Summary of findings:

1. Multivalent pneumococcal conjugate vaccines compared to placebo / other vaccine / no treatment for prevention of acute otitis media

Patient or population: Children aged 0-7 years.

Setting: Primary health care.

Intervention: Multivalent pneumococcal conjugate vaccines – 2 & 3 doses.

Comparison: Placebo / Other vaccine / No treatment.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens
		Without multivalent pneumococcal conjugate vaccines	**With multivalent pneumococcal conjugate vaccines**	**Difference**		
Risk of all-cause AOM (PCV 7 and PCV 10) assessed with: signs and symptoms of AOM and otoscopy follow up: range 2 to 2.75 years № of participants: 9258 (3 RCTs) [1,a]	**RR 0.93** (0.86 to 1.00)	22.3%	**20.7%** (19.2 to 22.3)	**1.6% fewer** (3.1 fewer to 0 fewer)	⨁⨁⨁⨁ HIGH	In children vaccinated with PCV compared to no PCV there is less all cause AOM at ~2 years follow-up. NNV ~63
Risk of pneumococcal AOM (PCV 7 and PCV10) assessed with: signs and symptoms of AOM and otoscopy follow up: range 2.6 to 2.75 years № of participants: 7581 (2 RCTs) [1,b]	**RR 0.57** (0.39 to 0.83)	2.0%	**1.1%** (0.8 to 1.7)	**0.9% fewer** (1.2 fewer to 0.3 fewer)	⨁⨁⨁⨁ HIGH [c,d]	In children vaccinated with PCV compared to no PCV vaccine there is less pneumococcal AOM at ~2 years follow-up. NNV ~111
Risk of vaccine-specific AOM (PCV7, PCV10 and PCV 11) assessed with: signs and symptoms of AOM and otoscopy follow up: range 6 months to 2.75 years № of participants: 52079 (5 RCTs) [1,e]	**RR 0.51** (0.43 to 0.60)	1.5%	**0.8%** (0.6 to 0.9)	**0.7% fewer** (0.8 fewer to 0.6 fewer)	⨁⨁⨁⨁ HIGH [c,f]	In children vaccinated with PCV compared to no PCV vaccine there is less vaccine serotype pneumococcal AOM at ~2 years follow-up. NNV ~143
Risk of recurrent AOM (PCV7) assessed with: signs and symptoms of AOM and otoscopy follow up: 2 years № of participants: 1758 (2 RCTs) [1,g]	**RR 0.87** (0.72 to 1.05)	23.0%	**20.0%** (16.6 to 24.2)	3.0% fewer (NS) (6.5 fewer to 1.2 more)	⨁⨁⨁◯ MODERATE [h]	In children vaccinated with PCV 7 compared to no PCV vaccine there are probably no fewer recurrent AOM episodes at 2 years follow-up. NNV Not Applicable

Summary of findings:

1. Multivalent pneumococcal conjugate vaccines compared to placebo / other vaccine / no treatment for prevention of acute otitis media

Patient or population: Children aged 0-7 years.

Setting: Primary health care.

Intervention: Multivalent pneumococcal conjugate vaccines – 2 & 3 doses.

Comparison: Placebo / Other vaccine / No treatment.

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without multivalent pneumococcal conjugate vaccines	**With multivalent pneumococcal conjugate vaccines**	**Difference**		
Insertion of tympanostomy tubes (PCV 7) follow up: range 2 years to 3.5 years № of participants: 41142 (4 RCTs) [2,3,4,5,j]	**RR 0.80** (0.71 to 0.89)	3.1%	**2.5%** (2.2 to 2.8)	**0.6% fewer** (0.9 fewer to 0.3 fewer)	⨁⨁⨁◯ MODERATE [j]	In children vaccinated with PCV 7 compared to no PCV vaccine there are probably fewer TTs at 2-3.5 years follow-up. NNV ~167
Outpatient antibiotic purchases (PCV 10) assessed with: national insurance register follow up: range 14 to 46 months № of participants: 45974 (1 RCT) [6,k]	-	The mean outpatient antibiotic purchases was **1.55** purchases per person-year	-	MD **0.12 purchases per person-year fewer** (0.01 fewer to 0.23 fewer)	⨁⨁⨁◯ MODERATE [l]	In children receiving PCV 10 compared to no PCV there are probably less outpatient antibiotic purchases during 1-4 years follow-up. NNV not evaluable

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm; NNV: Number needed to vaccinate; **MD:** Mean difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: Ewald Meta-analysis 2016 (Eskola 2001, Veenhoven 2003, Tregnaghi 2014)
b. Studies taken from: Ewald Meta-analysis 2016 (Veenhoven 2003, Tregnaghi 2014)
c. Inconsistency: Different vaccines used however low heterogeneity with pooled data.
d. Imprecision: Low event rate however large sample size.
e. Studies taken from: Ewald Meta-analysis 2016 (Black 2000, Eskola 2001, Veenhoven 2003, Tregnaghi 2014, Prymula 2006)
f. Risk of Bias: Black 2000 stopped early for benefit, therefore high risk of over-estimation of effect. However in meta-analysis this trial only contributes 3% weight and removal does not effect estimate of effect. Not rated down.
g. Studies taken from: Ewald Meta-analysis 2016 (Eskola 2001, Gisselsson-Solen 2011)
h. Risk of bias: Lack of blinding. Parental threshold to consult ENT may be lower in children allocated to control treatment (no vaccination) than in those allocated to PCV, which may have introduced (detection) bias. Attrition bias (Gisselsson-Solen 2011)
i. Studies: Meta-analysis of Eskola 2001, Fireman 2003, O'Brien 2008, Palmu 2004.

j. Risk of bias: Attrition bias in follow-up of Black 2000/Fireman 2003. Potential for selection bias in Palmu.
k. Study: Palmu 2014
l. Indirectness: Data for indication not available for all purchases (indication only available for 52% purchases). Assumption made that certain specified antibiotics were prescribed for AOM. Secondary outcome.

References

1. Ewald H, Briel M, Vuichard D, Kreutle V, Zhydkov A, Gloy V. The Clinical Effectiveness of Pneumococcal Conjugate Vaccines: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Deutsches Arzteblatt international. 2016;113(9):139-46. Epub 2016/03/19. doi: 10.3238/arztebl.2016.0139. PubMed PMID: 26987462; PubMed Central PMCID: PMCPMC4802351.
2. Fireman B, Black SB, Shinefield HR, Lee J, Lewis E, Ray P. Impact of the pneumococcal conjugate vaccine on otitis media. The Pediatric infectious disease journal. 2003;22(1):10-6. Epub 2003/01/25. doi: 10.1097/01.inf.0000045221.96634.7c. PubMed PMID: 12544402.
3. Eskola J, Kilpi T, Palmu A, Jokinen J, Haapakoski J, Herva E, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. The New England journal of medicine. 2001;344(6):403-9. Epub 2001/02/15. doi: 10.1056/nejm200102083440602. PubMed PMID: 11172176.
4. O'Brien KL, David AB, Chandran A, Moulton LH, Reid R, Weatherholtz R, et al. Randomized, controlled trial efficacy of pneumococcal conjugate vaccine against otitis media among Navajo and White Mountain Apache infants. The Pediatric infectious disease journal. 2008;27(1):71-3. Epub 2007/12/29. doi: 10.1097/INF.0b013e318159228f. PubMed PMID: 18162944.
5. Palmu AA, Verho J, Jokinen J, Karma P, Kilpi TM. The seven-valent pneumococcal conjugate vaccine reduces tympanostomy tube placement in children. The Pediatric infectious disease journal. 2004;23(8):732-8. Epub 2004/08/06. PubMed PMID: 15295223.
6. Palmu AA, Jokinen J, Nieminen H, Rinta-Kokko H, Ruokokoski E, Puumalainen T, et al. Effect of pneumococcal Haemophilus influenzae protein D conjugate vaccine (PHiD-CV10) on outpatient antimicrobial purchases: a double-blind, cluster randomised phase 3-4 trial. The Lancet Infectious diseases. 2014;14(3):205-12. Epub 2013/11/30. doi: 10.1016/s1473-3099(13)70338-4. PubMed PMID: 24287186.

Summary of findings:

2. Seasonal influenza vaccine compared to placebo / no treatment for prevention of acute otitis media

Patient or population: Children aged 6 months to 6 years of age.

Setting: Primary health care.

Intervention: Seasonal influenza vaccine [Studies used: Trivalent, Live, Cold Adapted Influenza Vaccine (CAIV-T) 1-2 doses for 1-2 years, Live Attenuated Influenza Vaccine (LAIV) intra-nasally 1-2 doses for 1-2 years, trivalent sub virion influenza virus vaccine 1-2 doses, CAIV 3 doses intra-nasally 60 days apart).

Comparison: Placebo / No treatment.

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without seasonal influenza vaccine	**With seasonal influenza vaccine**	**Difference**		
At least one episode of AOM assessed with: otoscopy +/- tympanometry follow up: range 6 to 18 months № of participants: 4736 (5 RCTs) [1,a]	**RR 0.80** (0.67 to 0.96)	26.4%	**21.1%** (17.7 to 25.3)	**5.3% fewer** (8.7 fewer to 1.1 fewer)	⨁⨁⨁◯ MODERATE [b,c,d]	In children receiving seasonal influenza vaccine compared to placebo / no treatment there is probably less risk of OM during 6-18 months follow-up. NNV ~19
AOM by season (respiratory and influenza season) assessed with: otoscopy +/- tympanometry follow up: median 6 months № of participants: 899 (2 RCTs) [1,e]	not pooled	42.9%	not pooled	not pooled	⨁⨁◯◯ LOW [b,f,g]	In children receiving seasonal influenza vaccine compared to placebo / no treatment there is insufficient evidence for or against vaccination during respiratory and influenza season. NNV Not Applicable
Adverse events - Fever follow up: range 11 days to 8 months № of participants: 10199 (6 RCTs) [1,h]	**RR 1.15** (1.06 to 1.24)	17.4%	**20.0%** (18.4 to 21.5)	**2.6% more** (1 more to 4.2 more)	⨁⨁⨁◯ MODERATE [i]	In children receiving seasonal influenza vaccine compared to placebo / no treatment there are probably more adverse events of fever. NNH ~39
Courses of antibiotics assessed with: number antibiotic prescriptions. follow up: range 6 to 12 months № of participants: 1223 (2 RCTs) [1,j]	**RR 0.70** (0.59 to 0.83)	36.2%	**25.4%** (21.4 to 30.1)	**10.9% fewer** (14.9 fewer to 6.2 fewer)	⨁⨁⨁◯ MODERATE [k]	In children receiving seasonal influenza vaccine compared to placebo / no treatment there is probably fewer antibiotic courses over 6-12 months follow-up. NNV ~10

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm; NNV: Number needed to vaccinate; **MD:** Mean difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: Cochrane Review, Norhayati 2015 (Belshe 2000, Clements 1995, Hoberman 2003, Lum 2010, Vesikari 2006)
b. Risk of bias: Clements 1995 was a prospective cohort study where participants were not blinded, however outcome assessor blinded. Not rated down.
c. Inconsistency: High heterogeneity noted however estimate of effect in same direction.
d. Indirectness: Difference formulations and routes of vaccination given. Trivalent cold-adapted inactivated vaccine (CAIV), trivalent inactivated vaccines used in difference studies, given intramuscularly and intranasally. Not considered to have significant effect on results, therefore not rated down.
e. Studies taken from: Cochrane Review, Norhayati 2015 (Clements 1995, Hoberman 2003). Not pooled due to substantial heterogeneity.
f. Inconsistency: Two trials with effect estimates in opposite directions. High heterogeneity precluded meta-analysis.
g. Imprecision: Optimal information size not reached.
h. Studies taken from: Cochrane Review, Norhayati 2015 (Bracco 2009, Gruber 1996, Lum 2010, Swierkosz 1994, Tam 2007, Vesikari 2006)
i. Risk of Bias: Attrition bias in 2 studies (Swierkosz 1994, Bracco 2009)
j. Studies taken from: Cochrane Review, Norhayati 2015 (Marchisio 2002, Vesikari 2006)
k. Risk of bias: Single blinded study (participants not blinded - risk of under-reporting symptoms) Marchisio.

References

1. Norhayati MN, Ho JJ, Azman MY. Influenza vaccines for preventing acute otitis media in infants and children. The Cochrane database of systematic reviews. 2015(3):Cd010089. Epub 2015/03/25. doi: 10.1002/14651858.CD010089.pub2. PubMed PMID: 25803008.

Summary of findings:

3 Relative effect for association: breastfeeding compared to other feeding for prevention of otitis media

Patient or population: Children aged 0 to 8 years.

Setting: Community / Primary health care.

Intervention: Breastfeeding. Duration varied from 6 months to 8 years.

Comparison: Other feeding.

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Breastfeeding / Never / "Less" Breastfeeding	**With Breastfeeding / Ever / "More" Breastfeeding**	**Difference**		
Annual incidence rate of AOM episodes in the first two years of life - exclusive breast feeding compared with nonexclusive breastfeeding for the first 6 months of life. assessed with: physician/doctor diagnosed AOM, parent/self-reported AOM, or AOM recorded on health-related databases. follow up: median 2 years № of participants: 17735 (5 observational studies) [1,a]	**OR 0.57** (0.44 to 0.75)	No raw data available			⨁◯◯◯ VERY LOW [b,c]	In children exclusively breastfed for first 6 months of life compared nonexclusive breast feeding there are possibly fewer AOM episodes in first 2 years of life. NNT not evaluable
Annual incidence rate of AOM episodes in first two years of life - ever breast fed compared no never breast fed over those two years assessed with: physician/doctor diagnosed AOM, parent/self-reported AOM, or AOM recorded on health-related databases. follow up: median 2 years № of participants: 19650 (5 observational studies) [1,d]	**OR 0.67** (0.56 to 0.80)	No raw data available			⨁◯◯◯ VERY LOW [b,c]	In children breastfed compared to other feeding there are possibly fewer AOM episodes in first 2 years of life. NNT not evaluable

Summary of findings:

3 Relative effect for association: breastfeeding compared to other feeding for prevention of otitis media

Patient or population: Children aged 0 to 8 years.

Setting: Community / Primary health care.

Intervention: Breastfeeding. Duration varied from 6 months to 8 years.

Comparison: Other feeding.

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Breastfeeding / Never / "Less" Breastfeeding	**With Breastfeeding / Ever / "More" Breastfeeding**	**Difference**		
Annual incidence rate of AOM episodes in first two years of life: "more" versus "less" breastfeeding assessed with: physician/doctor diagnosed AOM, parent/self-reported AOM, or AOM recorded on health-related databases. follow up: median 2 years № of participants: 39380 (12 observational studies) [1,e]	**OR 0.67** (0.59 to 0.76)	No raw data available			⨁◯◯◯ VERY LOW [b,f]	In children breastfed "more" compared to "less" there are possibly fewer AOM episodes in first 2 years of life. NNT not evaluable
Risk of AOM beyond two years of age: "more" versus "less" breastfeeding assessed with: physician/doctor diagnosed AOM, parent/self-reported AOM, or AOM recorded on health-related databases. follow up: range 2 to 8 years № of participants: 3943 (7 observational studies) [1,g]	**OR 1.03** (0.59 to 1.79)	No raw data available			⨁◯◯◯ VERY LOW [b,h]	In children breastfed "more" compared to "less" there is possibly no difference in long term outcomes of AOM. NNT not evaluable

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: Bowatte 2015 (Duffy 1997, Hetzner 2009, Ladomenou 2010, Raisler 1999, Scariati 1997)
b. Risk of Bias: Recall bias; some studies had mailed questionnaires which may lead to mis-classification of disease process.
c. Inconsistency: High heterogeneity noted with complete data.
d. Studies taken from: Bowatte 2015 (Hetzner 2009, Labout 2011, Raisler 1999, Teele 1989, Scariati 1997)
e. Studies taken from: Bowatte 2015 (Alho 1990, Duffy 1997, Duncan 1993, Freeman 2007, Hetzner 2009, Kero 1987, Labout 2011, Ladomenou 2010, Raisler 1999, Teele 1989, Vernacchio 2004, Scariati 1997)
f. Inconsistency: High heterogeneity noted with complete data.
g. Studies taken from: Bowatte 2015 (Fridel 2014, Li 2014, Teele 1989, Hatakka 2010, Homoe 1999, Patel 2006, Voganzianos 2007)
h. Inconsistency: High heterogeneity

References

1. Bowatte G, Tham R, Allen KJ, Tan DJ, Lau M, Dai X, et al. Breastfeeding and childhood acute otitis media: a systematic review and meta-analysis. Acta paediatrica (Oslo, Norway : 1992). 2015;104(467):85-95. Epub 2015/08/13. doi: 10.1111/apa.13151. PubMed PMID: 26265016.

