulardii (I, A) (strong recommendation, low-quality evidence).

14.1.6.1.5 NHG acute diarrhea 2014

Probiotics are not recommended to treat acute diarrhea, to prevent antibiotic-associated diarrhea or to prevent travelers' diarrhea.

14.1.6.2 Other non-antibiotic treatment

14.1.6.2.1 Summary

All four guidelines mention the importance of preventing and correcting dehydration.

ESPGHAN/ESPID AGE 2015, DM acute GE 2010 and NHG acute diarrhea 2014 all recommend rehydration salts in patients where there is (a risk of) dehydration. DM acute GE 2010 and NHG acute diarrhea 2014 specifically recommend using commercial preparations. All three guidelines agree that the ORS should be offered frequently and in small quantities, and that it is a laborious task.
DM acute GE 2010 and ESPGHAN/ESPID AGE 2014 recommend using reduced osmolarity ORS rather than those with the WHO composition (which is tailored for cholera diarrhea).

Concerning food or nutrition during diarrhea, NHG acute diarrhea 2014 and DM acute GE 2014 both state that breastfeeding and formula can be continued undiluted. ESPGHAN/ESPID AGE 2014 speaks of interrupting formula. All three guidelines state that beverages with high sugar such as soft drinks and fruit juices should be avoided.

Nifuroxazide has no place in the treatment of acute gastro-enteritis according to BAPCOC 2012 and DM acute GE 2014.

Loperamide has no place in the treatment of acute gastro-enteritis according to ESPGHAN/ESPID AGE 2014, DM acute GE 2010 and NHG acute diarrhea 2014. The latter even gives an absolute contra-indication against loperamide in children under 3 years of age.

Adsorbents have no place in the treatment of acute gastro-enteritis according to DM acute GE 2010 and NHG acute diarrhea 2014, but ESPGHAN/ESPID AGE 2014 states that diosmectite can be considered.

Anti-emetics have no place in the treatment of acute gastro-enteritis according to BAPCOC 2012 and DM acute GE 2014.

14.1.6.2.2 BAPCOC 2012

Treatment of acute gastroenteritis should in the first place be aimed at preventing of correcting dehydration, and in case of severe dehydration - especially in children – hospitalization might be necessary.

The usefulness of intestinal antiseptics like nifuroxazide has not been proven (Grade 1C).

14.1.6.2.3 DM acute GE 2010

Food and nutrition:

- *Breastfeeding should continue undiminished, even if the infant is being treated with oral rehydration salts as well*
- *Infants who receive formula and show no signs of dehydration can receive their usual formula undiluted*

- *In case of dehydration formula should be interrupted during the rehydration period of 4 to 6 hours, but should be started again swiftly*
- *After successful rehydration, the usual, undiluted formula should be started again. Vomiting happens as often with undiluted as with progressively less diluted formula. The duration of diarrhea is shorter and the weight gain is better when undiluted formula is given.*
- *There is no reason to switch to hydrolised, low fat or low lactose formula after rehydration. Secondary lactose intolerance doesn't occur often anymore in the western world and there is no reason to give diluted formula*
- *Older children and adults with acute gastro-enteritis can eat anything, in accordance with how hungry they feel and for what. They are advised to drink more to compensate the loss of fluid from diarrhea. In case of nausea and abdominal cramps it is advised to take frequent small meals.*

Oral rehydration salts

- *The use of oral rehydration salts is indicated in patients with signs of mild dehydration and in patients at a high risk of developing dehydration.*
- *Compared with IV rehydration, oral rehydration is safer and almost always more effective. Enteral rehydration seldom fails (4% of children still do need IV rehydration), while parenteral rehydration usually has a higher risk of unwanted effects and lead to a longer hospitalization.*
- *In western countries hyposmotic oral rehydration (osmolarity < 250 mmol/l and Na 60 mEg/l) is favored above the standard WHO solution who was developed to treat cholera diarrhea.*
- *Oral rehydration salts from rice are not more effective than those based on glucose, except for cholera diarrhea.*
- *Commercial oral rehydration salts in Belgium contain 40-70 mEq/l sodium, 20-49 mEq/l potassium, and the osmolarity varies from 140 to 298 mOsm/l. Commercial rehydration must be used according to the prescribed dilution. Using commercial preparations has a lower risk of wrong composition than pharmaceutically compounded or home-prepared oral rehydration.*
- *It is not appropriate to add extra sugar or syrup to the oral rehydration salts to change the taste. Adding sugar changes the osmolarity of the solution and the balance between carbohydrates and sodium, and diminishes the efficacity of the rehydration solution.*
- *Oral rehydration salts should not be used to prepare formula for infants.*
- *Children with mild dehydration should get oral rehydration at a rate of 50 to 75 ml/kg every 4 to 6 hours (corresponding to a 5% dehydration plus further loss through diarrhea). It is best to present the solution very frequently and in small quantities per intake. Vomiting does not constitute a contra-indication.*
- *To present the oral rehydration in small quantities, it is best to administer them with small sips from a cup or a straw. Administering oral rehydration is laborious. It is common to administer oral rehydration through a nasogastric probe drip in infants with moderate dehydration.*
- *To prevent diarrhea in infants with a high risk of dehydration (<7 kg bodyweight, very frequent watery diarrhea and vomiting) one should offer 10 ml/kg per loose stool. If the solution is refused, the infants will generally not be dehydrated.*
- *Soft drinks, orange juice or apple juice can bring more fluids, but they can't be considered as rehydration solutions. Their osmolality is usually very high and the balance between*

electrolytes and carbohydrates not appropriate. Due to their high osmolality they can even help maintain the diarrhea if they're consumed in large quantities.

Intestinal antiseptics

- *There is no effect of nifuroxazide on dehydration or course of the diarrhea. Severe (although very rare) allergic reactions have been described. Due to these reasons nifuroxazide was removed from the Belgian market.*

Anti-motility drugs (loperamide)

- *The use of bowel movement inhibitors such as loperamide is advised against because of the risk of unwanted side effects. Loperamide is contra-indicated in children under two years due to the risk of respiratory depression.*

Adsorbents:

- *The use of adsorbentia (smectite, kaolin, pectin, attapulgite, activated charcoal) is not recommended due to the lack of evidence about their efficacity, or on the case of smectite, the very limited effect without clinical relevance. These products are, especially for children, difficult to ingest and can compromise the essential intake of fluid and food.*

Anti-emetics

- *Anti-emetics should not be used in acute gastro-enteritis*

14.1.6.2.4 ESPGHAN/ESPID AGE 2014

Oral rehydration:

- *Caregivers should be encouraged to have oral rehydration solution (ORS) at home and start administering it as soon as AGE symptoms begin in order to reduce complications and the need for a medical visit.*
- **Reduced osmolarity ORS (50/60 mmol/L Na) should be used as first-line therapy for the management of children with AGE (I, A) (strong recommendation, moderate-quality evidence).**
- **Reduced osmolarity ORS is more effective than fullstrength ORS as measured by such important clinical outcomes as reduced stool output, reduced vomiting, and reduced need for supplemental IV therapy (I, A) (strong recommendation, moderate-quality evidence).**
- **There is insufficient evidence to recommend in favor or against the universal addition of enriched ORS (II, B) (weak recommendation, low-quality evidence).**
- **There is limited evidence for similar efficacy of ORS with standard taste and ORS with improved taste (II, B) (weak recommendation, moderate-quality evidence).**
- **Frozen fruit-flavored ORS is better tolerated than conventional ORS (III, C) (weak recommendation; very low quality evidence)**

Food and nutrition:

- **Early resumption of feeding after rehydration therapy is recommended. Further studies are, however, needed to determine whether the timing of refeeding affects the duration of**

diarrhea, total stool output, or weight gain in childhood acute diarrhea (I, A) (strong recommendation, low-quality evidence).

- **The routine use of lactose-free feeds is presently not recommended in outpatient setting (I, A) (strong recommendation, low-quality evidence).**
- **There is insufficient evidence to recommend in favor or against the use of diluted lactose-containing milk (I, A) (weak recommendation, low-quality evidence).**
- **The bread, rice, apple, toast (BRAT) diet has not been studied and is not recommended (Vb, D) (strong recommendation, low-quality evidence).**
- **Beverages with a high sugar content should not be used (III, C) (strong recommendation, low-quality evidence).**

Anti-emetics:

- **There is no evidence to support the use of other antiemetics** (other than odansetron) **(II, B) (strong recommendation, low-quality evidence).**

Anti-motility drugs:

- **Loperamide is not recommended in the management of AGE in children (II, B) (strong recommendation, very low quality evidence).**

Adsorbents:

- **Diosmectite can be considered in the management of AGE (II, B) (weak recommendation, moderate-quality evidence).**
- **Other absorbents (namely, kaolin–pectin and attapulgite-activated charcoal) are not recommended (III, C) (weak recommendation, very low-quality evidence).**

14.1.6.2.5 NHG acute diarrhea 2014

Food and nutrition:

- *The patient can eat what he feels like eating. Taking in sufficient calories helps the patient's well-being; the intestines are able to take in half of the calories even in the case of strong watery diarrhea. In case of cramps it is advised to eat smaller portions.*
- *Drinking more than usual in small quantities is necessary, also in the case of vomiting. Regularly administering small amounts of fluid can be laborious. When there is no (risk of) dehydration it can be sufficient to add some fluids (like broth, tea and water).*
- *Breastfeeding and formula are continued as usual, there is no need to dilute.*
- *If patients (except for infants) have diarrhea during more than 7 days, it is possible that a temporary intolerance for lactose has set in. Avoiding all lactose is not necessary, but diminishing the consumption of milk is advised.*
- *In the case of persistent diarrhea one should also limit fruit juices, especially apple juice, sof drinks and diet or "light" products, because overuse or diminished intake of those products can lead to osmotic diarrhea, especially in toddlers.*

Oral rehydration salts:

- *In case of (a risk of) dehydration, ambulant therapy is possible. ORS are a first choice, are safe and effective.*

- *In case of heightened risk of dehydration, give as follows:*
    - *Children up to 6 years: 10 ml/kg after each loose stool*
    - *Children older than 6 years: up to 300 ml ORS after each loose stool*
- *In case of dehydration, give as follows:*
    - *Children and adults: 15-25 ml/kg/hour during 4 hours*
    - *Re-evaluate after 4 hours, fluid balance must be restored*
- *Explain to the caregiver that giving rehydration is laborious; the caregiver should give a few sips, if needed with a spoon or bottle, preferably sitting half-upright. A dehydrated patient is thirsty and will most likely drink. Vomiting is no reason not to start oral rehydration, the ORS are taken in very quickly and the patient takes in more than he vomits.*
- *Give clear instructions for the preparation of ORS (variable between brands).*
- *Recommend using commercial brands to make ORS, the osmolarity of those products is (in accordance to the WHO advice) around 245 mmol/l. Advise against home-made ORS.*
- *Advice against the use of sportdrinks or soft drinks.*

Loperamide

- *Use of loperamide in children under 8 years is advised against due to the risk of obstipation and (sub)ileus. Small children are more sensible to this, and also more sensible to central side effects such as lethargy.*
- *Absolute contra-indications: under 3 years of age, fever, bloody stool, persistent diarrhea after antibiotics, pregnancy*

Other:

- Do not recommend adsorbents such as activated charcoal, or preparations with tannins.
- Do not use anti-emetics to avoid vomiting, because this symptomatic treatment has no added value for recovery, and can lead to severe side effects in children and elderly.

14.1.7 Referrals

14.1.7.1 Summary

Four out of four guidelines agree that hospitalization is necessary in case of deterioration of general health. Three mention more details: severe dehydration, failure of rehydration, suspected comorbidities or worsening conditions, absence of dependable caretaker. One gives a strong recommendation with low levels of evidence. One guideline mentions that children under 3 months with suspicion of dehydration should be referred earlier, and also to refer in case of suspected HUS.

14.1.7.2 BAPCOC 2012

Hospitalization for (intravenous) antibiotic treatment is recommended for patients with a sepsis presentation, severe deterioration of general health and bloody stools (GRADE 1C).

14.1.7.3 DM acute GE 2010

Indications for hospital transfer:

- Severe dehydration with shock

- Sepsis presentation with severe deterioration of general health

- Neurological symptoms (lethargy, convulsions)
- Continued vomiting leading to failure of oral rehydration
- Infants with bloody diarrhea
- Infants with a body weight lower than 7kg without dependable caretakers
- Young children with signs of moderate dehydration who cannot be evaluated 6 to 8 hours after starting oral rehydration
- Young children with signs of moderate dehydration without dependable caretakers

Immediate referral is indicated in case of suspected hemolytic uremic syndrome.

14.1.7.4 ESPGHAN/ESPID AGE 2014

The recommendations for hospital admission are based on consensus and include any of the following conditions (Vb, D) (strong recommendation, low-quality evidence):

- **Shock**
- **Severe dehydration (>9% of body weight)**
- **Neurological abnormalities (lethargy, seizures, etc)**
- **Intractable or bilious vomiting**
- **Failure of oral rehydration**
- **Suspected surgical condition**
- **Conditions for a safe follow-up and home management are not met**

14.1.7.5 NHG acute diarrhea 2014

Indications for consultation or referral are the following:

- *Being severely ill*
- *Heightened chance of the disease being very serious, for example due to comorbidity*
- *Serious dehydration (with confusion or diminution of consciousness, deep and fast breathing or severe hypotension)*
- *In case of a rehydration attempt: continuing negative fluid balance, clinical degradation*
- *Children with (suspicion of) dehydration, consult or refer earlier with children under 3 months*
- *Patients with dehydration, when the patient or caretaker isn't able to ensure sufficient fluid intake*
- *Suspicion of HUS with infectious diarrhea caused by EHEC*
- *Diarrhea with heavy rectal blood loss*
- *In case of residence in a nursing home or in a child care center: consult the GGD* ("Gemeentelijke gezondheidsdienst": communal health service) *if necessary*

14.2 Evidence tables and conclusions

14.2.1 Antibiotics versus placebo or no treatment

14.2.1.1 AB vs placebo or no treatment without prior identification of pathogen

14.2.1.1.1 Clinical evidence profile

Systematic review: NICE 2009{National Collaborating Centre for Women's and Children's Health, 2009 #100} “Diarrhoea and vomiting caused by gastroenteritis - diagnosis, assessment and management in children younger than 5 years”
Inclusion criteria:
Infants and young children from birth up to their fifth birthday presenting to healthcare professionals with acute diarrhoea (lasting 14 days or fewer) due to gastroenteritis, on its own or with vomiting.
Setting: Community care, primary care and secondary care, and indications for referral.
Search strategy:
“Systematic searches to answer the clinical questions formulated and agreed by the GDG were executed using the following databases on the OVID platform: MEDLINE (1950 onwards); Embase (1980 onwards); Cumulative Index to Nursing and Allied Health Literature (1982 onwards); Cochrane Central Register of Controlled Trials (1991 to 3rd quarter 2008); Cochrane Database of Systematic Reviews (3rd quarter 2008); and Database of Abstracts of Reviews of Effects (1991 to 3rd quarter 2008).
Search strategies combined relevant controlled vocabulary and natural language in an effort to balance sensitivity and specificity. Unless advised by the GDG, searches were not date specific. Language restrictions were applied to searches – searches were limited to English language papers only. Both generic and specially developed methodological search filters were used appropriately.”
Assessment of quality of included trials: yes

Table 1.1 Levels of evidence for intervention studies

Level	Source of evidence
1++	High-quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1–	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies; high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies (for example, case reports, case series)
4	Expert opinion, formal consensus

Other methodological remarks: NICE found 4 RCTs for this comparison; they did not perform a meta-analysis. Of the 4 RCTs, 3 RCTs had sample sizes of less than 40 participants per arm. We reported only the one RCT that met our inclusion criteria.

Table 361

Oberhelman 1987 [153] Location : Mexico	Study Type RCT Evidence Level 1-	**Total number of participants** *n* = 141 Randomised into two treatment arms Group 1 Intervention : Trimethoprim/sulfamethoxazole *n* = 73 Group 2 Intervention : placebo *n* = 68	**Inclusion criteria**: Children aged 3–84 months seen in hospital with diarrhoea as chief complaint. Three or more unformed stools in previous 24 hours, <72 hours duration of diarrhoea, no antibiotic treatment in prior 7 days, absence of severe dehydration. **Exclusion criteria** : Not stated **Withdrawal criteria** : Not stated 74/141 had identifiable enteric pathogen 56/74 had a bacterial pathogen 6/31 ETEC mixed with others 25/31 ETEC only 7/10 patients had EPEC only 3/10 EPEC mixed with others	**Comparison** Intervention details: **Group 1**: 10 mg/kg per day trimethoprim + 50 mg/kg per day sulfamethoxazole oral suspension in two divided doses per day for 5 days **Group 2**: Placebo oral suspension in two doses per day for 5 days	**Follow up** **Daily assessments for 5 days except weight at day 5 and on assessment at 2 weeks post-treatment** **Outcome measures**: **Mean time to last illness stool** : All patients Group 1 = 58.2 Group 2 = 75.5 *P* = 0.021 Patients with fever Group 1 = 59.6 Group 2 = 94.6 *P* = 0.046 Patients with faecal leucocytes (>3/HPF) Group 1 = 57.7 Group 2 = 106.5 *P* = 0.025	**Funding** : Burroughs Wellcome Company Grant AI 23049 National Institutes of Health Applicable to UK Baseline comparability Similar for age, prior duration of illness, mean no stools in 24 hours prior to therapy, fever, dehydration, three faecal leucocytes per high-power field. Allocation concealment : Not stated Sequence generation : Not stated Blinding of outcome assessors : Daily assessments blinded – made by parents. Other assessments unclear Loss to follow up : None

			12 patients had Shigella 9 patients had Campylobacter 2 patients had Salmonella 4 patients had Cryptosporidium 6 patients had Giardia lablia		***Mean no of unformed stools in 5 day period*** : All patients Group 1 = 9.8 Group 2 = 12.5 *P* = NS Patients with fever Group 1 = 9.1 Group 2 = 17.3 *P* = NS Patients with faecal leucocytes (>3/HPF) Group 1 = 10.1 Group 2 = 18.1 *P* = 0.041 ***Post treatment no of unformed stools in wk1 and wk2*** All patients Patients with fever Patients with faecal leucocytes (>3/HPF) Group 1 Group 2 *P* = NS	Intention to treat analysis : Not stated Power calculation : Not stated 50/141 partipants had body weight <3rd percentile for age (Mexican standards)

Figure 18 study details, as evaluated by NICE 2009

Ref: Oberhelman 1987{Oberhelman, 1987 #333}

14.2.1.1.2 Summary and conclusions

AB vs placebo or no treatment without prior identification of pathogen
Bibliography: NICE 2009{National Collaborating Centre for Women's and Children's Health, 2009 #100}

Table 362

NICE found 4 RCTs for this comparison. They did not perform a meta-analysis. Of the 4 RCTs, 3 RCTs had sample sizes of less than 40 participants per arm. We reported only the one RCT that met our inclusion criteria.

This trial, Oberhelman 1987{Oberhelman, 1987 #333}, examined the effect of oral trimethoprim/sulfamethoxazole (10/50 mg/kg/day in two doses for 5 days) versus placebo. 141 Children aged 3-84 months were included. They were followed for 2 weeks.

The *mean time to last diarrhoeal stool* was statistically significantly **shorter** with antibiotic use compared with placebo (58.2 versus 75.5; p=0.021)

There were **no** statistically significant **differences** between both groups for the *mean number of unformed stools in a 5 day period* and *in week 1 and week 2*.

GRADE: VERY LOW quality of evidence

14.2.1.2 AB vs placebo or no treatment in Salmonella infection

14.2.1.2.1 Clinical evidence profile

Systematic review: NICE 2009{National Collaborating Centre for Women's and Children's Health, 2009 #100} “Diarrhoea and vomiting caused by gastroenteritis - diagnosis, assessment and management in children younger than 5 years”

Inclusion criteria:
Infants and young children from birth up to their fifth birthday presenting to healthcare professionals with acute diarrhoea (lasting 14 days or fewer) due to gastroenteritis, on its own or with vomiting.
Setting: Community care, primary care and secondary care, and indications for referral.

Search strategy:
“Systematic searches to answer the clinical questions formulated and agreed by the GDG were executed using the following databases on the OVID platform: MEDLINE (1950 onwards); Embase (1980 onwards); Cumulative Index to Nursing and Allied Health Literature (1982 onwards); Cochrane Central Register of Controlled Trials (1991 to 3rd quarter 2008); Cochrane Database of Systematic Reviews (3rd quarter 2008); and Database of Abstracts of Reviews of Effects (1991 to 3rd quarter 2008).
Search strategies combined relevant controlled vocabulary and natural language in an effort to balance sensitivity and specificity. Unless advised by the GDG, searches were not date specific. Language restrictions were applied to searches – searches were limited to English language papers only. Both generic and specially developed methodological search filters were used appropriately.”
Assessment of quality of included trials: yes
Other methodological remarks: NICE found 4 RCTs for this comparison. They did not perform a meta-analysis. Of the 4 RCTs, 3 RCTs had sample sizes of less than 40 participants per arm. We reported only the one RCT that met our inclusion criteria.

Table 363

Bibliographic information	Study type and evidence level	Study details	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
Garcia de Olarte 1974 [144] Location : Colombia	Study Type RCT Evidence Level 1+	**Total number of participants** *n* = 282 Randomised into two treatment arms Group 1 Intervention : Ampicillin *n* = 142 Group 2 Intervention : Placebo *n* = 140	**Inclusion criteria:** Infants and children admitted with diarrhoea as a major symptom. Subsequent culture confirmation of Shigella or Salmonella, or *E. coli* in under 2 years age required. 1 patient without recognised pathogens per 2 patients with Shigella, Salmonella, or *E. coli* were entered into study **Exclusion criteria :** Other illness requiring antibiotic therapy, age under 6 weeks, history of allergy to penicillin or its derivatives **Withdrawal criteria :** Not stated Rectal swab and stool sample examined	**Comparison** Ampicillin vs placebo Intervention details: *Year 1* **Group 1:** IM ampicillin **Group 2:** Injection of sterile fructose ***1) Year 2*** **(ii) Group 1** Oral suspension of ampicillin 100 mg/kg in equally divided doses every 6 hours for 5 days (One half Salmonella patients given 100 mg/kg in equally divided doses every 12 hours for 5 days **Group 2 :** Oral suspension of placebo in doses every 6 hours for 5 days	**Follow up** Daily rectal swabs until 10 days, thereafter if still hospitalised, every three days. Daily clinical examination **Outcome measures:** ***Mean number of days until diarrhoea improved*** Shigella *n* = 37 Group 1 = 2.4 Group 2 =4.6 Salmonella *n* = 110 Group 1 = 2.9 Group 2 = 2.4 *E. coli n* = 35 Group 1 = 2.8 Group 2 = 4.9 No Pathogens *n* = 96 Group 1 = 2.7 Group 2 = 2.9 ***Mean number of days until diarrhoea ceased*** Shigella Group 1 = 4.4 Group 2 =6.8 Salmonella	**Funding :** Applicable to UK Baseline comparability Similar for sex, race, *E. coli* group younger than other groups. Blood and mucus present in stools, lethargy and convulsions found in greater proportion of shigella group than other groups. Allocation concealment : Random number table Sequence generation : Random number table Blinding of outcome assessors : Yes Loss to follow up 4/282 Intention to treat analysis : Not stated Power calculation : Not stated

Bibliographic information	Study type and evidence level	Study details	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					Group 1 = 5.2 Group 2 = 4.8 *E. coli* Group 1 = 4.2 Group 2 = 6.4 No Pathogens Group 1 = 4.2 Group 2 = 4.2 ***Mean number of days until patient afebrile*** Shigella Group 1 = <0.5 Group 2 =1.6 *P* < 0.05 Salmonella Group 1 = 0.8 Group 2 = 1.0 *E. coli* Group 1 = 0.3 Group 2 = 0.9 No Pathogens Group 1 = 0.7 Group 2 = 0.8 ***Mean number of days until culture negative*** Shigella Group 1 = 0.9 Group 2 = 2 *P* < 0.05	

Bibliographic information	Study type and evidence level	Study details	Patient characteristics	Intervention and comparison	Outcome measures, follow-up and effect size	Comments
					Salmonella Group 1 = 1.8 Group 2 = 1.7 *E. coli* Group 1 = 3.4 Group 2 = 3.0 No Pathogens – not rel	

Figure 19 study details, as evaluated by NICE 2009

Ref Garcia de Olarte{Garcia de Olarte, 1974 #334}

14.2.1.2.2 Summary and conclusions

AB vs placebo or no treatment in Salmonella infection
Bibliography: NICE 2009{National Collaborating Centre for Women's and Children's Health, 2009 #100}

Table 364

NICE found 4 RCTs for this comparison. They did not perform a meta-analysis. Of the 4 RCTs, 3 RCTs had sample sizes of less than 40 participants per arm. We reported only the one RCT that met our inclusion criteria.

This trial, de Olarte 1974{Garcia de Olarte, 1974 #334}, examined the effect of ampicillin (IM in the first year of the study, oral suspension of 100 mg/kg/day in four doses for 5 days in the second year) versus placebo. 110 of 282 malnourished children and infants under 2 years of age had salmonella isolated from stool specimens.

In malnourished children with salmonella infection, there were **no** statistically significant **differences** between treatment with ampicillin and placebo for the *mean number of days until diarrhoea improved or ceased* or for the *mean number of days until the patient became afebrile or culture negative.*

GRADE: LOW quality of evidence

14.2.1.3 Antibiotics versus placebo or no treatment in Campylobacter infection

14.2.1.3.1 Clinical evidence profile

Systematic review: NICE 2009{National Collaborating Centre for Women's and Children's Health, 2009 #100} “Diarrhoea and vomiting caused by gastroenteritis - diagnosis, assessment and management in children younger than 5 years”

Inclusion criteria:
Infants and young children from birth up to their fifth birthday presenting to healthcare professionals with acute diarrhoea (lasting 14 days or fewer) due to gastroenteritis, on its own or with vomiting.
Setting: Community care, primary care and secondary care, and indications for referral.

Search strategy:
“Systematic searches to answer the clinical questions formulated and agreed by the GDG were executed using the following databases on the OVID platform: MEDLINE (1950 onwards); Embase (1980 onwards); Cumulative Index to Nursing and Allied Health Literature (1982 onwards); Cochrane Central Register of Controlled Trials (1991 to 3rd quarter 2008); Cochrane Database of Systematic Reviews (3rd quarter 2008); and Database of Abstracts of Reviews of Effects (1991 to 3rd quarter 2008).
Search strategies combined relevant controlled vocabulary and natural language in an effort to balance sensitivity and specificity. Unless advised by the GDG, searches were not date specific. Language restrictions were applied to searches – searches were limited to English language papers only. Both generic and specially developed methodological search filters were used appropriately.”
Assessment of quality of included trials: yes
Other methodological remarks: NICE found 3 RCTs for this comparison. They did not perform a meta-analysis. All of the 3 RCTs had sample sizes of less than 40 participants per arm. Therefore we did not report these RCTs.

Table 365

14.2.1.3.2 Summary and conclusions

AB vs placebo or no treatment in Campylobacter infection
Bibliography: NICE 2009{National Collaborating Centre for Women's and Children's Health, 2009 #100}

Table 366

NICE found 3 RCTs for this comparison. They did not perform a meta-analysis. All of the 3 RCTs had sample sizes of less than 40 participants per arm. Therefore we did not report these RCTs.

14.2.1.4 Antibiotics versus placebo in Yersinia infection

14.2.1.4.1 Clinical evidence profile

Systematic review: NICE 2009{National Collaborating Centre for Women's and Children's Health, 2009 #100} “Diarrhoea and vomiting caused by gastroenteritis - diagnosis, assessment and management in children younger than 5 years”

Inclusion criteria:
Infants and young children from birth up to their fifth birthday presenting to healthcare professionals with acute diarrhoea (lasting 14 days or fewer) due to gastroenteritis, on its own or with vomiting.
Setting: Community care, primary care and secondary care, and indications for referral.

Search strategy:
“Systematic searches to answer the clinical questions formulated and agreed by the GDG were executed using the following databases on the OVID platform: MEDLINE (1950 onwards); Embase (1980 onwards); Cumulative Index to Nursing and Allied Health Literature (1982 onwards); Cochrane Central Register of Controlled Trials (1991 to 3rd quarter 2008); Cochrane Database of Systematic Reviews (3rd quarter 2008); and Database of Abstracts of Reviews of Effects (1991 to 3rd quarter 2008).
Search strategies combined relevant controlled vocabulary and natural language in an effort to balance sensitivity and specificity. Unless advised by the GDG, searches were not date specific. Language restrictions were applied to searches – searches were limited to English language papers only. Both generic and specially developed methodological search filters were used appropriately.”
Assessment of quality of included trials: yes
Other methodological remarks: NICE found only one RCT for this comparison. It had a sample sizes of less than 40 participants per arm. Therefore we did not report this RCT.

Table 367

14.2.1.4.2 Summary and conclusions

AB vs placebo or no treatment in Yersinia infection
Bibliography: NICE 2009{National Collaborating Centre for Women's and Children's Health, 2009 #100}

Table 368

NICE found only one RCT for this comparison. It had a sample sizes of less than 40 participants per arm. Therefore we did not report this RCT.

14.2.1.5 Antibiotics versus placebo or no treatment in suspected Shigella infection

14.2.1.5.1 Clinical evidence profile

Meta-analysis: Christopher 2010{Christopher Prince, 2010 #103} "Antibiotic therapy for Shigella dysentery"
Inclusion criteria:
RCTs
Population: Adults and children with clinical symptoms suggestive of Shigella dysentery. Both hospitalized and non-hospitalized participants were included.
Intervention: Antibiotics, irrespective of the dose or route of administration.
Control: placebo, or no drug.
We included trials that used additional interventions if the interventions were used in all treatment arms.
Search strategy:
"We searched the following databases using the strategies and search terms set out in Table 2: the Cochrane Infectious Diseases Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2008, issue 4); MEDLINE (1966 to June 2009); EMBASE (1974 to June 2009); and LILACS (1982 to June 2009). We also searched the metaRegister of Controlled Trials (mRCT) using 'shigell*' as the search term (June 2009).
"...conference proceedings searched for relevant abstracts, individual researchers working in this field contacted, organizations and pharmaceutical companies contacted to identify unpublished and ongoing trials. We also checked the reference lists of all studies identified by the above methods."
Assessment of quality of included trials: yes
Other methodological remarks: This systematic review and meta-analysis included studies in adults and children. Where subanalyses for children are provided, we have reported these. In other cases, we have reported the outcomes for a mixed group of children and adults and provided the details of studies that included children below.

Table 369

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Christopher 2010{Christopher Prince, 2010 #103}	Antibiotic therapy versus no drug or placebo	N=1 n=76 (Rodriguez 1989)	**Diarrhoea on follow up (cotrimoxazole versus no drug)**	Crude AR: 9/52 vs 14/24 **RR 0.30 [0.15, 0.59]** **SS**

Table 370

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
Rodriguez 1989{Rodriguez, 1989 #335}	248	children, aged 2 months to 59 months; passage of 3 or more watery stools in the previous 24 hours; history of diarrhoea up to 5 days before admission; and polymorphonuclear leucocytes and blood in stool samples	6 days follow-up	Furazolidone (7.5 mg/kg/day, in 4 equally divided doses) versus Cotrimoxazole (Trimethoprim (8 mg/kg/day) + sulphamethoxazole (40 mg/kg/day) in 2 equally divided doses Versus Control group (no antimicrobials)	ADEQUATE SEQUENCE GENERATION? Unclear ("...randomised into three groups" but the method not mentioned. Neither the author nor the journal could be contacted for clarifications) ALLOCATION CONCEALMENT? Unclear (Not mentioned) BLINDING? No ("Single blind"; not mentioned which group was blinded; blinding of the dosage schedules of the trial drugs in the 3 arms not done) INCOMPLETE OUTCOME DATA ADDRESSED? No ("...two patients in the control group were voluntarily withdrawn from the study". They were not included in the analysis. 98% follow up) FREE OF SELECTIVE REPORTING? Yes FREE OF OTHER BIAS? No (Baseline imbalance, patients in furazolidone group had fewer days with diarrhoea (P value < 0.02))

Table 371

Author's conclusions:

NOTE: pertains to mixed group of adults and children:

Antibiotics reduce the duration of Shigella dysentery.

Regularly updated local or regional antibiotic sensitivity patterns to different species and strains of Shigella are required to guide empiric therapy. More trials adhering to standard guidelines are required to evaluate the role of antibiotics in the treatment of severe forms of Shigella dysentery and in groups who are at high risk of complications.

Remarks:

Outcomes *time to cessation of fever*, *time to cessation of diarrhoea*, *time to cessation of blood in stools and Other adverse events* not described in our report because only studies with IV antibiotics were included in the meta-analysis.

14.2.1.5.2 Summary and conclusions

Antibiotic therapy versus no drug or placebo for suspected Shigella dysentery			
Bibliography: Christopher 2010{Christopher Prince, 2010 #103}			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Diarrhoea on follow up (at 6 d) **(cotrimoxazole versus no drug)**	76 (1 study)	**RR 0.30 [0.15, 0.59]** **SS** **(less diarrhoea with cotrimoxazole)**	⨁⊖⊖⊖: **VERY LOW** As assessed by Cochrane group

Table 372

In this meta-analysis, a treatment with antibiotic therapy was compared to no drug or placebo for suspected Shigella dysentery.

One study was found where cotrimoxazole was compared to no drug.

This study was performed in children aged 2 to 59 months.

The dose of the treatment was trimethoprim 8 mg/kg/day + sulphamethoxazole 40 mg/kg/day in 2 equally divided doses.

As there is only trial with methodological limitations (unclear randomisation and allocation concealment, single blind), our confidence in these results are severely limited.