Summary of findings:

4. Hygiene promotion programs compared to no intervention for prevention of acute otitis media

Patient or population: Children with mean age of 3.5 years.

Setting: Primary health care / Community Day Care Centres.

Intervention: Hygiene promotion programs - The infection prevention program consisted of intensified handwashing, the use of an alcohol-based oilydisinfectant, directions on the use of disposable towels, cleaning of the child-care centres and regular washing of the toys, or if that was not possible, circulation of the toys so that they were taken out of use for at least every other week. One healthy adult person always served food and tooth brushing was withdrawn. Attention was paid to diaper changing practices and the places where this was done. The personnel were encouraged to take sick leave at first appearance of symptoms (exact procedures and instructions given to the personnel are available on request). Duration was over 15 months.

Comparison: No intervention

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without hygiene promotion programs	**With hygiene promotion programs**	**Difference**		
Mean number of days with ear ache (symptom) per person year at risk < 3years of age assessed with: parental report follow up: median 8 months № of participants: 661 (1 RCT) [1,a]	-	The mean number of days with ear ache (symptom) per person year at risk < 3years of age was **6.8** per person year	-	MD **1.9 per person year fewer** (1.43 fewer to 2.3 fewer)	⨁⨁◯◯ LOW [b,c]	In children <3 years attending daycare centres with hygiene promotion programs compared to no intervention there are possibly fewer days with ear ache per person year at risk. NNT not evaluable
Mean number of days with ear ache (symptom) per person year at risk > 3 years of age assessed with: parental report follow up: median 8 months № of participants: 861 (1 RCT) [1,a]	-	The mean number of days with ear ache (symptom) per person year at risk > 3 years of age was **2** per person year	-	MD **0.6 per person year fewer** (0.5 fewer to 0.9 fewer)	⨁⨁◯◯ LOW [b,c]	In children >3 years attending daycare centres with hygiene promotion programs compared to no intervention there are possibly fewer days with ear ache per person year at risk. NNT not evaluable

Summary of findings:

4. Hygiene promotion programs compared to no intervention for prevention of acute otitis media

Patient or population: Children with mean age of 3.5 years.

Setting: Primary health care / Community Day Care Centres.

Intervention: Hygiene promotion programs - The infection prevention program consisted of intensified handwashing, the use of an alcohol-based oilydisinfectant, directions on the use of disposable towels, cleaning of the child-care centres and regular washing of the toys, or if that was not possible, circulation of the toys so that they were taken out of use for at least every other week. One healthy adult person always served food and tooth brushing was withdrawn. Attention was paid to diaper changing practices and the places where this was done. The personnel were encouraged to take sick leave at first appearance of symptoms (exact procedures and instructions given to the personnel are available on request). Duration was over 15 months.

Comparison: No intervention

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without hygiene promotion programs	**With hygiene promotion programs**	**Difference**		
Mean number of days with ear ache (infectious episode separated by at least 3 symptom free days) per person year at risk <3 years of age assessed with: parental report follow up: median 8 months № of participants: 661 (1 RCT) [1,a]	-	The mean number of days with ear ache (infectious episode separated by at least 3 symptom free days) per person year at risk <3 years of age was **2** per person year	-	MD **0.4 per person year fewer** (0.2 fewer to 0.7 fewer)	⨁⨁◯◯ LOW [b,c]	In children <3 years attending daycare centres with hygiene promotion programs compared to no intervention there are possibly less infectious episodes characterised by ear ache per person year at risk. NNT not evaluable
Mean number of days with ear ache (infectious episode separated by at least 3 symptom free days) per person year at risk >3 years of age assessed with: parental report follow up: median 8 months № of participants: 861 (1 RCT) [1,a]	-	The mean number of days with ear ache (infectious episode separated by at least 3 symptom free days) per person year at risk >3 years of age was **0.7** per person year	-	MD **0.1 per person year fewer** (0.02 fewer to 0.29 fewer)	⨁⨁◯◯ LOW [b,c]	In children >3 years attending daycare centres with hygiene promotion programs compared to no intervention there are possibly less infectious episodes characterised by ear ache per person year at risk. NNT not evaluable

Summary of findings:

4. Hygiene promotion programs compared to no intervention for prevention of acute otitis media

Patient or population: Children with mean age of 3.5 years.

Setting: Primary health care / Community Day Care Centres.

Intervention: Hygiene promotion programs - The infection prevention program consisted of intensified handwashing, the use of an alcohol-based oilydisinfectant, directions on the use of disposable towels, cleaning of the child-care centres and regular washing of the toys, or if that was not possible, circulation of the toys so that they were taken out of use for at least every other week. One healthy adult person always served food and tooth brushing was withdrawn. Attention was paid to diaper changing practices and the places where this was done. The personnel were encouraged to take sick leave at first appearance of symptoms (exact procedures and instructions given to the personnel are available on request). Duration was over 15 months.

Comparison: No intervention

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without hygiene promotion programs	**With hygiene promotion programs**	**Difference**		
Mean number of visits to a doctor because of an attack of acute otitis media (all ages) assessed with: parental report follow up: median 8 months № of participants: 1522 (1 RCT) [1,a]	-	The mean number of visits to a doctor because of an attack of acute otitis media (all ages) was **1.5** visits/child/year	-	MD **0.4 visits/child/year fewer**	⨁⨁◯◯ LOW [c,d]	In children attending daycare centres with hygiene promotion programs compared to no intervention there are possibly fewer doctor visits for AOM.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm; **MD:** Mean difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Study: Uhari 1999
b. Risk of Bias: Noted that open label, however complete blinding difficult in study circumstances. Not rated down.
c. Indirectness: Otitis media not primary outcome. Only children in daycare centres studied. Ear ache used as a surrogate for middle ear disease.
d. Indirectness: Diagnostic criteria for otitis media not standardised (by parental report).

References

1. Uhari M, Mottonen M. An open randomized controlled trial of infection prevention in child day-care centers. The Pediatric infectious disease journal. 1999;18(8):672-7. Epub 1999/08/26. PubMed PMID: 10462334.

Summary of findings:

5. Relative effect for association: Parental counselling to restrict pacifier/dummy use compared to unrestricted pacifier/dummy use for prevention of acute otitis media

Patient or population: Children aged 0 to 7.24 years of age.

Setting: Primary health care / Day-care centres / Community.

Intervention: Parental counselling to restrict pacifier/dummy use (limit to moments of falling asleep after 6 months and discontinue use after 10 months of age). Single counselling session was provided.

Comparison: Unrestricted pacifier/dummy use.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens
		Without Parental counselling to restrict pacifier/dummy use	**With Parental counselling to restrict pacifier/dummy use**	**Difference**		
AOM per person-months at risk assessed with: parental report follow up: median 4.6 months № of participants: 484 (1 RCT) [1,a]	Study in Finland found that with parental counselling against pacifier use there was a 29% lower occurrence of AOM/PMR in the intervention group. In the total series the occurrence of AOM/PMR was 33% higher in the group of children who used pacifier continuously than in those not using one or using it when falling asleep. [b]				⨁⨁◯◯ LOW [c,d,e]	In children who have restricted pacifier use compared to unrestricted pacifier use there is possibly less AOM per person months at risk. NNT Not able to be calculated (raw data not available)
Risk of rAOM (>3 episodes of AOM) assessed with: physician diagnosed AOM follow up: range 10 months to 5.6 years № of participants: 884 (2 observational studies) [2,3,f]	**RR 0.49** (0.36 to 0.68)	21.6%	**10.6%** (7.8 to 14.7)	**11.0% fewer** (13.8 fewer to 6.9 fewer)	⨁◯◯◯ VERY LOW [g,h,i]	In children who have restricted pacifier use compared to no pacifier use there are possibly fewer with rAOM at up to ~5 years follow-up. NNT 10

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm; **MD:** Mean difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Study: Niemela 2000
b. Raw data not reported.
c. Risk of Bias: Nature of intervention makes blinding difficult.
d. Indirectness: Diagnosis of AOM was not made according predefined criteria or by trained staff but during routine visits to health care centres or private practices.
e. Imprecision: Single, small study
f. Studies: Rovers 2008 and Niemela 1995
g. Inconsistency: Pacificer use only measured at baseline in Rovers 2008. Diagnosis of AOM made by different physicians with differing pre-defined criteria. Short term follow-up in Niemela 1995 (median 10 months).
h. Imprecision: Optimal information size not reached.

i. Possible confounding: All children in Niemela 1995 attended daycare centres - not adjusted.

References

1. Niemela M, Pihakari O, Pokka T, Uhari M. Pacifier as a risk factor for acute otitis media: A randomized, controlled trial of parental counseling. Pediatrics. 2000;106(3):483-8. Epub 2000/09/02. PubMed PMID: 10969091.
2. Niemela M, Uhari M, Mottonen M. A pacifier increases the risk of recurrent acute otitis media in children in day care centers. Pediatrics. 1995;96(5 Pt 1):884-8. Epub 1995/11/01. PubMed PMID: 7478830.
3. Rovers MM, Numans ME, Langenbach E, Grobbee DE, Verheij TJ, Schilder AG. Is pacifier use a risk factor for acute otitis media? A dynamic cohort study. Family practice. 2008;25(4):233-6. Epub 2008/06/20. doi: 10.1093/fampra/cmn030. PubMed PMID: 18562333.

Summary of findings:

6. Relative effect of association: household tobacco smoke exposure compared to no household tobacco smoke exposure for prevention of acute otitis media

Patient or population: Children aged 0 to18 years

Setting: Community / Primary health care.

Intervention: Household tobacco smoke exposure. Duration ranged from 6 months to 10 years.

Comparison: No household tobacco smoke exposure.

Outcome No. of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens
		Without household tobacco smoke exposure	**With household tobacco smoke exposure**	**Difference**		
Risk of middle ear infection (includes AOM, OME, recurrent otitis media, chronic otitis media) with any household member smoking assessed with: parental report / health record review follow up: median 2 years (37 observational studies) [1,a]	**OR 1.32** (1.20 to 1.45)	Raw data not available.			⨁◯◯◯ VERY LOW [c,d]	In children exposed to household smoking compared to no household smoking there is possibly an increased risk of OM during 2 years follow-up. NNT not evaluable
Risk of middle ear infection (includes AOM, OME, recurrent otitis media, chronic otitis media) with postnatal maternal smoking assessed with: parental report / health record review follow up: range 6 months to 10 years (14 observational studies) [1,b]	**OR 1.53** (1.22 to 1.92)	Raw data not available			⨁◯◯◯ VERY LOW [c,d]	In children exposed to postnatal maternal smoking compared to no smoking there is possibly an increased risk of OM between 6 months to 10 years of age. NNT not evaluable

Summary of findings:

6. Relative effect of association: household tobacco smoke exposure compared to no household tobacco smoke exposure for prevention of acute otitis media

Patient or population: Children aged 0 to18 years

Setting: Community / Primary health care.

Intervention: Household tobacco smoke exposure. Duration ranged from 6 months to 10 years.

Comparison: No household tobacco smoke exposure.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens
		Without household tobacco smoke exposure	**With household tobacco smoke exposure**	**Difference**		
Risk of requiring surgery for middle ear disease with any household member smoking assessed with: parental report / health record review follow up: median 12 months (11 observational studies) [1,e]	**R 1.62** (1.31 to 1.98)	Raw data not available			⨁◯◯◯ VERY LOW [c,d]	In children exposed to household smoking compared to no household smoking there is possibly an increased risk of requiring surgery for OM during 12 months follow-up.
Diagnosis of OM (AOM, OME, TM perforation with or without discharge) - observational study in Indigenous children. assessed with: ENT examination, otoscopy, pneumatic otoscopy and tympanometry follow up: median 12 months № of participants: 80 (1 observational study) [2,f]	**OR 3.54** (1.68 to 7.47)	55.2%	**81.3%** (67.4 to 90.2) [g]	**26.2% more** (12.2 more to 35 more)	⨁◯◯◯ VERY LOW [h,i]	In Aboriginal children exposed to household tobacco smoke compared to no household tobacco smoke there are possibly more OM episodes at 12 months follow-up. NNT not evaluable

Summary of findings:

6. Relative effect of association: household tobacco smoke exposure compared to no household tobacco smoke exposure for prevention of acute otitis media

Patient or population: Children aged 0 to18 years

Setting: Community / Primary health care.

Intervention: Household tobacco smoke exposure. Duration ranged from 6 months to 10 years.

Comparison: No household tobacco smoke exposure.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens
		Without household tobacco smoke exposure	**With household tobacco smoke exposure**	**Difference**		
Post-operative tympanostomy tube otorrhoea with household smoking assessed with: parental report follow up: mean 323 days № of participants: 191 (1 observational study) [3,j]	**OR 2.310** (1.734 to 6.028)	45.3%	**65.7%** (58.9 to 83.3)	**20.4% more** (13.6 more to 38 more)	⨁◯◯◯ VERY LOW [k,l]	In children exposed to household tobacco smoke compared to no tobacco smoke there is possibly more post-operative TTO at ~1 year follow-up. NNT not evaluable

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

OR: Odds ratio; **CI:** Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: Jones Systematic Review and Meta-analysis 2012 (Adair-Bischoff and Sauve 1998, Alho 1993, Apostolopoulos 1998, Barr and Coatesworth 1991, Bentdal 2007, Collet 1995, da Costa 2004, Daly 2007, Engel 1999, Etzel 1992, Froom 2001, Gliddon and Sutton 2001, Gryczyska1999, Gultekin 2010, Hinton and Buckley 1988, Homøe 1999, Inversen 1985, Jacoby 2008, Lasisi 2007, Lee 2003, Lieuand Feinstein 2002, Lubianca Neto 1999, Paradise 1997, Pukander 1985, Rylander and Mégarand 2000, Safavi Naini 2002, Saim 1997, Salazar 1997, Shiva 2003, Sophia 2010, Stathis 1999, Stenström 1993, Stachan and Cook 1990, Tainio 1998, Teele 1989, Zenellis 2005, Zielhui 1989.

b. Risk of Bias: Recall bias in some studies as AOM is by parental report.

c. Inconsistency: High heterogeneity.

d. Studies taken from: Adair-Bischoff and Sauve 1998, Barr and Coatesworth 1991, Bennett and Haggard 1998, Daigler 1991, Daly 2007, Ey 1995, Gliddon and Sutton 2001, Green and Cooper 1991, Gultekin 2010, Håberg 2010, Hammarén-Malmi 2005, Hammarén-Malmi 2007, Lieu and Feinstein 2002, Stenström and Ingvarsson 1997.

e. Studies taken from: Jones Systematic Review and Meta-analysis 2012 (Hinton 1989, Hinton 1993, Ilicali 1999, Ilicali 2001, Kitchens 1995, Kraemer 1983, Rasmussen 1993, Rowe-Jones and Brockbank 1992, Said 1978, Stahlberg 1986, Willat 1986).

f. Study: Jacoby 2008

h. Risk of Bias: Risk of reporter bias as tobacco smoke exposure recorded as per carer report.

i. Imprecision: Small, single study

j. Study: Bizzell 2017

k. Risk of Bias: Risk of recall bias as outcome based on parental report.

l. Imprecision: Small, single study.

References

1. Jones LL, Hassanien A, Cook DG, Britton J, Leonardi-Bee J. Parental smoking and the risk of middle ear disease in children: a systematic review and meta-analysis. Archives of pediatrics & adolescent medicine. 2012;166(1):18-27. Epub 2011/09/07. doi: 10.1001/archpediatrics.2011.158. PubMed PMID: 21893640.
2. Jacoby PA, Coates HL, Arumugaswamy A, Elsbury D, Stokes A, Monck R, et al. The effect of passive smoking on the risk of otitis media in Aboriginal and non-Aboriginal children in the Kalgoorlie-Boulder region of Western Australia. The Medical journal of Australia. 2008;188(10):599-603. Epub 2008/05/20. PubMed PMID: 18484936.
3. Bizzell JG, Cox MD, Wang AR, Richter GT, Nolder AR. The impact of tobacco exposure on development of otorrhea after myringotomy tube placement. International journal of pediatric otorhinolaryngology. 2017;92:67-9. Epub 2016/12/26. doi: 10.1016/j.ijporl.2016.10.024. PubMed PMID: 28012536.

Summary of findings:

7 Second-hand smoke prevention program compared to no intervention for prevention of acute otitis media

Patient or population: Australian Aboriginal and Maori children aged 4 to 12 months of age.

Setting: Community / Primary health care.

Intervention: Second-hand smoke (SHS) prevention program – three "behavioural coaching" face-to-face sessions for 3 months.

Comparison: No intervention.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens
		Without intervention	**With SHS prevention program**	**Difference**		
New episodes of otitis media assessed with: parental report and clinician review of medical record follow up: median 12 months № of participants: 293 (1 RCT) [1,a]	**RR 1.13** (0.74 to 1.73)	64.2%	**72.5%** (47.5 to 100.0)	8.3% more (NS) (16.7 fewer to 46.9 more)	⨁⨁◯◯ LOW [b,c]	In Australian Aboriginal and Maori children whose parents receive SHS intervention programs there is possibly no reduction in new episodes of OM during 12 months. NNT not applicable

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm; **SHS**: Second Hand Smoke

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Study: Walker 2015
b. Risk of Bias: Participants not blinded to intervention. Outcome assessors blinded.
c. Imprecision: Small, single study

References

1. Walker N, Johnston V, Glover M, Bullen C, Trenholme A, Chang A, et al. Effect of a family-centered, secondhand smoke intervention to reduce respiratory illness in indigenous infants in Australia and New Zealand: a randomized controlled trial. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2015;17(1):48-57. Epub 2014/08/27. doi: 10.1093/ntr/ntu128. PubMed PMID: 25156527; PubMed Central PMCID: PMCPMC4282121.

Summary of findings:

8. Probiotics compared to placebo for prevention of acute otitis media

Patient or population: Children aged 0 to 18 years.

Setting: Community / Primary health care.

Intervention: Probiotics (Studies used: Lactobacillus rhamnosus GG, multi-probiotic formula, Bifidobacterium animalis subsp. lactis BB-12). Duration varied from 3 to 12 months.

Comparison: Placebo.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens
		Without probiotics	**With probiotics**	**Difference**		
Incidence of AOM during treatment with probiotics (Lactobacillus rhamnosus GG) assessed with: physician diagnosed AOM follow up: range 3 to 12 months № of participants: 1805 (4 RCTs) [1,a]	**RR 0.76** (0.64 to 0.91)	24.4%	**18.5%** (15.6 to 22.2)	**5.9% fewer** (8.8 fewer to 2.2 fewer)	⨁⨁◯◯ LOW [b,c]	In children receiving probiotics (LGG) compared to placebo there is possibly fewer episodes of AOM at 3-12 months follow-up. NNT ~17
≥1 episodes of AOM during treatment with multi-probiotic formula in children aged 7-13 months at high risk of AOM assessed with: physician assessment follow up: median 1 years № of participants: 224 (1 RCT) [2,d,e]	**RR 1.0** (0.8 to 1.2)	71.4%	**71.4%** (57.1 to 85.7)	0.0% fewer (NS) (14.3 fewer to 14.3 more)	⨁⨁◯◯ LOW [f]	In children 7-13 months at high risk of AOM receiving probiotics (multi-probiotic formula) compared to placebo there is possibly no difference in AOM episodes during 1 year follow-up. NNT Not Applicable
Episodes of AOM (any) during treatment with Bifidobacterium animalis subsp. lactis BB-12 in well infants from 1 month of age assessed with: parental report of doctor diagnosed AOM follow up: median 8 months № of participants: 69 (1 RCT) [3,g]	**RR 1.54** (0.62 to 3.87)	17.1%	**26.4%** (10.6 to 66.3)	9.3% more (NS) (6.5 fewer to 49.2 more)	⨁◯◯◯ VERY LOW [h,i]	In infants receiving probiotics (BB-12) compared to placebo there is possibly no reduction in AOM episodes during 8 months follow-up. NNT Not Applicable

Summary of findings:

8. Probiotics compared to placebo for prevention of acute otitis media

Patient or population: Children aged 0 to 18 years.

Setting: Community / Primary health care.

Intervention: Probiotics (Studies used: Lactobacillus rhamnosus GG, multi-probiotic formula, Bifidobacterium animalis subsp. lactis BB-12). Duration varied from 3 to 12 months.

Comparison: Placebo.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens
		Without probiotics	**With probiotics**	**Difference**		
Adverse events (gastrointestinal and dermatological) follow up: range 3 to 12 months № of participants: 586 (3 RCTs) [2,4,5,j,k]	**RR 0.88** (0.52 to 1.47)	24.2%	**21.3%** (12.6 to 35.6)	2.9% fewer (NS) (11.6 fewer to 11.4 more)	⨁⨁◯◯ LOW [c]	In children receiving probiotics compared to placebo there is possibly no difference in adverse events during 3-12 months follow-up. NNH Not Applicable.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm; **MD:** Mean difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: Liu Meta-analysis 2013 (Hatakka 2001, Hojsak 2010, Kukkonen 2008, Rautava 2009)
b. Indirectness: Differences in probiotic composition (however all contained Lactobacillus rhamnosus GG). Differences in regimens used. Poor definition of outcome measures between studies. However estimate if effect similar amongst studies. Not rated down.
c. Imprecision: Optimal information size not reached. Low event rate with many studies reporting no adverse events.
d. Defined as high risk if exposed to other children (day-care center attendance or with 2 siblings) and those with history of at least 1 episode of AOM before the current one.
e. Study: Cohen 2013
f. Imprecision: Broad estimate of effect. Small study.
g. Study: Taipale 2011
h. Risk of Bias: Recall bias
i. Imprecision: Small single trial. Broad estimate of effect.
j. Several other studies reported no differences in adverse events between probiotics and control groups however raw data not available.
k. Studies: Meta-analysis of Cohen 2013, Hojsak 2010, Rautava 2009.

References

1. Liu S, Hu P, Du X, Zhou T, Pei X. Lactobacillus rhamnosus GG supplementation for preventing respiratory infections in children: a meta-analysis of randomized, placebo-controlled trials. Indian pediatrics. 2013;50(4):377-81. Epub 2013/05/15. PubMed PMID: 23665598.
2. Cohen R, Martin E, de La Rocque F, Thollot F, Pecquet S, Werner A, et al. Probiotics and prebiotics in preventing episodes of acute otitis media in high-risk children: a randomized, double-blind, placebo-controlled study. The Pediatric infectious disease journal. 2013;32(8):810-4. Epub 2013/02/23. doi: 10.1097/INF.0b013e31828df4f3. PubMed PMID: 23429555.
3. Taipale T, Pienihakkinen K, Isolauri E, Larsen C, Brockmann E, Alanen P, et al. Bifidobacterium animalis subsp. lactis BB-12 in reducing the risk of infections in infancy. The British journal of nutrition. 2011;105(3):409-16. Epub 2010/09/25. doi: 10.1017/s0007114510003685. PubMed PMID: 20863419.
4. Hojsak I, Snovak N, Abdovic S, Szajewska H, Misak Z, Kolacek S. Lactobacillus GG in the prevention of gastrointestinal and respiratory tract infections in children who attend day care centers: a randomized, double-blind, placebo-controlled trial. Clinical nutrition (Edinburgh, Scotland). 2010;29(3):312-6. Epub 2009/11/10. doi: 10.1016/j.clnu.2009.09.008. PubMed PMID: 19896252.
5. Rautava S, Salminen S, Isolauri E. Specific probiotics in reducing the risk of acute infections in infancy--a randomised, double-blind, placebo-controlled study. The British journal of nutrition. 2009;101(11):1722-6. Epub 2008/11/07. doi: 10.1017/s0007114508116282. PubMed PMID: 18986600.

Summary of findings:

9. Vitamin D supplementation compared to placebo for prevention of acute otitis media

Patient or population: Children aged 1 to 5 years who are otitis prone (defined as at least 3 episodes of AOM in the preceding 6 months or at least 4 episodes in the preceding 12 months, with the most recent episode in the previous 2–8 weeks)

Setting: Primary health care.

Intervention: Vitamin D supplementation (1000 IU per day of Vitamin D_3). Duration was for 4 months.)

Comparison: Placebo.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens
		Without Vitamin D supplementation	**With Vitamin D supplementation**	**Difference**		
>1 AOM episode (includes AOMwiP and AOMwoP) assessed with: fever, earache, irritability and otoscopy +/- tympanometry follow up: range 1 to 6 months № of participants: 116 (1 RCT) [1,a]	**RR 0.68** (0.49 to 0.96)	65.5%	**44.6%** (32.1 to 62.9)	**21.0% fewer** (33.4 fewer to 2.6 fewer)	⨁⨁◯◯ LOW [b,c]	In otitis prone children treated with vitamin D supplementation compared to placebo there is possibly a reduction in AOM (includes AOMwiP and AOMwoP) episodes at 1-6 months follow up. NNT ~5
>1 episode of AOMwoP assessed with: fever, earache, irritability and otoscopy +/- tympanometry follow up: range 1 to 6 months № of participants: 116 (1 RCT) [1,a]	**RR 0.34** (0.19 to 0.64)	50.0%	**17.0%** (9.5 to 32.0)	**33.0% fewer** (40.5 fewer to 18 fewer)	⨁⨁◯◯ LOW [b,c]	In otitis prone children treated with vitamin D supplementation compared to placebo there is possibly a reduction in uncomplicated AOM episodes at 1-6 months follow up. NNT ~3
Adverse Events (reported as "significant", not defined) № of participants: 116 (1 RCT) [1,a]	not estimable	0.0%	**0.0%** (0.0 to 0.0)	0.0% fewer (0 fewer to 0 fewer)	⨁⨁◯◯ LOW [b,c]	In otitis prone children treated with vitamin D supplementation compared to placebo there is possibly no increase in on adverse events. NNH Not evaluable

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm; **MD:** Mean difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Study: Marchisio 2013
b. Indirectness: Children studied during European winter (may not be applicable to warmer environments).Only children with rAOM studied.
c. Imprecision: Single, small study

References

1. Marchisio P, Consonni D, Baggi E, Zampiero A, Bianchini S, Terranova L, et al. Vitamin D supplementation reduces the risk of acute otitis media in otitis-prone children. The Pediatric infectious disease journal. 2013;32(10):1055-60. Epub 2013/05/23. doi: 10.1097/INF.0b013e31829be0b0. PubMed PMID: 23694840.

Summary of findings:

10 Xylitol (administered as syrup, gum or lozenge) compared to placebo for prevention of acute otitis media

Patient or population: Children aged 6 months to 7 years.

Setting: Primary health care.

Intervention: Xylitol administered as syrup, gum or lozenge. (Studies used doses 5-10 grams per day, in 3-5 divided doses). Duration was for 2-3 months.

Comparison: Placebo. [a]

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens
		Without xylitol (administered as syrup, gum or lozenge)	**With xylitol (administered as syrup, gum or lozenge)**	**Difference**		
Final diagnosis of at least one episode of AOM assessed with: otoscopy / pneumatic otoscopy +/- tympanometry + signs / symptoms of AOM follow up: range 2 to 3 months № of participants: 1826 (3 RCTs) [1,b]	**RR 0.75** (0.65 to 0.88)	29.9%	**22.4%** (19.4 to 26.3)	**7.5% fewer** (10.5 fewer to 3.6 fewer)	⨁⨁⨁◯ MODERATE [c,d,e]	In children receiving xylitol compared to placebo there is probably a reduction in AOM episodes during treatment. NNT ~14
Final diagnosis of at least one episode of AOM - during respiratory infection assessed with: tympanometry + pneumatic otoscopy follow up: median 3 weeks № of participants: 1253 (1 RCT) [1,f]	**RR 1.13** (0.83 to 1.53)	11.5%	**13.0%** (9.5 to 17.6)	1.5% more (NS) (2 fewer to 6.1 more)	⨁⨁⨁◯ MODERATE [c,g,h]	In children receiving xylitol compared to placebo during respiratory infection there is probably no reduction in AOM episodes during 3 weeks follow-up. NNT Not applicable
Final diagnosis of at least one episode of AOM - Otitis-prone children assessed with: physician diagnosed AOM on medical record and/or parental report follow up: median 3 months № of participants: 326 (1 RCT) [1,i]	**RR 0.90** (0.67 to 1.21)	36.7%	**33.1%** (24.6 to 44.5)	3.7% fewer (NS) (12.1 fewer to 7.7 more)	⨁⨁◯◯ LOW [h,j,k]	In otitis prone children receiving xylitol compared to placebo there is possibly no reduction in AOM episodes at ~3 months follow-up. NNT Not Applicable.

Summary of findings:

10 Xylitol (administered as syrup, gum or lozenge) compared to placebo for prevention of acute otitis media

Patient or population: Children aged 6 months to 7 years.

Setting: Primary health care.

Intervention: Xylitol administered as syrup, gum or lozenge. (Studies used doses 5-10 grams per day, in 3-5 divided doses). Duration was for 2-3 months.

Comparison: Placebo. [a]

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens
		Without xylitol (administered as syrup, gum or lozenge)	**With xylitol (administered as syrup, gum or lozenge)**	**Difference**		
Adverse events (gastrointestinal related) assessed with: parental report follow up: range 2 to 3 months № of participants: 1826 (3 RCTs) [1,b]	**RR 1.43** (0.74 to 2.75)	1.7%	**2.4%** (1.3 to 4.7)	0.7% more (NS) (0.4 fewer to 3 more)	⨁⨁⨁◯ MODERATE [l]	In children receiving xylitol compared to placebo there is probably no more gastrointestinal-related adverse events at ~3 months follow-up. NNT Not Applicable.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm; **MD:** Mean difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Placebo was sucrose alternative (Uhari 1996), sorbitol (Vernacchio 2014) or low dose xylitol 0.5g (Uhari 1998, Hautalahti 2007, Tapiainen 2002)
b. Studies taken from: Cochrane Review, Azarpazhooh 2016 (Uhari 1996, 1998, Hautalahti 2007).
c. Risk of Bias: Xylitol treatment syrup sweeter than control (so not truly blinded) but not considered sufficient to rate down.
d. Inconsistency: High heterogeneity
e. Indirectness: In one study mean age was 5 years and some children had already suffered AOM and undergone adenoidectomy. Not rated down.
f. Studies taken from: Cochrane Review, Azarpazhooh 2016 (Tapiainen 2002)
g. Indirectness: Xylitol syrup administered by parents once symptoms of respiratory tract infection occurred - this judgement was not standardised and parents may have different threshold for administration. Not rated down.
h. Imprecision: Single study, optimal information size not reached. CI includes appreciable benefit and harm.
i. Studies taken from: Cochrane Review, Azarpazhooh 2016 (Vernacchio 2014)
j. Risk of Bias: Attrition bias.
k. Indirectness: AOM diagnosed by different healthcare providers or by parental report (no consistency).
l. Imprecision: 95% CIs are wide and imprecise. Moreover, there are few events and the CI includes appreciable benefit and harm.

References

1. Azarpazhooh A, Lawrence HP, Shah PS. Xylitol for preventing acute otitis media in children up to 12 years of age. The Cochrane database of systematic reviews. 2016(8):Cd007095. Epub 2016/08/04. doi: 10.1002/14651858.CD007095.pub3. PubMed PMID: 27486835.

Summary of findings:

11 Zinc supplementation compared to placebo for prevention of acute otitis media

Patient or population: Children aged 0-31 months.

Setting: Primary health care.

Intervention: Zinc supplementation. (Studies used: 10-20mg elemental zinc daily) Duration was for 4-6 months.

Comparison: Placebo.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens
		Without Zinc supplementation	**With Zinc supplementation**	**Difference**		
Any AOM assessed with: otoscope +/- otorrhoea follow up: range 4 to 6 months № of participants: 3191 (2 RCTs) [1,a]	**RR 1.05** (0.82 to 1.36)	6.8%	**7.2%** (5.6 to 9.3)	0.3% more (NS) (1.2 fewer to 2.5 more)	⨁⨁⨁◯ MODERATE [b,c]	In children receiving zinc supplements compared to placebo there is probably no reduction in AOM during 4-6 months follow up. NNT Not Applicable
>1 episode of definite otitis media assessed with: physician diagnosed AOM follow up: median 4 months № of participants: 2482 (1 RCT) [1,d]	**RR 1.08** (0.50 to 2.36)	1.0%	**1.0%** (0.5 to 2.3)	0.1% more(NS) (0.5 fewer to 1.3 more)	⨁⨁⨁◯ MODERATE [b,c]	In children receiving zinc supplements compared to placebo there is probably no difference in recurrent AOM episodes during 4-6 months follow up. NNT Not Applicable
Adverse events - discontinued supplement due to vomiting assessed with: parental report follow up: median 4 months № of participants: 2482 (1 RCT) [1,d]	**RR 17.00** (0.98 to 294.21)	0.0%	**0.6%** (0.0 to 0.0)	0.6% fewer (NS) (0 fewer to 0 fewer)	⨁⨁◯◯ LOW [b,c]	In children treated with zinc supplements compared to placebo for prevention of AOM there are possibly more adverse effects (vomiting) which have lead to discontinuation of treatment. NNT Not Applicable
Adverse events - Days with vomiting during intervention (per child for period of follow-up) assessed with: parental report follow up: median 4 months № of participants: 2482 (1 RCT) [1,d]	-	The mean days with vomiting during intervention (per child for period of follow-up) was **2.6** days	-	MD **1.7 days higher** (1.31 higher to 2.09 higher)	⨁⨁◯◯ LOW [b,e]	Children receiving zinc supplements compared to placebo for prevention of AOM possibly experience more mean days with vomiting during 4 months follow up.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm; **MD:** Mean difference

Summary of findings:

11 Zinc supplementation compared to placebo for prevention of acute otitis media

Patient or population: Children aged 0-31 months.