In children *with suspected Shigella dysentery* a treatment with cotrimoxazole, compared to no drug, **did** result in a statistically significant **decrease** in *diarrhoea on follow-up (at 6 days)*.
GRADE: VERY LOW quality of evidence

14.2.2 Antibiotic A versus antibiotic B

14.2.2.1 Fluoroquinolones versus beta-lactams in for suspected Shigella dysentery

14.2.2.1.1 Clinical evidence profile

Meta-analysis: Christopher 2010{Christopher Prince, 2010 #103} "Antibiotic therapy for Shigella dysentery"
Inclusion criteria:
RCTs
Population: Adults and children with clinical symptoms suggestive of Shigella dysentery. Both hospitalized and non-hospitalized participants were included.
Intervention: Antibiotics, irrespective of the dose or route of administration.
Control: Other antibiotic of a different class (irrespective of the dose or route of administration)
We included trials that used additional interventions if the interventions were used in all treatment arms.
Search strategy:
"We searched the following databases using the strategies and search terms set out in Table 2: the Cochrane Infectious Diseases Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2008, issue 4); MEDLINE (1966 to June 2009); EMBASE (1974 to June 2009); and LILACS (1982 to June 2009). We also searched the metaRegister of Controlled Trials (mRCT) using 'shigell*' as the search term (June 2009).
"...conference proceedings searched for relevant abstracts, individual researchers working in this field contacted, organizations and pharmaceutical companies contacted to identify unpublished and ongoing trials. We also checked the reference lists of all studies identified by the above methods."
Assessment of quality of included trials: yes
Other methodological remarks: This systematic review and meta-analysis included studies in adults and children. Where subanalyses for children are provided, we have reported these. In other cases, we have reported the outcomes for a mixed group of children and adults and provided the details of studies that included children below.

Table 373

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Christopher 2010{Christopher Prince, 2010 #103}	**Fluoroquinolones versus beta-lactams**	N=5 n=559 (Alam 1994, Haltalin 1973,	**Diarrhoea on follow-up (SUBGROUP: children)**	Crude AR: 69/276 vs 65/283 RR 1.46 [0.64, 3.34] NS

		Leibovitz 2000, Salam 1988, Salam 1998)		
		N=3 n=357 (Haltalin 1973, Leibovitz 2000, Salam 1998)	**Relapse**	Crude AR: 7/172 vs 13/185 RR 0.91 [0.11, 7.55] NS
		N=1 n=221 (Leibovitz 2000)	**Serious adverse events** (those that are life-threatening or require hospitalization)	Crude AR: 5/111 vs 0/110 RR 10.90 [0.61, 194.82] NS
		N=4 n=570 (Bennish 1990, Leibovitz 2000, Salam 1988, Salam 1998)	**Other adverse events** (not specified)	Crude AR: 52/282 vs 51/288 RR 1.03 [0.77, 1.39] NS

Table 374

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
Alam 1994{Alam, 1994 #336}	80	children of both sexes between 1 and 8 years of age; having bloody diarrhoea lasting less than 72 hours	6 days follow-up	(1) Pivmecillinam (50 mg/kg/day, by mouth, in 4 divided doses, for 5 days)	ADEQUATE SEQUENCE GENERATION? Yes

				(2) Nalidixic acid (60 mg/kg/day, by mouth, in 4 divided doses, for 5 days)	ALLOCATION CONCEALMENT? Yes BLINDING? Yes INCOMPLETE OUTCOME DATA ADDRESSED? No (80 entered the study; 71 had Shigella in culture; no data regarding participants with non-Shigella dysentery (9) who were randomized according to the inclusion criteria. Outcomes reported only for all 71 (89%) with culture confirmed Shigella dysentery) FREE OF SELECTIVE REPORTING? Yes FREE OF OTHER BIAS? Yes
Haltalin 1973{Haltalin, 1973 #337}	36	infants and children; acute diarrhoeal disease	5 days follow-up	(1) Nalidixic acid (13.75 mg/kg, orally, every 6 hours for 5 days) (2) Ampicillin (25 mg/kg, orally, every 6 hours for 5 days)	ADEQUATE SEQUENCE GENERATION? Unclear ("...randomly assigned"; but the method of sequencing not mentioned. In a previous trial done by the same author (Haltalin 1967) randomization was done based on the terminal digit number of the hospital record. The author could not be contacted for details since there was no mail ID. The journal's present editorial team did not have any details of the study) ALLOCATION CONCEALMENT?

					Unclear (Not mentioned) BLINDING? Unclear (Not mentioned) INCOMPLETE OUTCOME DATA ADDRESSED? Yes FREE OF SELECTIVE REPORTING? Yes Free of other bias? Yes
Leibovitz 2000{Leibovitz, 2000 #338}	221	ambulatory infants and children; 6 months to 11 years; community acquired; acute invasive diarrhoea; illness that started less than 7 days before enrolment; grossly bloody-mucoid stools on examination; more than or equal to soft or liquid stools within the last 24 hours; temperature more than or equal to 38 ºC, more than 15 white blood cells/high-power microscopic field; able to take oral medication	21 ±5 days	(1) Ciprofloxacin suspension (10 mg/kg, every 12 hours for 3 days + placebo intramuscular injection, one shot per day for 3 days) (2) Ceftriaxone (intramuscular injection, 50 mg/kg/day, once daily for 3 days, maximal dose of 1 g per day + placebo suspension, one dose every 12 hours for 3 days)	ADEQUATE SEQUENCE GENERATION? Yes ALLOCATION CONCEALMENT? Yes BLINDING? Yes INCOMPLETE OUTCOME DATA ADDRESSED? No (“Sixteen and four patients from the ciprofloxacin and ceftriaxone group respectively, were excluded from the efficacy analysis because they are withdrawn from the study before its completion”. 91% follow up) FREE OF SELECTIVE REPORTING? Yes FREE OF OTHER BIAS? Yes
Salam 1988{Salam, 1988 #339}	90	age between 6months and 12 years; history of blood,mucoid diarrhoea and a stool specimen that had grossly visible	6 days	(1) Nalidixic acid (55 mg/kg/day, in 4 equally divided doses for 5 days)	ADEQUATE SEQUENCE GENERATION? Yes

		blood and mucus; illness duration less than 72 hours		(2) Ampicillin (100 mg/kg/day in 4 equally divided doses for 5 days)	ALLOCATION CONCEALMENT? Yes BLINDING? Yes INCOMPLETE OUTCOME DATA ADDRESSED? No ("data were analysed only from patients with culture-confirmed cases of shigellosis who remained in the study for at least 24 hours." 90 enrolled, 74 eligible for analysis, 64 analysed. 10 drop-outs - 6 withdrawn by their parents, reasons not provided, 4 withdrawn because of lack of clinical improvement. 82% follow up) FREE OF SELECTIVE REPORTING? Yes FREE OF OTHER BIAS? Yes
Salam 1998{Salam, 1998 #340}	143	children aged 2 years to 15 years; dysentery	180 days	1. Ciprofloxacin suspension (10 mg/kg, every 12 hours, maximum of 500 mg, for 5 days, total 10 doses with placebo of pivmecillinam) 2. Pivmecillinam (15 to 20 mg/kg, maximum of 300 mg, every 8 hours for 5 days, total 15 doses with placebo of ciprofloxacin)	ADEQUATE SEQUENCE GENERATION? Yes ALLOCATION CONCEALMENT? Yes BLINDING? Yes INCOMPLETE OUTCOME DATA ADDRESSED? No (13/143 (6 in the ciprofloxacin group and 7 in the pivmecillinam group) were excluded from analysis because they were found not

					eligible (12 did not grow Shigella in their stool culture and 1 had taken nalidixic acid before study entry). Further 10 (5 in each group) withdrew before study completion. 84% follow up) FREE OF SELECTIVE REPORTING? Yes FREE OF OTHER BIAS? Yes

Table 375

Author's conclusions:

NOTE: concerns mixed group of adults and children:

Antibiotics reduce the duration of Shigella dysentery.

Regularly updated local or regional antibiotic sensitivity patterns to different species and strains of Shigella are required to guide empiric therapy. More trials adhering to standard guidelines are required to evaluate the role of antibiotics in the treatment of severe forms of Shigella dysentery and in groups who are at high risk of complications.

Remarks: outcome "fever at follow up" and "Development of severe complications" were not reported because all the included trials compared antibiotics not available in Belgium.

14.2.2.1.2 Summary and conclusions

Fluoroquinolones versus beta-lactams in for suspected Shigella dysentery			
Bibliography: Christopher 2010{Christopher Prince, 2010 #103}			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Diarrhoea on follow up (at 5-180 d) **(SUBGROUP CHILDREN)**	559 (5 studies)	RR 1.46 [0.64, 3.34] NS	⨁⊖⊖⊖: **VERY LOW** As assessed by Cochrane group
Relapse	357 (3 studies)	RR 0.91 [0.11, 7.55] NS	⨁⊖⊖⊖: **VERY LOW** As assessed by Cochrane group
Serious adverse events (those that are life-threatening or require hospitalization)	221 (1 study)	RR 10.90 [0.61, 194.82] NS	⨁⊖⊖⊖: **VERY LOW** As assessed by Cochrane group
Other adverse events (not specified)	570 (4 studies)	RR 1.03 [0.77, 1.39] NS	⨁⊖⊖⊖: **VERY LOW** As assessed by Cochrane group

Table 376

In this meta-analysis, a treatment with fluoroquinolones was compared to beta-lactams for suspected Shigella dysentery.

The children included in the studies ranged from 6 months to 12 years of age. Follow-up ranged from 5 days to 180 days.

The fluoroquinolones used in the studies were nalidixic acid and ciprofloxacin 20 mg/kg/day, in 2 doses for 3-5 days).

The beta-lactams used in the studies were pivmecillinam, ampicillin (100 mg/kg/ day in 4 doses 5 days),and ceftriaxone IM (50 mg/kg/day, once daily for 3 days).

In children *with suspected Shigella dysentery* a treatment with a fluoroquinolone, compared a beta-lactam, **did not** result in a statistically significant difference in *diarrhoea on follow-up, relapse, serious adverse events* or *other adverse events*.
GRADE: VERY LOW quality of evidence

14.2.2.2 Cotrimoxazole versus beta-lactams in for suspected Shigella dysentery

14.2.2.2.1 Clinical evidence profile

Meta-analysis: Christopher 2010{Christopher Prince, 2010 #103} "Antibiotic therapy for Shigella dysentery"
Inclusion criteria:
RCTs
Population: Adults and children with clinical symptoms suggestive of Shigella dysentery. Both hospitalized and non-hospitalized participants were included.
Intervention: Antibiotics, irrespective of the dose or route of administration.
Control: Other antibiotic of a different class (irrespective of the dose or route of administration)
We included trials that used additional interventions if the interventions were used in all treatment arms.
Search strategy:
"We searched the following databases using the strategies and search terms set out in Table 2: the Cochrane Infectious Diseases Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2008, issue 4); MEDLINE (1966 to June 2009); EMBASE (1974 to June 2009); and LILACS (1982 to June 2009). We also searched the metaRegister of Controlled Trials (mRCT) using 'shigell*' as the search term (June 2009).
"...conference proceedings searched for relevant abstracts, individual researchers working in this field contacted, organizations and pharmaceutical companies contacted to identify unpublished and ongoing trials. We also checked the reference lists of all studies identified by the above methods."
Assessment of quality of included trials: yes
Other methodological remarks: This systematic review and meta-analysis included studies in adults and children. Where subanalyses for children are provided, we have reported these. In other cases, we have reported the outcomes for a mixed group of children and adults and provided the details of studies that included children below.

Table 377

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Christopher 2010{Christopher Prince, 2010 #103}	Cotrimoxazole versus beta-lactams	N=2 n=89 (Nelson 1976, Prado 1993)	**Diarrhoea on follow-up**	Crude AR: 6/45 vs 10/44 RR 0.59 [0.23, 1.49] NS

		N=2 n=89 (Nelson 1976, Prado 1993)	**Other adverse events** (not specified)	Crude AR: 5/45 vs 6/44 RR 0.81 [0.27, 2.45] NS

Table 378

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
Nelson 1976{Nelson, 1976 #341}	28	infants and children, diarrhoeic form of shigellosis (abrupt onset with high fever, prostration followed by large volume watery stools containing mucus, no blood); dysenteric form of shigellosis (onset is less abrupt, with a 1- to 3-day period of increasing loose stools with blood, abdominal cramps and tenesmus)	14-21 days	(1) Cotrimoxazole suspension (40 mg trimethoprim and 200 mg sulphamethoxazole in each 5 ml, by mouth 1.25 ml/kg, daily in 2 doses every 12 hours for 5 days, total 10 doses) (2) Ampicillin trihydrate suspension, by mouth, 100 mg/kg/day in divided doses every 6 hours for 5 days, total 20 doses	ADEQUATE SEQUENCE GENERATION? Yes ALLOCATION CONCEALMENT? Unclear (Not mentioned) BLINDING? No (Ampicillin was given 4 times a day and cotrimoxazole was given 2 times a day without dummies) INCOMPLETE OUTCOME DATA ADDRESSED? Yes FREE OF SELECTIVE REPORTING? Yes FREE OF OTHER BIAS? Yes
Prado 1993{Prado, 1993 #342}	150	children, age range 6 months to 13 years; clinical syndrome of dysentery	11-13 days	(1) Pivmecillinam (40 mg/kg/day in 4 doses per day) (2) Cotrimoxazole (40 mg/kg/day in 4 doses per	ADEQUATE SEQUENCE GENERATION? Yes ALLOCATION CONCEALMENT? Yes

				day)	BLINDING? Yes INCOMPLETE OUTCOME DATA ADDRESSED? No (59/150 (39%) of randomized participants were not included in the analysis as Shigella strains not isolated. 2 patients who withdrew from the study on first day of treatment were not included in the analysis) FREE OF SELECTIVE REPORTING? Yes FREE OF OTHER BIAS? Yes

Table 379

Author's conclusions:

NOTE: concerns mixed group of adults and children:

Antibiotics reduce the duration of Shigella dysentery.

Regularly updated local or regional antibiotic sensitivity patterns to different species and strains of Shigella are required to guide empiric therapy. More trials adhering to standard guidelines are required to evaluate the role of antibiotics in the treatment of severe forms of Shigella dysentery and in groups who are at high risk of complications.

Remarks: outcomes "*Time to cessation of diarroea (hours)", "Time to cessation of fever (hours)",* and "*Time to cessation of visible blood in stools*" not reported because only antibiotic not available in Belgium in this comparison.

14.2.2.2.2 Summary and conclusions

Cotrimoxazole versus beta-lactams in for suspected Shigella dysentery			
Bibliography: Christopher 2010{Christopher Prince, 2010 #103}			
Outcomes	**N° of participants (studies) Follow up**	**Results (95%CI)**	**Quality of the evidence (GRADE)**
Diarrhoea on follow up (at 11-21 days)	89 (2 studies)	RR 0.59 [0.23, 1.49] NS	⨁⊖⊖⊖: **VERY LOW** As assessed by Cochrane group
Other adverse events (not specified)	89 (2 studies)	RR 0.81 [0.27, 2.45] NS	⨁⊖⊖⊖: **VERY LOW** As assessed by Cochrane group

Table 380

In this meta-analysis, a treatment with cotrimoxazole was compared to beta-lactams for suspected Shigella dysentery.

The children included in the studies ranged from 6 months to 13 years of age. Follow-up ranged from 11 days to 21 days.

Cotrimoxazole was given in a dose of 10mg TMP+50mg SMX/kg/day in 2 doses for 5 days in one trial and 40 mg/kg/day in 4 doses in another trial.

The beta-lactams used in the studies were pivmecillinam and ampicillin (100 mg/kg/ day in 4 doses for 5 days).

In children *with suspected Shigella dysentery* a treatment with cotrimoxazole, compared to a beta-lactam, **did not** result in a statistically significant difference in *diarrhoea on follow-up,* or *other adverse events*.
GRADE: VERY LOW quality of evidence

14.2.3 Probiotics in acute infectious diarrhoea

14.2.3.1 S. boulardii vs placebo or no treatment for acute infectious diarrhoea in children

14.2.3.1.1 Clinical evidence profile

Meta-analysis: Feizizadeh 2014{Feizizadeh, 2014 #102} "Efficacy and safety of Saccharomyces boulardii for acute diarrhea"
Inclusion criteria:
"All randomized controlled trials regardless of language or publication date or state (published, unpublished, in press, and in progress) were included. Participants had to be children (0 to18 years of age), male or female of any ethnic group with acute diarrhoea (≤14 days). We were flexible about definition of diarrhoea.
Patients in the experimental groups had to receive S. boulardii at any dose and in any form (eg, capsule, sachet, yogurt). Trials investigating products that do not label S. boulardii dose were not considered. Patients in the control groups had to receive placebo or no treatment control."
Search strategy:
"We searched Medline, Embase, CINAHL, Scopus, and The Cochrane Library up to September 2013. We checked the reference lists of all studies identified by the above methods. We additionally searched the following sources of gray literature"
Assessment of quality of included trials: yes, risk for bias of each study was assessed by 2 reviewers based on the Cochrane Collaboration's risk for bias tool** see Figure 10 Details and quality of studies, as assessed by Lassi 2014
Other methodological remarks:

Table 381

Ref	Comparison	N/n (n= total number included in studies, number analysed in MA not specified)	Outcomes	Result (95% CI)
Feizizadeh 2014{Feizizadeh, 2014 #102}	**S. Boulardii vs placebo or no treatment**	N=17 n=3133 (Cetina-Sauri 1994, Urganci	**Mean duration of diarrhea (hours)**	**SE= -19.70 (-26.05 to -13.34) SS**

		2001, Hafeez 2002, Kurugol 2005, Billoo 2006, Canani 2007, Vandenplas 2007, Villarruel 2007, Htwe 2008, Savas-Erdeve 2009, Dinleyici 2009, Grandy 2010, Dalgic 2011, Erdogan 2012, Khan 2012, Riaz 2012, Burande 2013)		
		N=5 n=1277 (Cetina-Sauri 1994, Urganci 2001, Canani 2007, Ozkan 2007, Khan 2012)	**Mean stool frequency on day 2 (hours)**	**SE= 0.74 (-1.38 to -0.10)** **SS**
		N=6 n=1386 (Cetina-Sauri 1994, Hafeez 2002, Billoo	**Mean stool frequency on day 3 (hours)**	**SE= -1.24 (-2.13 to -0.35)** **SS**

		2006, Canani 2007, Ozkan 2007, Khan 2012)		
		N=9 n=1247 (Chapoy 1985, Cetina-Sauri 1994, Hernandez 1998, Urganci 2001, Hafeez 2002, Kurugol 2005, Villarruel 2007, Htwe 2008, Khan 2012)	**Risk of diarrhea on day 4**	**RR= 0.38 (0.24 to 0.59)** **SS**
		N=8 n=1248 (Cetina-Sauri 1994, Hernandez 1998, Hafeez 2002, Kurugol 2005, Htwe 2008, Dinleyici 2009, Correa 2011, Khan 2012)	**Risk of diarrhea on day 3**	**RR 0.41 (0.27 to 0.60)** **SS**

Table 382

* Characteristics of included studies: see below

TABLE 1 Characteristics of Studies Included in the Systematic Review

Study, Year/Country	Design	Duration	Participants	Intervention		Outcome Measure	Results
				Probiotic	Control		
Chapoy et al, 1985[39]/ France	Controlled trial	Not stated	38 inpatient children who had acute diarrhea	*S. boulardii* (500 mg/d for 5 d)	ORS	Mean number of stools, mean stool weight, and carmine red transit time on days 1 and 4 Consistency of stools on day 4	Comparison between *S. boulardii* group and control group on days 1 and 4 revealed a significant difference on 4 clinical criteria: number of stools, weight and consistency of stools, and carmine red transit time
Cetina-Sauri et al, 1994[51]/Mexico	Double-blind, placebo-controlled study	11 mo; April 1, 1988 to March 15, 1989	130 children aged 3 mo to 3 y who had acute diarrhea	*S. boulardii* (live *Saccharomyces cerevisiae* Hansen CBS 5926; 600 mg/d; diluted in 5 mL cold water); duration was not stated	Glucose placebo (600 mg diluted in 5 mL cold water)	Number of stools per day First day stools formed	Evaluation of the percentage of clinical cure after 48 and 96 h showed significant differences from the control group.
Hernandez et al, 1998[40]/ Mexico	Randomized controlled trial	Not stated	50 inpatients who had uncomplicated acute diarrhea	*S. boulardii* (600 mg /d for 5 d)	Placebo	Stool frequency Persistence of diarrhea	Persistence of diarrhea was lower in *S. boulardii* group compared with control group
Urganci et al, 2001[42]/Turkey	Double-blind, placebo-controlled study	1 y; June 2000 to May 20, 2001	100 consecutive inpatients aged 2 to 29 mo who had acute, non-bacterial diarrhea (lasting >48 h)	Lyophilized *S. boulardii* (250 mg/d in 5 mL cold liquid)	250 mg glucose daily in 5 mL cold liquid	Stool frequency and consistency at 48 and 96 h Percentage of cases cured after 48 and 96 h	After 48 and 96 h, children treated with *S. boulardii* scored better than controls.
Hafeez et al, 2002[47]/Pakistan	Randomized controlled trial	2 months	109 outpatients aged 6 mo to 5 y who had acute watery diarrhea	Lyophilized *S. boulardii* (500 mg/d for 6 d)	Standard treatment (oral rehydration and feeds)	Frequency and consistency (loose versus formed) of stools Duration of illness (definition of end of diarrhea not stated)	At day 3 the frequency reduced significantly in the *S. boulardii* group compared with the control group. The consistency of stool showed a positive trend in the *S. boulardii* group compared with the control group at days 3 and 6. The average duration of the illness also decreased by a mean of 1.1 days.
Kurugöl et al, 2005[41]/ Turkey	Double-blind, placebo-controlled study	Not stated	200 inpatients aged 3 mo to 7 y who had acute diarrhea	*S. boulardii* (250 mg/d given with water or juice for 5 d)	Placebo (no details given)	Number stools/d and number watery stools/d	The stool frequency after the second day of the treatment was significantly lower in the *S. boulardii* group than in the placebo group.

TABLE 1 Continued

Study, Year/Country	Design	Duration	Participants	Intervention		Outcome Measure	Results
				Probiotic	Control		
						Duration of diarrhea	The duration of diarrhea significantly reduced in the *S. boulardii* group compared with the placebo group.
						Duration of vomiting and fever	The duration of hospital stay was shorter in the *S. boulardii* group than in the placebo group.
						Duration of hospital stay	
Billoo et al, 2006[13]/ Pakistan	Randomized controlled clinical trial	Not stated	100 inpatients aged 2 mo to 12 y who had acute watery diarrhea	*S. boulardii* (500 mg/d for 5 d) Enflor 250 mg 5×10^9	ORS and nutritional support only	Stoppage of diarrhea (not defined)	The duration of diarrhea and stool frequency were lower in the *S. boulardii* group compared with the control group.
						Weight gain	Weight gain was similar in the 2 groups.
						Daily stool frequency and consistency	
Canani et al, 2007[14]/Italy	Prospective, single-blind, randomized, controlled trial	October 1999 to September 2000	600 outpatients aged 3 to 36 mo who had diarrhea (<48 h)	*S. boulardii* (1×10^{10} live microorganisms/d for 5 d)	ORS alone	Mean duration of diarrhea Stool frequency	There was no effect on duration of diarrhea and stool frequency.
Ozkan et al, 2007[50]/Turkey	Randomized, double-blind, placebo-controlled study	October 2004 to March 2005	27 inpatient and outpatient previously healthy children aged 6 mo and 10 y who had acute diarrhea	*S. boulardii* (500 mg/d in 5 mL of water for 7 d)	Placebo	Number, characteristics, and frequency of stools	Stool frequency on day 2 was similar in the 2 groups.
						Blood tests	Stool frequency on day 3 was lower in the *S. boulardii* group compared with the control group.
Vandenplas et al, 2007[38]/ India and Indonesia	Double-blind, randomized, placebo-controlled trial	Not stated	202 children presenting with acute infectious gastroenteritis	ORS with 500 mg/d *S. boulardii* for 5 d	ORS with placebo	Duration of diarrhea Daily stool frequency and consistency Vomiting Weight gain Side effects	Administration of *S. boulardii* as add-on to standard WHO recommendations (ORS and realimentation) results in a social benefit, as more children were cured on day 3.
Villarruel et al, 2007[48]/ Argentina	Double-blind, randomized, placebo-controlled trial	1 y	100 outpatients aged 3 mo to 2 y who had acute diarrhea	*S. boulardii* (250–500 mg/d according to age for 6 d)	Placebo	Duration of diarrhea	Duration of diarrhea was significantly shorter in the *S. boulardii* group.
						Number of stools on days 4 and 7	Number of stools on days 4 and 7 was lower in the *S. boulardii* group.

TABLE 1 Continued

Study, Year/Country	Design	Duration	Participants	Intervention		Outcome Measure	Results
				Probiotic	Control		
						Number of participants who had diarrhea >7 d Number of participants who had liquid stools on days 4 and 7	
Htwe et al, 2008[17]/ Myanmar	Randomized controlled trial	No information	100 inpatients aged 3 mo to 10 y who had acute watery diarrhea	*S. boulardii* (500 mg/d for 5 d)	ORS according to WHO protocol	Mean duration of diarrhea Stool frequency Consistency of stools	*S. boulardii* shortens the duration of diarrhea and normalizes stool consistency and frequency.
Savas-Erdeve et al, 2009[52]/Turkey	Randomized open-prospective study	January 2006 to April 2007	90 children aged 1 to 15 y who presented with *E. histolytica*-associated diarrhea	*S. boulardii* (250 mg [5×10^8 living microorganisms]/d) plus metronidazole 30 to 50 mg/kg/d orally for 10 d (maximum: 500–750 mg)	Metronidazole 30 to 50 mg/kg/d orally for 10 d (maximum, 500–750 mg)	Duration of diarrhea Duration of bloody diarrhea Duration of vomiting Duration of fever Duration of abdominal pain Fever	The duration of diarrhea and duration of bloody diarrhea, fever, abdominal pain, and vomiting were similar in the 2 groups.
Dinleyici et al, 2009[46]/Turkey	Prospective, randomized open-label clinical trial	January 2006 to September 2007	53 outpatient children who had fever and acute bloody diarrhea	*S. boulardii* (500 mg/d) plus metronidazole 60 mg/kg/d for 7 d	Metronidazole (60 mg/kg/d for 7 d)	Duration of diarrhea	The duration of bloody diarrhea was significantly shorter in the *S. boulardii* group.
						Duration of bloody diarrhea	On day 5, amebic cysts had disappeared in all children in the *S. boulardii* group, whereas in the control group, amebic cysts were still present in 6 children.
						At day 3, bloody diarrhea and diarrhea At day 5, bloody diarrhea and diarrhea cyst passage	On day 10, all children were cured and cysts had disappeared in all.
Grandy et al, 2010[44]/Bolivia	Prospective double-blind randomized	July 2007 to February 2008	194 inpatients aged 1 to 23 mo who had acute diarrhea	ORS plus *S. boulardii* (4×10^{10} lyophilized cells for 5 d)	ORS	Duration of diarrhea	The median duration of diarrhea in children who received *S. boulardii* was shorter than in controls.
						Duration of hospitalization Fever	The duration of fever was significantly shorter in the group receiving *S. boulardii* (as compared with controls).

TABLE 1 Continued

Study, Year/Country	Design	Duration	Participants	Intervention		Outcome Measure	Results
				Probiotic	Control		
						Vomiting	There was no effect on duration of hospitalization and duration of vomiting.
Correa et al, 2011[43]/ Brazil	Double-blind, randomized, controlled trial	April 2007 to September 2008	186 inpatients aged 6 to 48 mo who had acute diarrhea	*S. boulardii* (400 mg/d for 5 d)	Placebo (400 mg/d for 5 d)	Frequency of diarrhea 3 d after beginning of intervention	There was a reduction in diarrhea duration when *S. boulardii* was given to children within 72 h after the onset of acute diarrhea.
Dalgic et al, 2011[16]/ Turkey	Prospective, randomized, single-blind, controlled trial	September 2008 to June 2010	480 inpatients aged 1 to 28 mo diagnosed with rotavirus diarrhea (<96 h)	*S. boulardii* (250 mg/d for 5 d)	Oral and/or parenteral rehydration solutions	Duration of diarrhea Time to resolution of vomiting Duration of hospitalization Fever	No statistically significant difference was found between the 2 groups.
Huseynova et al, 2011[18]/Azerbaijan	Trial	No information	43 inpatients aged 1 to 9 y who had diarrhea	Orally *S. boulardii* (500–750 mg/d for 7–10 d) 250 mg	No information	Frequency of diarrhea Pathologic and microbiological status of stool Dehydration status	The frequency of stool in days 5 and 7 was lower in the *S. boulardii* group as compared with the control group.
Erdogan et al, 2012[49]/Turkey	Prospective randomized trial	October 2009 to May 2010	75 outpatients and inpatients aged 5 mo to 5 y who had diarrhea in the last 48 h	Oral rehydration therapy and rapid refeeding with a normal diet with 282.5 mg/d *S. boulardii*	Oral rehydration therapy and rapid refeeding with a normal diet	Duration of diarrhea Vomiting	The duration of diarrhea was significantly shorter in the *S. boulardii* group as compared with the placebo group.
Khan et al, 2012[19]/ Pakistan	Randomized controlled trial	6 mo; June 2009 to November 2009	420 inpatients aged 2 mo to 5 y who had acute watery diarrhea	Orally *S. boulardii* (500 mg/d for 5 d) diluted in water or mixed with semisolid food	Standard treatment (oral rehydration and feeds)	Stool consistency and frequency	Statistically significant differences in terms of stool consistency and frequency were noted in the *S. boulardii* group from day 2 of treatment onward.
						Duration of diarrhea	The *S. boulardii* group also showed reduction in mean duration of diarrhea by 1.1 d compared with the control group.
Riaz et al, 2012[45]/India	Double-blind, randomized, controlled trial	May 2008 through September 2009	108 inpatients aged 3 to 59 mo who had acute-onset diarrhea (<48 h)	*S. boulardii* (500 mg/d for 5 d)	Placebo (puffed rice powder 500 mg/d for 5 d)	Mean duration of diarrhea	Mean post-intervention duration of diarrhea and mean time of appearance of first semi-formed stool were significantly shorter in the *S. boulardii* group as compared with the placebo group.

TABLE 1 Continued

Study, Year/Country	Design	Duration	Participants	Intervention		Outcome Measure	Results
				Probiotic	Control		
						Stool frequency	No statistically significant difference was found in the rest of the parameters.
						Consistency of stools	
						Weight gain	
						Total ORS consumed	
						Total IVF needed	
Burande et al, 2013[57]/India	Prospective, parallel, single-blind, randomized, controlled clinical trial	July 2009 to July 2011	72 outpatient children who had acute diarrhea	*S. boulardii* 500 mg/d for 5 d as lyophilized powder	Standard treatment (oral rehydration and feeds)	Time for recovery from diarrhea	The *S. boulardii* group had significantly early recovery from diarrhea and vomiting.
						Vomiting	
						Side effects	

IVF, intravenous fluids.

Figure 20 study details, as evaluated by Feizizadeh 2014

References in this table:

Chapoy 1985{Chapoy, 1985 #346}, Cetina-Sauri 1994{Cetina-Sauri, 1994 #364}, Hernandez 1998{Hernandez, 1998 #363}, Urganci 2001{Urganci, 2001 #366}, Hafeez 2002{Hafeez, 2002 #367}, Kurugol 2005{Kurugol, 2005 #351}, Billoo 2006{Billoo, 2006 #350}, Canani 2007{Canani, 2007 #349}, Ozkan 2007{Ozkan, 2007 #348}, Vandenplas 2007{Vandenplas, 2007 #362}, Villarruel 2007{Villarruel, 2007 #347}, Htwe 2008{Htwe, 2008 #352}, Savas-Erdeve 2009{Savas-Erdeve, 2009 #353}, Dinleyici 2009{Dinleyici, 2009 #356}, Grandy 2010{Grandy, 2010 #355}, Correa 2011{Correa, 2011 #94}, Dalgic 2011{Dalgic, 2011 #93}, Huseynova{Hüseynova, 2011 #365} 2011, Erdogan 2012{Erdogan, 2012 #357}, Khan 2012{Dalgic, 2011 #93}, Riaz 2012{Dalgic, 2011 #93}, Burande 2013{Burande, 2013 #96})

SUPPLEMENTAL TABLE 3 Study Quality and Risk for Bias Assessment of Included Studies

Study	Sequence Generation	Allocation Concealment	Blinding	Follow-Up	Overall Quality
Chapoy et al, 1985	−	−	−	+	Poor
Cetina-Sauri et al 1994	+	?	?	?	Fair
Hernandez et al, 1998	?	?	?	+	Fair
Urganci et al, 2001	?	?	?	?	Fair
Hafeez et al, 2002	−	−	−	+	Poor
Kurugöl et al, 2005	?	?	+	−	Fair
Billoo et al, 2006	?	?	−	+	Fair
Canani et al, 2007	+	+	−	−	Fair
Ozkan et al, 2007	?	?	+	+	Good
Vandenplas et al, 2007	?	?	?	+	Fair
Villarruel et al, 2007	+	+	+	−	Good
Htwe et al, 2008	−	−	−	+	Poor
Savas-Erdeve et al, 2009	?	?	−	−	Poor
Dinleyici et al, 2009	−	−	−	−	Poor
Grandy et al, 2010	?	?	+	−	Fair
Correa et al, 2011	+	+	+	+	Good
Dalgic et al, 2011	+	?	−	+	Fair
Huseynova et al, 2011	?	?	−	?	Fair
Erdogan et al, 2012	?	?	−	+	Fair
Khan et al, 2012	+	?	−	+	Fair
Riaz et al, 2012	+	+	+	−	Good
Burande et al, 2013	+	?	−	+	Fair

+, low risk; −, high risk; ?, unclear.