Setting: Primary health care.

Intervention: Zinc supplementation. (Studies used: 10-20mg elemental zinc daily) Duration was for 4-6 months.

Comparison: Placebo.

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Zinc supplementation	**With Zinc supplementation**	**Difference**		

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: Cochrane Review, Gulani 2012 (Bhandari 2002, Muller 2001)
b. Indirectness: Population with likely endemic malnutrition and probable zinc deficiency. Not rated down.
c. Imprecision: Optimal information size not reached, small event rates
d. Studies taken from: Cochrane Review, Gulani 2012 (Bhandari 2002)
e. Imprecision: Wide estimate of effect

References

1. Gulani A, Sachdev HS. Zinc supplements for preventing otitis media. The Cochrane database of systematic reviews. 2014(6):Cd006639. Epub 2014/06/30. doi: 10.1002/14651858.CD006639.pub4. PubMed PMID: 24974096.

Summary of findings:

12 Antibiotics compared to placebo / no treatment / unproven therapy for children with otitis media with effusion

Patient or population: Children aged 0 to 15 years who have otitis media with effusion.

Setting: Primary health care

Intervention: Antibiotics (Studies used: amoxicillin (20-50 mg/kg/day in single or 3 divided doses for 14 days to 6 months), trimethoprim-sulfamethoxazole (8 mg and 40 mg/kg/day in 2-3 divided doses for 2-4 weeks) and amoxycillin/clavulanic acid (40 mg/kg/day in 3 divided doses (maximum 750 mg/day) for 2 weeks to 3 months).

Comparison: Placebo / No treatment / Unproven therapy.

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without antibiotics	**With antibiotics**	**Difference**		
Hearing outcomes assessed with: pure tone average and speech reception threshold follow up: range 2 to 4 weeks № of participants: 784 (2 RCTs) [1,a,b]	Mandel 1987 reported no statistically significant differences in mean speech recognition threshold between antibiotic and placebo groups at 4 weeks. Mandel 1991 reported a statistically significant difference in the mean speech recognition threshold between antibiotic and placebo groups at 2 weeks (left and right ears). At 4 weeks a statistically significant result was only found in the right ears.				⊕◯◯◯ VERY LOW [c,d,e]	In children with OME treated with antibiotics compared to placebo / no treatment / unproven treatment there is possibly no improvement in hearing outcomes at 2-4 weeks. NNT Not Applicable
Complete resolution of OME assessed with: tympanometry +/- pneumatic otoscopy follow up: range 2 to 3 months № of participants: 484 (6 RCTs) [1,f]	**RR 2.00** (1.58 to 2.53)	24.7%	**49.3%** (39.0 to 62.4)	**24.7% more** (14.3 more to 37.7 more)	⊕⊕◯◯ LOW [e,g,h]	In children with OME treated with antibiotics compared to placebo / no treatment / unproven treatment there is possibly more resolution of OME at 2-3 months follow-up. NNT ~ 5
Complete resolution of OME (long term) assessed with: tympanometry +/- pneumatic otoscopy follow up: median 6 months № of participants: 606 (5 RCTs) [1,i]	**RR 1.75** (1.41 to 2.18)	25.5%	**44.5%** (35.9 to 55.5)	**19.1% more** (10.4 more to 30 more)	⊕⊕◯◯ LOW [e,j]	In children with OME treated with antibiotics compared to placebo / no treatment / unproven treatment there is possibly more resolution of OME at 6 months follow-up. NNT ~ 6
Adverse effects (diarrhoea, vomiting or skin rash) follow up: range 2 to 8 weeks № of participants: 742 (5 RCTs) [1,k]	**RR 2.15** (1.29 to 3.60)	4.5%	**9.7%** (5.8 to 16.2)	**5.2% more** (1.3 more to 11.7 more)	⊕⊕◯◯ LOW [e,l,m]	In children with OME treated with antibiotics compared to placebo / no treatment / unproven treatment there are possibly more adverse events at 2-8 weeks follow-up. NNH ~ 20
Tympanic membrane perforation assessed with: pneumatic otoscopy + tympanometry follow up: median 6 months № of participants: 103 (1 RCT) [1,n]	**RR 0.42** (0.18 to 1.01)	27.5%	**11.5%** (4.9 to 27.7)	15.9% fewer (NS) (22.5 fewer to 0.3 more)	⊕⊕◯◯ LOW [o]	In Aboriginal children with OME treated with antibiotics compared to placebo there is possibly a reduction in tympanic membrane perforation during therapy.

Summary of findings:

12 Antibiotics compared to placebo / no treatment / unproven therapy for children with otitis media with effusion

Patient or population: Children aged 0 to 15 years who have otitis media with effusion.

Setting: Primary health care

Intervention: Antibiotics (Studies used: amoxicillin (20-50 mg/kg/day in single or 3 divided doses for 14 days to 6 months), trimethoprim-sulfamethoxazole (8 mg and 40 mg/kg/day in 2-3 divided doses for 2-4 weeks) and amoxycillin/clavulanic acid (40 mg/kg/day in 3 divided doses (maximum 750 mg/day) for 2 weeks to 3 months).

Comparison: Placebo / No treatment / Unproven therapy.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens
		Without antibiotics	With antibiotics	Difference		
Insertion of tympanostomy tubes follow up: range 3 to 6 months № of participants: 121 (2 RCTs) [1,p]	**RR 0.90** (0.46 to 1.78)	18.5%	**16.7%** (8.5 to 33.0)	1.9% fewer (NS) (10 fewer to 14.4 more)	⊕⊕◯◯ LOW [e,q]	In children with OME treated with antibiotics compared to placebo / no treatment / unproven treatment there is possibly no reduction of TT insertion within 3 to 6 months. NNT Not Applicable

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm; **MD:** Mean difference; **TT**: tympanostomy tubes

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: Cochrane Review, Venekamp 2016 (Mandel 1991, Mandel 1987)
b. Studies taken from: Cochrane Review, Venekamp 2016 (Mandel 1987, 1991)
c. Inconsistency: inconsistency of effect estimates across individual trials and incomplete outcome reporting
d. Indirectness: 4 week follow-up may be too early to detect important differences in hearing
e. Imprecision: Optimal information size not met
f. Studies taken from: Cochrane Review, Venekamp 2016 (Ardehali 2008, Chen 2013, Marchisio 1998, Podoshin 1990, Safak 2001, Schwartz 1982)
g. Risk of Bias: Performance bias across several studies, attrition bias (Podoshin), selection bias (Schwartz). However on sensitivity analysis same estimate of effect achieved. Not rated down
h. Indirectness: Different antibiotic regimens used, differing definitions for OME (Marchisio diagnosed OME >1 month of effusion vs other studies >3 months of effusion)
i. Studies taken from: Cochrane Review, Venekamp 2016 (Chuong 2008, Leach 2008, Otten 1990, Principi 1989, Thomsen 1989)
j. Risk of bias: Performance bias (lack blinding Chuong 2008) & attrition bias (Principi 1989, Thomsen 1989)
k. Studies taken from: Cochrane Review, Venekamp 2016 (Hemlin 1997, Marchisio 1998, Moller 1990, Thomsen 1989, van Balen 1996)
l. Risk of Bias: Attrition bias across several studies, differing baseline characteristics shown to be prognostic factor (van Balen)
m. Imprecision: Low event rate
n. Study taken from: Cochrane Review, Venekamp 2016 (Leach 2008)
o. Imprecision: Small, single study.
p. Studies taken from: Cochrane Review, Venekamp 2016 (Chen 2013, Choung 2008)
q. Risk of bias: Performance bias due to open label trials.

References

1. Venekamp RP, Burton MJ, van Dongen TM, van der Heijden GJ, van Zon A, Schilder AG. Antibiotics for otitis media with effusion in children. The Cochrane database of systematic reviews. 2016(6):Cd009163. Epub 2016/06/13. doi: 10.1002/14651858.CD009163.pub3. PubMed PMID: 27290722

Summary of findings:

13. Tympanostomy tubes compared to no surgical intervention for otitis media with effusion

Patient or population: Children aged 6 months to 12 years with otitis media with effusion.

Setting: Hospital.

Intervention: Tympanostomy tubes (TTs) (Teflon biflanged, Donaldson and Bevel Bobbins ventilation tubes).

Comparison: No surgical intervention

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Tympanostomy tubes	**With Tympanostomy tubes**	**Difference**		
By child hearing level assessed with: Binaural mean hearing level on pure tone audiometry 500-4000Hz follow up: median 3 months № of participants: 215 (1 RCT) [1,a]	-	The mean by child hearing level was **26.3** dB HL	-	MD **11.9 dB HL lower** (9.6 lower to 14.2 lower) [b]	⨁⨁⨁◯ MODERATE [c,d]	In children with OME treated with TTs compared to no surgical intervention there is probably better hearing at 3 months follow-up. NNT not evaluable
By child hearing level assessed with: pure tone audiometry (500-4000Hz) or portable visual reinforcement audiometry follow up: range 6 to 9 months № of participants: 523 (3 RCTs) [2,e]	-	The mean by child hearing level was **30.1** dB HL	-	MD **4.2 dB HL lower** (6 lower to 2.4 lower) [b]	⨁⨁⨁◯ MODERATE [d,f,g]	In children with OME treated with TTs compared to no surgical intervention there is probably better hearing at 6-9 months follow-up. NNT not evaluable
By child hearing level assessed with: pure tone audiometry (500-4000Hz) or portable visual reinforcement audiometry follow up: median 12 months № of participants: 328 (2 RCTs) [2,h]	-	The mean by child hearing level was **27** dB HL	-	MD 0.41 dB HL (NS) lower (2.37 lower to 1.54 higher) [b]	⨁⨁⨁◯ MODERATE [d,f,g]	In children with OME treated with TTs compared to no surgical intervention there is possibly no difference in hearing outcomes at 12 months.

Summary of findings:

13. Tympanostomy tubes compared to no surgical intervention for otitis media with effusion

Patient or population: Children aged 6 months to 12 years with otitis media with effusion.

Setting: Hospital.

Intervention: Tympanostomy tubes (TTs) (Teflon biflanged, Donaldson and Bevel Bobbins ventilation tubes).

Comparison: No surgical intervention

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Tympanostomy tubes	**With Tympanostomy tubes**	**Difference**		
Comprehensive language development assessed with: Reynell test follow up: range 6 to 9 months № of participants: 394 (3 RCTs) [2,i]	-	-	-	SMD 0.09 higher (NS) (0.21 lower to 0.39 higher)	⨁⨁⨁◯ MODERATE [d]	In children with OME treated with TTs compared to no surgical intervention there is probably no difference in comprehensive language development at 6-9 months.
Expressive language development assessed with: Reynell, Schlichting follow up: range 6 to 9 months № of participants: 393 (3 RCTs) [2,i]	-		-	MD 0.03 SD higher (NS) (0.42 lower to 0.49 higher)	⨁⨁⨁◯ MODERATE [d]	In children with OME treated with TTs compared to no surgical intervention there is probably no difference in expressive language development at 6-9 months.
Time (proportion) with effusion in first year assessed with: otoscope and tympanometry № of participants: 574 (3 RCTs) [2,j]	-	The mean time (proportion) with effusion in first year was **0.6**	-	MD **0.32 lower** (0.48 lower to 0.17 lower)	⨁⨁◯◯ LOW [k,l]	In children with OME treated with TTs compared to no surgical intervention there is possibly less time spent with effusion at 12 months follow up.
Quality of life assessed with: TAIQOL survey follow up: median 2 years № of participants: 187 (1 RCT) [2,m]	Quality of life improved in six subdomains, whereas the number of complaints concerning appetite, anxiety, and aggression increased. Except for anxiety, children treated with tympanostomy tubes (TTs) showed greater improvement or less deterioration than the watchful waiting group. However, the differences were not statistically significant.				⨁◯◯◯ VERY LOW [d,n]	In children with OME treated with TTs compared to no surgical intervention there is insufficient evidence to report on quality of life scores.

Summary of findings:

13. Tympanostomy tubes compared to no surgical intervention for otitis media with effusion

Patient or population: Children aged 6 months to 12 years with otitis media with effusion.

Setting: Hospital.

Intervention: Tympanostomy tubes (TTs) (Teflon biflanged, Donaldson and Bevel Bobbins ventilation tubes).

Comparison: No surgical intervention

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Tympanostomy tubes	**With Tympanostomy tubes**	**Difference**		
Adverse effects – otorrhoea follow up: range 12 to 24 months № of participants: 213 (1 observational study) [3,o]	Rates of TTs otorrhoea vary widely between RCTs; MRC TARGET trial found a rate of 2% over 24 months (mean age 60 months) whilst Rovers 2000 reported a rate of 83% over 12 months (mean age 19.5 months). Best data in Australian children is from Jassar 2009 (cohort study); 36% across 213 Indigenous and non-Indigenous children in the NT 1996-2004. [p]				⨁◯◯◯ VERY LOW [q,r]	In children with OME treated with TTs compared to no surgical intervention there is insufficient evidence to report on otorrhoea at 1 to 2 years.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm; **MD:** Mean difference; **SMD:** Standardised mean difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Study: MRC 2001
b. Lower mean difference corresponds to better hearing outcome.
c. Risk of Bias: Risk of selection bias however demographic, audiometric, tympanometric and otoscopic findings similar for randomised and non-randomised groups. Not rated down.
d. Imprecision: Small studies, optimal information size not met.
e. Studies taken from: Cochrane Review, Browning 2010 (Maw 1999, MRC: TARGET 2001, Rovers 2000)
f. Risk of Bias: attrition bias , selective reporting noted. Not rated down.
g. Indirectness: Only 1 frequency available for comparison in Maw 1999, whilst 4 frequency average measured in other studies. Not rated down.
h. Studies taken from: Cochrane Review, Browning 2010 (MRC: TARGET 2001, Rovers 2000)
i. Studies taken from: Cochrane Review, Browning 2010 (Maw 1999, Rach 1991, Rovers 2000)
j. Studies taken from: Cochrane review, Browning 2010 (Mandel 1992, Paradise 2001, Rovers 2000)
k. Risk of Bias: Ability to blind assessor as to the presence of a grommet or its sequelae is not possible.
l. Inconsistency: High heterogeneity
m. Study data: Rovers 2001
n. Indirectness: TAIQOL is a generic quality of life measure which has not been validated for otitis media, whereas other specific otitis media quality of life measurements are now available.
o. Study: Jassar 2009
p. Indirectness: Data from Jassar 2009 included children with TT insertion for OME and RAOM.

q. Risk of Bias: Only those attending follow-up appointments included in analysis
r. Imprecision: Small study

References

1. MRC. Surgery for persistent otitis media with effusion: generalizability of results from the UK trial (TARGET). Trial of Alternative Regimens in Glue Ear Treatment. Clinical otolaryngology and allied sciences. 2001;26(5):417-24. Epub 2001/10/27. PubMed PMID: 11678951.
2. Browning GG, Rovers MM, Williamson I, Lous J, Burton MJ. Grommets (ventilation tubes) for hearing loss associated with otitis media with effusion in children. The Cochrane database of systematic reviews. 2010(10):Cd001801. Epub 2010/10/12. doi: 10.1002/14651858.CD001801.pub3. PubMed PMID: 20927726.
3. Jassar P, Sibtain A, Marco D, Jose J, Hunter G. Infection rates after tympanostomy tube insertion, comparing Aboriginal and non-Aboriginal children in the Northern Territory, Australia: a retrospective, comparative study. The Journal of laryngology and otology. 2009;123(5):497-501. Epub 2008/06/26. doi: 10.1017/s002221510800306x. PubMed PMID: 18577271.