Figure 21 study quality, as evaluated by Feizizadeh 2014

References in this figure:

Chapoy 1985{Chapoy, 1985 #346}, Cetina-Sauri 1994{Cetina-Sauri, 1994 #364}, Hernandez 1998{Hernandez, 1998 #363}, Urganci 2001{Urganci, 2001 #366}, Hafeez 2002{Hafeez, 2002 #367}, Kurugol 2005{Kurugol, 2005 #351}, Billoo 2006{Billoo, 2006 #350}, Canani 2007{Canani, 2007 #349}, Ozkan 2007{Ozkan, 2007 #348}, Vandenplas 2007{Vandenplas, 2007 #362}, Villarruel 2007{Villarruel, 2007 #347}, Htwe 2008{Htwe, 2008 #352}, Savas-Erdeve 2009{Savas-Erdeve, 2009 #353}, Dinleyici 2009{Dinleyici, 2009 #356}, Grandy 2010{Grandy, 2010 #355}, Correa 2011{Correa, 2011 #94}, Dalgic 2011{Dalgic, 2011 #93}, Huseynova{Hüseynova, 2011 #365} 2011, Erdogan 2012{Erdogan, 2012 #357}, Khan 2012{Dalgic, 2011 #93}, Riaz 2012{Dalgic, 2011 #93}, Burande 2013{Burande, 2013 #96})

Author's conclusions:

"This review and meta-analysis show that S. boulardii is safe and has clear beneficial effects in children who have acute diarrhea. However, additional studies using head-to-head comparisons are needed to define the best dosage of S. boulardii for diarrhea with different causes."

14.2.3.1.2 Summary and conclusions

S. Boulardii vs placebo or no treatment for acute infectious diarrhoea in children			
Bibliography: Feizizadeh 2014{Feizizadeh, 2014 #102}			
Outcomes	**N° of participants (studies) Follow up**	**Results (95%CI)**	**Quality of the evidence (GRADE)**
Mean duration of diarrhoea (hours)	3133 (17 studies)	**SE= -19.70 (-26.05 to -13.34) SS (shorter duration of diarrhoea with S. Boulardii)**	⊕⊕⊕⊖: **MODERATE** Study quality:-1 (unclear rando, allocation concealment, blinding) Consistency: ok Directness: ok Imprecision: ok
Mean stool frequency on day 2	1277 (5 studies)	**SE=- 0.74 (-1.38 to -0.10) SS (lower stool frequency with S. boulardii)**	⊕⊕⊖⊖: **LOW** Study quality: -1 (unclear rando, allocation concealment, blinding) Consistency: -1 (I^2= 91.6%) Directness: ok Imprecision:ok
Mean stool frequency on day 3	1386 (6 studies)	**SE= -1.24 (-2.13 to -0.35) SS (lower stool frequency with S. boulardii)**	⊕⊕⊖⊖: **LOW** Study quality: -1 (unclear rando, allocation concealment, blinding) Consistency: -1 (I^2=93.9%) Directness: ok Imprecision:ok
Risk of diarrhoea on day 4	1247 (9 studies)	**RR= 0.38 (0.24 to 0.59) SS (lower risk of diarrhoea with S. boulardii)**	⊕⊕⊖⊖: **LOW** Study quality: -1 (unclear rando, allocation concealment, blinding) Consistency: -1 (I^2=71.1%) Directness: ok Imprecision:ok
Risk of diarrhoea on day 3	1248 (8 studies)	**RR 0.41 (0.27 to 0.60) SS (lower risk of diarrhoea with S. boulardii)**	⊕⊕⊖⊖: **LOW** Study quality: -1 (unclear rando, allocation concealment, blinding) Consistency: -1 (I^2=84.7%) Directness: ok Imprecision:ok

Table 383

In this meta-analysis, a treatment with Sacchoromyces boulardii was compared to placebo or no treatment for acute infectious diarrhoea in children.

The children in the 22 studies ranged from 1 month to 15 years.

Duration of the intervention was 5 to 10 days. In 2 studies the duration of treatment was not stated.

There was significant heterogeneity between studies. In a sensitivity analysis, studies with adequate blinding showed no evidence of heterogeneity, while there was a high and significant heterogeneity in the results of inadequately blinded studies. The results for the outcome “mean duration of diarrhoea” was statistically significant for both adequately and inadequately blinded trials.

In children *with acute infectious diarrhoea*, a treatment with S. boulardii for 5-10 days, compared to placebo or no treatment, **did** result in a statistically significant **decrease** in *mean duration of diarrhoea*.
GRADE: MODERATE quality of evidence

In children *with acute infectious diarrhoea*, a treatment with S. boulardii for 5-10 days, compared to placebo or no treatment, **did** result in a statistically significant **decrease** in *mean stool frequency on day 2* and *on day 3,* and in *risk of diarrhoea on day 3* and *day 4.*
GRADE: LOW quality of evidence

14.2.3.2 Lactobacillus acidophilus LB vs placebo or no treatment for acute gastroenteritis in children

14.2.3.2.1 Clinical evidence profile

Meta-analysis: Szajewska 2014{Szajewska, 2014 #98} "Meta-analysis shows limited evidence for using Lactobacillus acidophilus LB to treat acute gastroenteritis in children"
Inclusion criteria: RCTs that compared the use of L. acidophilus LB with a placebo or no treatment were eligible for inclusion.
Search strategy:
"The Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library), MEDLINE and EMBASE databases were searched in August 2013. The principal search text word terms and MESH headings used were as follows: diarrhea/diarrhoea, diarrh*, gastroenteritis, probiotic*, L. acidophilus LB and Lacteol. No language restrictions were imposed. The reference lists from identified studies and key review articles, including previously published systematic reviews with or without a metaanalysis, were also searched to identify any other relevant studies."
Assessment of quality of included trials: yes, the Cochrane Collaboration's tool for assessing risk of bias was used.
Other methodological remarks:

Table 384

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Szajewska 2014{Szajewska, 2014 #98}	**Lactobacillus acidophilus LB vs placebo or no treatment**	N=4 n=224 (Lievin-Le Moal 2007, Boulloche 1994, Simakachorn 2000, Salazar-Lindo 2007)	**Duration of diarrhoea (hours)** **(shorter duration with L. acidophilus)**	**MD -21.57 (-26.54 to -16.61)** **SS**
		N=2 n=144 (Boulloche 1994, Simakachorn	**Cure on day 3**	Crude AR: 62/75 vs 55/69 RR 1.03 (0.88 to 1.21) NS

		2000)		
		N=2 n=153 (Lievin-Le Moal 2007, Simakachorn 2000)	**Cure on day 4** **(more cured with L. acidophilus)**	Crude Ar: 72/79 vs 47/74 **RR 1.44 (1.20 to 1.73)** **SS**

Table 385

* Characteristics of included studies: see below

Table 1 Characteristics of included trials

Study ID (country)	Patients	Exp/cont	Intervention	Total daily dose (CFU)	Comparison	Inclusion criteria	Aetiology of diarrhoea	Duration of diarrhoea (definition)	Funding
Boulloche et al. (10) France	N = 71 1–48 month, inpatients	38/33	*Lactobacillus acidophilus* LB (killed)	3×10^{10} on day one, then 2×10^{10} (for 3 days)	Placebo (no details provided)	Acute diarrhoea with at least 5% weight loss	18% positive stool culture; 49% positive virology tests. No more details	Time to passage of the last abnormal stool. Time to passage of the first normal stool	Not stated
Liévin-Le Moal et al. (12) Ecuador	N = 80 ≤24 month (mean age: 10 month); inpatients	42/38	*L. acidophilus* LB (heat-killed) plus their spent culture medium	3×10^{10} on day 1, then 2×10^{10} (for 3 days)	Placebo (sucrose, ferrous oxides, silicic acid and banana and orange flavouring)	Acute diarrhoea (four or more liquid stools/ 24 h of <72 h duration)	Only nonrotavirus diarrhoea. No more details	Time to passage of first normal stool	Lacteol Forte sachets and placebo provided free of charge from Laborat. Du Lacteol, France
Salazar-Lindo et al. (13) Peru	N = 80 3–48 month, outpatients	40/40	*L. acidophilus* LB (heat-killed) plus their spent culture medium	3×10^{10} on day 1, then 2×10^{10} until recovery; max. four and one half days)	Placebo (salicylic acid, banana and orange flavour, sucrose, and yellow and brown iron oxides)	Acute diarrhoea (three or more watery stools/ 24 h of <72 h duration)	RV 22.5%	Time to first normal stool followed by two consecutive normal stools or time to last diarrhoeic stool followed by 12 h without stools.	Axcan Pharma Sa, Houdin, France
Simakachorn et al. (14) Thailand	N = 73 3–24 month inpatients	37/36	*L. acidophilus* LB (heat-killed) plus their spent culture medium	2×10^{10} (five doses over 48 h)	Placebo (no bacteria and fermented culture medium; it contained the same excipients as active treatment and ferric oxides as dyes)	Acute watery diarrhoea for <5 days and mild to moderate dehydration.	RV 48%; bacterial 1.5%; unknown 50.5%	Two consecutive well-formed stools or no stool passed for 12 h.	Merck Ltd., Bangkok, Thailand Lactéol Fort sachets and placebo: Laboratoire du Lactéol, France

CFU, colony-forming units; RV, rotavirus.

Figure 22 study details, as evaluated by Szajewska 2014

Refs from figure: Boulloche{Boulloche, 1994 #360}, Liévin-Le Moal{Lievin-Le Moal, 2007 #358}, Salazar-Lindo{Salazar-Lindo, 2007 #359}, Simkachorn{Simakachorn, 2000 #354}

Table 2 Methodological assessment of included trials

Study ID	Adequacy of sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)
Boulloche et al. (10)	(+) Random number table	(?) Not described	(?) Not described. Only mentioned that the study was double blind.	(?) Not described.	(+) 61/72 (85%)
Liévin-Le Moal et al. (12)	(–) Sequential allocation. No details.	(+) The sachets were numerically coded. Sequential allocation.	(+) Identical placebo	(?) Not described.	(+) 100%
Salazar-Lindo et al. (13)	(?) Not described	(?) Probably sequential	(+) Double blind. Study codes were broken only after completion of the blind review.	(+) Study codes were broken only after completion of the blind review.	(+) 77/80 (96%)
Simakachorn et al. (14)	(+) Randomisation code	(+) Numerically coded package	(+) Identical placebo	(?) Not described.	(+) 100%

(+) indicates a low risk of bias; (–) indicates a high risk of bias; (?) indicates unclear risk of bias.

Figure 23 study quality, as evaluated by Szajewska 2014

Refs from figure: Boulloche{Boulloche, 1994 #360}, Liévin-Le Moal{Lievin-Le Moal, 2007 #358}, Salazar-Lindo{Salazar-Lindo, 2007 #359}, Simkachorn{Simakachorn, 2000 #354}

Author's conclusions:

"This systematic review and meta-analysis of RCTs document that the use of L. acidophilus LB compared with placebo reduces the duration of diarrhoea associated with AGE in hospitalised children. However, given the small number of trials and participants and the methodological limitations of the included trials, the evidence should be viewed with caution."

14.2.3.2.2 Summary and conclusions

Lactobacillus acidophilus LB vs placebo or no treatment for acute gastroenteritis in children			
Bibliography: Szajewska 2014{Szajewska, 2014 #98}			
Outcomes	**N° of participants (studies) Follow up**	**Results (95%CI)**	**Quality of the evidence (GRADE)**
Duration of diarrhoea (hours)	224 (4 studies)	**MD -21.57 (-26.54 to -16.61)** **SS** **(shorter duration with L. acidophilus)**	⨁⨁⨁⨀: **MODERATE** Study quality:-1 (unclear rando, allocation concealment, blinding) Consistency: ok Directness: ok Imprecision: ok
Cure on day 3	144 (2 studies)	RR 1.03 (0.88 to 1.21) NS	⨁⨁⨁⨀: **MODERATE** Study quality: -1 (unclear allocation concealment, blinding) Consistency: ok Directness: ok Imprecision:ok
Cure on day 4	153 (2 studies)	**RR 1.44 (1.20 to 1.73)** **SS** **(more cured with L. acidophilus)**	⨁⨁⨁⨀: **MODERATE** Study quality: -1 (unclear rando, allocation concealment, blinding) Consistency: ok Directness: ok Imprecision:ok

Table 386

In this meta-analysis, a treatment with Lactobacillus acidophilus LB was compared to placebo or no treatment for acute gastroenteritis in children.

The children in the 4 studies ranged from 1 to 48 months.

The duration of the intervention was 2-4 days.

In children *with acute gastroenteritis*, a treatment with L. acidophilus for 2-4 days, compared to placebo or no treatment, **did** result in a statistically significant **decrease** in *duration of diarrhoea*.
GRADE: MODERATE quality of evidence

In children *with acute gastroenteritis*, a treatment with L. acidophilus for 2-4 days, compared to placebo or no treatment, **did** result in a statistically significant **increase** in *cure on day 4.*
GRADE: MODERATE quality of evidence

In children *with acute gastroenteritis*, a treatment with L. acidophilus for 2-4 days, compared to placebo or no treatment, **did not** result in a statistically significant difference in *cure on day 3.*
GRADE: MODERATE quality of evidence

14.2.4 Probiotics for the prevention of diarrhoea following AB treatment

14.2.4.1 S. boulardii vs placebo or no treatment for prevention of diarrhoea following antibiotic treatment

14.2.4.1.1 Clinical evidence profile

Meta-analysis: Cochrane Goldenberg 2015{Goldenberg, 2015 #101} "Probiotics for the prevention of pediatric antibiotic-associated diarrhea"
Inclusion criteria:
All randomized controlled trials irrespective of language or publication status, in which a specified probiotic agent has been compared to placebo, active, or no treatment control
Children (0 to 18 years of age), male or female of any ethnic group being administered antibiotic therapy for any reason
Intervention group: specific, identified probiotic in any form (e.g. capsule, sachet, yogurt). Trials investigating non-specific probiotic or yogurt agents (e.g. products that do not label the probiotic strain and dose) were not considered. Trials combining probiotics with prebiotics were included if the prebiotic dose was less than 2.5 grams;
Control group: placebo, active, or no treatment control. All studies comparing probiotics to conventional care (i.e. diosmectite, loperamide) or probiotics plus conventional care versus conventional care plus placebo or no treatment were considered for the review.
Search strategy:
"In November 2014, a comprehensive search of the following relevant databases irrespective of publication status or language was conducted: The Cochrane Central Register of Controlled Trials (CENTRAL) on the Cochrane Library (2014) the trial registers of the Cochrane IBD/FBD Review Group, the Cochrane Complementary Medicine Field's Register of Controlled Trials, MEDLINE (1966 to 2014), EMBASE (1980 to 2014),CINAHL (1982 to 2014), AMED(1985 to 2014),Web of Science (1945 to 2014). HANDSEARCHES Bibliographies of randomised controlled trials and review articles were checked for additional studies not identified by the electronic searches."
Assessment of quality of included trials: yes
Other methodological remarks:

Table 387

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Cochrane Goldenberg 2015{Goldenberg, 2015 #101}	**S. boulardii vs placebo or no treatment**	N=4 n=1611 (Benhamou 1999, Erdeve	**Incidence of diarrhoea**	Crude AR: 54/829 vs 122/782 **RR 0.40 [0.17, 0.96]** **SS**

		2004, Kotowska 2005, Shan 2013)		

Table 388

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
Benhamou 1999{Benhamou, 1999 #361}	779	Age: 1 to 5 years	Period of follow-up: length of antibiotic intervention	Probiotic: SB (4.5 billion CFU/day) Control: Diosmectite 6 g/day (1 to 2 years), 9 g/day (> 2 years) (antibiotics not specified)	RANDOM SEQUENCE GENERATION Unclear risk (Mentioned randomization, otherwise not described) ALLOCATION CONCEALMENT Unclear risk (Not described) BLINDING Unclear risk(Described as “double blind” without further details) INCOMPLETE OUTCOME DATA High risk (Withdrawals/loss to follow-up: 163 participants (21%). The authors do not describe what happened to these patients) SELECTIVE REPORTING Low risk OTHER BIAS Unclear risk (No funding from industry or other sources mentioned)
Erdeve 2004{Erdeve, 2004 #343}	653	Age: 1 to 15 years	Not stated	Probiotic: SB (5 billion CFU/day)	RANDOM SEQUENCE GENERATION Low risk

				(Antibiotics: salbactam-ampicillin n = 234, azithromycin n = 232)	ALLOCATION CONCEALMENT Unclear risk (Not described) BLINDING Unclear risk (No mention is made of blinding) INCOMPLETE OUTCOME DATA High risk (Withdrawals/loss to follow-up: 187 participants (28.6%). There is no mention of which proportion of drop outs were from each group) SELECTIVE REPORTING Low risk OTHER BIAS Unclear risk (No mention of funding)
Kotowska 2005{Kotowska, 2005 #344}	269	Age: 6.2 to 182 months (5 months to 15 years)	Period of follow-up: 2 weeks after the end of antibiotic treatment	Probiotic: SB (10 billion CFU/day for duration of antibiotic treatment [range 7 to 9 days] (Antibiotics: cefuroxime axetil = 72, amoxicillin clavulanate = 46, amoxicillin = 33, cefuroxime (IV) = 39, penicillin = 33, clarithromycin = 20, roxithromycin = 13, other = 13)	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk BLINDING Low risk INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk OTHER BIAS Unclear risk (No mention of funding)
Shan 2013{Shan, 2013 #345}	333	Age: average 48 months	Period of follow-up: 2 weeks following	Probiotics: Saccharomyces boulardii 2×250 mg (10 billion CFU/day) (Antibiotics: cefepime,	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk

			end of antibiotic treatment	cefoperazone, sulbactam, cefuroxime, amoxicillin, clavulanic acid, erythromycin)	BLINDING High risk ("This study was an open, randomised, controlled clinical trial") Incomplete outcome data High risk (15% missing outcome data) SELECTIVE REPORTING Low risk OTHER BIAS Unclear risk (Funding source unclear. One of the authors is a consultant for a probiotics company)

Table 389

Author's conclusions:

Moderate quality evidence suggests a protective effect of probiotics in preventing AAD. Our pooled estimate suggests a precise (RR 0.46; 95% CI 0.35 to 0.61) probiotic effect with a NNT of 10. Among the various probiotics evaluated, Lactobacillus rhamnosus or Saccharomyces boulardii at 5 to 40 billion colony forming units/day may be appropriate given the modest NNT and the likelihood that adverse events are very rare. It is premature to draw conclusions about the efficacy and safety of other probiotic agents for pediatric AAD. Although no serious adverse events were observed among otherwise healthy children, serious adverse events have been observed in severely debilitated or immuno-compromised children with underlying risk factors including central venous catheter use and disorders associated with bacterial/fungal translocation. Until further research has been conducted, probiotic use should be avoided in pediatric populations at risk for adverse events. Future trials would benefit from a standard and valid outcomes to measure AAD.

Remarks:

We did not report the outcomes for all probiotics versus placebo, as most of the species are not registered as a medication in Belgium.

14.2.4.1.2 Summary and conclusions

S. boulardii vs placebo or no treatment for prevention of diarrhoea following antibiotic treatment			
Bibliography: Cochrane Goldenberg 2015{Goldenberg, 2015 #101}			
Outcomes	**N° of participants (studies) Follow up**	**Results (HR(95%CI))**	**Quality of the evidence (GRADE)**
Incidence of diarrhoea	1611 (4 studies)	**RR 0.40 [0.17, 0.96] SS (lower incidence of diarrhoea with S. boulardii)**	⨁⨁⨀⨀: **LOW** Study quality: -1(unclear allocation concealment, open lable in 1 study) Consistency: -1 (I^2=85%) Directness: ok Imprecision: ok

Table 390

In this meta-analysis, a treatment with S. boulardii was compared to placebo or no treatment for the prevention of diarrhoea following antibiotic treatment.

The children in these studies ranged from 1 to 15 years.

In children *treated with antibiotics,* a treatment with S. boulardii, compared to placebo or no treatment, **did** result in a statistically significant **decrease** in *incidence of diarrhoea*.
GRADE: LOW quality of evidence

14.2.4.2 L. acidophilus vs placebo or no treatment for prevention of diarrhoea following antibiotic treatmento

14.2.4.2.1 Clinical evidence profile

Meta-analysis: Cochrane Goldenberg 2015{Goldenberg, 2015 #101} "Probiotics for the prevention of pediatric antibiotic-associated diarrhea"
Inclusion criteria:
All randomized controlled trials irrespective of language or publication status, in which a specified probiotic agent has been compared to placebo, active, or no treatment control
Children (0 to 18 years of age), male or female of any ethnic group being administered antibiotic therapy for any reason
Intervention group: specific, identified probiotic in any form (e.g. capsule, sachet, yogurt). Trials investigating non-specific probiotic or yogurt agents (e.g. products that do not label the probiotic strain and dose) were not considered. Trials combining probiotics with prebiotics were included if the prebiotic dose was less than 2.5 grams;
Control group: placebo, active, or no treatment control. All studies comparing probiotics to conventional care (i.e. diosmectite, loperamide) or probiotics plus conventional care versus conventional care plus placebo or no treatment were considered for the review.
Search strategy:
"In November 2014, a comprehensive search of the following relevant databases irrespective of publication status or language was conducted: The Cochrane Central Register of Controlled Trials (CENTRAL) on the Cochrane Library (2014) the trial registers of the Cochrane IBD/FBD Review Group, the Cochrane Complementary Medicine Field's Register of Controlled Trials, MEDLINE (1966 to 2014), EMBASE (1980 to 2014),CINAHL (1982 to 2014), AMED(1985 to 2014),Web of Science (1945 to 2014). HANDSEARCHES Bibliographies of randomised controlled trials and review articles were checked for additional studies not identified by the electronic searches."
Assessment of quality of included trials: yes
Other methodological remarks:

Table 391

Remarks:

We did not report the results, as only one RCT with a very small sample size (<40 participants per arm) was found for this comparison.

14.2.4.2.2 Summary and conclusions

L. acidophilus vs placebo or no treatment for prevention of diarrhoea following antibiotic treatment
Bibliography: Cochrane Goldenberg 2015{Goldenberg, 2015 #101}

Table 392

In this meta-analysis, a treatment with L. acidophilus was compared to placebo or no treatment for the prevention of diarrhoea following antibiotic treatment.

We did not report the results, as only one RCT with a very small sample size (<40 participants per arm) was found for this comparison.

15 Impetigo

15.1 Guidelines

15.1.1 Method of reporting of the recommendations and notes

Formal recommendations, that are supplied with grades of recommendations or levels of evidence, are written in **bold**.

Text taken directly from the guidelines, that is not graded but provides supplemental information or a clarification of the formal recommendations, is written in *italics*.

Comments by the bibliography group are written in plain text.

15.1.2 General information on selected guidelines

15.1.2.1 Selected guidelines

The selected guidelines and their abbreviations as used in this report can be found in Table 393.

Abbreviation	Guideline
BAPCOC 2012{BAPCOC, 2012 #3}	BAPCOC - Belgische gids voor anti-infectieuze behandeling in de ambulante praktijk; editie 2012/ Guide Belge des traitements anti-infectieux en pratique ambulatoire; édition 2012

Table 393: Selected guidelines and their abbreviations as used in this report.

15.1.2.2 Grades of recommendation

Grades of recommendation and levels of evidence as defined in each guideline, can be found in Table 394.

BAPCOC 2012		
Grades of recommendation:	1	Strong recommendation
	2	Weak recommendation
Levels of evidence	A	High degree of evidence; RCTs without limitations or strong, compelling evidence from observational studies
	B	Medium level of evidence; RCTs with limitations or strong evidence from observational studies
	C	(very) low degree of evidence; observational

		studies or case studies

Table 394: Grades of recommendation and Level of evidence of BAPCOC 2012 guideline.

15.1.2.3 Agree II score

Information about the Agree II score can be found in the section "Methodology".

15.1.2.4 Included populations – interventions – main outcomes

In Table 395, the populations, interventions and main outcomes considered in the selected guidelines are represented.

BAPCOC 2012	
Population	Ambulant care patients (adults and children)
Interventions	Antibiotic treatment (indication, choice, dose, duration)
Outcomes	Not specified

Table 395: Included population, intervention and main outcomes of guideline.

15.1.2.5 Members of development group – target audience

Members of the development group that produced the guidelines, and the target audience for whom the guidelines are intended, can be found in Table 396

BAPCOC 2012	
Development group	General practitioners, microbiologists, pneumologists, infectiologists, paediatricians, pharmacists
Target audience	Physicians working in ambulant care

Table 396: Members of the development group and target audience of the BAPCOC 2012 guideline

15.1.3 Definition

15.1.3.1 Summary

No information.

15.1.3.2 BAPCOC 2012

The guideline doesn't define this term

15.1.4 Indications for antibiotic treatment

15.1.4.1 Summary

The BAPCOC 2012 guideline recommends local antibiotic treatment in case of limited lesions (strong recommendation, high level of evidence) and oral antibiotics in case of failure of local treatment, adenopathy or systemic symptoms (strong recommendation but low levels of evidence).

15.1.4.2 BAPCOC 2012

For limited skin lesions a local treatment is sufficient (GRADE 1A)

For extended lesions, in case of failure of the local treatment, adenopathy or systemic symptoms antibiotics per os are indicated (GRADE 1C)

15.1.5 Choice of antibiotic, dose and duration

15.1.5.1 Summary

The BAPCOC 2012 guideline strongly recommends, with high levels of evidence, fusidic acid or retapamuline (which is not available in Belgium) as first choice for local antibiotic therapy.

For oral antibiotics the first choice is flucloxacillin (strong recommendation, moderate levels of evidence). In case of IgE-mediated penicillin allergy second choices can be: clarithromycin, azithromycin or roxythromycin (strong recommendation, low levels of evidence).

15.1.5.2 BAPCOC 2012

- *Local treatment*

First choice (GRADE 1A):

  - **Fusidic adic 2%, 3 to 4 applications per day during 7 days**
  - **Retapamuline 1%, 2 applications per day during 5 days**

Alternative treatment (GRADE 2A):

  - **Mupirocine 2%, 3 applications per day during 7 days**

- *Per os treatment*

First choice (GRADE 1B):

  - **Flucloxacillin - Child: 25-50 mg/kg/day in 3 to 4 doses during 7 days**

Alternative treatment in case of IgE-mediated penicillin allergy (GRADE 1C)

  - **Clarithromycin - Child: 15 mg/kg/day in 2 doses during 7 days**
  - **Azithromycin – Child: 10 mg/kg per day in 1 dose during 3 days or 10 mg/kg in 1 dose on the first day then 5 mg/kg in one dose during 4 days.**
  - **Roxythromycin – Child: 300 mg/day in 2 doses during 7 days**

15.1.6 Non-antibiotic treatment

15.1.6.1 Summary

No information was found in the guideline.

15.1.7 Referrals

15.1.7.1 Summary

No information was found in the guideline.

15.1.7.2 BAPCOC 2012

No information found in the guideline.

15.2 Evidence tables and conclusions

15.2.1 Antibiotics versus placebo or no treatment for impetigo

15.2.1.1 Oral antibiotics versus placebo or no treatment for non-bullous impetigo

15.2.1.1.1 Clinical evidence profile

Meta-analysis: Koning 2012{Koning, 2012 #214} “Interventions for impetigo” Inclusion criteria: RCTs People who have impetigo or impetigo contagiosa diagnosed by a medically trained person (and preferably confirmed by bacterial culture). We included any program of topical or systemic (oral, intramuscular, or intravenous) treatment, including antibiotics, disinfectants, or any other intervention for impetigo, such as ’awaiting natural response’. We excluded studies that only compared different dosages of the same drug. Search strategy: We updated our searches of the following databases on 27 July 2010: the Cochrane Skin Group Specialised Register using the following search terms: (impetig* or pyoderma or ((staphylococc* or streptococc*) and skin and infection*)) and (therap* or treatment* or intervention*); CENTRAL, MEDLINE, EMBASE, LILACS A final prepublication search for this review was undertaken on 16 August 2011. Assessment of quality of included trials: yes Other methodological remarks:

Table 397

This systematic review found 1 RCT for this comparison, which did not meet our inclusion criteria (sample size too small).

15.2.1.1.2 Summary and conclusions

Oral Antibiotics vs placebo or no treatment for non-bullous impetigo
Bibliography: Koning 2012{Koning, 2012 #214}

Table 398

In this meta-analysis, RCTs that compared oral antibiotics to placebo or no treatment for non-bullous impetigo were sought.

It found 1 RCT for this comparison, which did not meet our inclusion criteria

15.2.1.2 Topical antibiotics versus placebo or no treatment for non-bullous impetigo

15.2.1.2.1 Clinical evidence profile

Meta-analysis: Koning 2012{Koning, 2012 #214} "Interventions for impetigo" Inclusion criteria: RCTs people who have impetigo or impetigo contagiosa diagnosed by a medically trained person (and preferably confirmed by bacterial culture). We included any programof topical or systemic (oral, intramuscular, or intravenous) treatment, including antibiotics, disinfectants, or any other intervention for impetigo, such as 'awaiting natural response'. We excluded studies that only compared different dosages of the same drug. Search strategy: We updated our searches of the following databases on 27 July 2010: the Cochrane Skin Group Specialised Register using the following search terms: (impetig* or pyoderma or ((staphylococc* or streptococc*) and skin and infection*)) and (therap* or treatment* or intervention*); CENTRAL, MEDLINE, EMBASE, LILACS A final prepublication search for this review was undertaken on 16 August 2011. Assessment of quality of included trials: yes Other methodological remarks:

Table 399

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Koning 2012{Koning, 2012 #214}	Topical Antibiotics vs placebo	N=6 n=575 (Eells 1986, Gould 1984, Rojas 1985, Koning 2003, Ruby 1973, Koning 2008)	**Cure/improvement** Cure as defined by clearance of crusts, blisters, and redness as assessed by the investigator	Crude AR 220/312 vs 77/263 **RR 2.24 [1.61, 3.13]** **SS**

Table 400

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
Eells 1986{Eells, 1986 #251}	38	7 months to 13 years	8 days	A: mupirocin ointment 2%, 3 td, 7 to 9 days B: vehicle control, 3 td, 7 to 9 days	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Unclear risk (Insufficient information was available.) BLINDING Low risk INCOMPLETE OUTCOME DATA High risk (14/52 participants were omitted in the analysis: 8/26 in the mupirocin group (5 were "unavailable for follow-up", 3 for several reasons (specified)), 6/26 in the vehicle group (2 were "unavailable for follow- up", 3 for several reasons (specified)). There were more than 20% withdrawals and dropouts) SELECTIVE REPORTING Unclear risk (This was unclear.) OTHER BIAS Unclear risk (There was no baseline imbalance. Compliance was not reported) RANDOMISED? Low risk WERE BOTH INCLUSION AND EXCLUSION CRITERIA SPECIFIED? Low risk

Gould 1984{Gould, 1984 #245}	129	**Average age 18.7 (all participants); % children unknown**	Not reported	A: mupirocin ointment 2%, once daily, until cleared B: placebo cream, once daily, until cleared	RANDOM SEQUENCE GENERATION Unclear risk (Quote: "Patient swere allocated a trial number in the consecutive order of their entry in the study. The study was performed under double blind conditions. Medication appropriate to the trial number, either mupirocin or placebo ointment, was dispensed according to a pre-determined randomization which ensured that in each group of four patients, two received treatment with mupirocin and two with placebo ointment." The process for selecting the blocks was not specified) ALLOCATION CONCEALMENT Unclear risk (Insufficient information was available.) BLINDING PATIENT Unclear risk (Quote: "The study was performed under double-blind conditions." It is unclear whether, and how, the outcome assessor, caregiver, and participant were blinded) INCOMPLETE OUTCOME DATA Unclear risk 514/107 participants were omitted in the analysis: 10/54 in the mupirocin group (they were classified as clinically unassessable, 7 did not return for final assessment (5 were traced later and found to

					have clinically improved), 3 developed other diseases requiring systemic treatment), 4/53 in the placebo group (3 did not return for final assessment (2 of whom were later found to have improved and one worsened and sought alternative treatment), 1 developed other disease requiring systemic treatment) . < 20%, 3 vs 1 impetigo participant not evaluable° SELECTIVE REPORTING Unclear risk (This was unclear.) OTHER BIAS Unclear risk (Quote: "...well matched". There was no compliance data.) RANDOMISED? Low risk WERE BOTH INCLUSION AND EXCLUSION CRITERIA SPECIFIED? Low risk
Koning 2003{Koning, 2002 #252}	160	< 12, average age 5.0 years	7 days	A: fusidic acid cream 2%, 3 td + povidone iodine shampoo, 2 td B: placebo cream, 3 td + povidone iodine shampoo, 2 td	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk BLINDING Low risk INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Unclear risk (This was unclear.) OTHER BIAS

					Unclear risk (There was no baseline imbalance. There was more non-compliance in the placebo group) RANDOMISED? Low risk WERE BOTH INCLUSION AND EXCLUSION CRITERIA SPECIFIED? Low risk
Koning 2008{Koning, 2008 #253}	210	0 to 73 years of age, mean age around 11 years	7 days	A: topical retapamulin 1% 2 td for 5 days B: topical placebo 2 td for 5 days	RANDOM SEQUENCE GENERATION Unclear risk (Insufficient information was available.) ALLOCATION CONCEALMENT Low risk BLINDING Low risk INCOMPLETE OUTCOME DATA High risk (50/213 participants missing in total: 18/ 140 in the retapamulin group (1 did not receive intervention, 17 withdrawals (5 lack of efficacy, 3 disease progression, 2 decided to withdraw, 1 adverse event, 5 lost to follow up)), 33/73 in the placebo group (2 did not receive intervention, 31 withdrawals (18 lack of efficacy, 9 disease progression, 1 adverse event, 3 lost to follow up)). > 20% missing data) SELECTIVE REPORTING Unclear risk (This was unclear.) OTHER BIAS Unclear risk (Quote: “The mean

					total lesion area at baseline was larger in the retapamulin group compared with the placebo group." There was an imbalance for age. There were no compliance data) RANDOMISED? Low risk WERE BOTH INCLUSION AND EXCLUSION CRITERIA SPECIFIED? Low risk
Rojas 1985{Rojas, 1985 #246}	Not found	**Age not reported**	7-12 days	A: mupirocin ointment 2%, 3 td, 10 to 12 days B: placebo/vehicle, 3 td, 10 to 12 days	RANDOM SEQUENCE GENERATION Unclear risk (Insufficient information was available.) ALLOCATION CONCEALMENT Unclear risk (Insufficient information was available.) BLINDING Unclear risk (Quote: "The medication was numerically labelled; the protocol ensured double-blind comparisons." Bactroban ointment versus vehicle ointment. It is not clear whether the caregiver and outcome assessor are the same person. There was unclear blinding of the outcome assessor. The participant and the caregiver were probably blinded) INCOMPLETE OUTCOME DATA High risk (Quote: "Fifty patients completed the study. " The number of participants that entered into the study was not specified)

					SELECTIVE REPORTING Unclear risk (This was unclear.) OTHER BIAS Unclear risk (There was no baseline data. There were no compliance data.) RANDOMISED? Low risk WERE BOTH INCLUSION AND EXCLUSION CRITERIA SPECIFIED? High risk (Quote: “Patients with...entered in the study sequentially.” No exclusion criteria was specified)
Ruby 1973{Ruby, 1973 #254}	102	Children, age not reported	5 days	5 arms: A: phenoxymethyl penicillin 40 to 60,000 units/kg/day in 3 doses + Hexachlorophene scrubs (HS) B: phenoxymethyl penicillin 40 to 60,000 units/kg/day in 3 doses C: HS + placebo D: placebo, 3 td E: bacitracin ointment, 2 td	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT High risk (Quote: “Patients were assigned to one of five treatment groups by a random numbers list.” Quote: “When more than one child from an household was entered in the study, all those children received the same treatment. ” Investigators knew that children in the same household got the same treatment) BLINDING High risk (Quote: “Phenoxymethyl penicillin suspension and placebo were coded as ’impecillin’ and ’tigocillin”’. Also, ointment versus suspension. The bacitracin was not

					placebo controlled Comment: The outcome assessor, caregiver, and participant were probably not blinded) INCOMPLETE OUTCOME DATA High risk(24/102 participants were omitted in the analysis: 0/20 in group A (penicillin + hexachlorophene), 2/20 in group B (penicillin) (2 not streptococcal positive) , 12/23 in group C (placebo) (6 not streptococcal positive, 6 failed to return for first follow-up), 4/17 in group D (placebo+hexachlorophene) (2 not streptococcal positive, 2 failed to return for first follow-up;), 6/22 in group E (bacitracin) (2 not streptococcal positive, 4 failed to return for first follow-up)) SELECTIVE REPORTING Unclear risk (This was unclear.) OTHER BIAS Unclear risk (There was no baseline imbalance. Compliance was good for penicillin (based on urine test) but not reported for other therapy) RANDOMISED? Low risk WERE BOTH INCLUSION AND EXCLUSION CRITERIA SPECIFIED? High risk (Quote: “Children with... were excluded.” Quote: “All

					patients were seen”.)