Summary of findings:

14 Adenoidectomy +/- tympanostomy tubes compared to tympanostomy tubes alone or no surgery for otitis media with effusion

Patient or population: Children aged 3 months to 18 years with otitis media with effusion

Setting: Hospital

Intervention: Adenoidectomy +/- tympanostomy tubes

Comparison: Tympanostomy tubes alone or no surgery

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Without Adenoidectomy +/- tympanostomy tubes	**With Adenoidectomy +/- tympanostomy tubes**	**Difference**		
Hearing outcome assessed with: mean binaural hearing level measured over 4 frequency average follow up: range 12 to 24 months № of participants: 254 (1 RCT) [1,a]	-	The mean hearing outcome was **20.1** dB	-	MD **4.2 dB lower** (2.6 lower to 5.7 lower) [b]	⨁⨁⨁◯ MODERATE [c]	In children with OME treated with adenoidectomy plus TTs compared to TT s alone there is probably better hearing at 12-24 months. NNT Not quantifiable
Treatment Failure in children ≥4 years of age follow up: median 12 months № of participants: 737 (8 RCTs) [2,d,e]	**RR 0.77** (0.68 to 0.86)	69.6%	**53.6%** (47.4 to 59.9)	**16.0% fewer** (22.3 fewer to 9.7 fewer)	⨁⨁◯◯ LOW [f,g]	In children >4 years with OME treated with adenoidectomy +/- TTs compared with non-surgical treatment or TTs only there is possibly less treatment failure at 12 months follow-up. NNT~6
Treatment Failure in children < 4 years of age follow up: median 12 months № of participants: 239 (8 RCTs) [2,d,e]	**RR 0.98** (0.69 to 1.38)	29.7%	**29.1%** (20.5 to 41.0)	0.6% fewer (NS) (9.2 fewer to 11.3 more)	⨁⨁◯◯ LOW [f,g]	In children <4 years treated with adenoidectomy +/- TTs compared with non-surgical treatment or TTs only there is possibly no fewer treatment failures at 12 months follow-up. NNT Not Applicable
Resolution of OME (randomised by ear) assessed with: tympanometry follow up: median 6 months № of participants: 297 (3 RCTs) [3,h]	**RR 2.29** (1.52 to 3.43)	17.0%	**38.9%** (25.8 to 58.3)	**21.9% more** (8.8 more to 41.3 more)	⨁⨁◯◯ LOW [ci]	In children with OME treated with adenoidectomy plus TTs compared to TTs alone there is possibly more resolution of OME at 6 months follow-up. NNT ~5

Summary of findings:

14 Adenoidectomy +/- tympanostomy tubes compared to tympanostomy tubes alone or no surgery for otitis media with effusion

Patient or population: Children aged 3 months to 18 years with otitis media with effusion

Setting: Hospital

Intervention: Adenoidectomy +/- tympanostomy tubes

Comparison: Tympanostomy tubes alone or no surgery

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Without Adenoidectomy +/- tympanostomy tubes	**With Adenoidectomy +/- tympanostomy tubes**	**Difference**		
Resolution of OME assessed with: tympanometry follow up: median 12 months № of participants: 298 (3 RCTs) [3,h]	**RR 2.33** (1.36 to 4.01)	20.0%	**46.6%** (27.2 to 80.2)	**26.6% more** (7.2 more to 60.2 more)	⨁⨁◯◯ LOW [ci]	In children with OME treated with adenoidectomy plus TTs compared to TTs alone there is probably more resolution of OME at 12 months. NNT ~4.
Complications of surgery (post-operative bleeding) № of participants: 508 (2 RCTs) [1,3 i]	**RR 3.02** (0.32 to 28.87)	0.0%	**0.0%** (0.0 to 0.0)	0.0% fewer (NS) (0 fewer to 0 fewer)	⨁⨁◯◯ LOW [c,j]	In children with OME treated with adenoidectomy plus TTs compared to TTs alone there is possibly on complications post surgery.
Repeat tympanostomy tube surgery follow up: range 2 to 5 years № of participants: 879 (4 RCTs) [1, k]	**RR 0.44** (0.35 to 0.54)	38.3%	**16.9%** (13.4 to 20.7)	**21.5% fewer** (24.9 fewer to 17.6 fewer)	⨁⨁⨁◯ MODERATE [l]	In children with OME treated with adenoidectomy plus TTs compared to TTs alone there is possibly less repeat TTs surgery. NNT ~5
Repeat tympanostomy tube surgery follow up: range 1 to 5 years № of participants: 200 (10 observational studies) [5,m,n]	**RR 0.54** (0.52 to 0.57)	32.0% [o]	**17.3%** (16.6 to 18.2) [o]	**14.7% fewer** (15.4 fewer to 13.8 fewer)	⨁◯◯◯ VERY LOW [p]	In children with OME treated with adenoidectomy plus TT compared to TT alone there is possibly less repeat tympanostomy tube surgery. NNT ~7

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm; **MD:** Mean difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Study data taken from: MRC Multicentre Otitis Media Study Group 2012

b. Lower mean difference corresponds to better hearing outcome.
c. Imprecision: Small numbers. Optimal information size not reached.
d. Treatment failure defined as: ≥4 AOM episodes (including episodes of otorrhoea) per year, presence of effusion for ≥ 50% of the time (i.e. effusion for > 6 months), need for additional surgery, hearing improved by < 10 dB.
e. Studies taken from: Boonacker Individual Patient Data Meta-analysis 2014 (Black 1990, Casselbrant 2009, Dempster 1993, Hammeren-Malmi 2005, Maw and Bawden 1993, Maw and Herod 1986, MRC Multicentre Otitis Media Study 2012, Nguyen 2004)
f. Risk of Bias: Attrition bias and Re-call bias (Nguyen 2004)
g. Publication Bias: 5 studies not included as individual patient data not supplied or unavailable, however there is no change is estimate of effect.
h. Studies taken from: Cochrane Review, van den Aardweg 2010 (Black 1990, Dempster 1993, Maw 1986)
i. Studies taken from: Cochrane Review, van den Aardweg 2010 (Gates 1987) and MRC 2012
j. Imprecision: low event rate / rare event
k. Studies taken from: (1) Mikals, 2014 (Meta-analysis with raw data provided for RCT's; Gates 1987, Black 1990, Maw & Bawden 1994), (2) Multicentre Otitis Media Study Group 2012
l. Imprecision: Optimal information size not reached.
m. Meta-analysis (Mikals 2014) combined RCT and observational studies looking at children undergoing adenoidectomy & tympanostomy tubes vs tympanostomy tubes for recurrent acute otitis media, otitis media with effusion and hearing loss.
n. Studies taken from: Mikals, 2014 (includes observational retrospective studies and RCT's)
o. No raw data available. Percentages extracted from published data (represented as rate %).
p. Inconsistency: High heterogeneity with lumping of data from a variety of studies which broad outcomes.

References

1. MRC. Multicentre O, Media, Study, Group. Adjuvant adenoidectomy in persistent bilateral otitis media with effusion: hearing and revision surgery outcomes through 2 years in the TARGET randomised trial. Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery. 2012;37(2):107-16. Epub 2012/03/27. doi: 10.1111/j.1749-4486.2012.02469.x. PubMed PMID: 22443163.
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Summary of findings:

15. Autoinflation devices compared to watchful waiting for otitis media with effusion

Patient or population: Children aged 3 to 11 years with otitis media with effusion

Setting: Primary health care and Hospital

Intervention: Autoinflation devices (Otovent®, carnival blower + balloon and Politzer devices) for a duration of 1 week to 3 months (ranged across studies)

Comparison: Watchful waiting

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Without Autoinflation	**With Autoinflation**	**Difference**		
Hearing - average improvement >= 10 dB assessed with: pure-tone audiogram (250 Hz to 2000 Hz) follow up: range 3 weeks to 3 months № of participants: 125 (2 RCTs) [1,a]	**Relative Risk 0.80** (0.22 to 2.88)	27.0% [b]	**21.6%** (5.9 to 77.8)	5.4% fewer (NS) (21.1 fewer to 50.8 more)	⨁⨁◯◯ LOW [c,d]	In children with OME who have autoinflation therapy compared to watchful waiting there is insufficient evidence to show a difference of >10dB in hearing during 3 weeks to 3 months follow-up. NNT Not Applicable
Pure-tone threshold assessed with: pure-tone audiogram (250 Hz to 2000 Hz) follow up: median 7 weeks № of participants: 179 (2 RCTs) [1,e]	-		-	MD 7.02 higher (NS) (6.92 lower to 20.96 higher)	⨁⨁◯◯ LOW [f,g,h]	In children with OME who have autoinflation therapy compared to watchful waiting there is insufficient evidence to show a difference in hearing at 7 weeks follow-up. NNT Not Applicable
Tympanogram improvement - B to C1/A assessed with: tympanometry follow up: median 1 months № of participants: 508 (4 RCTs) [1,2,i]	**Relative risk 1.72** (1.23 to 2.40)	35.6% [j]	**61.2%** (43.8 to 85.5)	**25.6% more** (8.2 more to 49.8 more)	⨁⨁◯◯ LOW [c,k]	In children with OME who have autoinflation therapy compared to watchful waiting there is possibly tympanogram improvement at up to 1 month follow-up. NNT ~4
Tympanogram improvement - B/C2 to C1/A assessed with: tympanometry follow up: median 1 months № of participants: 588 (6 RCTs) [1,2,l]	**Relative risk 1.48** (0.88 to 2.48)	35.6% [j]	**52.7%** (31.3 to 88.3)	17.1% more (NS) (4.3 fewer to 52.7 more)	⨁⨁◯◯ LOW [c,g,k]	In children with OME who have autoinflation therapy compared to watchful waiting there is possibly no tympanogram improvement <1 month follow-up. NNT Not Applicable

Summary of findings:

15. Autoinflation devices compared to watchful waiting for otitis media with effusion

Patient or population: Children aged 3 to 11 years with otitis media with effusion

Setting: Primary health care and Hospital

Intervention: Autoinflation devices (Otovent®, carnival blower + balloon and Politzer devices) for a duration of 1 week to 3 months (ranged across studies)

Comparison: Watchful waiting

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Without Autoinflation	**With Autoinflation**	**Difference**		
Tympanogram improvement - B/C2 to C1/A follow up: range 1 to 3 months № of participants: 530 (5 RCTs) [1,2,m]	**Relative Risk 1.27** (1.07 to 1.49)	38.3%	**48.7%** (41.0 to 57.1)	**10.4% more** (2.7 more to 18.8 more)	⨁⨁◯◯ LOW [c,k]	In children with OME who have autoinflation therapy compared to watchful waiting there is possibly tympanogram improvement at 1-3 months follow-up. NNT ~10
Adverse effects - Nosebleeds and Ear Pain assessed with: parental report follow up: median 3 months № of participants: 320 (1 RCT) [2,n]	**RR 0.90** (0.55 to 1.45)	16.3%	**14.6%** (8.9 to 23.6)	1.6% fewer (NS) (7.3 fewer to 7.3 more)	⨁⨁◯◯ LOW [o,p]	In children with OME who have autoinflation therapy compared to watchful waiting there are possibly no more adverse events (nosebleeds or ear pain) at 3 months follow-up. NNT Not Applicable
Disease specific quality of life assessed with: standardised change in OMQ-14 score follow up: mean 3 months № of participants: 247 (1 RCT) [2,n]	-	-	-	SMD **0.42 SD lower** (0.63 lower to 0.22 lower) [q]	⨁⨁◯◯ LOW [r]	In children with OME who have autoinflation therapy compared to watchful waiting there is possibly lower OMQ-14 score indicating better QOL at 3 months follow-up. NNT Not quantifiable

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio; **SMD:** Standardised mean difference; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: (1) Cochrane Review, Perera 2013 (Blanshard 1993, Brooker 1992)
b. Raw data not available from Cochrane Review. Baseline risk taken from watchful waiting group in Brooker 1992
c. Risk of Bias: Blinding not possible of participants. Unclear blinding of outcome assessors.
d. Imprecision: Broad estimate of effect. Includes benefit and harm.
e. Studies taken from: (1) Cochrane Review, Perera 2013 (Arick 2005, Fraser 1977)
f. Risk of Bias: Lack of blinding of participants, however audiologists blinded to otologic findings (Arick 2005). Unclear blinding Fraser 1977. Not rated down.
g. Inconsistency: High heterogeneity. Not rated down.
h. Imprecision: Optimal information size not reached. Broad estimate of effect.

i. Studies taken from: (1) Cochrane Review, Perera 2013 (Blanshard 1993, Ercan 2005, Stangerup 1992), (2) Williamson 2015
j. Raw data not available from Cochrane Review. Baseline risk taken from watchful waiting group in Williamson 2015
k. Indirectness: Tympanostomy is a surrogate for functional hearing. Not rated down.
l. Studies taken from: (1) Cochrane Review, Perera 2013 (Blanshard 1993, Brooker 1992, DeNobili 2008, Ercan 2005, Stangerup 1992), (2) Williamson 2015
m. Studies taken from: (1) Cochrane Review, Perera 2013 (Blanshard 1993, DeNobili 2008, Ercan 2005, Stangerup 1992), (2) Williamson 2015
n. Study: Williamson 2015
o. Risk of Bias: Lack of participant blinding. Otalgia and nosebleed reported anecdotally.
p. Imprecision: Single study with small numbers. Broad estimate of effect.
q. Lower score denotes better QOL.
r. Risk of Bias: Lack of participant blinding.

References

1. Perera R, Glasziou PP, Heneghan CJ, McLellan J, Williamson I. Autoinflation for hearing loss associated with otitis media with effusion. The Cochrane database of systematic reviews. 2013(5):Cd006285. Epub 2013/06/04. doi: 10.1002/14651858.CD006285.pub2. PubMed PMID: 23728660.
2. Williamson I, Vennik J, Harnden A, Voysey M, Perera R, Breen M, et al. An open randomised study of autoinflation in 4- to 11-year-old school children with otitis media with effusion in primary care. Health technology assessment (Winchester, England). 2015;19(72):1-150. Epub 2015/09/18. doi: 10.3310/hta19720. PubMed PMID: 26377389; PubMed Central PMCID: PMCPMC4781307.

Summary of findings:

16. Topical / intranasal steroids compared to placebo for otitis media with effusion

Patient or population: Children aged 2 to 12 years with otitis media with effusion.

Setting: Primary health care.

Intervention: Topical / Intranasal steroids (Studies used: Aerosolised dexamethasone1 spray each nostril, 3 times a day and mometasone furoate 50 - 200mcg once daily.) Duration was for 3 to 16 weeks.

Comparison: Placebo.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens
		Without Topical / Intranasal steroids	**With Topical / Intranasal steroids**	**Difference**		
Hearing Loss assessed with: Fail audiometry sweep at 25dB HL; fail on more than two out of five frequencies in both ears follow up: 9 months № of participants: 141 (1 RCT) [1,a]	**RR 1.17** (0.87 to 1.58)	50.7%	**59.4%** (44.1 to 80.2)	8.6% more (NS) (6.6 fewer to 29.4 more)	⨁⨁◯◯ LOW [b,c]	In children with OME treated with intranasal steroids compared to placebo there is possibly no improvement in hearing outcomes at 9 months. NNT Not applicable
Resolution OME - short term assessed with: pneumo-otoscopy +/- tympanometry follow up: range 3 weeks to 4 weeks № of participants: 238 (2 RCTs) [1,d]	**RR 0.85** (0.63 to 1.15)	46.3%	**39.3%** (29.2 to 53.2)	6.9% fewer (NS) (17.1 fewer to 6.9 more)	⨁⨁⨁◯ MODERATE [c,e]	In children with OME treated with intranasal steroids compared to placebo there is probably no difference in resolution of OME in the short term. NNT Not applicable
Resolution OME - medium term assessed with: pneumo-otoscopy +/- tympanometry follow up: range 3 to 6 months № of participants: 234 (2 RCTs) [1,2,f]	**RR 1.42** (0.85 to 2.37)	51.7%	**73.4%** (43.9 to 100.0)	21.7% more (NS) (7.8 fewer to 70.8 more)	⨁⨁◯◯ LOW [c,g,h]	In children with OME treated with intranasal steroids compared to placebo there is insufficient evidence to report on resolution of OME at 3-6 months. NNT Not applicable
Resolution OME - long term assessed with: pneumo-otoscopy +/- tympanometry follow up: median 9 months № of participants: 144 (1 RCT) [1,a]	**RR 0.85** (0.65 to 1.11)	65.3%	**55.5%** (42.4 to 72.5)	9.8% fewer (NS) (22.8 fewer to 7.2 more)	⨁⨁◯◯ LOW [b,h]	In children with OME treated with intranasal steroids compared to placebo there is insufficient evidence to report on resolution of OME at 9 months. NNT Not applicable

Summary of findings:

16. Topical / intranasal steroids compared to placebo for otitis media with effusion

Patient or population: Children aged 2 to 12 years with otitis media with effusion.

Setting: Primary health care.

Intervention: Topical / Intranasal steroids (Studies used: Aerosolised dexamethasone1 spray each nostril, 3 times a day and mometasone furoate 50 - 200mcg once daily.) Duration was for 3 to 16 weeks.

Comparison: Placebo.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens
		Without Topical / Intranasal steroids	**With Topical / Intranasal steroids**	**Difference**		
Adverse effects (No major adverse effects reported. Minor adverse effects during treatment includes: cough, dry throat, epistaxis, nasal stinging) assessed with: parental report follow up: range 2 weeks to 6 months № of participants: 234 (2 RCTs) [1,2,f]	**RR 1.21** (0.78 to 1.89)	22.0%	**26.7%** (17.2 to 41.6)	4.6% more (NS) (4.8 fewer to 19.6 more)	⨁⨁⨁◯ MODERATE [c,h]	In children with OME treated with intranasal steroids compared to placebo there is probably no difference in adverse effects. NNT Not applicable
Quality of life score assessed with: Glasgow Children Benefit Inventory follow up: mean 24 weeks № of participants: 62 (1 RCT) [2 i]	Glasgow Children Benefit Inventory showed statistically significant improvement in QOL with score of 37.11 +/- 25.5 (topical steroids) vs 11.02 +/-19.8 (placebo) (p value 0.0001).				⨁⨁◯◯ LOW [c,i]	In children with OME treated with intranasal steroids compared to placebo there is possibly some improvement in QOL scores.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm; **MD:** Mean difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: Cochrane Review, Simpson 2011 (Williamson 2009)
b. Risk of Bias: Attrition bias
c. Imprecision: Broad estimate of effect. Confidence interval covers significant benefit and harm. Single, small study.
d. Studies taken from: Cochrane Review, Simpson 2011 (Shapiro 1982, Williamson 2009)
e. Inconsistency: Different measures for OME resolution between studies, however low heterogeneity between studies on statistical analysis.

f. Studies taken from: Cochrane Review, Simpson 2011 (Williamson 2009) and Bhargava 2014
g. Inconsistency: High heterogeneity - rate of OME clearance very different between studies which may be due to inclusion criteria. Bhargava recruited via tertiary ENT service with adenoid hypertrophy, whilst Williamson recruited via primary care with 3 months of OME.
h. Imprecision: Optimal information size not met.
i. Indirectness: Not specifically evaluated for children with hearing loss due to OME

References

1. Simpson SA, Lewis R, van der Voort J, Butler CC. Oral or topical nasal steroids for hearing loss associated with otitis media with effusion in children. The Cochrane database of systematic reviews. 2011(5):Cd001935. Epub 2011/05/13. doi: 10.1002/14651858.CD001935.pub3. PubMed PMID: 21563132.
2. Bhargava R, Chakravarti A. A double-blind randomized placebo-controlled trial of topical intranasal mometasone furoate nasal spray in children of adenoidal hypertrophy with otitis media with effusion. American journal of otolaryngology. 2014;35(6):766-70. Epub 2014/08/26. doi: 10.1016/j.amjoto.2014.06.006. PubMed PMID: 25151658.

Summary of findings:

17. Oral steroids compared to placebo for otitis media with effusion

Patient or population: Children aged 6 months to 14 years with otitis media with effusion

Setting: Primary health care.

Intervention: Oral steroids [Prednisolone (0.5-1.5 mg/kg daily (max 30 mg) in divided dose tapering over 7 or 14 days), Dexamethasone (0.15 mg/kg daily in divided dose tapering over 14 days) and Betamethasone (6mg as single dose)]

Comparison: Placebo

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens
		Without Oral steroids	**With Oral steroids**	**Difference**		
Hearing loss (Proportion of children who fail to improve by >10dB in either ear) assessed with: pure tone audiometry follow up: 6 weeks № of participants: 49 (1 RCT) [1,a]	**RR 1.09** (0.80 to 1.49)	73.9%	**80.6%** (59.1 to 100.0)	6.7% more(NS) (14.8 fewer to 36.2 more)	⨁⨁◯◯ LOW [b,c,d]	In children with OME treated with oral steroids compared to placebo there is possibly no difference in hearing improvement of > 10 dB at 6 weeks. NNT Not Applicable.
OME resolution (two weeks) assessed with: pneumo-otoscopy & tympanometry № of participants: 108 (3 RCTs) [1,e]	**RR 3.80** (0.93 to 15.52)	5.8%	**21.9%** (5.4 to 89.5)	16.2% more(NS) (0.4 fewer to 83.8 more)	⨁⨁⨁◯ MODERATE [c,f]	In children with OME treated with oral steroids compared to placebo there is probably no increase in OME resolution at 2 weeks. NNT Not Applicable
OME resolution assessed with: pneumo-otoscopy & tympanometry follow up: range 4 to 6 weeks № of participants: 106 (3 RCTs) [1,e]	**RR 1.54** (0.76 to 3.14)	17.6%	**27.2%** (13.4 to 55.4)	9.5% more(NS) (4.2 fewer to 37.8 more)	⨁⨁◯◯ LOW [c,f,g]	In children with OME treated with oral steroids compared to placebo there possibly no increase in OME resolution at 4-6 weeks. NNT Not applicable.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: Cochrane Review, Simpson 2011 (Macknin 1985)
b. Risk of bias: Study terminated early due to concern that steroid was impairing resolution. Likely to result in lack of power rather than bias.
c. Imprecision: Small numbers / optimal information size not reached
d. Imprecision: single study
e. Studies taken from: Cochrane Review, Simpson 2011 (Giebink 1990, Macknin 1985, Niederman 1984)
f. Inconsistency: Different treatments and regimens between studies, however low heterogeneity of pooled data.

g. Risk of Bias: Attrition bias (Niederman 1984), some imbalance in baseline characteristics (Niederman 1984), allocation concealment / selection bias not described across all studies.

References

1. Simpson SA, Lewis R, van der Voort J, Butler CC. Oral or topical nasal steroids for hearing loss associated with otitis media with effusion in children. The Cochrane database of systematic reviews. 2011(5):Cd001935. Epub 2011/05/13. doi: 10.1002/14651858.CD001935.pub3. PubMed PMID: 21563132.

Summary of findings:

18 Oral steroids compared to placebo for otitis media with effusion (antibiotics in both arms of studies)

Patient or population: Children aged 6 months to 15 years with otitis media with effusion

Setting: Primary health care and Hospital

Intervention: Oral steroids [Prednisolone (0.5-1.5 mg/kg daily (max 30 mg) in divided dose tapering over 7 or 14 days), Dexamethasone (0.15 mg/kg daily in divided dose tapering over 14 days) and Betamethasone (6mg as single dose)] and Antibiotics [Amoxicillin (0.5 mg/kg twice daily on days 1 through 10 (total daily dose 1 mg/kg, maximum 30 mg/d), then days 11 through 14 given once daily (total daily dose 0.5 mg/kg, maximum 15 mg/d); then 40 mg/kg/d in 3 divided doses from days 15 through 28), Trimethoprim/sulfamethoxazole (5mg/kg/dose twice daily 30 days or 50 mg/kg/day twice daily for 7 days) and Cefixime for 10 days used across studies).

Comparison: Placebo and Antibiotics (Amoxicillin, Trimethoprim/sulfamethoxazole and Cefixime used across studies)

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens
		Without Oral steroids	**With Oral steroids**	**Difference**		
OME resolution (short term follow-up) assessed with: otoscopy, pneumatic otoscope, tympanometry +/- audiometry. follow up: range 7 to 28 days № of participants: 409 (5 RCTs) [1,a]	**RR 1.99** (1.14 to 3.49)	23.1%	**46.0%** (26.4 to 80.7)	**22.9% more** (3.2 more to 57.6 more)	⨁⨁◯◯ LOW [b,c,d]	In children with OME treated antibiotics, adjunct oral steroids compared to placebo there is possibly improve resolution of OME at 7 to 28 days. NNT ~5
Adverse effects - mild to moderate Assessed with: parental report follow up: range 2 weeks to 6 months № of participants: 255 (2 RCTs) [1,e,f]	**RR 1.34** (0.84 to 2.14)	18.1%	**24.3%** (15.2 to 38.8)	6.2% more (NS) (2.9 fewer to 20.6 more)	⨁⨁⨁◯ MODERATE [g,b,h]	In children with OME treated antibiotics, adjunct oral steroids compared to placebo there is there is probably no difference in adverse events. NNT Not applicable.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: Cochrane Review, Simpson 2011 (Berman 1990, Hemlin 1997, Lambert 1986, Mandel 2002, Schwartz 1980)
b. Imprecision: Small numbers / optimal information size not reached
c. Risk of bias: attrition bias (Berman 1990). Poor reporting with unclear risk of bias on many aspects of several studies. Not rated down.
d. Inconsistency: High heterogeneity likely due to different medications and regimens used in pooled studies.
e. Adverse effects included: dermatological, gastrointestinal, hyperactivity and irritability. No serious adverse effects reported. In Mandel 2002 treatments were administered in two phases (four-arm study analysed as two-arm) and adverse effects reported separately for both phases; data from end of first phase (completion of two-week steroid treatment) used in meta-analysis. No patients withdrew medications due to steroids. In Hemlin 1997 follow-up was until 6 months however treatment failures at visit 2 were not followed up beyond that time frame.
f. Studies taken from: Cochrane Review, Simpson 2011 (Hemlin 1997, Mandel 2002)
g. Risk of bias: Study terminated early due to concern that steroid was impairing resolution. Likely to result in lack of power rather than bias.
h. Inconsistency: Different treatments and regimens between studies, however low heterogeneity of pooled data.

References

1. Simpson SA, Lewis R, van der Voort J, Butler CC. Oral or topical nasal steroids for hearing loss associated with otitis media with effusion in children. The Cochrane database of systematic reviews. 2011(5):Cd001935. Epub 2011/05/13. doi: 10.1002/14651858.CD001935.pub3. PubMed PMID: 21563132.

Summary of findings:

19 Antihistamines and/or decongestants compared to placebo for otitis media with effusion

Patient or population: Children aged 5 months to 15 years with otitis media with effusion

Setting: Primary health care

Intervention: Antihistamines and/or decongestants (Studies used: chlorpheniramine & pseudoephedrine, ebastine, cinnarizine, oxymetazoline, phenylpropanolamine, phenylpropanolamine & brompheniramine, triprolidine & pseudoephedrine, phenylephrine, diphenhydrinate & pseudoephedrine)

Comparison: Placebo

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Antihistamines and/or decongestants	**With Antihistamines and/or decongestants**	**Difference**		
Hearing assessed with: <20dB hearing improvement or no improvement follow up: median 1 months № of participants: 358 (3 RCTs) [1,a]	**RR 1.08** (0.93 to 1.27)	60.2%	**65.0%** (56.0 to 76.5)	4.8% more (NS) (4.2 fewer to 16.3 more)	⨁⨁◯◯ LOW [b,c]	In children with OME treated with antihistamines and/or decongestants compared with placebo there is possibly no hearing improvement during 1 month follow-up. NNT Not Applicable
Hearing assessed with: <20dB hearing improvement or no improvement follow up: median 1 years № of participants: 48 (1 RCT) [1,d]	**RR 1.50** (0.63 to 3.56)	25.0%	**37.5%** (15.8 to 89.0)	12.5% more(NS) (9.3 fewer to 64 more)	⨁⨁◯◯ LOW [c]	In children with OME treated with antihistamines and/or decongestants compared with placebo there is possibly no hearing improvement at 1 year. NNT Not Applicable
Persistent OME assessed with: tympanometry and otoscopy follow up: median 1 months № of participants: 1177 (6 RCTs) [1,e]	**RR 0.99** (0.92 to 1.05)	74.9%	**74.1%** (68.9 to 78.6)	0.7% fewer (NS) (6 fewer to 3.7 more)	⨁⨁⨁◯ MODERATE [b,f]	In children with OME treated with antihistamines and/or decongestants compared with placebo there is probably no difference in persistent OME at or before 1 month. NNT Not applicable
Persistent OME assessed with: tympanometry and otoscopy follow up: range 1 to 3 months № of participants: 580 (7 RCTs) [1,g]	**RR 1.06** (0.92 to 1.22)	55.0%	**58.3%** (50.6 to 67.1)	3.3% more(NS) (4.4 fewer to 12.1 more)	⨁⨁⨁◯ MODERATE [b]	In children with OME treated with antihistamines and/or decongestants compared with placebo there is probably no difference in persistent OME at 1-3 months. NNT Not applicable

Summary of findings:

19 Antihistamines and/or decongestants compared to placebo for otitis media with effusion

Patient or population: Children aged 5 months to 15 years with otitis media with effusion

Setting: Primary health care

Intervention: Antihistamines and/or decongestants (Studies used: chlorpheniramine & pseudoephedrine, ebastine, cinnarizine, oxymetazoline, phenylpropanolamine, phenylpropanolamine & brompheniramine, triprolidine & pseudoephedrine, phenylephrine, diphenhydrinate & pseudoephedrine)

Comparison: Placebo

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Antihistamines and/or decongestants	**With Antihistamines and/or decongestants**	**Difference**		
Persistent OME assessed with: tympanometry and otoscopy follow up: range 3 to 12 months № of participants: 119 (2 RCTs) [1,h]	**RR 1.24** (0.72 to 2.13)	27.3%	**33.8%** (19.6 to 58.1)	6.5% more (NS) (7.6 fewer to 30.8 more)	⨁⨁◯◯ LOW [b,c,i]	In children with OME treated with antihistamines and/or decongestants compared with placebo there is possibly no difference of OME after 3 -12 months. NNT Not applicable
Adverse effects (most commonly irritability, sedation and gastrointestinal upset) assessed with: parental report follow up: median 1 months № of participants: 1144 (6 RCTs) [1,j]	**RR 2.70** (1.87 to 3.88)	6.4%	**17.4%** (12.0 to 25.0)	**10.9% more** (5.6 more to 18.5 more)	⨁⨁⨁◯ MODERATE [b,k]	In children with OME treated with antihistamines and/or decongestants compared with placebo there are probably more adverse events. NNH ~10
Surgery required (tympanostomy, myringotomy) follow up: range 1 to 3 months № of participants: 295 (4 RCTs) [1,l]	**RR 1.07** (0.81 to 1.41)	40.3%	**43.2%** (32.7 to 56.9)	2.8% more (NS) (7.7 fewer to 16.5 more)	⨁⨁◯◯ LOW [b,c,f]	In children with OME treated with antihistamines and/or decongestants compared with placebo there is possibly no difference in need for surgical interventions. NNT Not Applicable

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm; **MD:** Mean difference

Summary of findings:

19 Antihistamines and/or decongestants compared to placebo for otitis media with effusion

Patient or population: Children aged 5 months to 15 years with otitis media with effusion

Setting: Primary health care

Intervention: Antihistamines and/or decongestants (Studies used: chlorpheniramine & pseudoephedrine, ebastine, cinnarizine, oxymetazoline, phenylpropanolamine, phenylpropanolamine & brompheniramine, triprolidine & pseudoephedrine, phenylephrine, diphenhydrinate & pseudoephedrine)

Comparison: Placebo

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Antihistamines and/or decongestants	**With Antihistamines and/or decongestants**	**Difference**		

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: Cochrane Review, Griffin 2011 (Cantekin 1991, Haugeto 1981a, Haugeto 1981b, O'Shea 1980)
b. Inconsistency: Different treatment regimens used between studies.
c. Imprecision: Small studies, Optimal informational size not reached
d. Studies taken from: Cochrane Review, Griffin 2011 (O'Shea 1980)
e. Studies taken from: Cochrane Review, Griffin 2011 (Cantekin 1983, Cantekin 1991, Fabian 1986, Haugeto 1981a, Haugeto 1981b, Hayden 1984, Saunte 1978)
f. Risk of bias: risk selection bias (not clear in several studies), attrition bias (Saunte 1978, Hayden 1984) - however removal of these studies does not influence the outcome - not rated down.
g. Studies taken from: Cochrane Review, Griffin 2011 (Choung 2008, Dusdieker 1985, Edstrom 1977, Fabian 1986, Hughes 1984, Lesser 1986, O'Shea 1980).
h. Studies taken from: Cochrane Review, Griffin 2011 (Hughes 1984, O'Shea 1980)
i. Indirectness: Noted to have wide range of time points for outcome, data converted from outcome measure of ears in meta-analysis. Not rated down.
j. Studies taken from: Cochrane Review, Griffin 2011 (Cantekin 1983, Cantekin 1991, Fabian 1986, Lesser 1986, O'Shea 1980, Saunte 1978).
k. Imprecision: Optimal information size not reached, but significant difference noted. Not rated down.
l. Studies taken from: Cochrane Review, Griffin 2011 (Choung 2008, Fabian 1986, Hughes 1984, Saunte 1978)

References

1. Griffin G, Flynn CA. Antihistamines and/or decongestants for otitis media with effusion (OME) in children. The Cochrane database of systematic reviews. 2011(9):Cd003423. Epub 2011/09/09. doi: 10.1002/14651858.CD003423.pub3. PubMed PMID: 21901683.