Table 401

15.2.1.2.2 Summary and conclusions

Topical antibiotics vs placebo or for non-bullous impetigo			
Bibliography: Koning 2012{Koning, 2012 #214}			
Outcomes	**N° of participants (studies) Follow up**	**Results (RR(95%CI))**	**Quality of the evidence (GRADE)**
Cure/improvement	575 (6 studies)	**RR 2.24 [1.61, 3.13]** **SS** (more cure/improvement with topical AB)	⨁⨁⨀⨀: **LOW** Study quality:-1 (unclear rando in 3, inadequate blinding in 3) Consistency: ok Directness: -1 (mixed adults and children) Imprecision: ok

Table 402

In this meta-analysis, a treatment with topical antibiotics was compared placebo for non-bullous impetigo.

Six RCTs were found. Three included children only. Two included both adults and children. The percentage of children in these studies is unknown. One RCT did not report the ages of the participants.

The topical antibiotics used in these trials were mupirocin, fusidic acid, retapamulin and bacitracin. Retapamulin is not available in Belgium.

In one of the trials, there was additional use of povidone iodine in both study arms.

In children and adults *with non-bullous impetigo*, a treatment with a topical antibiotic, compared to placebo, **did** result in a statistically significant increase in *cure or improvement*.

GRADE: LOW quality of evidence

15.2.2 Antibiotic A versus antibiotic B

15.2.2.1 Oral cephalexin vs oral cefadroxil for non-bullous impetigo

15.2.2.1.1 Clinical evidence profile

Meta-analysis: Koning 2012{Koning, 2012 #214} "Interventions for impetigo" Inclusion criteria: RCTs People who have impetigo or impetigo contagiosa diagnosed by a medically trained person (and preferably confirmed by bacterial culture). We included any programof topical or systemic (oral, intramuscular, or intravenous) treatment, including antibiotics, disinfectants, or any other intervention for impetigo, such as 'awaiting natural response'. We excluded studies that only compared different dosages of the same drug. Search strategy: We updated our searches of the following databases on 27 July 2010: the Cochrane Skin Group Specialised Register using the following search terms: (impetig* or pyoderma or ((staphylococc* or streptococc*) and skin and infection*)) and (therap* or treatment* or intervention*); CENTRAL, MEDLINE, EMBASE, LILACS A final prepublication search for this review was undertaken on 16 August 2011. Assessment of quality of included trials: yes Other methodological remarks:

Table 403

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Koning 2012{Koning, 2012 #214	Cephalexin vs cefadroxil	N=1 n=96 (Hains 1989)	**Cure/improvement** Cure as defined by clearance of crusts, blisters, and redness as assessed by the investigator	Crude AR 41/45 vs 47/51 RR 0.99 [0.88, 1.12] NS

Table 404

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review

Hains 1989{Hains, 1989 #250}	Not found	1 to 18 years	14 days	A: cefadroxil 30 mg/kg/day, max 1 g, in 1 dd, 10 days B: cephalexin 30 mg/kg/day, max 1 g, in 2 dd, 10 days	RANDOM SEQUENCE GENERATION Unclear risk (Insufficient information was available) ALLOCATION CONCEALMENT Unclear risk (Quote: “Patients were randomly assigned to receive either...” It is unclear whether participants and investigators enrolling patients could foresee assignment) BLINDING High risk (Participants in both groups received different administrations of study drugs daily. The outcome assessor, caregiver, and participant were probably not blinded) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Unclear risk (This was unclear) OTHER BIAS Unclear risk (There was baseline data. Compliance was good in both groups.) RANDOMISED? Low risk WERE BOTH INCLUSION AND EXCLUSION CRITERIA SPECIFIED? Low risk

Table 405

15.2.2.1.2 Summary and conclusions

Oral cephalexin vs oral cefadroxil for non-bullous impetigo			
Bibliography: Koning 2012{Koning, 2012 #214}			
Outcomes	**N° of participants (studies) Follow up**	**Results (RR(95%CI))**	**Quality of the evidence (GRADE)**
Cure/improvement	96 (1 study)	RR 0.99 [0.88, 1.12] NS	⨁⨁⨁⨀: **MODERATE** Study quality:-1 (open label, unclear rando and allocation concealment) Consistency: na Directness: ok Imprecision: ok

Table 406

In this meta-analysis, a treatment with oral cephalexin was compared to oral cefadroxil for non-bullous impetigo.

One study was found. The children in this study were aged 1 to 18 years. They were followed for 14 days.

Cephalexin was given in a dose of 30 mg/kg/day for 10 days.

Cefadroxil was given in a dose of 30 mg/kg/day for 10 days.

In children *with non-bullous impetigo*, a treatment with oral cephalexin for 10 days, compared to oral cefadroxil for 10 days, **did not** result in a statistically significant difference in *cure or improvement*.

GRADE: MODERATE quality of evidence

15.2.2.2 Oral erythromycin vs oral amoxicillin for non-bullous impetigo

15.2.2.2.1 Clinical evidence profile

Meta-analysis: Koning 2012{Koning, 2012 #214} "Interventions for impetigo" Inclusion criteria: RCTs people who have impetigo or impetigo contagiosa diagnosed by a medically trained person (and preferably confirmed by bacterial culture). We included any programof topical or systemic (oral, intramuscular, or intravenous) treatment, including antibiotics, disinfectants, or any other intervention for impetigo, such as 'awaiting natural response'. We excluded studies that only compared different dosages of the same drug. Search strategy: We updated our searches of the following databases on 27 July 2010: the Cochrane Skin Group Specialised Register using the following search terms: (impetig* or pyoderma or ((staphylococc* or streptococc*) and skin and infection*)) and (therap* or treatment* or intervention*); CENTRAL, MEDLINE, EMBASE, LILACS A final prepublication search for this review was undertaken on 16 August 2011. Assessment of quality of included trials: yes Other methodological remarks:

Table 407

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Koning 2012{Koning, 2012 #214}	Erythromycin vs amoxicillin	N=1 n=129 (Faye 2007)	**Cure/improvement** Cure as defined by clearance of crusts, blisters, and redness as assessed by the investigator	Crude AR 58/65 vs 57/64 RR 1.00 [0.89, 1.13] NS

Table 408

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review

Faye 2007{Faye, 2007 #249}	132	Inclusion > 1 year of age Mean age 8.5 years	7 days	A: oral amoxicillin 50 mg/kg/day + topical 10% povidone iodine for 7 days B: oral erythromycin 30 mg/kg/day + topical 10% povidone iodine for 7 days	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Unclear risk (Insufficient information was available.) BLINDING High risk (Quote: "....an open randomized trial." Quote: "Patients and investigators were not blinded." The outcome assessor, participant, and caregiver were not blinded) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Unclear risk (This was unclear.) OTHER BIAS Unclear risk (There was no baseline comparison. There were no compliance data) RANDOMISED? Low risk WERE BOTH INCLUSION AND EXCLUSION CRITERIA SPECIFIED? Low risk

Table 409

15.2.2.2.2 Summary and conclusions

Oral erythromycin vs oral amoxicillin for non-bullous impetigo			
Bibliography: Koning 2012{Koning, 2012 #214}			
Outcomes	**N° of participants (studies) Follow up**	**Results (RR(95%CI))**	**Quality of the evidence (GRADE)**
Cure/improvement	129 (1 study)	RR 1.00 [0.89, 1.13] NS	⨁⨁⨁⊖: **MODERATE** Study quality:-1 (open label) Consistency: na Directness: ok Imprecision: ok

Table 410

In this meta-analysis, a treatment with oral erythromycin was compared to oral amoxicillin for non-bullous impetigo.

One study was found. The children in this study had a mean age of 8.5 years. They were followed for 7 days.

Amoxicillin was given in a dose of 50 mg/kg/day for 7 days.

Erythromycin was given in a dose of 30 mg/kg/day for 7 days.

In both study arms, there was additional use of topical povidone iodine.

In children *with non-bullous impetigo*, a treatment with oral erythromycin for 7 days, compared to oral amoxicillin for 7 days, **did not** result in a statistically significant difference in *cure or improvement*.

GRADE: MODERATE quality of evidence

15.2.2.3 Oral co-trimoxazole vs IM benzathine benzylpenicillin

15.2.2.3.1 Summary and conclusions

Oral cotrimoxazole versus intramuscular benzathine benzylpenicillin for impetigo in a highly endemic region
Bibliography: Bowen 2012{Bowen, 2014 #213}

Table 411

In this open-label non-inferiority trial, a treatment with oral cotrimoxazole was compared to intramuscular benzathine benzylpenicillin in 508 Indigenous Australian children with non-bullous impetigo.

The children were aged 3 months to 13 years and were followed for 7 days.

Cotrimoxazole was given in a dose of 8 mg/kg/day + 40 mg/kg/day, either in two daily doses for 3 days, or in one daily dose for 5 days.

Benzathine benzylpenicillin was given according to weight (weight band ≤6 kg, dose 225 mg; 6 –10 kg, 337·5 mg; 10·–15 kg, 450 mg; 15·–20 kg, 675 mg; >20 kg, 900 mg [1·2 million units]).

The primary outcome was treatment success at day 7; cotrimoxazole in both dosing schemes showed non-inferiority (margin 10%) to benzathine penicillin.

Adverse events occurred in 54 children, 49 (90%) of whom received benzathine benzylpenicillin.

Interpretation of the authors:
"The findings of this study are applicable to the severe and highly prevalent disease of impetigo which is seen in Australian Indigenous children or children in Oceania, Brazil and Africa. For these children, topical treatment is impractical and likely to induce antimicrobial resistance. Treatment in these settings usually consists of systemic antibiotics, often benzathine benzylpenicillin, which is painful and not likely to be active against staphylococcal disease. "

Thus, these findings are unlikely to be applicable to the Belgian context.

GRADE: LOW quality of evidence

15.2.2.4 Topical mupirocin vs oral erythromycin for non-bullous impetigo

15.2.2.4.1 Clinical evidence profile

Meta-analysis: Koning 2012{Koning, 2012 #214} "Interventions for impetigo" Inclusion criteria: RCTs people who have impetigo or impetigo contagiosa diagnosed by a medically trained person (and preferably confirmed by bacterial culture). We included any program of topical or systemic (oral, intramuscular, or intravenous) treatment, including antibiotics, disinfectants, or any other intervention for impetigo, such as 'awaiting natural response'. We excluded studies that only compared different dosages of the same drug. Search strategy: We updated our searches of the following databases on 27 July 2010: the Cochrane Skin Group Specialised Register using the following search terms: (impetig* or pyoderma or ((staphylococc* or streptococc*) and skin and infection*)) and (therap* or treatment* or intervention*); CENTRAL, MEDLINE, EMBASE, LILACS A final prepublication search for this review was undertaken on 16 August 2011. Assessment of quality of included trials: yes Other methodological remarks:

Table 412

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Koning 2012{Koning, 2012 #214}	Mupirocin vs erythromycin	N=10 n=581 (Barton 1989, Britton 1990, Dagan 1992, Dux 1986, Esterly 1991, Goldfarb 1988, Gratton 1987,	**Cure/improvement** Cure as defined by clearance of crusts, blisters, and redness as assessed by the investigator	Crude AR 270/298 vs 242/283 **RR 1.07 [1.01, 1.13]** **SS**

		McLinn 1988, Mertz 1989, Rice 1992)		

Table 413

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
Barton 1989{Barton, 1989 #255}	97	3 months to 16 years	7 days	A: erythromycin 40 mg/kg/day in 3 dd, 7 days B: mupirocin ointment 2%, 3 td, 7 days	RANDOM SEQUENCE GENERATION Unclear risk (Insufficient information was available.) ALLOCATION CONCEALMENT Unclear risk (This was not mentioned in the article.) BLINDING PATIENT High risk (Participant and caregiver were not blinded because they received either capsules or ointment. It is not mentioned in the article whether the outcome assessor was blinded (probably not, because the caregiver and participant were not blinded)) INCOMPLETE OUTCOME DATA Low SELECTIVE REPORTING Unclear risk (This was unclear.) OTHER BIAS Unclear risk (Compliance was not reported.)

					RANDOMISED? Low risk WERE BOTH INCLUSION AND EXCLUSION CRITERIA SPECIFIED? Low risk
Britton 1990{Britton, 1990 #256}	44	2 months to 12 years	10 days	A: erythromycin 40 mg/kg/day in 4 dd + placebo cream B: mupirocin ointment 2%, 3 td + placebo susp	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk BLINDING PATIENT Low risk INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Unclear risk (This was unclear.) OTHER BIAS High risk (Baseline characteristics were imbalanced (sex, severity), and compliance was also skewed) RANDOMISED? Low risk
Dagan 1992{Dagan, 1992 #257}	102	< 16 years	7 days	A: erythromycin susp 50 mg/kg/day 3 td + placebo ointment, 7 days B: mupirocin ointment 2% 3 td + oral placebo susp, 7 days	RANDOM SEQUENCE GENERATION Unclear risk (Insufficient information was available.) ALLOCATION CONCEALMENT Low risk (Quote: “The randomized code was prepared by Beecham Pharmaceutical and was not known to the investigators until after the raw data were tabulated.”) BLINDING PATIENT Low risk INCOMPLETE OUTCOME

					Low risk SELECTIVE REPORTING Unclear risk (This was unclear.) OTHER BIAS Unclear risk RANDOMISED? Low risk WERE BOTH INCLUSION AND EXCLUSION CRITERIA SPECIFIED? Low risk
Dux 1986{Dux, 1986 #247}	149	**Average age 22 years; % children unknown**	7 days	A: mupirocin ointment 2%, 3 td, 7 days B: erythromycin 250 mg, 4 td, 7 days C: cloxacillin 250 mg, 4 td, 7 days	RANDOM SEQUENCE GENERATION Unclear risk (Insufficient information about the sequence generation process was available, and there was unexpected distribution (78 vs 50 vs 20)) ALLOCATION CONCEALMENT Unclear risk (Quote: "...were randomized into two treatment groups by each investigator." Comment: It is unclear whether participants and investigators enrolling participants could foresee assignment) BLINDING PATIENT Unclear risk (Quote: "...single-blind". Comment: It is not clear who was blinded and how this was done. Also, participants in both groups did not receive the same administrations of study drugs daily. Participants were probably not blinded. The blinding of outcome

					assessor and caregiver is unclear) INCOMPLETE OUTCOME DATA Low risk OTHER BIAS Unclear risk (Compliance was not reported. There was a large age difference between groups (mean 22 vs 31 years), unknown for impetigo participants) RANDOMISED? Low risk WERE BOTH INCLUSION AND EXCLUSION CRITERIA SPECIFIED? Low risk
Esterly 1991{Esterly, 1991 #258}	?	3 months to 14 years, average 4.3 years	Not reported	A: mupirocin (dose not reported) B: erythromycin (dose not reported)	RANDOM SEQUENCE GENERATION Unclear risk (Insufficient information was available.) ALLOCATION CONCEALMENT Unclear risk (It is unclear whether participants and investigators enrolling participants could foresee assignment) BLINDING PATIENT High risk (oral versus topical treatment. The outcome assessor, caregiver, and participant were probably not blinded) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Unclear risk (This was unclear.) OTHER BIAS Unclear risk (There were no baseline

					characteristics per group. There were no compliance data) RANDOMISED? Low risk WERE BOTH INCLUSION AND EXCLUSION CRITERIA SPECIFIED? High risk (This was not mentioned in the article.)
Goldfarb 1988{Goldfarb, 1988 #259}	62	5 months to 13 years, average 3.8	8 days	A: mupirocin ointment 2%, 3 td, 8 days B: erythromycin 40 mg/kg/day in 4 dd, 8 days	RANDOM SEQUENCE GENERATION Unclear risk (Insufficient information was available.) ALLOCATION CONCEALMENT Unclear risk (It is unclear whether participants and investigators enrolling participants could foresee assignment) BLINDING PATIENT High risk (Topical versus oral treatment. The outcome assessor, caregiver, and participant were probably not blinded) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Unclear risk (This was unclear.) OTHER BIAS Unclear risk (The severity of impetigo was not compared between the 2 groups. There was a difference in age (range vs mean). Compliance was not reported) RANDOMISED? Low risk

					WERE BOTH INCLUSION AND EXCLUSION CRITERIA SPECIFIED? Low risk
Gratton 1987{Gratton, 1987 #260}	Not found	**Age not reported**	7 days	A: mupirocin ointment 2%, 3 td, 7 days B: erythromycin 250 mg, 4 td, 7 days	RANDOM SEQUENCE GENERATION Unclear risk (Insufficient information was available.) ALLOCATION CONCEALMENT Unclear risk (Quote: "...were randomly divided into two treatment groups." It is unclear whether participants and investigators enrolling participants could foresee assignment) BLINDING PATIENT High risk (Topical versus oral treatment. The outcome assessor, caregiver, and participant were probably not blinded) Incomplete outcome data Low SELECTIVE REPORTING Unclear risk (This was unclear.) OTHER BIAS Unclear risk (There was no baseline data. There were no compliance data) RANDOMISED? Low risk WERE BOTH INCLUSION AND EXCLUSION CRITERIA SPECIFIED? High risk (Quote: "Sixty patients with primary and secondary skin infections were randomly divided."

					No exclusion criteria was specified)
McLinn 1988{McLinn, 1988 #261}	60	> 6 months, average 5.5 years	8-12 days	A: mupirocin ointment 2%, 3 td, 7 to 9 days B: erythromycin 30 to 40/mg/kg/day in 3 to 4 doses, 7 to 9 days	Random sequence generation Low risk ALLOCATION CONCEALMENT Low risk BLINDING PATIENT High risk (Quote: “The investigator was blinded to the treatment the patient was to receive at the time of patient entry andwas unblinded only in those cases where lesions persisted requiring additional culturing.” Quote: “. ..open-label”. This was not blinded for all participants. Also topical versus oral treatment. The outcome assessor and caregiver were not blinded) INCOMPLETE OUTCOME DATA Low risk . SELECTIVE REPORTING Unclear risk (This was unclear.) OTHER BIAS Unclear risk (There was a severe baseline imbalance, more fever in erythromycin group (12 versus 3), but they seem to have adjusted for this in the analysis. There were no compliance data) RANDOMISED? Low WERE BOTH INCLUSION AND EXCLUSION CRITERIA SPECIFIED? Low risk

Mertz 1989{Mertz, 1989 #262}	53	6 months to 32 years, average 5.4 years	7-9 days	A: mupirocin ointment 2%, 3 td, 7 to 9 days C: erythromycin 30 to 50 mg/kg/day in 2 doses, 7 to 9 days	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk BLINDING PATIENT Unclear risk (Quote: "...were examined in a investigator-blinded study." Quote: "The randomization was predetermined by the sponsor and the schedule for distribution of medications was entrusted to a team member whose assignment was to dispense medication." Also, there was treatment with ointment versus capsules. The outcome assessor was blinded. The caregiver and the participant were not blinded) INCOMPLETE OUTCOME DATA High risk (22/75 participants were omitted in the analysis: 9 were missing in the mupirocin group (unclear why), 13weremissing in the in the erythromycin group (unclear why)) SELECTIVE REPORTING Unclear risk (This was unclear) OTHER BIAS Unclear risk (There was an imbalance for sex: 17/28 versus 10/25 boys (assessable participants) = 61% vs 40%. There was no compliance data)

					RANDOMISED? Low risk WERE BOTH INCLUSION AND EXCLUSION CRITERIA SPECIFIED? Low risk
Rice 1992{Rice, 1992 #263}	83	3 months to 16 years	9-11 days	A: erythromycin ethynyl succinate 40 mg/kg/day in 4 doses, 10 days B: mupirocin ointment 2%, 3 td, 10 days	RANDOM SEQUENCE GENERATION Unclear risk (Insufficient information was available.) ALLOCATION CONCEALMENT Unclear risk (It is unclear whether participants and investigators enrolling participants could foresee assignment) BLINDING PATIENT High risk (Quote: “In any clinical trial that is not blinded...” Also, oral versus topical treatment. The outcome assessor, caregiver, and participant were not blinded) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Unclear risk (This was unclear.) OTHER BIAS Low risk RANDOMISED? Low risk WERE BOTH INCLUSION AND EXCLUSION CRITERIA SPECIFIED? Low risk

Table 414

15.2.2.4.2 Summary and conclusions

Topical mupirocin vs oral erythromycin for non-bullous impetigo			
Bibliography: Koning 2012{Koning, 2012 #214}			
Outcomes	**N° of participants (studies) Follow up**	**Results (RR(95%CI))**	**Quality of the evidence (GRADE)**
Cure/improvement	581 (10 studies)	**RR 1.07 [1.01, 1.13]** **SS** **(more cure/improvement with topical AB)**	⨁⨁⊖⊖: **LOW** Study quality:-1 (inadequate blinding in 8 trials, unclear rando in 7) Consistency: ok Directness: -1 (adults and children) Imprecision: ok

Table 415

In this meta-analysis, a treatment with topical mupirocin was compared to oral erythromycin for non-bullous impetigo.

Ten RCTs were found. Seven included children only. One included both adults and children. The percentage of children in this trial is unknown. One RCT did not report the ages of the participants. In one RCT only the average age is given, which was 22 years.

Mupirocin ointment 2% was given 3x/day for 7-10 days.

Erythromycin was given in a dose of 30-50 mg/kg/day in2- 4 doses for 7-10 days

In children and adults *with non-bullous impetigo*, a treatment with a topical mupirocin, compared to oral erythromcyin, **did** result in a statistically significant **increase** in *cure or improvement*.

GRADE: LOW quality of evidence

15.2.2.5 Topical mupirocin vs topical fusidic acid for non-bullous impetigo

15.2.2.5.1 Clinical evidence profile

Meta-analysis: Koning 2012{Koning, 2012 #214} "Interventions for impetigo" Inclusion criteria: RCTs people who have impetigo or impetigo contagiosa diagnosed by a medically trained person (and preferably confirmed by bacterial culture). We included any program of topical or systemic (oral, intramuscular, or intravenous) treatment, including antibiotics, disinfectants, or any other intervention for impetigo, such as 'awaiting natural response'. We excluded studies that only compared different dosages of the same drug. Search strategy: We updated our searches of the following databases on 27 July 2010: the Cochrane Skin Group Specialised Register using the following search terms: (impetig* or pyoderma or ((staphylococc* or streptococc*) and skin and infection*)) and (therap* or treatment* or intervention*); CENTRAL, MEDLINE, EMBASE, LILACS A final prepublication search for this review was undertaken on 16 August 2011. Assessment of quality of included trials: yes Other methodological remarks: This review and meta-analysis included trials in both adults and children. A subanalysis with only pediatric participants was not performed. The trials that were included in this comparison were all mixed trials, with both adults and children. We don't have information about the percentage of children included in these studies.

Table 416

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Koning 2012{Koning, 2012 #214}	Mupirocin vs fusidic acid	N=4 n=440 (Gilbert 1989, Morley 1988, Sutton 1992, White 1989)	**Cure/improvement** Cure as defined by clearance of crusts, blisters, and redness as assessed by the investigator	Crude AR 199/236 vs 174/204 RR 1.03 [0.95, 1.11] NS

Table 417

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
Gilbert 1989{Gilbert, 1989 #265}	70	**Age not reported**	7 days	A: mupirocin ointment 2%, 3 td, 7 days B: fusidic acid cream 2%, 3 td, 7 days	RANDOM SEQUENCE GENERATION Unclear risk (Insufficient information was available) ALLOCATION CONCEALMENT Unclear risk (Insufficient information was available.) BLINDING PATIENT Unclear risk (The abstract reported the study was double- blind, but it is not explained in the article. There is unclear blinding of the outcome assessor, caregiver, and participant) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Unclear risk (This was unclear.) OTHER BIAS Unclear risk (There was no baseline imbalance, and compliance was not reported) RANDOMISED? Low risk WERE BOTH INCLUSION AND EXCLUSION CRITERIA SPECIFIED? Low risk
Morley 1988{Morley, 1988 #266}	324	**1 to 92 years, average 33 years (all participants); % children unknown**	6-8 days	A: fusidic acid ointment 2%, 3 td, up to 7 days B: mupirocin ointment 2%, 3 td, up to 7 days	RANDOM SEQUENCE GENERATION Unclear risk (Insufficient information was available) ALLOCATION CONCEALMENT

					Low risk BLINDING PATIENT Unclear risk (Quote: “On entry, patients were allocated at random to receive one or the other treatment, tubes of the ointment being provided in plain sealed numbered containers so that the investigator was unaware of the treatment given.” Comment: The participants were probably blinded because the tubes were plain sealed. The outcome assessor was blinded. It is unclear whether the caregiver was blinded (it is unclear if the outcome assessor was also the caregiver) Incomplete outcome data Low risk SELECTIVE REPORTING Unclear risk (This was unclear.) OTHER BIAS Unclear risk (There was baseline comparison for sex, age, and severity. There were no compliance data) RANDOMISED? Low risk WERE BOTH INCLUSION AND EXCLUSION CRITERIA SPECIFIED? Low risk
Sutton 1992{Sutton, 1992 #248}	177	**1 months to 77 years, average 22 years; % children unknown**	8 days	A: fusidic acid cream 3 td, 6 to 8 days	RANDOM SEQUENCE GENERATION Unclear risk (Insufficient

				B: mupirocin ointment 3 td, 6 to 8 days	information was provided.) ALLOCATION CONCEALMENT Unclear risk (Insufficient information was provided.) BLINDING PATIENT Unclear risk (Quote: “Investigators were not aware of the treatment given until the study was completed.” Quote: “Treatment was allocated randomly in a double-blind manner, medication [was] dispensed in numbered, sealed containers.” There was unclear blinding of the caregivers because it is unclear whether this is the same person as the outcome assessor. The participants were blinded) INCOMPLETE OUTCOME DATA High risk (24/201 were omitted in the analysis: 93 were left in the fusidic acid group, 84 were left in the mupirocin group (not further specified). 177/201 were in the analysis. Of the 24 participants who were not analysed for efficacy, 20 returned for follow-up after more than 8 days, 2 defaulted, and 2 violated the study protocol) SELECTIVE REPORTING Unclear risk (This was unclear.) OTHER BIAS Unclear risk(There was no baseline imbalance. There were no

					compliance data) RANDOMISED? Low risk Quote WERE BOTH INCLUSION AND EXCLUSION CRITERIA SPECIFIED? Low risk
White 1989{White, 1989 #267}	155	**Age 11 months to 84 years; % children unknown**	7 days	A: mupirocin ointment 2%, 2 td, 7 days B: fusidic acid ointment 2%, 3 td, 7 days	RANDOM SEQUENCE GENERATION Unclear risk (Insufficient information was available.) ALLOCATION CONCEALMENT Low risk BLINDING PATIENT Unclear risk (Quote: “Four plain tubes containing the preparations were supplied for each patient. These were labelled with instructions for use but the name of the antibiotic was omitted. Mupirocin was to be applied twice daily and sodium fusidate thrice daily.” Quote: “The tubes were supplied in a sealed box labelled with the patient’s number. Thereby the observer did not know which antibiotic a patient was receiving.” The outcome assessor was blinded. The caregiver and participant were probably not blinded because they did not receive the same administrations of study drugs daily) INCOMPLETE OUTCOME DATA High risk (23/413 participants were

					omitted in the analysis: 12/275 in the mupirocin group (8 failed to attend for assessment, 1 withdrew due to revised diagnosis, 3 were prescribed antibiotics for reasons other than lack of efficacy), 11/138 in the sodium fusidate group (3 failed to attend for assessment, 1 withdrew due to revised diagnosis, 2 were prescribed antibiotics for reasons other than lack of efficacy, 4 due to noncompliance, 1 due to inadequate data). < 20% dropouts, but reasons were not balanced between the groups) SELECTIVE REPORTING Unclear risk (his was unclear.) OTHER BIAS Unclear risk (Quote: “There was a similar distribution of type and severity of infection between the two treatment groups”. There were no compliance data) RANDOMISED? Low risk WERE BOTH INCLUSION AND EXCLUSION CRITERIA SPECIFIED? Low risk

Table 418

15.2.2.5.2 Summary and conclusions

Topical mupirocin vs topical fusidic acid for non-bullous impetigo in adults and children			
Bibliography: Koning 2012{Koning, 2012 #214}			
Outcomes	**N° of participants (studies) Follow up**	**Results (RR(95%CI))**	**Quality of the evidence (GRADE)**
Cure/improvement	440 (4 studies)	RR 1.03 [0.95, 1.11] NS	⊕⊕⊖⊖: **LOW** Study quality:-1 (unclear rando, blinding) Consistency: ok Directness: -1 (adults and children) Imprecision: ok

Table 419

In this meta-analysis, a treatment with topical mupirocin was compared to topical fusidic acid for non-bullous impetigo.

Four RCTs were found. Three included both adults and children. The percentage children in these studies is unknown. A fourth study did not report the age of its participants.

Fusidic acid 2% was given 3 times a day for 6-8 days.

Mupirocin 2% was given 2-3 times a day for 6-8 days.

In children and adults *with non-bullous impetigo*, a treatment with topical mupirocin, compared to topical fusidic acid, **did not** result in a statistically significant difference in *cure or improvement*.

GRADE: LOW quality of evidence

15.2.2.6 Topical fusidic acid vs tetracycline/polymyxin B for non-bullous impetigo

15.2.2.6.1 Clinical evidence profile

Meta-analysis: Koning 2012{Koning, 2012 #214} "Interventions for impetigo" Inclusion criteria: RCTs people who have impetigo or impetigo contagiosa diagnosed by a medically trained person (and preferably confirmed by bacterial culture). We included any program of topical or systemic (oral, intramuscular, or intravenous) treatment, including antibiotics, disinfectants, or any other intervention for impetigo, such as 'awaiting natural response'. We excluded studies that only compared different dosages of the same drug. Search strategy: We updated our searches of the following databases on 27 July 2010: the Cochrane Skin Group Specialised Register using the following search terms: (impetig* or pyoderma or ((staphylococc* or streptococc*) and skin and infection*)) and (therap* or treatment* or intervention*); CENTRAL, MEDLINE, EMBASE, LILACS A final prepublication search for this review was undertaken on 16 August 2011. Assessment of quality of included trials: yes Other methodological remarks: This review and meta-analysis included trials in both adults and children. A subanalysis with only pediatric participants was not performed. The trial that was included in this comparison was a mixed trial, with both adults and children. We don't have information about the percentage of children included in this study.

Table 420

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Koning 2012{Koning, 2012 #214}	Fusidic acid vs tetracycline/ polymyxin B	N=1 n=87 (Vainer 1986)	**Cure/improvement** Cure as defined by clearance of crusts, blisters, and redness as assessed by the investigator	Crude AR 26/43 vs 25/44 RR 1.06 [0.75, 1.52] NS

Table 421

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
Vainer 1986{Vainer, 1986 #264}	128	Age 1 to 77, average 11 years; % children unknown	1 week	3 arms: A: fusidic acid cream 2% B: tetracycline/polymyxin B ointment C: neomycin/bacitracin ointment	RANDOM SEQUENCE GENERATION Unclear risk (Insufficient information was available) ALLOCATION CONCEALMENT Unclear risk (Insufficient information was available) BLINDING PATIENT Unclear risk (Quote: “Undersøgelsen var således blindet for lægen, men ikke for patienten.” [The study was blinded for the doctor, but not for the patient.] The outcome assessor and caregiver were blinded. Participants were not blinded) INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Unclear risk (This was unclear) OTHER BIAS Unclear risk (There was no baseline imbalance for severity. The used medication is in table 2.There were no compliance data) RANDOMISED? Low risk WERE BOTH INCLUSION AND EXCLUSION CRITERIA SPECIFIED? Low risk

Table 422

15.2.2.6.2 Summary and conclusions

Topical fusidic acid vs topical tetracycline/polymyxin B for non-bullous impetigo			
Bibliography: Koning 2012{Koning, 2012 #214}			
Outcomes	**N° of participants (studies) Follow up**	**Results (RR(95%CI))**	**Quality of the evidence (GRADE)**
Cure/improvement	87 (1 study)	RR 1.06 [0.75, 1.52] NS	⨁⨁⊖⊖: **LOW** Study quality:-1 (unclear rando, allocation concealment, blinding) Consistency: na Directness: -1 (adults and children) Imprecision: ok

Table 423

In this meta-analysis, a treatment with topical fusidic acid was compared to topical tetracycline/polymyxin B for non-bullous impetigo.