Summary of findings:

20. Oral analgesia compared to placebo for pain relief in acute otitis media

Patient or population: Children aged 1 to 6.75 years with acute otitis media and pain

Setting: Primary health care

Intervention: Oral analgesia (Paracetamol 10mg/kg/dose three times daily and NSAID - ibuprofen 10mg/kg/dose three times daily)

Comparison: Placebo

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Placebo	**With paracetamol / NSAID**	**Difference**		
Pain - Paracetamol compared to placebo assessed with: parental report follow up: median 48 hours № of participants: 148 (1 RCT) [1, a]	**RR 0.38** (0.17 to 0.85)	25.3%	**9.6%** (4.3 to 21.5)	**15.7% fewer** (21 fewer to 3.8 fewer)	⨁⨁◯◯ LOW [b,c]	In children with AOM treated with Paracetamol compared to placebo there is possibly less pain reported at 48 hours. NNT ~6
Pain - NSAID compared to placebo assessed with: parental report follow up: median 48 hours № of participants: 146 (1 RCT) [1,a]	**RR 0.28** (0.11 to 0.70)	25.3%	**7.1%** (2.8 to 17.7)	**18.2% fewer** (22.5 fewer to 7.6 fewer)	⨁⨁◯◯ LOW [b,c]	In children with AOM treated with NSAIDs compared to placebo there is possibly less pain reported at 48 hours. NNT ~6
Adverse events (nausea, vomiting, abdominal pain & cutaneous rash) - Paracetamol compared to placebo assessed with: parental report follow up: median 48 hours № of participants: 148 (1 RCT) [1,a]	**RR 1.03** (0.21 to 4.93)	4.0%	**4.1%** (0.8 to 19.7)	0.1% more(NS) (3.2 fewer to 15.7 more)	⨁◯◯◯ VERY LOW [b,c,d]	In children with AOM treated with Paracetamol compared to placebo there is insufficient evidence to report on adverse events. NNH Not Applicable

Summary of findings:

20. Oral analgesia compared to placebo for pain relief in acute otitis media

Patient or population: Children aged 1 to 6.75 years with acute otitis media and pain

Setting: Primary health care

Intervention: Oral analgesia (Paracetamol 10mg/kg/dose three times daily and NSAID - ibuprofen 10mg/kg/dose three times daily)

Comparison: Placebo

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens
		Placebo	With paracetamol / NSAID	Difference		
Adverse events (nausea, vomiting, abdominal pain & cutaneous rash) - NSAID compared to placebo assessed with: parental report follow up: median 48 hours № of participants: 146 (1 RCT) [1,a]	**RR 1.76** (0.44 to 7.10)	4.0%	**7.0%** (1.8 to 28.4)	3.0% more(NS) (2.2 fewer to 24.4 more)	⨁◯◯◯ VERY LOW [b,d]	In children with AOM treated with NSAIDs compared to placebo there is insufficient evidence to report on adverse events. NNH Not Applicable

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: Cochrane Review, Sjoukes 2016 (Bertin 1996)
b. Indirectness: Antibiotics given to patient concurrently with analgesia during study
c. Imprecision: Optimal information size not met.
d. Imprecision: Broad estimate of effect.

References

1. Sjoukes A, Venekamp RP, van de Pol AC, Hay AD, Little P, Schilder AG, et al. Paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs, alone or combined, for pain relief in acute otitis media in children. The Cochrane database of systematic reviews. 2016;12:Cd011534. Epub 2016/12/16. doi: 10.1002/14651858.CD011534.pub2. PubMed PMID: 27977844.

Summary of findings:

21. NSAIDs +/- Paracetamol compared to paracetamol for pain relief in acute otitis media

Patient or population: Children aged 6 months to 18 years with acute otitis media and pain

Setting: Primary health care

Intervention: NSAID (ibuprofen) 10mg/kg/dose 6-8 hourly (maximum 3 doses in 24 hours) +/- Paracetamol 10-15mg/kg/dose 4-6 hourly (maximum 3-4 doses in 24 hours)

Comparison: Paracetamol 10-15mg/kg/dose 4-6 hourly (maximum 3-4 doses in 24 hours) alone

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Paracetamol	**NSAID +/- Paracetamol**	**Difference**		
Pain - NSAID vs Paracetamol assessed with: patient/parental report follow up: median 24 hours № of participants: 39 (2 RCTs) [1,b]	**RR 0.83** (0.59 to 1.18)	77.8%	**64.6%** (45.9 to 91.8)	13.2% fewer (NS) (31.9 fewer to 14 more)	⨁⨁◯◯ LOW [a,c,d]	In children with AOM treated with NSAIDs compared to Paracetamol there is possibly no difference in pain reported at 24 hours. NNT Not Applicable
Pain - NSAID + Paracetamol vs Paracetamol assessed with: patient/parental report follow up: median 24 hours № of participants: 41 (2 RCTs) [1,b]	**RR 1.07** (0.78 to 1.47)	70.6%	**75.5%** (55.1 to 100.0)	4.9% more (NS) (15.5 fewer to 33.2 more)	⨁⨁◯◯ LOW [a,c,d]	In children with AOM treated with NSAID + Paracetamol compared with Paracetamol there is possibly no difference in pain reported at 24 hours. NNT Not applicable.
Adverse events (gastrointestinal, cutaneous and wheeze) - NSAID vs Paracetamol assessed with: patient/parental report follow up: 2 days to 2 weeks № of participants: 197 (2 RCTs) [1,e]	**RR 1.71** (0.43 to 6.90)	3.0%	**5.1%** (1.3 to 20.7)	2.1% more (NS) (1.7 fewer to 17.7 more)	⨁◯◯◯ VERY LOW [a,c,d]	In children with AOM treated with NSAIDs compared to Paracetamol there is possibly no difference to report on adverse events. NNH Not Applicable

Summary of findings:

21. NSAIDs +/- Paracetamol compared to paracetamol for pain relief in acute otitis media

Patient or population: Children aged 6 months to 18 years with acute otitis media and pain

Setting: Primary health care

Intervention: NSAID (ibuprofen) 10mg/kg/dose 6-8 hourly (maximum 3 doses in 24 hours) +/- Paracetamol 10-15mg/kg/dose 4-6 hourly (maximum 3-4 doses in 24 hours)

Comparison: Paracetamol 10-15mg/kg/dose 4-6 hourly (maximum 3-4 doses in 24 hours) alone

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Paracetamol	**NSAID +/- Paracetamol**	**Difference**		
Adverse events (gastrointestinal, cutaneous and wheeze - NSAID + Paracetamol vs Paracetamol assessed with: patient/parental report follow up: 2 weeks № of participants: 56 (1 RCT) [1,f]	not estimable	0.0%	**0.0%** (0.0 to 0.0)	0.0% fewer (0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW [a,c]	In children with AOM treated with NSAID + Paracetamol compared to Paracetamol there was insufficient data to report on adverse events. NNH Not Applicable

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Imprecision: Optimal information size not met.
b. Studies taken from: Cochrane Review, Sjoukes 2016 (Little 2013, Hay 2009)
c. Risk of Bias: Performance bias (lack of blinding) (Little 2013)
d. Imprecision: Broad estimate of effect.
e. Studies taken from: Cochrane Review, Sjoukes 2016 (Bertin 1996, Little 2013)
f. Studies taken from: Cochrane Review, Sjoukes 2016 (Little 2013)

References

1. Sjoukes A, Venekamp RP, van de Pol AC, Hay AD, Little P, Schilder AG, et al. Paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs, alone or combined, for pain relief in acute otitis media in children. The Cochrane database of systematic reviews. 2016;12:Cd011534. Epub 2016/12/16. doi: 10.1002/14651858.CD011534.pub2. PubMed PMID: 27977844.

Summary of findings:

22. Topical analgesia as an adjunct to simple oral analgesia compared to placebo ear drops for immediate pain relief in acute otitis media

Patient or population: Children aged 3 to 19 years with acute otitis media and pain.

Setting: Emergency departments

Intervention: Topical analgesic ear drops as an adjunct to simple oral analgesia (Studies used: 2% aqueous lignocaine or antipyrine benzocaine glycerine. Both studies offered paracetamol 15mg/kg/dose single dose). Single dose of ear drops given on presentation to emergency department.

Comparison: Placebo ear drops (Studies used: Normal saline or olive oil. Both studies offered paracetamol 15mg/kg/dose single dose)

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Topical analgesia as an adjunct to simple oral anagesia	**With Topical analgesia as an adjunct to simple oral anagesia**	**Difference**		
50% reduction in ear pain assessed: two visual analogue scales follow up: median 10 minutes № of participants: 117 (2 RCTs) [1, a]	**RR 2.13** (1.19 to 3.80)	20.3%	**43.3%** (24.2 to 77.3)	**23.0% more** (3.9 more to 56.9 more)	⨁⨁◯◯ LOW [b,c]	Children with AOMwoP who have local anaesthetic ear drops administered by a health professional compared to placebo possibly have a reduction in pain score by 50% at 10 minutes. NNT ~5.
50% reduction in ear pain assessed: two visual analogue scales follow up: median 20 minutes № of participants: 117 (2 RCTs) [1,a]	**RR 1.24** (0.88 to 1.74)	47.5%	**58.8%** (41.8 to 82.6)	**11.4% more** (5.7 fewer to 35.1 more)	⨁⨁◯◯ LOW [b,c]	Children with AOMwoP who have local anaesthetic ear drops administered by a health professional compared to placebo possibly have no reduction in pain score by 50% at 20 minutes. NNT Not Applicable
50% reduction in ear pain assessed: two visual analogue scales follow up: median 30 minutes № of participants: 117 (2 RCTs) [1,a]	**RR 1.43** (1.12 to 1.81)	59.3%	**84.8%** (66.4 to 100.0)	**25.5% more** (7.1 more to 48.1 more)	⨁⨁◯◯ LOW [b,c]	Children with AOMwoP who have local anaesthetic ear drops administered by a health professional compared to placebo possibly have a reduction in pain score by 50% at 30 minutes. NNT ~4

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm; **AOMwoP:** Acute otitis media without perforation

Summary of findings:

22. Topical analgesia as an adjunct to simple oral analgesia compared to placebo ear drops for immediate pain relief in acute otitis media

Patient or population: Children aged 3 to 19 years with acute otitis media and pain.

Setting: Emergency departments

Intervention: Topical analgesic ear drops as an adjunct to simple oral analgesia (Studies used: 2% aqueous lignocaine or antipyrine benzocaine glycerine. Both studies offered paracetamol 15mg/kg/dose single dose). Single dose of ear drops given on presentation to emergency department.

Comparison: Placebo ear drops (Studies used: Normal saline or olive oil. Both studies offered paracetamol 15mg/kg/dose single dose)

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Topical analgesia as an adjunct to simple oral anagesia	**With Topical analgesia as an adjunct to simple oral anagesia**	**Difference**		

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: Cochrane Review, Foxlee 2008 (Bolt 2008, Hoberman 1997).
b. Indirectness: Studies of children 3-18 years of age. Peak incidence AOM is 6-15 months of age.
c. Imprecision: Small studies

References

1. Foxlee R, Johansson A, Wejfalk J, Dawkins J, Dooley L, Del Mar C. Topical analgesia for acute otitis media. The Cochrane database of systematic reviews. 2006(3):Cd005657. Epub 2006/07/21. doi: 10.1002/14651858.CD005657.pub2. PubMed PMID: 16856108.

Summary of findings:

23. Antibiotics compared to placebo for acute otitis media - short term outcomes

Patient or population: Children aged 2 months to 12 years with acute otitis media

Setting: Primary health care

Intervention: Antibiotics (Studies used: amoxycillin 40-90mg/kg/day three times daily, amoxicillin with clavulanate 40-90 / 5.7-6.4mg/kg/day twice daily, ampicillin 100 mg/kg/day four times daily, phenoxymethyl penicillin 50 mg/kg/day twice daily and penicillin 500-1500mg/day four times daily with dose adjusted with age. Duration was from 5-14 days.)

Comparison: Placebo

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Antibiotics	**With Antibiotics**	**Difference**		
Pain assessed with: parental report +/- clinical assessment follow up: median 24 hours № of participants: 1394 (6 RCTs) [1,b,c]	**RR 0.89** (0.78 to 1.01)	42.6%	**37.9%** (33.2 to 43.1)	4.7% fewer (NS) (9.4 fewer to 0.4 more)	⨁⨁⨁⨁ HIGH	In children with AOM treated with antibiotics compared to placebo there is no reduction in pain at 24 hours. NNT Not Applicable
Pain assessed with: parental report +/- clinical assessment follow up: range 2 to 3 days № of participants: 2320 (7 RCTs) [1,b,d]	**RR 0.70** (0.57 to 0.86)	15.9%	**11.1%** (9.0 to 13.7)	**4.8% fewer** (6.8 fewer to 2.2 fewer)	⨁⨁⨁◯ MODERATE [e]	In children with AOM treated with antibiotics compared to placebo there is probably a reduction in pain at 2-3 days. NNT ~21
Pain assessed with: parental report +/- clinical assessment follow up: range 4 to 7 days № of participants: 1347 (8 RCTs) [1,b,f]	**RR 0.76** (0.63 to 0.91)	24.1%	**18.3%** (15.2 to 22.0)	**5.8% fewer** (8.9 fewer to 2.2 fewer)	⨁⨁⨁◯ MODERATE [e]	In children with AOM treated with antibiotics compared to placebo there is probably a reduction in pain at 4-7 days. NNT ~18
Pain assessed with: parental report +/- clinical assessment follow up: range 10 to 12 days № of participants: 278 (1 RCT) [1,b,g]	**RR 0.33** (0.17 to 0.66)	21.6%	**7.1%** (3.7 to 14.2)	**14.5% fewer** (17.9 fewer to 7.3 fewer)	⨁⨁◯◯ LOW [e,h]	In children with AOM treated with antibiotics compared to placebo there is possibly a reduction in pain at 10-12 days. NNT ~7

Summary of findings:

23. Antibiotics compared to placebo for acute otitis media - short term outcomes

Patient or population: Children aged 2 months to 12 years with acute otitis media

Setting: Primary health care

Intervention: Antibiotics (Studies used: amoxycillin 40-90mg/kg/day three times daily, amoxicillin with clavulanate 40-90 / 5.7-6.4mg/kg/day twice daily, ampicillin 100 mg/kg/day four times daily, phenoxymethyl penicillin 50 mg/kg/day twice daily and penicillin 500-1500mg/day four times daily with dose adjusted with age. Duration was from 5-14 days.)