One RCT was found. It included both adults and children from age 1 to 77. The average age was 11 years. The percentage of children in the study is unknown.

In children and adults *with non-bullous impetigo*, a treatment with topical fusidic acid, compared to topical tetracyclin/polymyxin B, **did not** result in a statistically significant difference in *cure or improvement*.

GRADE: LOW quality of evidence

16 Cellulitis and erysipelas

16.1 Guidelines

16.1.1 Method of reporting of the recommendations and notes

Formal recommendations, that are supplied with grades of recommendations or levels of evidence, are written in **bold**.

Text taken directly from the guidelines, that is not graded but provides supplemental information or a clarification of the formal recommendations, is written in *italics*.

Comments by the bibliography group are written in plain text.

16.1.2 General information on selected guidelines

16.1.2.1 Selected guidelines

The selected guidelines and their abbreviations as used in this report can be found in Table 424.

Abbreviation	Guideline
BAPCOC 2012{BAPCOC, 2012 #3}	BAPCOC - Belgische gids voor anti-infectieuze behandeling in de ambulante praktijk; editie 2012/ Guide Belge des traitements anti-infectieux en pratique ambulatoire; édition 2012

Table 424: Selected guidelines and their abbreviations as used in this report.

16.1.2.2 Grades of recommendation

Grades of recommendation and levels of evidence as defined in each guideline, can be found in table Table 425.

BAPCOC 2012		
Grades of recommendation:	1	Strong recommendation
	2	Weak recommendation
Levels of evidence	A	High degree of evidence; RCTs without limitations or strong, compelling evidence from observational studies
	B	Medium level of evidence; RCTs with limitations or strong evidence from observational studies
	C	(very) low degree of evidence; observational studies or case studies

Table 425: Grades of recommendation and Level of evidence of NICE CKD 2014 guideline.

16.1.2.3 Agree II score

Information about the Agree II score can be found in the section "Methodology".

A summary of the assessment by the literature group of the individual items of the domain score for each guideline can be found in Table 426. The total domain score is also reported in this table.

Rigour of development item	7	8	9	10	11	12	13	14	Total	Domain score
										%

Table 426: AGREE score of selected guidelines on item "Rigour of development", see 1.1.2.6 for a description of the items.

16.1.2.4 Included populations – interventions – main outcomes

In Table 427, the populations, interventions and main outcomes considered in the selected guidelines are represented.

BAPCOC 2012	
Population	Ambulant care patients (adults and children)
Interventions	Antibiotic treatment (indication, choice, dose, duration)
Outcomes	Not specified

Table 427: Included population, intervention and main outcomes of guideline.

16.1.2.5 Members of development group – target audience

Members of the development group that produced the guidelines, and the target audience for whom the guidelines are intended, can be found in Table 428.

BAPCOC 2012	
Development group	General practitioners, microbiologists, pneumologists, infectiologists, paediatricians, pharmacists
Target audience	Physicians working in ambulant care

Table 428: Members of the development group and target audience of the BAPCOC 2012 guideline

16.1.3 Definition

16.1.3.1 Summary

No information.

16.1.3.2 BAPCOC 2012

The guideline doesn't define this term.

16.1.4 Indications for antibiotic treatment

16.1.4.1 Summary

The BAPCOC 2012 always recommends an antibiotic treatment.

16.1.4.2 BAPCOC 2012

Antibiotic treatment is always indicated.

16.1.5 Choice of antibiotic, dose and duration

16.1.5.1 Summary

The BAPCOC 2012 guideline states that due to the difficulty of identifying the pathogen, experts have opted for cloxacillin or flucloxacillin as first choice, but the clinician can deviate from this if clinical symptoms make him suspect an infection through streptococcus,. In that case a penicillin is preferred. (Weak recommendation, low level of evidence)

16.1.5.2 BAPCOC 2012

First choice (GRADE 2C)

Because it is very difficult to identify solely on the base of clinical symptoms if an infection is due to streptococci or staphylococci, experts have opted for cloxacillin or flucloxacillin. If there are clinical signs to suspect a streptococcus infection, penicillin can be used. If after 48 hours there is no improvement, a switch to cloxacillin or flucloxacillin is warranted.

- **Phenoxymethylpenicillin: 1.5g (0,8 million IU) in 3 doses during 10 days**
- **Flucloxacillin: (child) 25-50 mg/kg per day in 4 doses during 10 days**

Alternative in case of IgE-mediated penicillin allergy (GRADE 1C):

- **Clindamycin: (child) 25 mg/kg per day in 3 to 4 doses during 10 days.**

16.1.6 Non-antibiotic treatment

16.1.6.1 Summary

No information was found in the guideline.

16.1.7 Referrals

16.1.7.1 Summary

The BAPCOC 2012 recommends hospitalization in case of degradation of general health.

16.1.7.2 BAPCOC 2012

Hospitalization is indicated in case of degradation of the general health.

16.2 Evidence tables and conclusions

16.2.1 Antibiotics versus placebo or no treatment for cellulitis or erysipelas

16.2.1.1 Clinical evidence profile

Systematic review: Morris 2008 {Morris, 2008 #210} “Cellulitis and erysipelas” Inclusion criteria: “published systematic reviews and RCTs in any language, at least single blinded and containing more than 20 individuals, of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies.We excluded all studies described as “open”, “open label”, or not blinded unless blinding was impossible.” Search strategy: searched: Medline, Embase, The Cochrane Library and other important databases up to May 2007 Assessment of quality of included trials: yes, GRADE evaluation Other methodological remarks: This systematic review included trials in both adults and children. We will only report the trials including children.

Table 429

This systematic review found no direct information about whether antibiotics are better than no active treatment.

16.2.1.2 Summary and conclusions

Antibiotics vs placebo or no treatment for cellulitis or erysipelas
Bibliography: Morris 2008 {Morris, 2008 #210}

Table 430

This systematic review found no direct information about whether antibiotics are better than no active treatment.

16.2.2 Antibiotic A versus antibiotic B for cellulitis and erysipelas

16.2.2.1 Clindamycin vs trimethoprim-sulfamethoxazole

16.2.2.1.1 Clinical evidence profile

"Clindaymycin versus trimethoprim-sulfamethoxazole for uncomplicated skin infections"

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Miller 2015{Miller, 2015 #209} Design: RCT DB; PG Duration of follow-up: 1 month	n= 524, including 155 children Age <1y; n=11 Age 1-8y: n=87 Age 9-17y: n=57 Age >18y: n=369 <u>Inclusion</u> Patients were eligible if they had two or more of the following signs or symptoms for 24 or more hours: erythema, swelling or induration, local warmth, purulent drainage, and tenderness to pain or palpation. Patients were categorized as having cellulitis (defined as	Clindamycin (25-30 mg/kg/day) for 10 days Vs Trimethoprim-sulfamethoxazole (8-10 mg trimethoprim/day) for 10 days	Efficacy		RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (not described) BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Lost-to follow-up: 9.5 % Drop-out and Exclusions: 9.5 % • Described: yes • Balanced across groups: unclear ITT: Yes SELECTIVE REPORTING: no
			clinical cure 7 to 10 days after the end of treatment (PO)	Clindamycin: 70/81 Cotrimoxazole: 60/74 Risk difference: -5.3 (-18.6 to 7.9) NS	
			SUBGROUP CHILDREN	P= 0.39	

	inflammation of the skin and associated skin structures without signs of a drainable fluid collection), abscess (defined as a circumscribed, drainable collection of pus), or both (if lesions of both cellulitis and abscess were present). <u>Exclusion</u> superficial skin infections (e.g., impetigo), skin infection at a body site that requires specialized management (e.g., perirectal, genital, or hand infection), a human or animal bite at the infection site, high fever (oral temperature, >38.5°C [>38.0°C in children 6 to 11 months of age]), receipt of immunosuppressive medications or the presence of an immunocompromising condition such as diabetes or chronic renal			Sponsor: Supported by grants from the National Institutes of Allergy and Infectious Diseases and the National Center for Research Resources

	failure, morbid obesity (body-mass index [the weight in kilograms divided by the square of the height in meters], >40), surgical-site or prosthetic-device infection, and receipt of antibacterial therapy with antistaphylococcal activity in the previous 14 days. Patients were ineligible if they lived in a long-term care facility, had cancer or an inflammatory disorder that required treatment in the previous 12 months, or had major surgery in the previous 12 months.			

Table 431

16.2.2.1.2 Summary and conclusions

Clindamycin versus trimethoprim-sulfamethoxazole for uncomplicated skin infections			
Bibliography: Miller 2015{Miller, 2015 #209}			
Outcomes	**N° of participants (studies) Follow up**	**Results (95%CI)**	**Quality of the evidence (GRADE)**
clinical cure 7 to 10 days after the end of treatment	155 (1 study) Subgroup children	Risk difference: -5.3 (-18.6 to 7.9) NS	⨁⨁⨁⨀: **MODERATE** Study quality:-1 (unclear rando, allocation concealment) Consistency: na Directness: ok Imprecision: ok

Table 432

In this double blind RCT, a treatment with clindamycin was compared to cotrimoxazole in patients with cellulitis or abcesses.

This trial included children and adults. A subgroup analysis in children (<18y) was performed.

Clindamycin was given in a dose of 25-30 mg/kg/day for 10 days.
Cotrimoxazole was given in a dose of 8-10 mg/day (trimethoprim portion) for 10 days.

As this is only one study with a relatively small sample size, our confidence in the results is limited.

In children *with cellulitis or abcesses*, a treatment with clindamycin for 10 days, compared to cotrimoxazole for 10 days **did not** result in a statistically significant difference in *clinical cure 7 to 10 days after the end of treatment*.
GRADE: MODERATE quality of evidence

17 Conjunctivitis

17.1 Guidelines

17.1.1 Method of reporting of the recommendations and notes

Formal recommendations, that are supplied with grades of recommendations or levels of evidence, are written in **bold**.

Text taken directly from the guidelines, that is not graded but provides supplemental information or a clarification of the formal recommendations, is written in *italics*.

Comments by the bibliography group are written in plain text.

17.1.2 General information on selected guidelines

17.1.2.1 Selected guidelines

The selected guidelines and their abbreviations as used in this report can be found in Table 433.

Abbreviation	Guideline
BAPCOC 2012{BAPCOC, 2012 #3}	BAPCOC - Belgische gids voor anti-infectieuze behandeling in de ambulante praktijk; editie 2012/ Guide Belge des traitements anti-infectieux en pratique ambulatoire; édition 2012
AAoO conjunctivitis 2013{American Academy of Ophtalmology, 2013 #2}	American Academy of Ophthalmology – Preferred Practice Pattern Conjunctivitis ; 2013

Table 433: Selected guidelines and their abbreviations as used in this report

17.1.2.2 Grades of recommendation

Grades of recommendation and levels of evidence as defined in each guideline, can be found in table Table 434 to Table 435.

BAPCOC 2012		
Grades of recommendation:	1	Strong recommendation
	2	Weak recommendation
Levels of evidence	A	High degree of evidence; RCTs without limitations or strong, compelling evidence from observational studies

	B	Medium level of evidence; RCTs with limitations or strong evidence from observational studies
	C	(very) low degree of evidence; observational studies or case studies

Table 434: Grades of recommendation and levels of evidence of BAPCOC 2012 guideline

AAoO conjunctivitis 2013	
Individual studies are rated on a scale based on SIGN	
I++	Hig-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
I+	Well-conducted meta-analysis, systematic reviews of randomized controlled trials, or RCT with a low risk of bias
I-	Meta-analysis, systematic reviews of RCTs, or RCTs with a high risk of bias
II++	High-quality systematic reviews of case-control or cohort studies
II+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is casual
II-	case-control or cohort study with a high risk of confounding or bias and a significant risk that the relationship is not casual
III	Nonanalytic studies (e.g. case reports, case series)
Recommendations for care are formed based on the body of evidence. The body of evidence quality ratings are defined by GRADE as follows:	
Good quality	Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Insufficient quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is very uncertain.
Key recommandations for care are defined by GRADE as follows:	
Strong recommendation	Used when the desirable effects of an intervention clearly outweigh the undesirable effects or clearly not
Discretionary recommendation	Used when the trade-offs are less certain – either because of low-quality evidence or because evidence suggest that desirable and undesirable effects are closely balanced.

Table 435: Grades of recommendation and Level of evidence of AAoO conjunctivitis 2013 guideline

17.1.2.3 Agree II score

Information about the Agree II score can be found in the section “Methodology”.

A summary of the assessment by the literature group of the individual items of the domain score for each guideline can be found inTable 436. The total domain score is also reported in this table.

Rigour of development item	7	8	9	10	11	12	13	14	Total	Domain score
AAoO Conjunctivitis 2013	6	2	4	5	5	5	5	4	**36**	**64%**

Table 436: AGREE score of selected guidelines on item "Rigour of development", see 1.1.2.6 for a description of the items.

17.1.2.4 Included populations – interventions – main outcomes

In Table 437 to Table 438 , the populations, interventions and main outcomes considered in the selected guidelines are represented.

BAPCOC 2012	
Population	Ambulant care patients (adults and children)
Interventions	Antibiotic treatment (indication, choice, dose, duration)
Outcomes	Not specified

Table 437

AAoO conjunctivitis 2013	
Population	Individuals of all ages who present with symptoms and signs suggestive of conjunctivitis, such as red eye or discharge.
Interventions	Diagnosis, Diagnostic tests, prevention, treatment, provider and setting, counseling and referral, socioeconomic considerations
Outcomes	Patient outcome criteria: - Eliminate or reduce signs and symptoms of conjunctivitis - Restore or maintain normal visual function - Detect and treat the underlying systemic disease process when applicable - Prevent or reduce the likelihood of damage to the ocular surface

Table 438: Included population, intervention and main outcomes of guideline.

17.1.2.5 Members of development group – target audience

Members of the development group that produced the guidelines, and the target audience for whom the guidelines are intended, can be found in Table 439.

AAoO conjunctivitis 2013	
Development group	Cornea/External Disease preferred practice pattern panel members (all MDs except one methodologist, no further information given)
Target audience	No statement found

Table 439: Members of the development group and target audience of the BAPCOC 2012 guideline

17.1.3 Definition

17.1.3.1 Summary

The AAoO conjunctivitis 2013 guideline defines the term as an inflammation that affects the conjunctiva primarily.

17.1.3.2 BAPCOC 2012

The guideline doesn't define this term.

17.1.3.3 AAoO Conjunctivitis 2013

Conjunctivitis is an inflammation that affects the conjunctiva primarily.

17.1.4 Indications for antibiotic treatment

17.1.4.1 Summary

The BAPCOC 2012 guideline mentions that an antibiotic treatment against bacterial conjunctivitis is effective (strong recommendation, moderate levels of evidence) while the AAoO on the other hand mentions that mild bacterial conjunctivitis is usually self-limiting (also strong recommendation, but with high levels of evidence). However, the AAoO, while warning against indiscriminate use of topical antibiotics, also says that a topical antibacterial therapy is associated with earlier clinical and microbiological remission (Strong recommendation, high levels of evidence).
The AAoO conjunctivitis 2013 guideline also mentions that for conjunctivitis caused by certain sexually transmissible pathogens (n. gonorrhea and chlamydia) systemic antibiotic therapy is necessary (strong recommendation, high levels of evidence).

17.1.4.2 BAPCOC 2012

A local treatment with antibiotics is effective in proven cases of bacterial conjunctivitis (GRADE 1B) and probably also in case of suspected bacterial conjunctivitis – eyes glued shut in the morning, no itching, no previous conjunctivitis (GRADE 2C).

17.1.4.3 AAoO Conjunctivitis 2013

Indiscriminate use of topical antibiotics or corticosteroids should be avoided, because antibiotics can induce toxicity and corticosteroids can potentially prolong adenoviral infections and worsen herpes simplex virus infections. Viral conjunctivitis will not respond to anti-bacterial agents, and mild bacterial conjunctivitis is likely to be self-limited.
(Good, Strong)

Mild bacterial conjunctivitis is usually self-limited and typically resolves spontaneously without specific treatment in immune-competent adults (Good, Strong).

Use of topical antibacterial therapy is associated with earlier clinical and microbiological remission compared with placebo in days 2 to 5 of treatment (Good, Strong).

Systemic antibiotic therapy is necessary to treat conjunctivitis due to *Neisseria Gonorrhea* and *Chlamydia trachomatis* (Insufficient, Discretionary).

17.1.5 Choice of antibiotic, dose and duration

17.1.5.1 Summary

The AAoO conjunctivitis guideline doesn't recommend a specific option, but states that the most convenient broad-spectrum topical antibiotic can be used. The BAPCOC 2012 guideline recommends chlortetracycline or fusidic acid eye ointments. Both recommendations have low strength of recommendations and low levels of evidence.
For the pathogens in which systemic antibiotic therapy is indicated (see above "indications for AB treatment"), the AAoO guideline also doesn't recommend a specific one, stating that empirical therapy can be considered.

17.1.5.2 BAPCOC 2012

- Chlortetracycline eye ointment (GRADE 2C)
4 to 6 applications a day until 48 hours after recovery
- Fusidic acid eye ointment (GRADE 2C)
4 to 6 applications a day until 48 hours after recovery

17.1.5.3 AAoO conjunctivitis 2013

Because a 5-to-7 days course of a broad-spectrum topical antibiotic is usually effective, the most convenient or least expensive option can be selected (Insufficient, Discretionary)

Empiric antibiotic therapy can be considered in patients with symptoms and signs highly suggestive of chlamydia (Insufficient, Discretionary).

17.1.6 Non-antibiotic treatment

17.1.6.1 Summary

The AAoO conjunctivitis 2013 guideline mentions saline lavage in case of a gonococcal conjunctivitis. Artificial tears, topical antihistamines or cold compresses can be used to mitigate symptoms in adenoviral conjunctivitis.

17.1.6.2 BAPCOC 2012

No information found in the guideline.

17.1.6.3 AAoO conjunctivitis 2013

Saline lavage may promote comfort and more rapid resolution of inflammation in gonococcal conjunctivitis.

In the case of adenoviral conjunctivitis, artificial tears, topical antihistamines or cold compresses may be used to mitigate symptoms. (Insufficient, discretionary)

17.1.7 Referrals

17.1.7.1 Summary

The AAoO Conjunctivitis 2013 guideline states that most patients can be treated in outpatient treatment. Neonates however need to be hospitalized.
A referral to an ophthalmologist is indicated in case of visual loss, moderate or severe pain, severe discharge, corneal involvement, conjunctival scarring, recurrent episodes, history of Herpes Simplex eye diseases, or being immunocompromised.
All those recommendations are weak, with low levels of evidence.

17.1.7.2 BAPCOC 2012

No information found in the guideline.

17.1.7.3 AAoO Conjunctivitis 2013

Patients with conjunctivitis who are evaluated by non-ophthalmologist health care providers should be referred promptly to the ophthalmologist when visual loss, moderate or severe pain, severe, purulent discharge, corneal involvement, conjunctival scarring, lack of response to therapy, recurrent episodes, history of HSV (herpes simplex virus) **eye disease, or history of immunocompromised occur. (Insufficient, discretionary)**

A majority of patients with conjunctivitis can be treated effectively in outpatient setting. (Insufficient, Discretionary)

Hospitalization may be necessary to administer parenteral therapy for sever gonococcal conjunctivitis and is mandatory for neonatal conjunctivitis. (Insufficient, Discrectionary)

17.2 Evidence tables and conclusions

17.2.1 Antibiotics versus placebo or no treatment for conjunctivitis

17.2.1.1 Oral antibiotics versus placebo or no treatment for conjunctivitis

17.2.1.1.1 Clinical evidence profile

Systematic review: Epling 2012{Epling, 2012 #211} ”Bacterial conjunctivitis” Inclusion criteria: “[we] aimed to answer the following clinical questions: What are the effects of empirical treatment in adults and children with suspected bacterial conjunctivitis? What are the effects of treatment in adults and children with bacteriologically confirmed bacterial conjunctivitis? What are the effects of treatment in adults and children with clinically confirmed gonococcal conjunctivitis?” “published systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing >20 individuals of whom >80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits” Search strategy: Medline 1966 to August 2011, Embase 1980 to August 2011, and The Cochrane Database of Systematic Reviews, July 2011 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA).We also searched for retractions of studies included in the review Assessment of quality of included trials: GRADE evaluation for outcomes, not every individual trial assessed Other methodological remarks: This SR included trials in children and adults. No meta-analysis was performed. We will report only the RCTs performed in an exclusively pediatric population, or in a mixed population if a subgroup analysis in children exists, and pertaining to antibiotics which are available in Belgium.

Table 440

This systematic review found no RCTs for this comparison.

17.2.1.1.2 Summary and conclusions

Oral antibiotics versus placebo or no treatment for suspected or confirmed bacterial conjunctivitis
Bibliography: Epling 2012{Epling, 2012 #211}

Table 441

This meta-analysis sought SRs and RCTs that compared a treatment with oral antibiotics with placebo or no treatment for suspected or confirmed bacterial conjunctivitis.

No SRs or RCTs were found.

17.2.1.2 Topical chloramphenicol versus placebo or no treatment for conjunctivitis

17.2.1.2.1 Clinical evidence profile

Chloramphenicol versus placebo for suspected bacterial conjunctivitis

Systematic review: Sheikh 2012{Sheikh, 2012 #212} "Antibiotics versus placebo for acute bacterial conjunctivitis"
Inclusion criteria:
"Double-masked randomised controlled trials (RCTs) in which any form of antibiotic treatment had been compared with placebo/vehicle in the management of acute bacterial conjunctivitis. This included topical, systemic and combination (for example, antibiotics and steroids) antibiotic treatments. Participants were people with acute bacterial conjunctivitis, aged one month or older. The diagnosis of bacterial conjunctivitis may have been on clinical or microbiological grounds. 'Acute' was defined as symptoms of less than four weeks duration."
Search strategy:
"We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (The Cochrane Library 2012, Issue 7), MEDLINE (January 1950 to July 2012), EMBASE (January 1980 to July 2012), Open Grey (System for Information on Grey Literature in Europe) (www.opengrey.eu/), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) www.who.int/ictrp/search/en).We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 18 July 2012"
Assessment of quality of included trials: yes
Other methodological remarks: This systematic review and meta-analysis included trials in children and adults. It did not perform subanalyses for a pediatric population. We only reported the trials with a purely pediatric population, or in which a subanalysis in children was available, and pertaining to antibiotics available in Belgium.

Table 442

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Sheikh 2012{Sheikh, 2012 #212	**Chloramphenicol versus placebo**	N=1 n=326	**Clinical remission (early)** days two to five post-intervention	Crude AR: 123/163 vs 107/163 RR: 1.15 (1.00 to 1.32) NS

		N=1 n=326	**Clinical remission (late)** days six to 10 post-intervention	Crude AR: 140/163 vs 128/163 RR: 1.09 (0.99 to 1.21) NS

Table 443

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology scored by authors of review
Rose 2005{Rose, 2005 #239}	326	6 months to 12 years Clinical diagnosis of infective conjunctivitis	6 weeks	Treatment: chloramphenicol 0.5% Control: placebo	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk BLINDING OF PARTICIPANTS AND PERSONNEL Low risk BLINDING OF OUTCOME ASSESSMENT Low risk INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Low risk OTHER BIAS Low risk

Table 444

17.2.1.2.2 Summary and conclusions

Chloramphenicol versus placebo for suspected bacterial conjunctivitis			
Bibliography: Sheikh 2012{Sheikh, 2012 #212}			
Outcomes	**N° of participants (studies) Follow up**	**Results (RR(95%CI))**	**Quality of the evidence (GRADE)**
Clinical remission (early)	326 (1 study)	RR: 1.15 (1.00 to 1.32) NS	⨁⨁⨁⨁**:HIGH** Study quality:ok Consistency: na Directness: ok Imprecision: ok
Clinical remission (late)	326 (1 study)	RR: 1.09 (0.99 to 1.21) NS	⨁⨁⨁⨁**:HIGH** Study quality:ok Consistency: na Directness: ok Imprecision: ok

Table 445

In this meta-analysis, a treatment with topical chloramphenicol was compared to placebo for infective conjunctivitis.

One study was found, which included children aged 6 months to 12 years, with a clinical diagnosis of infective conjunctivitis. They were followed for 6 weeks.

Chloramphenicol 0.5% eye drops were instilled every 2 hours for the first 24 hours when the child was awake, and then 4 times daily until 48 hours after the infection had resolved.

In children *with suspected bacterial conjunctivitis*, a treatment with topical chloramphenicol, compared to placebo, **did not** result in a statistically significant difference in *early or late clinical remission*.

GRADE: HIGH quality of evidence

17.2.2 Topical AB A versus topical AB B in suspected bacterial conjunctivis

17.2.2.1 Moxifloxacin vs ofloxacin in suspected bacterial conjunctivis

17.2.2.1.1 Clinical evidence profile

Systematic review: Epling 2012{Epling, 2012 #211} "Bacterial conjunctivitis" Inclusion criteria: "[we] aimed to answer the following clinical questions: What are the effects of empirical treatment in adults and children with suspected bacterial conjunctivitis? What are the effects of treatment in adults and children with bacteriologically confirmed bacterial conjunctivitis? What are the effects of treatment in adults and children with clinically confirmed gonococcal conjunctivitis?" "published systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing >20 individuals of whom >80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits" Search strategy: Medline 1966 to August 2011, Embase 1980 to August 2011, and The Cochrane Database of Systematic Reviews, July 2011 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA).We also searched for retractions of studies included in the review Assessment of quality of included trials: GRADE evaluation for outcomes, not every individual trial assessed Other methodological remarks: This SR included trials in children and adults. No meta-analysis was performed. We will report only the RCTs performed in an exclusively pediatric population, or in a mixed population if a subgroup analysis in children exists, and pertaining to antibiotics which are available in Belgium.

Table 446

This systematic review found one systematic review that compared topical moxifloxacin versus topical ofloxacin. It found no significant difference between ofloxacin and moxifloxacin in treatment failure (1 RCT, 521 people; OR 1.81 (95%CI 0.38 to 4.12).

The Clinical Evidence review did not provide further details and we could not find this systematic review, nor the RCT it referenced, in the libraries of Ugent, KUL or ULB. Therefore, we do not know whether this RCT included children and we cannot score its methodology.

17.2.2.1.2 Summary and conclusions

Topical moxifloxacin versus topical ofloxacin for suspected bacterial conjunctivitis
Bibliography: Epling 2012{Epling, 2012 #211}

Table 447

This systematic review found one systematic review that compared topical moxifloxacin versus topical ofloxacin. It found no significant difference between ofloxacin and moxifloxacin in treatment failure (1 RCT, 521 people; OR 1.81 (95%CI 0.38 to 4.12).

The Clinical Evidence review did not provide further details and we could not find this systematic review, nor the RCT it referenced, in the libraries of Ugent, KUL or ULB. Therefore, we do not know whether this RCT included children and we cannot score its methodology.

17.2.2.2 Fusidic acid vs chloramphenicol in suspected bacterial conjunctivis

17.2.2.2.1 Clinical evidence profile

Systematic review: Epling 2012{Epling, 2012 #211} "Bacterial conjunctivitis"
Inclusion criteria:
"[we] aimed to answer the following clinical questions: What are the effects of empirical treatment in adults and children with suspected bacterial conjunctivitis? What are the effects of treatment in adults and children with bacteriologically confirmed bacterial conjunctivitis? What are the effects of treatment in adults and children with clinically confirmed gonococcal conjunctivitis?"
"published systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing >20 individuals of whom >80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits"
Search strategy: Medline 1966 to August 2011, Embase 1980 to August 2011, and The Cochrane Database of Systematic Reviews, July 2011 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA).We also searched for retractions of studies included in the review
Assessment of quality of included trials: GRADE evaluation for outcomes, not every individual trial assessed
Other methodological remarks: This SR included trials in children and adults. No meta-analysis was performed. We will report only the RCTs performed in an exclusively pediatric population, or in a mixed population if a subgroup analysis in children exists, and pertaining to antibiotics which are available in Belgium.

Table 448

Intervention	Number of participants	Age of participants	Proportion culture-positive	Microbiological cure rate	Clinical cure rate	Adverse effects
Fusidic acid 1% viscous drops twice daily *v* chloramphenicol 0.5% drops 4-hourly [37]	541	Over 1 year	17% culture-positive	Not reported	Success of treatment, assessed by investigator: 96% with fusidic acid *v* 97% with chloramphenicol cured; P = 0.56 Complete absence of symptoms: 71% with fusidic acid *v* 77% with chloramphenicol; P = 0.14	Bad taste: 11% with fusidic acid *v* 37% with chloramphenicol; P = 0.001
Fusidic acid 1% viscous drops twice daily after loading dose *v* chloramphenicol 0.5% drops 6 times daily after loading dose [38]	340	Adults and children (ratio not specified)	161/340 (47%) culture-positive	Not reported	>90% cured/improved; median: 6.6 days with fusidic acid *v* 6.2 days with chloramphenicol; no significant difference between fusidic acid and chloramphenicol	Itching, burning, blurred vision, bad taste: 31% with fusidic acid *v* 16% with chloramphenicol

Fusidic acid 1% suspension in carbomer gel twice daily after loading dose *v* chloramphenicol 0.5% drops 5 to 6 times daily after loading dose [39]	250	221 adults (16–89 years), 29 children (1–14 years)	Not all culture-confirmed	Not reported	Cured: 84% with fusidic acid *v* 81% with chloramphenicol (mean: 3.3 days with fusidic acid *v* 3.6 days with chloramphenicol); P = NS	Mild to moderate itching, stinging, local discomfort: 5% with fusidic acid *v* 14% with chloramphenicol
Fusidic acid viscous drops 1% twice daily for 5 to 7 days *v* chloramphenicol 1% ointment 3-hourly [41]	505 recruited; 16 lost to follow-up	1 to 90 years	27% of 486 culture-positive for pathogenic bacteria	Not reported	83% with fusidic acid *v* 84% with chloramphenicol; P = NS	Smarting, irritation, stinging, red eye, blurred vision: 15% with fusidic acid *v* 11% with chloramphenicol; treatment discontinuation because of adverse effects greater with chloramphenicol (P <0.01)

Figure 24 study details, as evaluated by Epling 2012

37: Carr 1998{Carr, 1998 #238}; 38: Horven 1993{Horven, 1993 #231}; 39: Hvidberg 1987{Hvidberg, 1987 #232}; 41: Sinclair 1988{Sinclair, 1988 #237}

Remarks: No RCTs in a purely pediatric population. In 4 RCTs inclusion of children as well as adults. No subgroup analyses for children. Ratio of children unknown.

The Clinical Evidence review did not provide further details and we could not find these RCTs in the libraries of Ugent, KUL or ULB. Therefore, we cannot score their methodology.

17.2.2.2.2 Summary and conclusions

Topical fusidic acid versus topical chloramphenicol for suspected bacterial conjunctivitis
Bibliography: Epling 2012{Epling, 2012 #211}

Table 449

In this systematic review, RCTs that compared two topical antibiotic treatments for suspected bacterial conjunctivitis were sought.

4 RCTs that included children were found for this comparison. None of these RCTs included a purely pediatric population. There were no subgroup analyses for children. The ratio of children in these RCTs is unknown.

All 4 RCTs reported no statistically significant difference between fusidic acid and chloramphenicol in clinical cure rate.

The Clinical Evidence review did not provide further details and we could not find these RCTs in the libraries of Ugent, KUL or ULB. Therefore, we cannot score their methodology.

17.2.3 Topical AB A versus topical AB B in confirmed bacterial conjunctivitis

17.2.3.1 Ciprofloxacin vs tobramycin in confirmed bacterial conjunctivitis

17.2.3.1.1 Clinical evidence profile

Systematic review: Epling 2012{Epling, 2012 #211} "Bacterial conjunctivitis"
Inclusion criteria:
"[we] aimed to answer the following clinical questions: What are the effects of empirical treatment in adults and children with suspected bacterial conjunctivitis? What are the effects of treatment in adults and children with bacteriologically confirmed bacterial conjunctivitis? What are the effects of treatment in adults and children with clinically confirmed gonococcal conjunctivitis?"
"published systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing >20 individuals of whom >80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits"
Search strategy: Medline 1966 to August 2011, Embase 1980 to August 2011, and The Cochrane Database of Systematic Reviews, July 2011 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA).We also searched for retractions of studies included in the review
Assessment of quality of included trials: GRADE evaluation for outcomes, not every individual trial assessed
Other methodological remarks: This SR included trials in children and adults. No meta-analysis was performed. We will report only the RCTs performed in an exclusively pediatric population, or in a mixed population if a subgroup analysis in children exists, and comparing antibiotics which are available in Belgium.

Table 450

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Epling 2012{Epling, 2012 #211}	Ciprofloxacin drops vs tobramycin drops	N=1 n=141 (Gross 1997)	**Clinical cure rate on day 7** *(not defined)*	87% vs 90% NS P=0.6

		N=1 n=257 (Gross 1997)	**Adverse effects**	3 people in each group had adverse effects (dry eye, pruritus, lid oedema, leukoderma, hyperaemia) 2 people using tobramycin withdrew as a result

Table 451

* Characteristics of included studies: see below

Intervention	Number of participants	Age of participants	Proportion culture-positive	Microbiological cure rate	Clinical cure rate	Adverse effects
Confirmed bacterial conjunctivitis						
Ciprofloxacin 0.3% drops 2-hourly for 2 days then 4 times daily for 5 more days *v* tobramycin drops 2-hourly for 2 days then 4 times daily for 5 more days [59]	257 (only 141 evaluated for efficacy, but all evaluated for safety)	0 to 12 years	100% culture-positive	Eradicated: 90% with ciprofloxacin *v* 84% with tobramycin; P = 0.29	Cured by investigator assessment on day 7: 87% with ciprofloxacin *v* 90% with tobramycin (P = 0.6)	3 people in each group had adverse effects (dry eye, pruritus, lid oedema, leukoderma, hyperaemia; significance not calculated); 2 people using tobramycin withdrew as a result

59: Gross 1997{Gross, 1997 #235}

The Clinical Evidence review did not provide further details and we could not find this RCT in the libraries of Ugent, KUL or ULB. Therefore, we cannot score its methodology.

17.2.3.1.2 Summary and conclusions

Topical ciprofloxacin versus topical tobramycin for confirmed bacterial conjunctivitis			
Bibliography: Epling 2012{Epling, 2012 #211}			
Outcomes	**N° of participants (studies) Follow up**	**Results (95%CI)**	**Quality of the evidence (GRADE)**
Clinical cure rate on day 7	141 (1 study)	87% vs 90% NS P=0.6	*Insufficient data*
Adverse effects	257 (1 study)	3 people in each group had adverse effects (dry eye, pruritus, lid oedema, leukoderma, hyperaemia) 2 people using tobramycin withdrew as a result	*Insufficient data*

Table 452

In this systematic review, RCTs comparing two topical antibiotic treatments for confirmed bacterial conjunctivitis were sought.

One study that compared topical ciprofloxacin with topical tobramycin in a pediatric population was found. The children were 0 to 12 years old.

They were either treated with ciprofloxacin 0.3% eye drops every 2 hours for 2 days, then 4 times daily for 5 more days, or with tobramycin drops every 2 hours for 2 days, then 4 times daily for 5 more days.

The Clinical Evidence review did not report a methodological assessment of this study, and we could not find this RCT in the libraries of Ugent, KUL or ULB. Therefore, we cannot score its methodology.

In children *with confirmed bacterial conjunctivitis*, a treatment with topical ciprofloxacin, compared to topical tobramycin, **did not** result in a statistically significant difference in *clinical cure rate*.
GRADE: Insufficient data

17.2.3.2 Fusidic acid vs chloramphenicol in confirmed bacterial conjunctivitis

17.2.3.2.1 Clinical evidence profile

Systematic review: Epling 2012{Epling, 2012 #211} "Bacterial conjunctivitis"
Inclusion criteria:
"[we] aimed to answer the following clinical questions: What are the effects of empirical treatment in adults and children with suspected bacterial conjunctivitis? What are the effects of treatment in adults and children with bacteriologically confirmed bacterial conjunctivitis? What are the effects of treatment in adults and children with clinically confirmed gonococcal conjunctivitis?"
"published systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing >20 individuals of whom >80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits"
Search strategy: Medline 1966 to August 2011, Embase 1980 to August 2011, and The Cochrane Database of Systematic Reviews, July 2011 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA).We also searched for retractions of studies included in the review
Assessment of quality of included trials: GRADE evaluation for outcomes, not every individual trial assessed
Other methodological remarks: This SR included trials in children and adults. No meta-analysis was performed. We will report only the RCTs performed in an exclusively pediatric population, or in a mixed population if a subgroup analysis in children exists, and pertaining to antibiotics which are available in Belgium.

Table 453

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Epling 2012{Epling, 2012 #211}	Fusidic acid gel vs chloramphenicol drops	N=1 n=139	**Clinical cure rate** *(not defined)*	**85% vs 48%** **SS** **P<0.0001**
		N=1 n=139	**Adverse events**	No adverse events associated with treatment reported by participants

Table 454

* Characteristics of included studies: see below

Intervention	Number of participants	Age of participants	Proportion culture-positive	Microbiological cure rate	Clinical cure rate	Adverse effects
Confirmed bacterial conjunctivitis						
Fusidic acid 1% gel *v* chloramphenicol 0.5% drops 4 to 6 times daily for 7 days [58]	139 (114 with fusidic acid *v* 25 with chloramphenicol) (248 total, but only the 139 culture-positive patients used to calculated success rates)	Up to 15 years	100% culture-positive (56% of the total 248)	Not reported (resistance: 16% with fusidic acid *v* 55% with chloramphenicol; statistical analysis not provided)	85% with fusidic acid *v* 48% with chloramphenicol; P <0.0001	No adverse events associated with treatment reported by participants

Figure 25 study details, as evaluated by Epling 2012

58: van Bijsterveld 1987{van Bijsterveld, 1987 #236}

Remarks:

The Clinical Evidence review did not provide further details and we could not find this RCT in the libraries of Ugent, KUL or ULB. Therefore, we cannot score its methodology.

17.2.3.2.2 Summary and conclusions

Topical fusidic acid versus topical chloramphenicol for confirmed bacterial conjunctivitis			
Bibliography: Epling 2012{Epling, 2012 #211}			
Outcomes	**N° of participants (studies) Follow up**	**Results (95%CI)**	**Quality of the evidence (GRADE)**
Clinical cure rate	139 (1 study)	**85% vs 48%** **SS** **P<0.0001** **(Higher clinical cure rate with fusidic acid)**	*Insufficient data*
Adverse effects	139 (1 study)	No adverse events associated with treatment reported by participants	*Insufficient data*

Table 455

In this systematic review, RCTs comparing two topical antibiotic treatments for confirmed bacterial conjunctivitis were sought.

One study that compared topical fusidic acid with topical chloramphenicol in a pediatric population was found. The children were up to 15 years old.

They were either treated with fusidic acid 1% gel, or with chloramphenicol 0.5% drops 4-6 times a day for 7 days.

The Clinical Evidence review did not report a methodological assessment of this study, and we could not find this RCT in the libraries of Ugent, KUL or ULB. Therefore, we cannot score its methodology.

In children *with confirmed bacterial conjunctivitis*, a treatment with topical fusidic acid, compared to topical chloramphenicol, **did** result in a statistically significant **increase** in *clinical cure rate*.
GRADE: Insufficient data

18 Safety of Fluoroquinolones in children

18.1 Clinical evidence profile

18.1.1 Systematic reviews on the safety of fluoroquinolones

Systematic review: Adefurin 2011{Adefurin, 2011 #301} "Ciprofloxacin safety in paediatrics; a systematic review" Inclusion criteria: all published articles, regardless of design, that involved the use of ciprofloxacin in any paediatric age group ≤17 years Search strategy: A systematic search of MEDLINE, EMBASE, CINAHL, CENTRAL and bibliographies of relevant articles was carried out Assessment of quality of included trials: no Other methodological remarks:

Table 456

Adefurin 2011{Adefurin, 2011 #301}					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results**
Design: SR Search date: (11/2009)	N= 105 (all types of studies, **of which 15 RCTs and 12 cohort studies**) n= 16 184 exposed to ciprofloxacin	children =< 17y	ciprofloxacin* use (no comparator)	Any adverse event	**AR: 7% (95% CI 3.2% to 14.0%)** The most frequent AEs were musculoskeletal problems, abnormal liver function tests, nausea, changes in white blood cell counts and vomiting
				Musculoskeletal events	**AR: 1.6%, (95% CI 0.9% to 2.6%)** **SS** **(more musculoskeletal events with ciprofloxacin)**

	Pooled safety data of controlled trials and cohort studies N=23 n= 6 481 cases and 17 441 controls		ciprofloxacin* use vs other antibiotic use	Arthropathy	**OR 1.57 (95% CI 1.26 to 1.97)** **SS (more arthropathy with ciprofloxacin)**
*studies that evaluated fluoroquinolones as a class were also included					

Table 457

Systematic review: Kaguelidou 2011{Kaguelidou, 2011 #302} "Ciprofloxacin use in neonates: a systematic review of the literature"

Inclusion criteria: all published articles, regardless of design, that reported efficacy and safety of ciprofloxacin in neonates

Search strategy: A systematic search of MEDLINE, EMBASE, Cochrane Database of Systematic Reviews and bibliographies of relevant articles

Assessment of quality of included trials: no

Other methodological remarks:

Kaguelidou 2011{Kaguelidou, 2011 #302}					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Design: SR Search date: (07/2009)	5 cohort studies, n=1000	Neonates with sepsis	Ciprofloxacin use vs other antibiotics	Musculoskeletal damage (clinical evaluation)	'no significant difference'

Table 458

A Spanish SR + MA by Rosanova 2011{Rosanova, 2010 #299} (not included in detail because of language reasons) studied the adverse musculoskeletal effects of fluoroquinolones. It found 3 RCTs and 5 observational studies with a total of 23166 patients. No statistically significant difference between fluoroquinolones and control (other antibiotics) was found (OR 1.02, 95% CI 0.76 to 1.38).

18.1.2 Additional RCT information on ciprofloxacin safety

"The use of systemic and topical fluoroquinolones"

Ref	Comparison	N/n	Outcomes	Result (95% CI)
US Food and Drug Administration. Drug approval package [ciprofloxacin]. Available at: www.accessdata.fda.gov/drugsatfda_docs/nda/2004/019537s49_19847s27_19857s31_20780s13TOC.cfm. Accessed by Bradley 2011 on June 30, 2010 (from: Bradley 2011{Bradley, 2011 #305}, Review)	Ciprofloxacin vs other antibiotic	RCTs in multiple countries, n=684	**Arthropathy (6 weeks)**	9.3% vs 6.0% ARI 3.3% (-0.8 to 7.2) non-inferiority trial: non-inferiority criterion of Cipro vs other antibiotics was not met
			Arthropathy (1 y)	13.7% vs 9.5% ARI 4.2% (-0.6 to 9.1) non-inferiority trial: non-inferiority criterion of Cipro vs other antibiotics was not met
			Neurologic adverse events	3% vs 2% 'similar'

Table 459

18.1.3 Additional RCTs on levofloxacin safety

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Noel 2007{Noel, 2007 #303} "Comparative safety profile of levofloxacin in 2523 children with a focus on four specific musculoskeletal disorders" (from: Bradley 2011{Bradley, 2011 #305}, Review)	levofloxacin vs other antibiotic	3 RCTs, n=2523	**Weight bearing joint disorders (2m)**	**1.9% vs 0.7%** **p=0.025** **SS more disorders with levofloxacin**
		unblinded 1y follow up: n=2233	**Weight bearing joint disorders (1y)**	**2.9%vs 1.6%** **p=0.047** **SS more disorders with levofloxacin** 85% of cases was joint pain, no structural abnormalities at 1y
Noel 2007{Noel, 2007 #303} (from: Bradley 2011{Bradley, 2011 #305}, Review)		3 RCTs, n=2523	**Neurologic adverse events**	'statistically similar'
Bradley 2014{Bradley, 2014 #300} 5y follow up (from Noel 2007)		n=207 children with tendon/joint abnormalities or diminished growth at 1 y follow-up	**musculoskeletal disorders** (including ongoing arthropathy, peripheral neuropathy, abnormal bone development, scoliosis, walking difficulty, myalgia, tendon disorder, hypermobility syndrome, and pain in the spine, hip, and shoulder)	2% vs 4% p-value not reported only 49% completed 5y follow-up No cases were assessed as 'likely related to study drug'

Table 460

18.2 Summary and conclusions

We found several systematic reviews that evaluate the safety of quinolones in children.
- A systematic review by Adefurin 2011{Adefurin, 2011 #301} collected all publications on **ciprofloxacin** (RCT, observational, case series…). From the pooled data of 23 (R)CTs and cohort studies, consisting of >23 000 patients, the calculated odds ratio for **arthropathy** with ciprofloxacin use versus other antibiotics was **1.57 (95%CI 1.26 to 1.97).** The author states that all cases of arthropathy resolved or improved with management.
- A systematic review by Kaguelidou 2011{Kaguelidou, 2011 #302} evaluated the safety of **ciprofloxacin in neonates** with sepsis. A pooled analysis from 5 cohort studies, consisting of 1000 children, found no significant difference between ciprofloxacin and other antibiotics for musculoskeletal damage. Most trials only did a clinical evaluation and did not have long-term follow-up.
- A systematic review by Rosanova 2011{Rosanova, 2010 #299} studied the adverse **musculoskeletal effects of fluoroquinolones**. It included 3 RCTs and 5 observational studies with a total of 23166 patients. No statistically significant difference between fluoroquinolones and control (other antibiotics) was found (OR 1.02, 95% CI 0.76 to 1.38). The inclusion criteria of this SR were stricter than for Adefurin 2011, but there was overlap in the studies they included.

We found additional information on ciprofloxacin safety from RCTs.
- FDA drug approval data on **ciprofloxacin** use in children were based on non-inferiority RCTs with a total of 684 children{Bradley, 2011 #305}. Compared to other antibiotics, the non-inferiority of ciprofloxacin for arthropathy at 6 weeks and at 1 year could not be established.
Neurologic adverse events were reported as 'similar'.

- We also found additional information on levofloxacin safety from RCTs.
A pooled analysis of 3 RCTs with a total of 2523 children by Noel 2007{Noel, 2007 #303} found more **disorders of weight-bearing joints** with **levofloxacin** compared to other antibiotics at 2 months (1.9% vs 0.7%, p=0.25) and at 1 year (2.9% vs 1.6%, p=0.047). At 1 year, 85% of these cases were joint pain. There were no cases of structural joint abnormalities.
207 of these children were followed up for a total of 5 years, because of certain joint abnormalities or diminished growth at 1 year. At 5 years, no significant difference in musculoskeletal disorders was found between levofloxacin-users and the users of other antibiotics (Bradley 2014{Bradley, 2014 #300}). No cases were assessed as 'likely related to the study drug'. However, only 49% of children completed the 5 year follow-up.

Conclusion:
There is some evidence of an increased risk of musculoskeletal disorders/arthropathy with the use of fluoroquinolones in children (low quality of evidence).

There is limited evidence that these adverse events are resolved with time and do not result in long-term musculoskeletal problems (very low quality of evidence).

19 Adverse effects of antibiotics and probiotics

- All antibacterial agents: diarrhea and yeast and fungal infections[10]
- Pseudomembranous colitis caused by proliferation of Clostridium difficile may occur following treatment with various antibiotics; more frequently with lincomycin and clindamycin[1]

19.1 Bèta-lactam antibiotics

- Acute interstitial nephritis[2]

19.1.1 Penicillins

- Allergic reactions, diarrhoea and candidiasis. [10]
- Allergy to penicillin :
    - Anaphylactic shock: 0.04% of all patients treated with penicillin. Less common after oral than parenteral administration. [11]
    - Only when there is a history of symptoms of anaphylaxis (<1 hour after ingestion) or symptoms such as urticaria, angioedema, hypotension, cardiac arrhythmia, laryngeal edema , and / or bronchospasm within 72 hours after ingestion, should a treatment with penicillin be withheld. [10]
    - In children, anaphylaxis after taking penicillin is even rarer.
    - Other, non- life-threatening reactions are type II (anemia or thrombocytopenia) or Type III (serum sickness) hypersensitivity reactions, and idiopathic reactions (maculopapular or morbilliform rash) [10]
    - Approximately 10 % of patients with IgE - mediated penicillin hypersensitivity is also allergic to cephalosporins of the first and second group; a cephalosporin of the third or fourth group- a monobactam or a carbapenem- can be administered to these patients[10]

19.1.1.1 Flucloxacilline

- Flucloxacillin is the most important cause of antimicrobial drug-induced hepatotoxicity in various countries. Estimated risk: 1 in 10000 to 1 in 30000 prescriptions. The hepatic injury is often severe and deaths have occurred. Female sex, increasing age, and duration and higher dose of therapy are risk factors. [11]

19.1.1.2 Oxacilline

- Oxacillin can cause hepatotoxicity. Incidence unknown. [11]

19.1.1.3 Aminopenicillines

- Dyspepsia and diarrhea , especially with high oral doses. [10]
- Patients who are allergic to other penicillins are also allergic to aminopenicillins, but the opposite is not necessarily true . [10]
- In addition to penicillin-allergy, there is also a risk with all aminopenicillins of maculopapular skin rash; This occurs more frequently in patients with infectious mononucleosis or lymphatic leukemia , and in concomitant treatment with allopurinol. [10]

19.1.1.3.1 Ampicilline

- Crystal precipitation with possible obstruction and interstitial reaction[2]

19.1.1.3.2 Amoxicilline

- A cohort study also suggest a link between the use of amoxicillin at an early age (especially before the age of 6 months) and the occurrence of tooth abnormalities (fluorosis , ie mottled tooth enamel) of the first permanent teeth (central teeth and first molars). The risk increased with the number of exposures to amoxicillin[3]

19.1.2 Cefalosporines

- Increased risk of nephrotoxicity in association with aminoglycosides or loop diuretics : rare.
- Disulfiram-like reaction with many cephalosporins in association with alcohol. [10]
- Virtually all cephalosporins can cause neutropenia and agranulocytosis. This has been associated with cefepime, ceftriaxone, and others. All of these cases were seen after high cumulative doses given in one treatment course. [11]
- Generalized pustular eruptions have been reported with different cephalosporins, such as cefaclor, cefazolin, cefalexin. The frequencies of rashes have been retrospectively investigated in 5923 children. 12.3% for cefaclor, 8.5% for sulfonamides, 7.4% for penicillins, and 2.6% for other cephalosporins. [11]

19.1.2.1.1 Ceftriaxon

- Intravenous ceftriaxone has been associated with autoimmune hemolytic anemia, *erythroblastocytopenia, and acute hepatitis. Of 10 patients with hemolysis due to ceftriaxone, seven died, six of them children*[11]
- *Ceftriaxone can displace bilirubin from its binding sites to albumin. Given the risk of bilirubin encephalopathy , it was decided that ceftriaxone should not be administered to premature babies and newborns with hyperbilirubinemia*[4]
- *Ceftriaxone , used in high doses or together with calcium-containing solutions, may lead to precipitation of ceftriaxone-calcium, which usually disappears after discontinuation of ceftriaxone . Rarely, formation of gallstones and kidney stones is reported , mainly in children; in some neonates (including premature infants), treated with ceftriaxone and calcium , the outcome was fatal, despite administration through different infusion lines and at different times. There is no data available about possible interactions between intravenous ceftriaxone and oral calcium or between intramuscular ceftriaxone and calcium orally or intravenously*[4]

19.2 Macrolides

19.2.1 Erythromycin

- Dyspepsia, abdominal pain. [10]
- Allergic reactions: rare . [10]
- Reversible elevated liver function tests ; rarely cholestatic hepatitis. [10]
- Ototoxicity in high doses . [10]
- Effects on central nervous system (psychotic reactions ,nightmares) . [10]
- QT prolongation with risk of torsades de pointes , particularly when erythromycin is too rapidly injected intravenously[10]

- Cardiovascular reactions are rare if macrolide antibiotics are used in the absence of susceptibility factors, which include drug interactions, increasing age, female sex, concomitant diseases, and co-morbidity[11]

19.2.2 Neomacrolides

- The adverse effects of the neo-macrolides resemble those of erythromycin, but the gastrointestinal adverse effects are less pronounced. [10]
- Prolongation of the QT interval and torsades de pointes have been described with clarithromycin and can not be ruled out for the other neo-macrolides[10]

19.2.2.1 Azithromycin

- In a prospective study of 47 previously healthy people, there was a modest statistically insignificant prolongation of the QTc interval without clinical consequences after the end of a course of azithromycin 3 g/day for 5 days[11]
- In a review of 12 clinical studies most of the adverse events in those taking azithromycin affected the gastrointestinal system, and were reported in 138 (8.5%) azithromycin-treated patients[11]

19.2.2.2 Clarithromycin

- Adverse events on the nervous system (in 3% of patients.) [11]
- Abnormal taste (17 of 175 patients treated with clarithromycin 250 mg bd for 10 days) [11]
- gastrointestinal disturbances : mild (in 13%) to moderate (in 11%) [11]
- Abnormal liver function tests (5%) and hepatomegaly [11]
- fixed drug eruptions and hypersensitivity reactions. [11]
- A cohort study evaluated the risk of cardiovascular mortality of clarithromycin and roxithromycin . Relative to penicillin V (2.5 deaths in 1,000 patients per year), there was a significantly increased risk of cardiovascular mortality with clarithromycin (5.3 deaths in 1,000 patients per year), but not with roxithromycin (2.5 deaths in 1,000 patients per year). Given the small number of cardiac deaths in this study these results are difficult to interpret[5]

19.2.2.3 Roxithromycin

- *In 304 infants and children under 14 years adverse effects occurred in 6.9%. Treatment was withdrawn in 10 children (two with vomiting, two diarrhea, and six rashes).* [11]
- *A cohort study evaluated the risk of cardiovascular mortality of clarithromycin and roxithromycin . Relative to penicillin V (2.5 deaths in 1,000 patients per year), there was a significantly increased risk of cardiovascular mortality with clarithromycin (5.3 deaths in 1,000 patients per year), but not with roxithromycin (2.5 deaths in 1,000 patients per year). Given the small number of cardiac deaths in this study these results are difficult to interpret*[5]

19.2.3 Other macrolides

19.2.3.1 Spiramycin

- The adverse effects of erythromycin[10]
- Hematological toxicity, including bone marrow suppression and hemolysis, has been observed, especially during combined treatment with spiramycin and pyrimethamine for toxoplasmosis. [11]

19.2.3.2 Telithromycin

- The adverse effects of erythromycin[10]
- Besides the risk of prolongation of the QT interval and arrhythmias , telithromycin is associated withs other serious adverse effects such as severe liver damage , worsening of myasthenia gravis, rhabdomyolysis, visual disturbances , and severe skin reactions. Given telithromycin has no added value compared to other macrolides and in view of the adverse effects , the risk - benefit ratio is unfavorable and its use is not recommended[5]

19.3 Tetracyclines

- Accumulation in bones and teeth when tetracyclines are used during growth (during pregnancy and in young children). This can lead to reversible delay of bone growth , to irreversible yellow discoloration of the teeth , and possibly to an increased risk of caries.
- Liver disorders , especially in renal insufficiency and in pregnant women. [10]
- Dyspepsia, nausea and diarrhoea, minder met doxycycline en minocycline, which are better resorbed. [10] The symptoms are usually mild and seldom necessitate withdrawal. Nausea occurs in 8–15% of patients[11]
- photodermatosis , especially with doxycycline. [10]
- Benign intracranial hypertension, especially with minocycline [10]

19.3.1 Doxycycline

- Doxycycline in all solid forms: esophageal ulcers, especially after incorrect intake (eg lying down, without fluids) . [10]
- Thirty centers for pharmacovigilance in France have reported 81 cases of esophageal damage after treatment with tetracyclines collected between 1985 and 1992. Two cases of esophagitis in children have been reported. [11]

19.3.2 Lymecycline

- Lymecycline : deterioration of an already impaired renal function [10]

19.3.3 Minocycline

- Minocycline : vestibular disorders, which disappear upon discontinuation of therapy , especially in young women[10]
- Drug reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome and lupus-like reactions with arthralgias during prolonged treatment (eg . Acne) [10]In a retrospective review of drug safety databases, minocycline was the only tetracycline derivative that caused drug-induced lupus. Minocycline-related lupus can also occur in adolescents. [11]
- Minocycline and nicotinamide therapy for bullous pemphigoid have been associated with severe pneumonitis[11]
- Minocycline has been associated with acute pancreatitis. [11]

19.4 Clindamycine and lincomycine

- Gastrointestinal disorders : nausea, vomiting and especially diarrhea[10] (10-20% or patient's) [11].
- Pseudomembranous colitis caused by proliferation of Clostridium difficile , even after parenteral administration[10]

19.5 Fluoroquinolones

- Gastrointestinal troubles. [10]
- Allergic manifestations (rarely anaphylaxis) . [10]
- Arthralgias , tendinitis and tendon rupture (especially in the elderly and in patients using corticosteroids) . [10]
- Photosensitization [10] (1:03 %)[11]
- Central nervous system complaints (especially vertigo , agitation , rarely convulsions). [10]
- Acute worsening of myasthenia gravis[6]
- Haematological and hepatic toxicity: rare. [10]
- QT prolongation with risk of torsades de pointes , especially with moxifloxacin and levofloxacin , and to a lesser extent with ciprofloxacin, norfloxacin and ofloxacin . [10]

19.5.1 Ciprofloxacin

- Prolongation of the QT interval ; 0.3 cases of torsade de pointes/10 million prescriptions (retrospective database analysis) [11]
- Headache (in 8% of patients), dizziness (in 6%)[11]
- confusion and general seizures, facial dyskinesia[11]
- partial or complete tendinitis. (Of 72 lung transplant recipients who received ciprofloxacin, 20 had Achilles tendon involvement (tendinitis 15, rupture 5)) [11]
- The available data suggest that the incidence of arthrotoxicity in children taking ciprofloxacin is the same as in adults; the use of other fluoroquinolones is too rare to obtain clear information about the risks in children. Data on more than 1500 children treated with ciprofloxacin suggest that the safety profile of ciprofloxacin in children and adolescents is similar to the profile in adults. Adverse events, mostly involving the gastrointestinal tract, were noted in 5–15% of patients. Reversible arthralgia occurred in 36 of 1113 patients, but there was no radiographic evidence of cartilage damage. [11]

19.5.2 Levofloxacin

- Anaphylactic and anaphylactoid reactions are rare adverse events after the administration of fluoroquinolones (about 0.46–1.2 per 100 000 patients). [11]
- Surveillance data reported low adverse event rates: nausea 0.8%, rash 0.5%, abdominal pain 0.4%, and diarrhea, dizziness, and vomiting 0.3%. The adverse drug reactions rate for levofloxacin is still one of the lowest of any fluoroquinolone, at 2% compared with 2–10% for other fluoroquinolones[11]
- Levofloxacin can cause seizures. In one study convulsions occurred in two per million prescriptions[11]
- 5.4 cases of torsade de pointes/10 million prescriptions.(retrospective database analysis) [11]
- In a study based on European and international data from about 130 million prescriptions, the adverse effects profile of levofloxacin was compared with that of other fluoroquinolones; there was a low rate of hepatic abnormalities (1/650 000) [11]
- Tendon rupture (less than four per million prescriptions) [11]

19.5.3 Moxifloxacin

- Dizziness (observed in 2.8% of patients) [11]
- Heart failure in the elderly , severe skin reactions , fulminant hepatitis . [10]

19.5.4 Norfloxacin

- Acute hepatitis [11]
- pancreatitis[11]

19.5.5 Ofloxacin

- Headache (9%)[11]
- can cause fatal hepatic failure[11]
- Acute renal insufficiency [11]

19.6 Co-trimoxazole (sulfamethoxazole + trimethoprim)

- Allergic reactions : rash, hematological abnormalities and serum sickness ; cross reaction with hypoglycemic sulfonylureas . [10]
- Liver and kidney disorders : rare. [10]
- Drug reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome [10]
- Stevens-Johnson syndrome and Lyell's syndrome ; possibly fatal: rare. [10]
- Interference of trimethoprim with the metabolism of folic acid, leading to hematologic abnormalities. [10]
- Hyperkalemia [10] (In one study with standard dosages of co-trimoxazole, up to 62% of patients developed a peak serum potassium concentration of over 5.0 mmol/l and 21% a peak concentration of over 5.5.mmol/l) [11]
- The adverse effects were more frequent in patients infected with HIV. [10] Nausea and possibly vomiting occur in a few to 20% of adult patients taking normal dosages of co-trimoxazole[11]

19.7 Urinary antibacterial agents

19.7.1 Nitrofuranes

- Nausea and vomiting. [10]
- Allergic skin reactions (1–2%). The frequency of serious cutaneous reactions (erythema multiforme, Stevens–Johnson syndrome, or toxic epidermal necrolysis) after nitrofurantoin has been estimated to be 7 cases per 100 000 exposed individuals [11]
- Pulmonary fibrosis and cholestatic jaundice in prolonged administration[7]
- Peripheral neuropathy with prolonged use[10] (rare)[8]

19.7.1.1 Nitrofurantoin

- Acute respiratory reactions to nitrofurantoin include dyspnea, cough, interstitial pneumonitis, and pleural effusion, while interstitial pneumonitis and fibrosis are common chronic reactions. The frequency of acute severe pulmonary disease has been estimated to be one in every 5000 first administrations. Women aged 40–50 years are mainly affected.. Acute lung reactions to nitrofurantoin are extremely rare in children[11]
- More than 140 cases of toxic polyneuropathy have been reported. The frequency depends on dose, tissue concentration, and renal function: in up to 90% of cases polyneuropathy occurred in patients with renal insufficiency[11]
- About 20 cases of a lupus-like syndrome have been described[11]

19.7.2 Trimethoprim

- Nausea and vomiting[10].

- Allergic skin reactions[10].
- Hematologic abnormalities , such as macrocytic anemia by interfering with the metabolism of folic acid : rare. [10]
- Slight increase in serum creatinine by inhibition of tubular secretion of creatinine. [10]
- Hyperkalemia[10]

19.8 Probiotics

19.8.1 Saccharomyces boulardii

- systemic infections with Saccharomyces boulardii, in critically ill patients with a central venous catheter and who were treated with high doses (rare).[9]

19.9 Topical AB (ophtalmology)

Topical ophtalmic agents in general:

- Allergic reactions to ophthalmic agents are frequent. [10]
- Local agents used can theoretically cause the undesirable effects that occur in their systemic administration. In view of the low quantity that reaches the general circulation, this risk is likely to be very small. [10]
- Preservatives: most drugs for ophthalmic use contain a preservative; which can also give rise to allergic reactions (in particular benzalkonium chloride), and may interfere with the stability of the tear film. In patients with problems related to the tear film or with allergic conjunctivitis, products which do not contain any preservative are preferred. [10]
- Eye ointments may interfere with the stability of the tear film and deteriorate dryness of the eyes. [10]

Topical opthalmic antibiotics

- Allergy (especially with neomycin). [10]
- The notion that there would be a risk of aplastic anemia in local application of chloramphenicol has been abandoned. [10]

19.9.1 Chloramphenicol

- Erythema multiforme caused by local treatment with chloramphenicol eye-drops has been described[11]

19.9.2 Tobramycin

- Allergic contact dermatitis causing conjunctivitis and blepharitis has been reported with topical ophthalmic tobramycin[11]

19.9.3 bacitracine + neomycine

- Bacitracin is one of the most important clinical allergens. Anaphylaxis rarely occurs after topical administration of bacitracin ointment[11]

19.9.4 oxytetracycline + polymyxine

- In 145 patients with eczema of the external ear canal, allergic contact dermatitis was diagnosed in one-third; topical therapeutic agents, especially neomycin sulfate and probably polymyxin B, were the dominating allergens[11]

19.10 Topical AB (dermatology)

- Allergic reactions, more frequent with chloramphenicol, neomycin, polymyxin B , bacitracin and sulphonamides . Sulfonylureas alone or in association may not be used locally because of the risk of allergy; sulfacetamide does cause less allergy. Silver sulfadiazine and mupirocin rarely cause contact allergy. [10]
- The notion that there would be a risk of aplastic anemia with local application of chloramphenicol has been abandoned . [10]

19.10.1 Mupirocin

- Mupirocin ointment can occasionally cause allergic contact dermatitis[11]

19.11 References

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20 Appendix 1: search

20.1 Acute sore throat

("Child"[Mesh] OR "Infant"[Mesh] OR "Adolescent"[Mesh] OR child*[Title/Abstract] OR infan*[Title/Abstract] OR adolescen*[Title/Abstract] OR pediatr*[Title/Abstract] OR paediatr*[Title/Abstract]) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo[tiab] OR systematic[sb] OR medline[TIAB]) AND ("Anti-Bacterial Agents"[Mesh] OR "beta-Lactams"[Mesh] OR "Macrolides"[Mesh] OR "Tetracycline"[Mesh] OR "Lincomycin"[Mesh] OR "Fluoroquinolones"[Mesh] OR "Sulfamethoxazole"[Mesh] OR "Nitrofurans"[Mesh] OR "Trimethoprim"[Mesh] OR "Fosfomycin"[Mesh] OR Anti-Bacterial Agent*[Title/Abstract] OR beta-Lactam*[Title/Abstract] OR Macrolide*[Title/Abstract] OR Tetracycline*[Title/Abstract] OR Lincomycin*[Title/Abstract] OR Fluoroquinolone*[Title/Abstract] OR Sulfamethoxazole*[Title/Abstract] OR Nitrofuran*[Title/Abstract] OR Trimethoprim[Title/Abstract] OR Fosfomycin[Title/Abstract] OR anti-microbial*[Title/Abstract] OR antimicrobial*[Title/Abstract] OR antibacterial*[Title/Abstract] OR anti-bacterial*[Title/Abstract] OR antibiotic*[Title/Abstract] OR penicillin*[Title/Abstract] OR Penicillin*[Title/Abstract] OR Benzylpenicillin*[Title/Abstract] OR phenoxymethylpenicillin*[Title/Abstract] OR Flucloxacillin*[Title/Abstract] OR Oxacillin*[Title/Abstract] OR Ampicillin*[Title/Abstract] OR Amoxicillin*[Title/Abstract] OR Clavulan*[Title/Abstract] OR Cephalosporin*[Title/Abstract] OR Cefalosporin*[Title/Abstract] OR Cefadroxil*[Title/Abstract] OR Cephadroxil*[Title/Abstract] OR Cephalexin*[Title/Abstract] OR Cefalexin*[Title/Abstract] OR Cefazolin*[Title/Abstract] OR Cephazolin*[Title/Abstract] OR Cefuroxim*[Title/Abstract] OR Cephuroxim*[Title/Abstract] OR Ceftriaxone*[Title/Abstract] OR Monobactam*[Title/Abstract] OR Aztreonam*[Title/Abstract] OR Erythromycin*[Title/Abstract] OR Azithromycin*[Title/Abstract] OR Clarithromycin*[Title/Abstract] OR Roxithromycin*[Title/Abstract] OR Spiramycin*[Title/Abstract] OR Telithromycine*[Title/Abstract] OR Doxycycline*[Title/Abstract] OR Lymecycline*[Title/Abstract] OR Minocycline*[Title/Abstract] OR Quinolone*[Title/Abstract] OR Ciprofloxacin*[Title/Abstract] OR Levofloxacin*[Title/Abstract] OR Moxifloxacin*[Title/Abstract] OR Norfloxacin*[Title/Abstract] OR Ofloxacin*[Title/Abstract] OR Co-Trimoxazol*[Title/Abstract] OR Nifurtoinol*[Title/Abstract] OR Phosphomycin*[Title/Abstract]) AND **("2007/10/14"[Date - Entrez] :** "2016/01/01"**[Date - Entrez]) AND ("Pharyngitis"[Mesh] OR sore throat[Title/Abstract] OR pharyngit*[Title/Abstract] OR tonsillit*[Title/Abstract]OR painful throat[Title/Abstract] OR throat pain[Title/Abstract] OR strep throat[Title/Abstract])**

20.2 Acute Otitis media

("Child"[Mesh] OR "Infant"[Mesh] OR "Adolescent"[Mesh] OR child*[Title/Abstract] OR infan*[Title/Abstract] OR adolescen*[Title/Abstract] OR pediatr*[Title/Abstract] OR paediatr*[Title/Abstract]) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo[tiab] OR systematic[sb] OR medline[TIAB]) AND ("Anti-Bacterial Agents"[Mesh] OR "beta-Lactams"[Mesh] OR "Macrolides"[Mesh] OR "Tetracycline"[Mesh] OR "Lincomycin"[Mesh] OR "Fluoroquinolones"[Mesh] OR "Sulfamethoxazole"[Mesh] OR "Nitrofurans"[Mesh] OR "Trimethoprim"[Mesh] OR

"Fosfomycin"[Mesh] OR Anti-Bacterial Agent*[Title/Abstract] OR beta-Lactam*[Title/Abstract] OR Macrolide*[Title/Abstract] OR Tetracycline*[Title/Abstract] OR Lincomycin*[Title/Abstract] OR Fluoroquinolone*[Title/Abstract] OR Sulfamethoxazole*[Title/Abstract] OR Nitrofuran*[Title/Abstract] OR Trimethoprim[Title/Abstract] OR Fosfomycin[Title/Abstract] OR anti-microbial*[Title/Abstract] OR antimicrobial*[Title/Abstract] OR antibacterial*[Title/Abstract] OR anti-bacterial*[Title/Abstract] OR antibiotic*[Title/Abstract] OR penicillin*[Title/Abstract] OR Penicillin*[Title/Abstract] OR Benzylpenicillin*[Title/Abstract] OR phenoxymethylpenicillin*[Title/Abstract] OR Flucloxacillin*[Title/Abstract] OR Oxacillin*[Title/Abstract] OR Ampicillin*[Title/Abstract] OR Amoxicillin*[Title/Abstract] OR Clavulan*[Title/Abstract] OR Cephalosporin*[Title/Abstract] OR Cefalosporin*[Title/Abstract] OR Cefadroxil*[Title/Abstract] OR Cephadroxil*[Title/Abstract] OR Cephalexin*[Title/Abstract] OR Cefalexin*[Title/Abstract] OR Cefazolin*[Title/Abstract] OR Cephazolin*[Title/Abstract] OR Cefuroxim*[Title/Abstract] OR Cephuroxim*[Title/Abstract] OR Ceftriaxone*[Title/Abstract] OR Monobactam*[Title/Abstract] OR Aztreonam*[Title/Abstract] OR Erythromycin*[Title/Abstract] OR Azithromycin*[Title/Abstract] OR Clarithromycin*[Title/Abstract] OR Roxithromycin*[Title/Abstract] OR Spiramycin*[Title/Abstract] OR Telithromycine*[Title/Abstract] OR Doxycycline*[Title/Abstract] OR Lymecycline*[Title/Abstract] OR Minocycline*[Title/Abstract] OR Quinolone*[Title/Abstract] OR Ciprofloxacin*[Title/Abstract] OR Levofloxacin*[Title/Abstract] OR Moxifloxacin*[Title/Abstract] OR Norfloxacin*[Title/Abstract] OR Ofloxacin*[Title/Abstract] OR Co-Trimoxazol*[Title/Abstract] OR Nifurtoinol*[Title/Abstract] OR Phosphomycin*[Title/Abstract]) AND **("2009/10/11"[Date - Entrez] :** "2016/01/01"**[Date - Entrez]) AND ("Otitis Media"[Mesh] OR otitis[Title/Abstract] OR ear infection*[Title/Abstract] OR recurrent otitis[Title/Abstract] OR AOM[Title/Abstract] OR earache[Title/Abstract] OR otalgia[Title/Abstract])**

20.3 Acute rhinosinusitis

("Child"[Mesh] OR "Infant"[Mesh] OR "Adolescent"[Mesh] OR child*[Title/Abstract] OR infan*[Title/Abstract] OR adolescen*[Title/Abstract] OR pediatr*[Title/Abstract] OR paediatr*[Title/Abstract]) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo[tiab] OR systematic[sb] OR medline[TIAB]) AND ("Anti-Bacterial Agents"[Mesh] OR "beta-Lactams"[Mesh] OR "Macrolides"[Mesh] OR "Tetracycline"[Mesh] OR "Lincomycin"[Mesh] OR "Fluoroquinolones"[Mesh] OR "Sulfamethoxazole"[Mesh] OR "Nitrofurans"[Mesh] OR "Trimethoprim"[Mesh] OR "Fosfomycin"[Mesh] OR Anti-Bacterial Agent*[Title/Abstract] OR beta-Lactam*[Title/Abstract] OR Macrolide*[Title/Abstract] OR Tetracycline*[Title/Abstract] OR Lincomycin*[Title/Abstract] OR Fluoroquinolone*[Title/Abstract] OR Sulfamethoxazole*[Title/Abstract] OR Nitrofuran*[Title/Abstract] OR Trimethoprim[Title/Abstract] OR Fosfomycin[Title/Abstract] OR anti-microbial*[Title/Abstract] OR antimicrobial*[Title/Abstract] OR antibacterial*[Title/Abstract] OR anti-bacterial*[Title/Abstract] OR antibiotic*[Title/Abstract] OR penicillin*[Title/Abstract] OR Penicillin*[Title/Abstract] OR Benzylpenicillin*[Title/Abstract] OR phenoxymethylpenicillin*[Title/Abstract] OR Flucloxacillin*[Title/Abstract] OR Oxacillin*[Title/Abstract] OR Ampicillin*[Title/Abstract] OR Amoxicillin*[Title/Abstract] OR Clavulan*[Title/Abstract] OR Cephalosporin*[Title/Abstract] OR Cefalosporin*[Title/Abstract] OR Cefadroxil*[Title/Abstract] OR Cephadroxil*[Title/Abstract] OR Cephalexin*[Title/Abstract] OR Cefalexin*[Title/Abstract] OR Cefazolin*[Title/Abstract] OR Cephazolin*[Title/Abstract] OR

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20.4 Acute bronchitis

("Child"[Mesh] OR "Infant"[Mesh] OR "Adolescent"[Mesh] OR child*[Title/Abstract] OR infan*[Title/Abstract] OR adolescen*[Title/Abstract] OR pediatr*[Title/Abstract] OR paediatr*[Title/Abstract]) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo[tiab] OR systematic[sb] OR medline[TIAB]) AND ("Anti-Bacterial Agents"[Mesh] OR "beta-Lactams"[Mesh] OR "Macrolides"[Mesh] OR "Tetracycline"[Mesh] OR "Lincomycin"[Mesh] OR "Fluoroquinolones"[Mesh] OR "Sulfamethoxazole"[Mesh] OR "Nitrofurans"[Mesh] OR "Trimethoprim"[Mesh] OR "Fosfomycin"[Mesh] OR Anti-Bacterial Agent*[Title/Abstract] OR beta-Lactam*[Title/Abstract] OR Macrolide*[Title/Abstract] OR Tetracycline*[Title/Abstract] OR Lincomycin*[Title/Abstract] OR Fluoroquinolone*[Title/Abstract] OR Sulfamethoxazole*[Title/Abstract] OR Nitrofuran*[Title/Abstract] OR Trimethoprim[Title/Abstract] OR Fosfomycin[Title/Abstract] OR anti-microbial*[Title/Abstract] OR antimicrobial*[Title/Abstract] OR antibacterial*[Title/Abstract] OR anti-bacterial*[Title/Abstract] OR antibiotic*[Title/Abstract] OR penicillin*[Title/Abstract] OR Penicillin*[Title/Abstract] OR Benzylpenicillin*[Title/Abstract] OR phenoxymethylpenicillin*[Title/Abstract] OR Flucloxacillin*[Title/Abstract] OR Oxacillin*[Title/Abstract] OR Ampicillin*[Title/Abstract] OR Amoxicillin*[Title/Abstract] OR Clavulan*[Title/Abstract] OR Cephalosporin*[Title/Abstract] OR Cefalosporin*[Title/Abstract] OR Cefadroxil*[Title/Abstract] OR Cephadroxil*[Title/Abstract] OR Cephalexin*[Title/Abstract] OR Cefalexin*[Title/Abstract] OR Cefazolin*[Title/Abstract] OR Cephazolin*[Title/Abstract] OR Cefuroxim*[Title/Abstract] OR Cephuroxim*[Title/Abstract] OR Ceftriaxone*[Title/Abstract] OR Monobactam*[Title/Abstract] OR Aztreonam*[Title/Abstract] OR Erythromycin*[Title/Abstract] OR Azithromycin*[Title/Abstract] OR Clarithromycin*[Title/Abstract] OR Roxithromycin*[Title/Abstract] OR Spiramycin*[Title/Abstract] OR Telithromycine*[Title/Abstract] OR Doxycycline*[Title/Abstract] OR Lymecycline*[Title/Abstract] OR Minocycline*[Title/Abstract] OR Quinolone*[Title/Abstract] OR Ciprofloxacin*[Title/Abstract] OR Levofloxacin*[Title/Abstract] OR Moxifloxacin*[Title/Abstract] OR Norfloxacin*[Title/Abstract] OR Ofloxacin*[Title/Abstract] OR Co-Trimoxazol*[Title/Abstract] OR Nifurtoinol*[Title/Abstract] OR Phosphomycin*[Title/Abstract]) AND **("2013/12/15"[Date - Entrez] :** "2016/01/01"**[Date - Entrez]) AND ("Bronchitis"[Mesh] OR bronchit*[Title/Abstract] OR lower respiratory tract infection[Title/Abstract])**

20.5 **Bronchiolitis**

("Child"[Mesh] OR "Infant"[Mesh] OR "Adolescent"[Mesh] OR child*[Title/Abstract] OR infan*[Title/Abstract] OR adolescen*[Title/Abstract] OR pediatr*[Title/Abstract] OR paediatr*[Title/Abstract]) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo[tiab] OR systematic[sb] OR medline[TIAB]) AND ("Anti-Bacterial Agents"[Mesh] OR "beta-Lactams"[Mesh] OR "Macrolides"[Mesh] OR "Tetracycline"[Mesh] OR "Lincomycin"[Mesh] OR "Fluoroquinolones"[Mesh] OR "Sulfamethoxazole"[Mesh] OR "Nitrofurans"[Mesh] OR "Trimethoprim"[Mesh] OR "Fosfomycin"[Mesh] OR Anti-Bacterial Agent*[Title/Abstract] OR beta-Lactam*[Title/Abstract] OR Macrolide*[Title/Abstract] OR Tetracycline*[Title/Abstract] OR Lincomycin*[Title/Abstract] OR Fluoroquinolone*[Title/Abstract] OR Sulfamethoxazole*[Title/Abstract] OR Nitrofuran*[Title/Abstract] OR Trimethoprim[Title/Abstract] OR Fosfomycin[Title/Abstract] OR anti-microbial*[Title/Abstract] OR antimicrobial*[Title/Abstract] OR antibacterial*[Title/Abstract] OR anti-bacterial*[Title/Abstract] OR antibiotic*[Title/Abstract] OR penicillin*[Title/Abstract] OR Penicillin*[Title/Abstract] OR Benzylpenicillin*[Title/Abstract] OR phenoxymethylpenicillin*[Title/Abstract] OR Flucloxacillin*[Title/Abstract] OR Oxacillin*[Title/Abstract] OR Ampicillin*[Title/Abstract] OR Amoxicillin*[Title/Abstract] OR Clavulan*[Title/Abstract] OR Cephalosporin*[Title/Abstract] OR Cefalosporin*[Title/Abstract] OR Cefadroxil*[Title/Abstract] OR Cephadroxil*[Title/Abstract] OR Cephalexin*[Title/Abstract] OR Cefalexin*[Title/Abstract] OR Cefazolin*[Title/Abstract] OR Cephazolin*[Title/Abstract] OR Cefuroxim*[Title/Abstract] OR Cephuroxim*[Title/Abstract] OR Ceftriaxone*[Title/Abstract] OR Monobactam*[Title/Abstract] OR Aztreonam*[Title/Abstract] OR Erythromycin*[Title/Abstract] OR Azithromycin*[Title/Abstract] OR Clarithromycin*[Title/Abstract] OR Roxithromycin*[Title/Abstract] OR Spiramycin*[Title/Abstract] OR Telithromycine*[Title/Abstract] OR Doxycycline*[Title/Abstract] OR Lymecycline*[Title/Abstract] OR Minocycline*[Title/Abstract] OR Quinolone*[Title/Abstract] OR Ciprofloxacin*[Title/Abstract] OR Levofloxacin*[Title/Abstract] OR Moxifloxacin*[Title/Abstract] OR Norfloxacin*[Title/Abstract] OR Ofloxacin*[Title/Abstract] OR Co-Trimoxazol*[Title/Abstract] OR Nifurtoinol*[Title/Abstract] OR Phosphomycin*[Title/Abstract]) AND **("2014/05/16"[Date - Entrez] :** "2016/01/01"**[Date - Entrez]) AND ("Bronchiolitis"[Mesh] OR bronchiolit*[Title/Abstract])**

20.6 **Pneumonia**

("Child"[Mesh] OR "Infant"[Mesh] OR "Adolescent"[Mesh] OR child*[Title/Abstract] OR infan*[Title/Abstract] OR adolescen*[Title/Abstract] OR pediatr*[Title/Abstract] OR paediatr*[Title/Abstract]) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo[tiab] OR systematic[sb] OR medline[TIAB]) AND ("Anti-Bacterial Agents"[Mesh] OR "beta-Lactams"[Mesh] OR "Macrolides"[Mesh] OR "Tetracycline"[Mesh] OR "Lincomycin"[Mesh] OR "Fluoroquinolones"[Mesh] OR "Sulfamethoxazole"[Mesh] OR "Nitrofurans"[Mesh] OR "Trimethoprim"[Mesh] OR "Fosfomycin"[Mesh] OR Anti-Bacterial Agent*[Title/Abstract] OR beta-Lactam*[Title/Abstract] OR Macrolide*[Title/Abstract] OR Tetracycline*[Title/Abstract] OR Lincomycin*[Title/Abstract] OR Fluoroquinolone*[Title/Abstract] OR Sulfamethoxazole*[Title/Abstract] OR Nitrofuran*[Title/Abstract] OR Trimethoprim[Title/Abstract] OR Fosfomycin[Title/Abstract] OR anti-microbial*[Title/Abstract] OR antimicrobial*[Title/Abstract] OR antibacterial*[Title/Abstract] OR anti-bacterial*[Title/Abstract] OR antibiotic*[Title/Abstract] OR penicillin*[Title/Abstract] OR

Penicillin*[Title/Abstract] OR Benzylpenicillin*[Title/Abstract] OR phenoxymethylpenicillin*[Title/Abstract] OR Flucloxacillin*[Title/Abstract] OR Oxacillin*[Title/Abstract] OR Ampicillin*[Title/Abstract] OR Amoxicillin*[Title/Abstract] OR Clavulan*[Title/Abstract] OR Cephalosporin*[Title/Abstract] OR Cefalosporin*[Title/Abstract] OR Cefadroxil*[Title/Abstract] OR Cephadroxil*[Title/Abstract] OR Cephalexin*[Title/Abstract] OR Cefalexin*[Title/Abstract] OR Cefazolin*[Title/Abstract] OR Cephazolin*[Title/Abstract] OR Cefuroxim*[Title/Abstract] OR Cephuroxim*[Title/Abstract] OR Ceftriaxone*[Title/Abstract] OR Monobactam*[Title/Abstract] OR Aztreonam*[Title/Abstract] OR Erythromycin*[Title/Abstract] OR Azithromycin*[Title/Abstract] OR Clarithromycin*[Title/Abstract] OR Roxithromycin*[Title/Abstract] OR Spiramycin*[Title/Abstract] OR Telithromycine*[Title/Abstract] OR Doxycycline*[Title/Abstract] OR Lymecycline*[Title/Abstract] OR Minocycline*[Title/Abstract] OR Quinolone*[Title/Abstract] OR Ciprofloxacin*[Title/Abstract] OR Levofloxacin*[Title/Abstract] OR Moxifloxacin*[Title/Abstract] OR Norfloxacin*[Title/Abstract] OR Ofloxacin*[Title/Abstract] OR Co-Trimoxazol*[Title/Abstract] OR Nifurtoinol*[Title/Abstract] OR Phosphomycin*[Title/Abstract]) AND **("2012/10/07"[Date - Entrez] :** "2016/01/01"**[Date - Entrez])** AND **("Pneumonia"[Mesh] OR pneumon*[Title/Abstract] OR bronchopneumon*[Title/Abstract] OR CAP[Title/Abstract] OR lower respiratory tract infection[Title/Abstract])**

20.7 Urinary tract infection

("Child"[Mesh] OR "Infant"[Mesh] OR "Adolescent"[Mesh] OR child*[Title/Abstract] OR infan*[Title/Abstract] OR adolescen*[Title/Abstract] OR pediatr*[Title/Abstract] OR paediatr*[Title/Abstract]) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo[tiab] OR systematic[sb] OR medline[TIAB]) AND ("Anti-Bacterial Agents"[Mesh] OR "beta-Lactams"[Mesh] OR "Macrolides"[Mesh] OR "Tetracycline"[Mesh] OR "Lincomycin"[Mesh] OR "Fluoroquinolones"[Mesh] OR "Sulfamethoxazole"[Mesh] OR "Nitrofurans"[Mesh] OR "Trimethoprim"[Mesh] OR "Fosfomycin"[Mesh] OR Anti-Bacterial Agent*[Title/Abstract] OR beta-Lactam*[Title/Abstract] OR Macrolide*[Title/Abstract] OR Tetracycline*[Title/Abstract] OR Lincomycin*[Title/Abstract] OR Fluoroquinolone*[Title/Abstract] OR Sulfamethoxazole*[Title/Abstract] OR Nitrofuran*[Title/Abstract] OR Trimethoprim[Title/Abstract] OR Fosfomycin[Title/Abstract] OR anti-microbial*[Title/Abstract] OR antimicrobial*[Title/Abstract] OR antibacterial*[Title/Abstract] OR anti-bacterial*[Title/Abstract] OR antibiotic*[Title/Abstract] OR penicillin*[Title/Abstract] OR Penicillin*[Title/Abstract] OR Benzylpenicillin*[Title/Abstract] OR phenoxymethylpenicillin*[Title/Abstract] OR Flucloxacillin*[Title/Abstract] OR Oxacillin*[Title/Abstract] OR Ampicillin*[Title/Abstract] OR Amoxicillin*[Title/Abstract] OR Clavulan*[Title/Abstract] OR Cephalosporin*[Title/Abstract] OR Cefalosporin*[Title/Abstract] OR Cefadroxil*[Title/Abstract] OR Cephadroxil*[Title/Abstract] OR Cephalexin*[Title/Abstract] OR Cefalexin*[Title/Abstract] OR Cefazolin*[Title/Abstract] OR Cephazolin*[Title/Abstract] OR Cefuroxim*[Title/Abstract] OR Cephuroxim*[Title/Abstract] OR Ceftriaxone*[Title/Abstract] OR Monobactam*[Title/Abstract] OR Aztreonam*[Title/Abstract] OR Erythromycin*[Title/Abstract] OR Azithromycin*[Title/Abstract] OR Clarithromycin*[Title/Abstract] OR Roxithromycin*[Title/Abstract] OR Spiramycin*[Title/Abstract] OR Telithromycine*[Title/Abstract] OR Doxycycline*[Title/Abstract] OR Lymecycline*[Title/Abstract] OR Minocycline*[Title/Abstract] OR Quinolone*[Title/Abstract] OR

Ciprofloxacin*[Title/Abstract] OR Levofloxacin*[Title/Abstract] OR Moxifloxacin*[Title/Abstract] OR Norfloxacin*[Title/Abstract] OR Ofloxacin*[Title/Abstract] OR Co-Trimoxazol*[Title/Abstract] OR Nifurtoinol*[Title/Abstract] OR Phosphomycin*[Title/Abstract]) AND **("2010/10/28"[Date - Entrez] :** "2016/01/01"**[Date - Entrez]) AND ("Cystitis"[Mesh] OR "Urinary Tract Infections"[Mesh] OR "Pyelonephritis"[Mesh] OR cystit*[Title/Abstract] OR urinary tract infect*[Title/Abstract] OR pyelonephrit*[Title/Abstract] OR bacteriuria*[Title/Abstract] OR pyuri*[Title/Abstract] OR UTI[Title/Abstract] OR bladder infection*[Title/Abstract] OR renal infection* OR kidney infection*[Title/Abstract])**

20.8 Gastroenteritis

("Child"[Mesh] OR "Infant"[Mesh] OR "Adolescent"[Mesh] OR child*[Title/Abstract] OR infan*[Title/Abstract] OR adolescen*[Title/Abstract] OR pediatr*[Title/Abstract] OR paediatr*[Title/Abstract]) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo[tiab] OR systematic[sb] OR medline[TIAB]) AND ("Anti-Bacterial Agents"[Mesh] OR "beta-Lactams"[Mesh] OR "Macrolides"[Mesh] OR "Tetracycline"[Mesh] OR "Lincomycin"[Mesh] OR "Fluoroquinolones"[Mesh] OR "Sulfamethoxazole"[Mesh] OR "Nitrofurans"[Mesh] OR "Trimethoprim"[Mesh] OR "Fosfomycin"[Mesh] OR Anti-Bacterial Agent*[Title/Abstract] OR beta-Lactam*[Title/Abstract] OR Macrolide*[Title/Abstract] OR Tetracycline*[Title/Abstract] OR Lincomycin*[Title/Abstract] OR Fluoroquinolone*[Title/Abstract] OR Sulfamethoxazole*[Title/Abstract] OR Nitrofuran*[Title/Abstract] OR Trimethoprim[Title/Abstract] OR Fosfomycin[Title/Abstract] OR anti-microbial*[Title/Abstract] OR antimicrobial*[Title/Abstract] OR antibacterial*[Title/Abstract] OR anti-bacterial*[Title/Abstract] OR antibiotic*[Title/Abstract] OR penicillin*[Title/Abstract] OR Penicillin*[Title/Abstract] OR Benzylpenicillin*[Title/Abstract] OR phenoxymethylpenicillin*[Title/Abstract] OR Flucloxacillin*[Title/Abstract] OR Oxacillin*[Title/Abstract] OR Ampicillin*[Title/Abstract] OR Amoxicillin*[Title/Abstract] OR Clavulan*[Title/Abstract] OR Cephalosporin*[Title/Abstract] OR Cefalosporin*[Title/Abstract] OR Cefadroxil*[Title/Abstract] OR Cephadroxil*[Title/Abstract] OR Cephalexin*[Title/Abstract] OR Cefalexin*[Title/Abstract] OR Cefazolin*[Title/Abstract] OR Cephazolin*[Title/Abstract] OR Cefuroxim*[Title/Abstract] OR Cephuroxim*[Title/Abstract] OR Ceftriaxone*[Title/Abstract] OR Monobactam*[Title/Abstract] OR Aztreonam*[Title/Abstract] OR Erythromycin*[Title/Abstract] OR Azithromycin*[Title/Abstract] OR Clarithromycin*[Title/Abstract] OR Roxithromycin*[Title/Abstract] OR Spiramycin*[Title/Abstract] OR Telithromycine*[Title/Abstract] OR Doxycycline*[Title/Abstract] OR Lymecycline*[Title/Abstract] OR Minocycline*[Title/Abstract] OR Quinolone*[Title/Abstract] OR Ciprofloxacin*[Title/Abstract] OR Levofloxacin*[Title/Abstract] OR Moxifloxacin*[Title/Abstract] OR Norfloxacin*[Title/Abstract] OR Ofloxacin*[Title/Abstract] OR Co-Trimoxazol*[Title/Abstract] OR Nifurtoinol*[Title/Abstract] OR Phosphomycin*[Title/Abstract]) AND **("2008/04/01"[Date - Entrez] :** "2016/01/01"**[Date - Entrez]) AND ("Gastroenteritis"[Mesh] OR gastroenterit*[Title/Abstract] OR gastro-enterit*[Title/Abstract] OR enterit*[Title/Abstract] OR infectious diarrh*[Title/Abstract] OR** (acute**[Title/Abstract]** AND diarrh***[Title/Abstract]**))

20.9 Probiotics and diarrhoea

("Child"[Mesh] OR "Infant"[Mesh] OR "Adolescent"[Mesh] OR child*[Title/Abstract] OR infan*[Title/Abstract] OR adolescen*[Title/Abstract] OR pediatr*[Title/Abstract] OR paediatr*[Title/Abstract]) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo[tiab] OR systematic[sb] OR medline[TIAB]) AND **("2010/04/24"[Date - Entrez] :** "2016/01/01"**[Date - Entrez]) AND ("Probiotics"[Mesh] OR probiotic*[Title/Abstract] OR "Saccharomyces"[Mesh] OR "Lactobacillus"[Mesh] OR saccharomyces[Title/Abstract] OR lactobacillus[Title/Abstract]) AND ("Gastroenteritis"[Mesh] OR "Diarrhea"[Mesh] OR gastroenterit*[Title/Abstract] OR gastro-enterit*[Title/Abstract] OR diarrhea*[Title/Abstract] OR diarrhoea*[Title/Abstract] OR enterit*[Title/Abstract])**

20.10 Impetigo

("Child"[Mesh] OR "Infant"[Mesh] OR "Adolescent"[Mesh] OR child*[Title/Abstract] OR infan*[Title/Abstract] OR adolescen*[Title/Abstract] OR pediatr*[Title/Abstract] OR paediatr*[Title/Abstract]) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo[tiab] OR systematic[sb] OR medline[TIAB]) AND ("Anti-Bacterial Agents"[Mesh] OR "beta-Lactams"[Mesh] OR "Macrolides"[Mesh] OR "Tetracycline"[Mesh] OR "Lincomycin"[Mesh] OR "Fluoroquinolones"[Mesh] OR "Sulfamethoxazole"[Mesh] OR "Nitrofurans"[Mesh] OR "Trimethoprim"[Mesh] OR "Fosfomycin"[Mesh] OR Anti-Bacterial Agent*[Title/Abstract] OR beta-Lactam*[Title/Abstract] OR Macrolide*[Title/Abstract] OR Tetracycline*[Title/Abstract] OR Lincomycin*[Title/Abstract] OR Fluoroquinolone*[Title/Abstract] OR Sulfamethoxazole*[Title/Abstract] OR Nitrofuran*[Title/Abstract] OR Trimethoprim[Title/Abstract] OR Fosfomycin[Title/Abstract] OR anti-microbial*[Title/Abstract] OR antimicrobial*[Title/Abstract] OR antibacterial*[Title/Abstract] OR anti-bacterial*[Title/Abstract] OR antibiotic*[Title/Abstract] OR penicillin*[Title/Abstract] OR Penicillin*[Title/Abstract] OR Benzylpenicillin*[Title/Abstract] OR phenoxymethylpenicillin*[Title/Abstract] OR Flucloxacillin*[Title/Abstract] OR Oxacillin*[Title/Abstract] OR Ampicillin*[Title/Abstract] OR Amoxicillin*[Title/Abstract] OR Clavulan*[Title/Abstract] OR Cephalosporin*[Title/Abstract] OR Cefalosporin*[Title/Abstract] OR Cefadroxil*[Title/Abstract] OR Cephadroxil*[Title/Abstract] OR Cephalexin*[Title/Abstract] OR Cefalexin*[Title/Abstract] OR Cefazolin*[Title/Abstract] OR Cephazolin*[Title/Abstract] OR Cefuroxim*[Title/Abstract] OR Cephuroxim*[Title/Abstract] OR Ceftriaxone*[Title/Abstract] OR Monobactam*[Title/Abstract] OR Aztreonam*[Title/Abstract] OR Erythromycin*[Title/Abstract] OR Azithromycin*[Title/Abstract] OR Clarithromycin*[Title/Abstract] OR Roxithromycin*[Title/Abstract] OR Spiramycin*[Title/Abstract] OR Telithromycine*[Title/Abstract] OR Doxycycline*[Title/Abstract] OR Lymecycline*[Title/Abstract] OR Minocycline*[Title/Abstract] OR Quinolone*[Title/Abstract] OR Ciprofloxacin*[Title/Abstract] OR Levofloxacin*[Title/Abstract] OR Moxifloxacin*[Title/Abstract] OR Norfloxacin*[Title/Abstract] OR Ofloxacin*[Title/Abstract] OR Co-Trimoxazol*[Title/Abstract] OR Nifurtoinol*[Title/Abstract] OR Phosphomycin*[Title/Abstract] OR "Fusidic Acid"[Mesh] OR "Chloramphenicol"[Mesh] OR "Bacitracin"[Mesh] OR "Polymyxins"[Mesh] OR "Oxytetracycline"[Mesh] OR "Mupirocin"[Mesh] OR Fusidi*[tiab] OR Chloramphenicol*[tiab] OR Bacitracin*[tiab] OR Polymyxins*[tiab] OR Oxytetracycline*[tiab] OR Mupirocin*[tiab]) AND **("2010/04/03"[Date - Entrez] :** "2016/01/01"**[Date - Entrez]) AND ("Impetigo"[Mesh] OR impetig*[Title/Abstract] OR pyoderma*[Title/Abstract])**

20.11 Cellulitis and erysipelas

("Child"[Mesh] OR "Infant"[Mesh] OR "Adolescent"[Mesh] OR child*[Title/Abstract] OR infan*[Title/Abstract] OR adolescen*[Title/Abstract] OR pediatr*[Title/Abstract] OR paediatr*[Title/Abstract]) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo[tiab] OR systematic[sb] OR medline[TIAB]) AND ("Anti-Bacterial Agents"[Mesh] OR "beta-Lactams"[Mesh] OR "Macrolides"[Mesh] OR "Tetracycline"[Mesh] OR "Lincomycin"[Mesh] OR "Fluoroquinolones"[Mesh] OR "Sulfamethoxazole"[Mesh] OR "Nitrofurans"[Mesh] OR "Trimethoprim"[Mesh] OR "Fosfomycin"[Mesh] OR Anti-Bacterial Agent*[Title/Abstract] OR beta-Lactam*[Title/Abstract] OR Macrolide*[Title/Abstract] OR Tetracycline*[Title/Abstract] OR Lincomycin*[Title/Abstract] OR Fluoroquinolone*[Title/Abstract] OR Sulfamethoxazole*[Title/Abstract] OR Nitrofuran*[Title/Abstract] OR Trimethoprim[Title/Abstract] OR Fosfomycin[Title/Abstract] OR anti-microbial*[Title/Abstract] OR antimicrobial*[Title/Abstract] OR antibacterial*[Title/Abstract] OR anti-bacterial*[Title/Abstract] OR antibiotic*[Title/Abstract] OR penicillin*[Title/Abstract] OR Penicillin*[Title/Abstract] OR Benzylpenicillin*[Title/Abstract] OR phenoxymethylpenicillin*[Title/Abstract] OR Flucloxacillin*[Title/Abstract] OR Oxacillin*[Title/Abstract] OR Ampicillin*[Title/Abstract] OR Amoxicillin*[Title/Abstract] OR Clavulan*[Title/Abstract] OR Cephalosporin*[Title/Abstract] OR Cefalosporin*[Title/Abstract] OR Cefadroxil*[Title/Abstract] OR Cephadroxil*[Title/Abstract] OR Cephalexin*[Title/Abstract] OR Cefalexin*[Title/Abstract] OR Cefazolin*[Title/Abstract] OR Cephazolin*[Title/Abstract] OR Cefuroxim*[Title/Abstract] OR Cephuroxim*[Title/Abstract] OR Ceftriaxone*[Title/Abstract] OR Monobactam*[Title/Abstract] OR Aztreonam*[Title/Abstract] OR Erythromycin*[Title/Abstract] OR Azithromycin*[Title/Abstract] OR Clarithromycin*[Title/Abstract] OR Roxithromycin*[Title/Abstract] OR Spiramycin*[Title/Abstract] OR Telithromycine*[Title/Abstract] OR Doxycycline*[Title/Abstract] OR Lymecycline*[Title/Abstract] OR Minocycline*[Title/Abstract] OR Quinolone*[Title/Abstract] OR Ciprofloxacin*[Title/Abstract] OR Levofloxacin*[Title/Abstract] OR Moxifloxacin*[Title/Abstract] OR Norfloxacin*[Title/Abstract] OR Ofloxacin*[Title/Abstract] OR Co-Trimoxazol*[Title/Abstract] OR Nifurtoinol*[Title/Abstract] OR Phosphomycin*[Title/Abstract] OR "Fusidic Acid"[Mesh] OR "Chloramphenicol"[Mesh] OR "Bacitracin"[Mesh] OR "Polymyxins"[Mesh] OR "Oxytetracycline"[Mesh] OR "Mupirocin"[Mesh] OR Fusidi*[tiab] OR Chloramphenicol*[tiab] OR Bacitracin*[tiab] OR Polymyxins*[tiab] OR Oxytetracycline*[tiab] OR Mupirocin*[tiab]) AND ("2010/04/03"[Date - Entrez] : "2016/01/01"[Date - Entrez]) AND (**"Erysipelas"[Mesh] OR "Cellulitis"[Mesh] OR erysipelas[Title/Abstract] OR cellulit*[Title/Abstract])**

20.12 Conjunctivitis

("Child"[Mesh] OR "Infant"[Mesh] OR "Adolescent"[Mesh] OR child*[Title/Abstract] OR infan*[Title/Abstract] OR adolescen*[Title/Abstract] OR pediatr*[Title/Abstract] OR paediatr*[Title/Abstract]) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo[tiab] OR systematic[sb] OR medline[TIAB]) AND ("Anti-Bacterial Agents"[Mesh] OR "beta-Lactams"[Mesh] OR "Macrolides"[Mesh] OR "Tetracycline"[Mesh] OR "Lincomycin"[Mesh] OR "Fluoroquinolones"[Mesh] OR "Sulfamethoxazole"[Mesh] OR "Nitrofurans"[Mesh] OR "Trimethoprim"[Mesh] OR "Fosfomycin"[Mesh] OR Anti-Bacterial Agent*[Title/Abstract] OR beta-Lactam*[Title/Abstract] OR Macrolide*[Title/Abstract] OR Tetracycline*[Title/Abstract] OR

Lincomycin*[Title/Abstract] OR Fluoroquinolone*[Title/Abstract] OR Sulfamethoxazole*[Title/Abstract] OR Nitrofuran*[Title/Abstract] OR Trimethoprim[Title/Abstract] OR Fosfomycin[Title/Abstract] OR anti-microbial*[Title/Abstract] OR antimicrobial*[Title/Abstract] OR antibacterial*[Title/Abstract] OR anti-bacterial*[Title/Abstract] OR antibiotic*[Title/Abstract] OR penicillin*[Title/Abstract] OR Penicillin*[Title/Abstract] OR Benzylpenicillin*[Title/Abstract] OR phenoxymethylpenicillin*[Title/Abstract] OR Flucloxacillin*[Title/Abstract] OR Oxacillin*[Title/Abstract] OR Ampicillin*[Title/Abstract] OR Amoxicillin*[Title/Abstract] OR Clavulan*[Title/Abstract] OR Cephalosporin*[Title/Abstract] OR Cefalosporin*[Title/Abstract] OR Cefadroxil*[Title/Abstract] OR Cephadroxil*[Title/Abstract] OR Cephalexin*[Title/Abstract] OR Cefalexin*[Title/Abstract] OR Cefazolin*[Title/Abstract] OR Cephazolin*[Title/Abstract] OR Cefuroxim*[Title/Abstract] OR Cephuroxim*[Title/Abstract] OR Ceftriaxone*[Title/Abstract] OR Monobactam*[Title/Abstract] OR Aztreonam*[Title/Abstract] OR Erythromycin*[Title/Abstract] OR Azithromycin*[Title/Abstract] OR Clarithromycin*[Title/Abstract] OR Roxithromycin*[Title/Abstract] OR Spiramycin*[Title/Abstract] OR Telithromycine*[Title/Abstract] OR Doxycycline*[Title/Abstract] OR Lymecycline*[Title/Abstract] OR Minocycline*[Title/Abstract] OR Quinolone*[Title/Abstract] OR Ciprofloxacin*[Title/Abstract] OR Levofloxacin*[Title/Abstract] OR Moxifloxacin*[Title/Abstract] OR Norfloxacin*[Title/Abstract] OR Ofloxacin*[Title/Abstract] OR Co-Trimoxazol*[Title/Abstract] OR Nifurtoinol*[Title/Abstract] OR Phosphomycin*[Title/Abstract] OR "Fusidic Acid"[Mesh] OR "Chloramphenicol"[Mesh] OR "Tobramycin"[Mesh] OR "Bacitracin"[Mesh] OR "Neomycin"[Mesh] OR "Polymyxins"[Mesh] OR "Oxytetracycline"[Mesh] OR Fusidi*[tiab] OR Chloramphenicol*[tiab] OR Tobramycin*[tiab] OR Bacitracin*[tiab] OR Neomycin*[tiab] OR Polymyxins*[tiab] OR Oxytetracycline*[tiab]) AND ("2012/06/18"[Date - Entrez] : "2016/01/01"[Date - Entrez]) AND **("Conjunctivitis"[Mesh] OR conjunctivit*[Title/Abstract])**

20.13 Laryngitis

("Child"[Mesh] OR "Infant"[Mesh] OR "Adolescent"[Mesh] OR child*[Title/Abstract] OR infan*[Title/Abstract] OR adolescen*[Title/Abstract] OR pediatr*[Title/Abstract] OR paediatr*[Title/Abstract]) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo[tiab] OR systematic[sb] OR medline[TIAB]) AND ("Anti-Bacterial Agents"[Mesh] OR "beta-Lactams"[Mesh] OR "Macrolides"[Mesh] OR "Tetracycline"[Mesh] OR "Lincomycin"[Mesh] OR "Fluoroquinolones"[Mesh] OR "Sulfamethoxazole"[Mesh] OR "Nitrofurans"[Mesh] OR "Trimethoprim"[Mesh] OR "Fosfomycin"[Mesh] OR Anti-Bacterial Agent*[Title/Abstract] OR beta-Lactam*[Title/Abstract] OR Macrolide*[Title/Abstract] OR Tetracycline*[Title/Abstract] OR Lincomycin*[Title/Abstract] OR Fluoroquinolone*[Title/Abstract] OR Sulfamethoxazole*[Title/Abstract] OR Nitrofuran*[Title/Abstract] OR Trimethoprim[Title/Abstract] OR Fosfomycin[Title/Abstract] OR anti-microbial*[Title/Abstract] OR antimicrobial*[Title/Abstract] OR antibacterial*[Title/Abstract] OR anti-bacterial*[Title/Abstract] OR antibiotic*[Title/Abstract] OR penicillin*[Title/Abstract] OR Penicillin*[Title/Abstract] OR Benzylpenicillin*[Title/Abstract] OR phenoxymethylpenicillin*[Title/Abstract] OR Flucloxacillin*[Title/Abstract] OR Oxacillin*[Title/Abstract] OR Ampicillin*[Title/Abstract] OR Amoxicillin*[Title/Abstract] OR Clavulan*[Title/Abstract] OR Cephalosporin*[Title/Abstract] OR Cefalosporin*[Title/Abstract] OR Cefadroxil*[Title/Abstract] OR Cephadroxil*[Title/Abstract] OR Cephalexin*[Title/Abstract] OR Cefalexin*[Title/Abstract] OR Cefazolin*[Title/Abstract] OR Cephazolin*[Title/Abstract] OR

Cefuroxim*[Title/Abstract] OR Cephuroxim*[Title/Abstract] OR Ceftriaxone*[Title/Abstract] OR Monobactam*[Title/Abstract] OR Aztreonam*[Title/Abstract] OR Erythromycin*[Title/Abstract] OR Azithromycin*[Title/Abstract] OR Clarithromycin*[Title/Abstract] OR Roxithromycin*[Title/Abstract] OR Spiramycin*[Title/Abstract] OR Telithromycine*[Title/Abstract] OR Doxycycline*[Title/Abstract] OR Lymecycline*[Title/Abstract] OR Minocycline*[Title/Abstract] OR Quinolone*[Title/Abstract] OR Ciprofloxacin*[Title/Abstract] OR Levofloxacin*[Title/Abstract] OR Moxifloxacin*[Title/Abstract] OR Norfloxacin*[Title/Abstract] OR Ofloxacin*[Title/Abstract] OR Co-Trimoxazol*[Title/Abstract] OR Nifurtoinol*[Title/Abstract] OR Phosphomycin*[Title/Abstract]) AND **("1965/01/01"[Date - Entrez] :** "2016/01/01"**[Date - Entrez]) AND ("Laryngitis"[Mesh] OR "Croup"[Mesh] OR laryngit*[Title/Abstract] OR croup[Title/Abstract])**

20.14 Tracheitis

("Child"[Mesh] OR "Infant"[Mesh] OR "Adolescent"[Mesh] OR child*[Title/Abstract] OR infan*[Title/Abstract] OR adolescen*[Title/Abstract] OR pediatr*[Title/Abstract] OR paediatr*[Title/Abstract]) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo[tiab] OR systematic[sb] OR medline[TIAB]) AND ("Anti-Bacterial Agents"[Mesh] OR "beta-Lactams"[Mesh] OR "Macrolides"[Mesh] OR "Tetracycline"[Mesh] OR "Lincomycin"[Mesh] OR "Fluoroquinolones"[Mesh] OR "Sulfamethoxazole"[Mesh] OR "Nitrofurans"[Mesh] OR "Trimethoprim"[Mesh] OR "Fosfomycin"[Mesh] OR Anti-Bacterial Agent*[Title/Abstract] OR beta-Lactam*[Title/Abstract] OR Macrolide*[Title/Abstract] OR Tetracycline*[Title/Abstract] OR Lincomycin*[Title/Abstract] OR Fluoroquinolone*[Title/Abstract] OR Sulfamethoxazole*[Title/Abstract] OR Nitrofuran*[Title/Abstract] OR Trimethoprim[Title/Abstract] OR Fosfomycin[Title/Abstract] OR anti-microbial*[Title/Abstract] OR antimicrobial*[Title/Abstract] OR antibacterial*[Title/Abstract] OR anti-bacterial*[Title/Abstract] OR antibiotic*[Title/Abstract] OR penicillin*[Title/Abstract] OR Penicillin*[Title/Abstract] OR Benzylpenicillin*[Title/Abstract] OR phenoxymethylpenicillin*[Title/Abstract] OR Flucloxacillin*[Title/Abstract] OR Oxacillin*[Title/Abstract] OR Ampicillin*[Title/Abstract] OR Amoxicillin*[Title/Abstract] OR Clavulan*[Title/Abstract] OR Cephalosporin*[Title/Abstract] OR Cefalosporin*[Title/Abstract] OR Cefadroxil*[Title/Abstract] OR Cephadroxil*[Title/Abstract] OR Cephalexin*[Title/Abstract] OR Cefalexin*[Title/Abstract] OR Cefazolin*[Title/Abstract] OR Cephazolin*[Title/Abstract] OR Cefuroxim*[Title/Abstract] OR Cephuroxim*[Title/Abstract] OR Ceftriaxone*[Title/Abstract] OR Monobactam*[Title/Abstract] OR Aztreonam*[Title/Abstract] OR Erythromycin*[Title/Abstract] OR Azithromycin*[Title/Abstract] OR Clarithromycin*[Title/Abstract] OR Roxithromycin*[Title/Abstract] OR Spiramycin*[Title/Abstract] OR Telithromycine*[Title/Abstract] OR Doxycycline*[Title/Abstract] OR Lymecycline*[Title/Abstract] OR Minocycline*[Title/Abstract] OR Quinolone*[Title/Abstract] OR Ciprofloxacin*[Title/Abstract] OR Levofloxacin*[Title/Abstract] OR Moxifloxacin*[Title/Abstract] OR Norfloxacin*[Title/Abstract] OR Ofloxacin*[Title/Abstract] OR Co-Trimoxazol*[Title/Abstract] OR Nifurtoinol*[Title/Abstract] OR Phosphomycin*[Title/Abstract]) AND **("1965/01/01"[Date - Entrez] :** "2016/01/01"**[Date - Entrez]) AND ("tracheitis"[Mesh] OR tracheit*[Title/Abstract] OR laryngotrach*[Title/Abstract] OR bacterial trach*[Title/Abstract] OR tracheobronch*[Title/Abstract])**

20.15 Fluoroquinolones

Source document:
(Adefurin 2011)

Search **((("Child"[Mesh] OR "Infant"[Mesh] OR "Adolescent"[Mesh] OR child*[Title/Abstract]) AND ("Fluoroquinolones"[Mesh] OR Fluoroquinolone*[Title/Abstract] OR Quinolone*[Title/Abstract] OR Ciprofloxacin*[Title/Abstract] OR Levofloxacin*[Title/Abstract] OR Moxifloxacin*[Title/Abstract] OR Norfloxacin*[Title/Abstract] OR Ofloxacin*[Title/Abstract]) AND (Cohort*[tiab] OR Longitudinal[TIAB] OR Prospective[TIAB] OR Retrospective[TIAB] OR "Observational Study"[Publication Type])) AND (adverse event*[TIAB] OR adverse effect*[TIAB] OR arthropath*[TIAB] OR musculoskeletal*[TIAB]))**

From September 2009 to 1st januari 2016

32 references found
+ additional references provided by the organizing committee and the reading committee

21 Appendix 2: List of excluded articles

21.1 Sore throat

1. Altamimi S, Khalil A, Khalaiwi KA, et al. Short versus standard duration antibiotic therapy for acute streptococcal pharyngitis in children. Cochrane Database Syst Rev 2009:Cd004872.**n, update 2012 available**
2. Bax R. Development of a twice daily dosing regimen of amoxicillin/clavulanate. Int J Antimicrob Agents 2007;30 Suppl 2:S118-21.**n, no SR**
3. Bird JH, Biggs TC, King EV. Controversies in the management of acute tonsillitis: an evidence-based review. Clin Otolaryngol 2014;39:368-74.**n; is SR but only included references are the cochrane SR's, little numerical data, no appendix**
4. Bottaro G, Biasci P, Lo Giudice M, et al. [5 days Cefaclor vs. 10 days amoxicillin/clavulanate in the treatment of childhood streptococcal pharyngitis. Data from a randomized clinical trial]. Minerva Pediatr 2012;64:341-6.**n, language**
5. Chiappini E, Principi N, Mansi N, et al. Management of acute pharyngitis in children: summary of the Italian National Institute of Health guidelines. Clin Ther 2012;34:1442-58.e2.**n; guideline based on SR with end date search before that of cochranes**
6. Hersh AL, Jackson MA, Hicks LA. Principles of judicious antibiotic prescribing for upper respiratory tract infections in pediatrics. Pediatrics 2013;132:1146-54.**n; no SR**
7. Lennon D, Kerdemelidis M, Arroll B. Meta-analysis of trials of streptococcal throat treatment programs to prevent rheumatic fever. Pediatr Infect Dis J 2009;28:e259-64.**n, intervention (school/community-based treatment)**
8. Lennon DR, Farrell E, Martin DR, et al. Once-daily amoxicillin versus twice-daily penicillin V in group A beta-haemolytic streptococcal pharyngitis. Arch Dis Child 2008;93:474-8.**n, comparison**
9. Little P, Hobbs FD, Moore M, et al. PRImary care Streptococcal Management (PRISM) study: in vitro study, diagnostic cohorts and a pragmatic adaptive randomised controlled trial with nested qualitative study and cost-effectiveness study. Health Technol Assess 2014;18:vii-xxv, 1-101.**n; no subanalysis children**
10. Llerena Santa Cruz ED, Bunuel Alvarez JC, Porcar Farran D, et al. [Treatment of streptococcal tonsillitis with once-a-day amoxicillin: a meta-analysis]. An Pediatr (Barc) 2011;75:298-306.**n, language**
11. Rimoin AW, Hoff NA, Fischer Walker CL, et al. Treatment of streptococcal pharyngitis with once-daily amoxicillin versus intramuscular benzathine penicillin G in low-resource settings: a randomized controlled trial. Clin Pediatr (Phila) 2011;50:535-42.**n, low-resource setting; IM vs oral**
12. Uziel Y. Post streptococcal and beyond. Annals of the Rheumatic Disease 2013;71.**n, no SR**
13. Van Brusselen D, Vlieghe E, Schelstraete P, et al. Streptococcal pharyngitis in children: to treat or not to treat? Eur J Pediatr 2014;173:1275-83.**n, no SR**
14. Zeng L, Zhang L, Hu Z, et al. Systematic review of evidence-based guidelines on medication therapy for upper respiratory tract infection in children with AGREE instrument. PLoS One 2014;9:e87711.**n; study type**

21.2 Acute otitis media

1. Arguedas A, Soley C, Kamicker BJ, et al. Single-dose extended-release azithromycin versus a 10-day regimen of amoxicillin/clavulanate for the treatment of children with acute otitis media. Int J Infect Dis 2011;15:e240-8.**n; extended release azithromycin: not available in Be**
2. Clinical practice guidelines for the diagnosis and management of acute otitis media (AOM) in children in Japan. Auris Nasus Larynx 2012;39:1-8.**n; guideline; is based on SR but search date before other source documents**
3. Actrn, Reath J. A multi-centre open label randomised non-inferiority study to compare the efficacy of antibiotics versus watchful waiting for Acute Otitis Media without perforation in low-risk urban Aboriginal and Torres Strait Islander children. ANZCTR [wwwanzctrorgau] 2013.**n, trial registration, trial not yet completed**
4. Centre for Clinical Practice at N. National Institute for Health and Clinical Excellence: Guidance-Respiratory Tract Infections - Antibiotic Prescribing: Prescribing of Antibiotics for Self-Limiting Respiratory Tract Infections in Adults and Children in Primary Care. 2008.**n; search date older than Cochrane Venekamp**
5. Chhetri SS. Acute otitis media: a simple diagnosis, a simple treatment. Nepal Med Coll J 2014;16:33-6.**n, mixed population, no subgroup children**
6. Coker TR, Chan LS, Newberry SJ, et al. Diagnosis, microbial epidemiology, and antibiotic treatment of acute otitis media in children: a systematic review. Jama 2010;304:2161-9.**n; search comparable to shekelle but less comprehensive reporting**
7. Committee WGAbtGR. Recommendations for Management of Common Childhood Conditions: Evidence for Technical Update of Pocket Book Recommendations: Newborn Conditions, Dysentery, Pneumonia, Oxygen Use

and Delivery, Common Causes of Fever, Severe Acute Malnutrition and Supportive Care. 2012.**n; refers to cochrane, focuses on low income settings**
8. Courter JD, Baker WL, Nowak KS, et al. Increased clinical failures when treating acute otitis media with macrolides: a meta-analysis. Ann Pharmacother 2010;44:471-8.**n; search date older than AHRQ Shekelle and MA Coker, less comparisons**
9. Damoiseaux RA, Rovers MM. AOM in children. BMJ Clin Evid 2011;2011.**n; updated version is available**
10. Duodecim. [Update on current care guidelines: Acute otitis media]. Duodecim 2010;126:573-4.**n, guideline**
11. Ebell MH. Short course of antibiotics for acute otitis media treatment. Am Fam Physician 2011;83:37.**n, no SR**
12. Ellis VT, Jones-Ho KO. Evidence-based guidelines for the definition and management of children with acute otitis media. ORL Head Neck Nurs 2010;28:17.**n, guideline**
13. Gaboury I, Coyle K, Coyle D, et al. Treatment cost effectiveness in acute otitis media: A watch-and-wait approach versus amoxicillin. Paediatr Child Health 2010;15:e14-8.**n, cost-effectiveness**
14. Gamboa S, Park MK, Wanserski G, et al. Clinical inquiries. Should you use antibiotics to treat acute otitis media in children? J Fam Pract 2009;58:602-4.**n, no SR**
15. Hang A, Brietzke SE. Otitis media: epidemiology and management. Infect Disord Drug Targets 2012;12:261-6.**n, no SR**
16. Hersh AL, Jackson MA, Hicks LA. Principles of judicious antibiotic prescribing for upper respiratory tract infections in pediatrics. Pediatrics 2013;132:1146-54.**n, no SR**
17. Hoberman A, Ruohola A, Shaikh N, et al. Acute otitis media in children younger than 2 years. JAMA Pediatr 2013;167:1171-2.**n, opinion piece**
18. Kaur R, Casey JR, Pichichero ME. Relationship with original pathogen in recurrence of acute otitis media after completion of amoxicillin/clavulanate: bacterial relapse or new pathogen. Pediatr Infect Dis J 2013;32:1159-62.**n, not a research question**
19. Klein JO. Is acute otitis media a treatable disease? N Engl J Med 2011;364:168-9.**n, no SR**
20. Leach Amanda J, Morris Peter S. Antibiotics for the prevention of acute and chronic suppurative otitis media in children. Cochrane Database of Systematic Reviews 2006.**n; prevention of otitis in undifferentiated upper airway tract infections**
21. Lee HJ, Park SK, Choi KY, et al. Korean clinical practice guidelines: otitis media in children. J Korean Med Sci 2012;27:835-48.**n, guideline**
22. Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. Pediatrics 2013;131:e964-99.**n, is guideline**
23. Mandel EM, Casselbrant ML. Treatment of acute otitis media in young children. Curr Allergy Asthma Rep 2012;12:559-63.**n, no SR**
24. Marchisio P, Bellussi L, Di Mauro G, et al. Acute otitis media: From diagnosis to prevention. Summary of the Italian guideline. Int J Pediatr Otorhinolaryngol 2010;74:1209-16.**n, is guideline**
25. Marchisio P, Chonmaitree T, Leibovitz E, et al. Panel 7: Treatment and comparative effectiveness research. Otolaryngol Head Neck Surg 2013;148:E102-21.**n, searched 2007-2011**
26. McWilliams CJ, Goldman RD. Update on acute otitis media in children younger than 2 years of age. Can Fam Physician 2011;57:1283-5.**n, no SR**
27. Nesbit CE, Powers MC. An evidence-based approach to managing acute otitis media. Pediatr Emerg Med Pract 2013;10:1-26; quiz -7.**n, no SR**
28. Nikolopoulos TP. To give or not to give antibiotics in non-severe acute otitis media? The American Academy of Pediatrics guidelines that do not guide. Int J Pediatr Otorhinolaryngol 2014;78:983-4.**n, publication type**
29. Nitsche MP, Carreno M. Antibiotics for acute otitis media in children. Medwave 2015;15 Suppl 2:e6295.**n; full text not available from Ugent, ULB and KUL**
30. Paradise JL, Hoberman A, Rockette HE, et al. Treating acute otitis media in young children: what constitutes success? Pediatr Infect Dis J 2013;32:745-7.**n, no SR**
31. Reinhardt D. [Tympanostomy tubes and otorrhea - how to manage?]. MMW Fortschr Med 2014;156:33.**n; not available from Ugent, ULB and KUL**
32. Schoch AG, van Marwijk HW. [Acute otitis media: do not hesitate to treat]. Ned Tijdschr Geneeskd 2012;156:A4027.**n, opinion piece**
33. Tahtinen PA, Laine MK, Ruuskanen O, et al. Delayed versus immediate antimicrobial treatment for acute otitis media. Pediatr Infect Dis J 2012;31:1227-32.**n; posthoc**
34. Tahtinen PA, Laine MK, Ruuskanen O, et al. Delayed versus immediate antimicrobial treatment for acute otitis media. Pediatric infectious disease journal 2012;31:1227-32.**n; posthoc**
35. Thomas JP, Berner R, Zahnert T, et al. Acute otitis media--a structured approach. Dtsch Arztebl Int 2014;111:151-9; quiz 60.**n, no SR**
36. Thornton K, Parrish F, Swords C. Topical vs. systemic treatments for acute otitis media. Pediatr Nurs 2011;37:263-7, 42.**n; inclusion of RCTs focusing on OME and other comparisons**
37. Toll EC, Nunez DA. Diagnosis and treatment of acute otitis media: review. J Laryngol Otol 2012;126:976-83.**n; guidelines**
38. van Dongen TM, Schilder AG, Venekamp RP, et al. Cost-effectiveness of treatment of acute otorrhea in children with tympanostomy tubes. Pediatrics 2015;135:e1182-9.**n, cost-effectiveness study**

39. van Dongen TM, van der Heijden GJ, Venekamp RP, et al. A trial of treatment for acute otorrhea in children with tympanostomy tubes. N Engl J Med 2014;370:723-33.**n; intervention not available in Be**
40. Venekamp RP, Damoiseaux RA, Schilder AG. Acute otitis media in children. BMJ Clin Evid 2014;2014.**n; search date older than cochrane venekamp**
41. Venekamp RP, Sanders S, Glasziou PP, et al. Antibiotics for acute otitis media in children. Cochrane Database Syst Rev 2013;1:Cd000219.**n, update 2015 is available**
42. Wald ER, DeMuri GP. Commentary: antibiotic recommendations for acute otitis media and acute bacterial sinusitis in 2013--the conundrum. Pediatr Infect Dis J 2013;32:641-3.**n, not an SR**
43. WHO Guidelines Approved by the Guidelines Review Committee. Integrated Management of Childhood Illness for High HIV Settings. 2008.**n, subject**
44. Zeng L, Zhang L, Hu Z, et al. Systematic review of evidence-based guidelines on medication therapy for upper respiratory tract infection in children with AGREE instrument. PLoS One 2014;9:e87711.**n; guidelines**

21.3 Acute rhinosinusitis

1. Block SL. Comparative tolerability, safety and efficacy of tablet formulations of twice-daily clarithromycin 250 mg versus once-daily extended-release clarithromycin 500 mg in pediatric and adolescent patients. Clinical pediatrics 2006;45:641-8.**n, extended release azithromycin not available in Be**
2. Cervin A, Wallwork B. Efficacy and safety of long-term antibiotics (macrolides) for the treatment of chronic rhinosinusitis. Current Allergy and Asthma Reports 2014;14:416.**n, chronic sinusitis**
3. El-Hennawi DM, Abou-Halawa AS, Zaher SR. Management of clinically diagnosed subacute rhinosinusitis in children under the age of two years: a randomized, controlled study. Journal of laryngology and otology 2006;120:845-8.**n, subacute sinusitis**
4. Kenealy T, Arroll B. Antibiotics for the common cold and acute purulent rhinitis. Cochrane Database of Systematic Reviews 2013.**n; no seperate data for children**
5. Lari AR, Alinejad F, Alaghehbandan R, et al. Comparison of cefuroxime and co-amoxiclav in the treatment of acute sinusitis in a sample of the Iranian population. Infez Med 2012;20:251-5.**n; >12 y, no seperate analysis for children**
6. Morris Peter S, Leach Amanda J. Antibiotics for persistent nasal discharge (rhinosinusitis) in children. Cochrane Database of Systematic Reviews 2008.**n; review withdrawn**
7. Poachanukoon O, Tangsathapornpong A, Tanuchit S. A Comparison of Cefditoren Pivoxil 8-12 mg/kg/day and Cefditoren Pivoxil 16-20 mg/kg/day in Treatment of Children With Acute Presumed Bacterial Rhinosinusitis: A Prospective, Randomized, Investigator-Blinded, Parallel-Group Study. Clin Exp Otorhinolaryngol 2015;8:129-35.**n, not available in Be**
8. Ragab A, Farahat T, Al-Hendawy G, et al. Nasal saline irrigation with or without systemic antibiotics in treatment of children with acute rhinosinusitis. Int J Pediatr Otorhinolaryngol 2015;79:2178-86.**n, sample size**
9. Simon MW. A prospective randomized study comparing the efficacy of amoxicillin- clavulanate, erythromycin-sulfisoxazole, cefaclor, and cefprozil in treating acute sinusitis of childhood. Advances in therapy 1997;14:64-72.**n, not available via Ugent, KUL or ULB**
10. Sutter AI, Meyere MJ, Christiaens TC, et al. Does amoxicillin improve outcomes in patients with purulent rhinorrhea? A pragmatic randomized double-blind controlled trial in family practice. Journal of family practice 2002;51:317-23.**n, no subanalysis children**
11. Wald ER, Reilly JS, Casselbrant M, et al. Treatment of acute maxillary sinusitis in childhood: a comparative study of amoxicillin and cefaclor. Journal of pediatrics 1984;104:297-302.**n, cefaclor not in Be**
12. Wan KS, Wu WF, Chen TC, et al. Comparison of amoxicillin + clavulanate with or without intranasal fluticasone for the treatment of uncomplicated acute rhinosinusitis in children. Minerva Pediatr 2015;67:489-94.**n; sample size**

21.4 Acute bronchitis

1. Biondi E, McCulloh R, Alverson B, et al. Treatment of mycoplasma pneumonia: a systematic review. Pediatrics 2014;133:1081-90.**n; pneumonia**
2. Darelid J, Löfgren S, Malmvall BE. Erythromycin treatment is beneficial for longstanding Moraxella catarrhalis associated cough in children. Scandinavian journal of infectious diseases 1993;25:323-9.**n, longstanding cough**
3. Duodecim. [Current care guideline: lower respiratory tract infections in children]. Duodecim 2014;130:1560-1.**n; is guideline**
4. Farley R, Spurling GK, Eriksson L, et al. Antibiotics for bronchiolitis in children under two years of age. Cochrane Database Syst Rev 2014;10:Cd005189.**n; bronchiolitis**

5. Gadomski AM. Potential interventions for preventing pneumonia among young children: lack of effect of antibiotic treatment for upper respiratory infections. Pediatric infectious disease journal 1993;12:115-20.**n; prevention of pneumonia in upper respiratory tract infection**
6. Gardiner SJ, Gavranich JB, Chang AB. Antibiotics for community-acquired lower respiratory tract infections secondary to Mycoplasma pneumoniae in children. Cochrane Database Syst Rev 2015;1:Cd004875.**n; included for chapter "pneumonia"**
7. Laopaiboon M, Panpanich R, Swa Mya K. Azithromycin for acute lower respiratory tract infections. Cochrane Database of Systematic Reviews 2015.**n, included in chapter pneumonia**

21.5 Acute bronchiolitis

1. Baraldi E, Lanari M, Manzoni P, et al. Inter-society consensus document on treatment and prevention of bronchiolitis in newborns and infants. Ital J Pediatr 2014;40:65.**n, not an SR**
2. Chang AB, Grimwood K, White AV, et al. Randomized placebo-controlled trial on azithromycin to reduce the morbidity of bronchiolitis in Indigenous Australian infants: rationale and protocol. Trials 2011;12:94.**n, is protocol; trial publication not found**
3. Duodecim. [Current care guideline: lower respiratory tract infections in children]. Duodecim 2014;130:1560-1.**n, guideline**
4. Farley R, Spurling GK, Eriksson L, et al. Antibiotics for bronchiolitis in children under two years of age. Cochrane Database Syst Rev 2014;10:Cd005189.**n, NICE 2015 more recent search**
5. McCallum Gabrielle B, Morris Peter S, Chang Anne B. Antibiotics for persistent cough or wheeze following acute bronchiolitis in children. Cochrane Database of Systematic Reviews 2012.**n, persistent cough or wheeze after bronchiolitis**
6. National Collaborating Centre for Women's and Children's Health. Bronchiolitis: diagnosis and management of bronchiolitis in children. 2015.**n; most outcomes could not be reported because of small sample sizes (did not pool most studies); we will report cochrane farley instead**
7. Spurling GK, Doust J, Del Mar CB, et al. Antibiotics for bronchiolitis in children. Cochrane Database Syst Rev 2011:Cd005189.**n, older version of Cochrane Farley**

21.6 Community acquired pneumonia

1. Agweyu A, Gathara D, Oliwa J, et al. Oral amoxicillin versus benzyl penicillin for severe pneumonia among kenyan children: a pragmatic randomized controlled noninferiority trial. Clin Infect Dis 2015;60:1216-24.**n, children with comorbidities**
2. Alves Galvao MG, Rocha Crispino Santos MA, Alves da Cunha AJ. Antibiotics for preventing suppurative complications from undifferentiated acute respiratory infections in children under five years of age. Cochrane Database Syst Rev 2014;2:Cd007880.**n, not a research question**
3. Baraldi E, Lanari M, Manzoni P, et al. Inter-society consensus document on treatment and prevention of bronchiolitis in newborns and infants. Ital J Pediatr 2014;40:65.**n, bronchiolitis**
4. Behere S, Garber MD. Community-acquired pneumonia: judicious use of antibiotics or treatment failure? Hosp Pediatr 2013;3:180-1.**n, not an SR**
5. Berti E, Galli L, de Martino M, et al. International guidelines on tackling community-acquired pneumonia show major discrepancies between developed and developing countries. Acta Paediatr Suppl 2013;102:4-16.**n, guidelines**
6. Biondi E, McCulloh R, Alverson B, et al. Treatment of mycoplasma pneumonia: a systematic review. Pediatrics 2014;133:1081-90.**n; includes observational studies; Gardiner more recent**
7. Das RR, Singh M. Treatment of severe community-acquired pneumonia with oral amoxicillin in under-five children in developing country: a systematic review. PLoS One 2013;8:e66232.**n, severe pneumonia**
8. Duodecim. [Current care guideline: lower respiratory tract infections in children]. Duodecim 2014;130:1560-1.**n, guideline**
9. Esamai F, Tshefu AK, Ayede AI, et al. Ongoing trials of simplified antibiotic regimens for the treatment of serious infections in young infants in South Asia and sub-Saharan Africa: implications for policy. Pediatr Infect Dis J 2013;32 Suppl 1:S46-9.**n; not an SR**
10. Farley R, Spurling GK, Eriksson L, et al. Antibiotics for bronchiolitis in children under two years of age. Cochrane Database Syst Rev 2014;10:Cd005189.**n, bronchiolitis**
11. Ferrero F, Adrian Torres F, Dominguez P, et al. Efficacy and safety of a decision rule for using antibiotics in children with pneumonia and vaccinated against pneumococcus. A randomized controlled trial. Arch Argent Pediatr 2015;113:397-403.**n, sample size**

12. Hare KM, Grimwood K, Chang AB, et al. Nasopharyngeal carriage and macrolide resistance in Indigenous children with bronchiectasis randomized to long-term azithromycin or placebo. Eur J Clin Microbiol Infect Dis 2015;34:2275-85.**n, bronchiectasis**
13. Nascimento-Carvalho CM, Andrade DC, Vilas-Boas AL. An update on antimicrobial options for childhood community-acquired pneumonia: a critical appraisal of available evidence. Expert Opin Pharmacother 2015:1-26.**n, not an SR**
14. Osowicki J, Carr JP, Bryant PA, et al. Comment on: Comparison of oral amoxicillin given thrice or twice daily to children between 2 and 59 months old with non-severe pneumonia: a randomized controlled trial. J Antimicrob Chemother 2015;70:635-6.**n; comment on article**
15. Osowicki J, Carr JP, Bryant PA, et al. Comment on: Comparison of oral amoxicillin given thrice or twice daily to children between 2 and 59 months old with non-severe pneumonia: A randomized controlled trial. Journal of antimicrobial chemotherapy 2015;70:635-6.**n, comment**
16. Patel AB, Bang A, Singh M, et al. A randomized controlled trial of hospital versus home based therapy with oral amoxicillin for severe pneumonia in children aged 3 - 59 months: The IndiaCLEN Severe Pneumonia Oral Therapy (ISPOT) Study. BMC Pediatr 2015;15:186.**n; oral AB at home versus oral AB at the hospital for severe pneumonia: not a research question**
17. Principi N, Esposito S. Macrolide-resistant Mycoplasma pneumoniae: its role in respiratory infection. J Antimicrob Chemother 2013;68:506-11.**n, not an SR**
18. Soofi S, Ahmed S, Fox MP, et al. Effectiveness of community case management of severe pneumonia with oral amoxicillin in children aged 2-59 months in Matiari district, rural Pakistan: a cluster-randomised controlled trial. Lancet (London, England) 2012;379:729-37.**n, severe pneumonia, community intervention**
19. Stokholm J, Chawes BL, Vissing NH, et al. Azithromycin for episodes with asthma-like symptoms in young children aged 1-3 years: a randomised, double-blind, placebo-controlled trial. Lancet Respir Med 2015.**n; asthma-like symptoms**
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