Comparison: Placebo

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Antibiotics	**With Antibiotics**	**Difference**		
Adverse events (vomiting, diarrhoea or rash) assessed with: parental report follow up: range 7 days to 4 weeks № of participants: 2107 (8 RCTs) [1,i]	**RR 1.38** (1.19 to 1.59)	19.6%	**27.0%** (23.3 to 31.1)	**7.4% more** (3.7 more to 11.5 more)	⊕⊕⊕⊕ HIGH	In children with AOM treated with antibiotics compared to placebo there is more adverse events during 4 weeks follow-up. NNH ~14
Tympanic membrane perforation assessed with: otoscopy follow up: range 7 days to 4 weeks № of participants: 1075 (5 RCTs) [1 j]	**RR 0.37** (0.18 to 0.76)	4.8%	**1.8%** (0.9 to 3.6)	**3.0% fewer** (3.9 fewer to 1.2 fewer)	⊕⊕⊕◯ MODERATE [e]	In children with AOM treated with antibiotics compared to placebo there is probably fewer tympanic membrane perforations during 4 weeks follow-up. NNT ~34
Treatment failure (lack of substantial improvement, worsening of otoscopic signs, worsening clinical condition at any time) Assessed with: parental report +/- clinical	**Proportion of children > 2 years of age with unilateral AOM (№ of participants: 611; 6 RCTs)** [2,l,k]					
	RR 0.92 (0.85 to 1.01)	26.2% [m]	**24.1%** (22.3 to 26.5) [m]	2.1% fewer (NS) (3.9 fewer to 0.3 more)	⊕⊕⊕◯ MODERATE [e]	In children >2 years with unilateral AOM treated with antibiotics compared to placebo there is probably no difference in treatment failure at 3-5 days follow-up. NNT Not Applicable
	Proportion of children <2 years (№ of participants: 567; 6 RCTs) [2,l,k,m]					

assessment Follow up: range 3 to 5 days	**RR 0.77** (0.68 to 0.89)	47.6% [m]	**36.6%** (32.3 to 42.3) [m]	**10.9% fewer** (15.2 fewer to 5.2 fewer)	⨁⨁⨁◯ MODERATE [e]	In children <2 years treated with antibiotics compared to placebo there is probably fewer treatment failures during 3-5 days follow-up. NNT ~10
	Proportion of children with bilateral AOM at diagnosis (№ of participants: 456; 6 RCTs) [2,l,k]					
	RR 0.72 (0.62 to 0.84)	47.5% [m]	**34.2%** (29.4 to 39.9) [m]	**13.3% fewer** (18 fewer to 7.6 fewer)	⨁⨁⨁◯ MODERATE [e]	In children with bilateral AOM treated with antibiotics compared to placebo there is probably fewer treatment failures during 3-5 days follow-up. NNT ~8
	Proportion of children with otorrhoea through TM perforations at diagnosis (№ of participants: 116; 6 RCTs) [2,k,l]					
	RR 0.52 (0.37 to 0.73)	60.0% [m]	**31.2%** (22.2 to 43.8) [m]	**28.8% fewer** (37.8 fewer to 16.2 fewer)	⨁⨁⨁◯ MODERATE [e]	In children with AOM and otorrhoea at diagnosis treated with antibiotics compared to placebo there is probably fewer treatment failures at 3-5 days follow-up. NNT ~4
Proportion of children >2 years of age with treatment failure assessed with: pain, fever or both follow up: range 3 to 7 days № of participants: 1076 (6 RCTs) [2,l]	**RR 0.86** (0.80 to 0.93)	30.9%	**26.6%** (24.7 to 28.7)	**4.3% fewer** (6.2 fewer to 2.2 fewer)	⨁⨁⨁◯ MODERATE [e]	In children >2 years with AOM treated with antibiotics compared to placebo there is probably fewer treatment failures at 3-7 days follow-up. NNT ~24

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm; **MD:** Mean difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies include amoxicillin alone, amoxicillin with clavulanate, and penicillin
b. Proportion of children with any pain at timepoint - various instruments across studies
c. Studies taken from: Cochrane Review, Venekamp 2015 (Burke 1991, Le Saux 2005, Thalin 1985, Tahtinen 2011, van Buchem 1981a, van Buchem 1981b)
d. Studies taken from: Cochrane Review, Venekamp 2015 (Appleman 1991, Halsted 1968, Kaleida 1991, Le Saux 2005, Mygind 1981, Thalin 1985, Tahtinen 2011)
e. Imprecision: Optimal information size not reached
f. Studies taken from: Cochrane Review, Venekamp 2015 (Burke 1991, Damoiseaux 2000, Mygind 1981, Tapiainen 2014, Thalin 1985, Tahtinen 2011, van Buchem 1981a, van Buchem 1981b)
g. Studies taken from: Cochrane Review, Venekamp 2015 (Hoberman 2011)
h. Indirectness: Timepoint not specified a priori as an outcome of interest
i. Studies taken from: Cochrane Review, Venekamp 2015 (Burke 1991, Damoiseaux 2000, Hoberman 2011, Le Saux 2005, Mygind 1981, Tapiainen 2014, Thalin 1985, Tahtinen 2011)
j. Studies taken from: Cochrane Review, Venekamp 2015 (Tapiainen 2014, Hoberman 2011, Tahtinen 2011, Burke 1991, Mygind 1981)

k. Treatment failure - composite outcome of persisting pain and or fever, worsening of otoscopic signs, and/or deterioration of patient's overall condition

l. Studies taken from: Rovers meta-analysis with individual patient data (Appleman 1991, Burke 1991, Damoiseaux 2000, Little 2001, Le Saux 2005, McCormick 2005)

m. Some data estimated from published data

n. Note: Hoberman 2011, Tahtinen 2011 - <2 year old children, strict diagnostic criteria

References

1. Venekamp RP, Sanders SL, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. The Cochrane database of systematic reviews. 2015(6):Cd000219. Epub 2015/06/24. doi: 10.1002/14651858.CD000219.pub4. PubMed PMID: 26099233.

2. Rovers MM, Glasziou P, Appelman CL, Burke P, McCormick DP, Damoiseaux RA, et al. Antibiotics for acute otitis media: a meta-analysis with individual patient data. Lancet (London, England). 2006;368(9545):1429-35. Epub 2006/10/24. doi: 10.1016/s0140-6736(06)69606-2. PubMed PMID: 17055944.

Summary of findings:

24. Antibiotics compared to placebo for acute otitis media – long term outcomes

Patient or population: Children aged 6 months to 15 years with acute otitis media

Setting: Primary health care.

Intervention: Antibiotics (Studies used: amoxycillin 40-90mg/kg/day three times daily, amoxicillin with clavulanate 40-90 / 5.7-6.4mg/kg/day twice daily, ampicillin 100 mg/kg/day four times daily, phenoxymethyl penicillin 50 mg/kg/day twice daily and penicillin 500-1500mg/day four times daily with dose adjusted with age. Duration was from 5-14 days.)

Comparison: Placebo

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Antibiotics	**With Antibiotics**	**Difference**		
Abnormal tympanometry assessed by: tympanometry follow up: median 3 months № of participants: 809 (3 RCTs) [1,c,d]	**RR 0.97** (0.76 to 1.24)	24.1%	**23.4%** (18.3 to 29.9)	0.7% fewer (NS) (5.8 fewer to 5.8 more)	⨁⨁⨁◯ MODERATE [a]	In children with AOM treated with antibiotics compared to placebo there is probably no difference in tympanometry findings at 3 months. NNT Not Applicable
Contralateral otitis (in unilateral cases) assessed by: otoscopy follow up: range 1 to 12 months № of participants: 906 (4 RCTs) [e]	**RR 0.49** (0.25 to 0.95)	18.8%	**9.2%** (4.7 to 17.8)	**9.6% fewer** (14.1 fewer to 0.9 fewer)	⨁⨁◯◯ LOW [a,b]	In children with AOM treated with antibiotics compared to placebo there is possibly fewer contralateral AOM episodes during 12 months follow-up. NNT ~11
Late AOM recurrence assessed by: otoscope +/- parental report follow up: range 15 days to 6 months № of participants: 2200 (6 RCTs) [f]	**RR 0.93** (0.78 to 1.10)	20.1%	**18.7%** (15.6 to 22.1)	1.4% fewer (NS) (4.4 fewer to 2 more)	⨁⨁⨁⨁ HIGH	In children with AOM treated with antibiotics compared to placebo there is no difference in late AOM recurrences during 6 months follow-up. NNT Not applicable.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Imprecision: Optimal information size not reached
b. Inconsistency: High heterogeneity
c. Time point chosen since persistent effusion for 3 months post AOM warrants a diagnosis of persistent OME and specific management strategies.

d. Studies taken from: Cochrane Review, Venekamp 2015 (Burke 1991, Le Saux 2005, Mygind 1981)

e. Studies taken from: Cochrane Review, Venekamp 2015 (Burke 1991, Hoberman 2011, Mygind 1981, Thalin 1985)

f. Studies taken from: Cochrane Review, Venekamp 2015 (Hoberman 2011, Kaleida 1991, Le Saux 2005, Mygind 1981, Thalin 1985, van Buchem 1981a)

References

1. Venekamp RP, Sanders SL, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. The Cochrane database of systematic reviews. 2015(6):Cd000219. Epub 2015/06/24. doi: 10.1002/14651858.CD000219.pub4. PubMed PMID: 26099233.

Summary of findings:

25. Twice daily compared to three daily doses of Amoxycillin (+/- clavulanate) for acute otitis media

Patient or population: Children aged 2 months to 12 years with acute otitis media

Setting: Primary health care.

Intervention: Amoxycillin (+/- clavulanate) twice daily (Studies used: amoxycillin 40-60mg/kg/day, amoxycillin/clavulanate 40-70/10 mg/kg/day). Duration was 7 to 10 days.

Comparison: Amoxycillin (+/- clavulanate) three times daily (Studies used: amoxycillin 40-60mg/kg/day, amoxycillin/clavulanate 45-60 / 6.4-15 mg/kg/ day). Duration was 7 to 10 days.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens
		With Three daily doses	With Twice daily	Difference		
Clinical cure rate at the end of therapy assessed by: clinical, otoscopy +/- tympanometry follow up: range 7 to 10 days № of participants: 1601 (5 RCTs) [1,a]	**RR 1.03** (0.99 to 1.07)	86.4%	**89.0%** (85.6 to 92.5)	2.6% more (NS) (0.9 fewer to 6.1 more)	⨁⨁⨁◯ MODERATE [b]	In children with AOM treated with BD compared to TDS Amoxicillin there is probably no difference in cure rates at 7-10 days (end of therapy). NNT Not Applicable
Adverse reactions to medication (gastrointestinal and cutaneous) assessed by: parental report follow up: range 28 to 42 days № of participants: 878 (2 RCTs) [1,c]	**RR 0.92** (0.52 to 1.63)	29.9%	**27.5%** (15.6 to 48.8)	**2.4% fewer** (14.4 fewer to 18.8 more)	⨁⨁◯◯ LOW [b,d,e]	In children with AOM treated with BD compared to TDS Amoxicillin there is possibly no fewer adverse events during 42 days follow-up. NNT Not Applicable
AOM complications: Recurrent AOM after completion of therapy assessed by: clinical, otoscopy+/- tympanometry follow up: range 42 to 90 days № of participants: 1029 (3 RCTs) [1,f]	**RR 1.21** (0.52 to 2.81)	9.2%	**11.1%** (4.8 to 25.7)	**1.9% more** (4.4 fewer to 16.6 more)	⨁⨁◯◯ LOW [b,g,h]	In children with AOM treated with BD compared to TDS Amoxicillin there is possibly no more AOM recurrences during ~3months follow-up. NNT Not Applicable
Compliance rate assessed by: parental report follow up: range 7 to 14 days № of participants: 1520 (4 RCTs) [1,i]	**RR 1.04** (0.98 to 1.10)	81.8%	**85.1%** (80.2 to 90.0)	**3.3% more** (1.6 fewer to 8.2 more)	⨁⨁◯◯ LOW [b,d]	In children with AOM treated with BD compared to TDS Amoxicillin there is possibly no difference in compliance during therapy. NNT Not Applicable

Summary of findings:

25. Twice daily compared to three daily doses of Amoxycillin (+/- clavulanate) for acute otitis media

Patient or population: Children aged 2 months to 12 years with acute otitis media

Setting: Primary health care.

Intervention: Amoxycillin (+/- clavulanate) twice daily (Studies used: amoxycillin 40-60mg/kg/day, amoxycillin/clavulanate 40-70/10 mg/kg/day). Duration was 7 to 10 days.

Comparison: Amoxycillin (+/- clavulanate) three times daily (Studies used: amoxycillin 40-60mg/kg/day, amoxycillin/clavulanate 45-60 / 6.4-15 mg/kg/ day). Duration was 7 to 10 days.

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		With Three daily doses	**With Twice daily**	**Difference**		

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: Cochrane Review, Thanaviratananich 2013 (Principi1986, Murph 1993, Behre 1997, Hoberman 1997, Damrikarnlert 2000)
b. Risk of Bias: Attrition bias (Behre & Damrikarnlert), selective reporting (Murph 1993)
c. Studies taken from: Cochrane Review, Thanaviratananich 2013 (Behre 1997, Damrikarnlert 2000)
d. Imprecision: High heterogeneity
e. Imprecision: Optimal information size not met, noted and not rated down.
f. Studies taken from: Cochrane Review, Thanaviratananich 2013 (Principi1986, Hoberman 1997, Damrikarnlert 2000)
g. Inconsistency: Borderline high heterogeneity noted but not rated down.
h. Imprecision: Low event rate, optimal information size not reached
i. Studies taken from: Cochrane Review, Thanaviratananich 2013 (Murph 1993, Behre 1997, Hoberman 1997, Damrikarnlert 2000)

References

1. 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. The Cochrane database of systematic reviews. 2013(12):Cd004975. Epub 2013/12/18. doi: 10.1002/14651858.CD004975.pub3. PubMed PMID: 24338106.

Summary of findings:

26. Short course (3-5 days) compared to longer course (7-10 days) antibiotics for acute otitis media

Patient or population: Children aged 1 month to 14.3 years with acute otitis media

Setting: Primary health care.

Intervention: Short course (3-5 days) antibiotics (Studies used: Amoxycillin/clavulanate 80-90mg / 6.4-10mg/kg/day, Cefixime 8mg/kg/day, Cefpodoxime 8mg/kg/day, Ceflacor 40mg/kg/day, Cefuroxime 30mg/kg/day, Cefprozil 30mg/kg/day, Penicillin V 25mg/kg/day).

Comparison: longer course (7-10 days) antibiotics (Studies used: Amoxycillin/clavulanate 80-90mg / 6.4-10mg/kg/day, Cefixime 8mg/kg/day, Cefpodoxime 8mg/kg/day, Ceflacor 40mg/kg/day, Cefuroxime 30mg/kg/day, Cefprozil 30mg/kg/day, Penicillin V 25mg/kg/day).

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Short course (3-5 days)	**With Short course (3-5 days)**	**Difference**		
Treatment failure - Sensitivity Analysis: same antibiotic in treatment arms assessed by: clinical assessment and otoscopy follow up: median 1 months № of participants: 3788 (10 RCTs) [1,2,a]	**RR 1.57** (1.36 to 1.82)	14.3%	**22.4%** (19.4 to 25.9)	**8.1% more** (5.1 more to 11.7 more)	⨁⨁⨁◯ MODERATE [b]	In children with AOM treated with a shorter antibiotic course (3-5 days) compared to longer antibiotic course (7-10 days) there is probably more treatment failures at 1 month follow-up. NNH ~13
Treatment failure - Amoxicillin-clavulanate - 5 versus 10 days assessed by: clinical assessment and otoscopy follow up: median 1 months № of participants: 1409 (3 RCTs) [1,2,c]	**RR 1.82** (1.49 to 2.23)	16.6%	**30.1%** (24.7 to 36.9)	**13.6% more** (8.1 more to 20.4 more)	⨁⨁◯◯ LOW [d,e]	In children with AOM treated with a shorter 5 day course of amoxicillin-clavulanate compared to a longer 10 day course there is possibly more treatment failures at 1 month follow-up. NNH ~8
Adverse effects (gastrointestinal) assessed by: parental report follow up: median 1 months № of participants: 5433 (14 RCTs) [1,2,f]	**RR 0.79** (0.69 to 0.91)	15.1%	**12.0%** (10.4 to 13.8)	**3.2% fewer** (4.7 fewer to 1.4 fewer)	⨁⨁◯◯ LOW [b,g]	In children with AOM treated with a shorter course (3-5 days) compared to longer course (7-10 days) of antibiotics there are possibly fewer adverse effects at 1 month follow-up. NNT ~32

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm;

Summary of findings:

26. Short course (3-5 days) compared to longer course (7-10 days) antibiotics for acute otitis media

Patient or population: Children aged 1 month to 14.3 years with acute otitis media

Setting: Primary health care.

Intervention: Short course (3-5 days) antibiotics (Studies used: Amoxycillin/clavulanate 80-90mg / 6.4-10mg/kg/day, Cefixime 8mg/kg/day, Cefpodoxime 8mg/kg/day, Ceflacor 40mg/kg/day, Cefuroxime 30mg/kg/day, Cefprozil 30mg/kg/day, Penicillin V 25mg/kg/day).

Comparison: longer course (7-10 days) antibiotics (Studies used: Amoxycillin/clavulanate 80-90mg / 6.4-10mg/kg/day, Cefixime 8mg/kg/day, Cefpodoxime 8mg/kg/day, Ceflacor 40mg/kg/day, Cefuroxime 30mg/kg/day, Cefprozil 30mg/kg/day, Penicillin V 25mg/kg/day).

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Short course (3-5 days)	**With Short course (3-5 days)**	**Difference**		

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: (1) Cochrane Review, Kozyrskyj 2010 (Adam 2000, Catania 2004, Cohen 1998, 2000, Gooch 1996, Hendrickse 1988, Hoberman 1997, Ingvarsson 1982, Kafetzis 1997), (2) Hoberman 2016
b. Risk of bias: Selection bias (many studies), reporting bias, attrition bias
c. Studies taken from: (1) Cochrane Review, Kozyrskyj 2010 (Cohen 1998, Hoberman 1997), (2) Hoberman 2016
d. Risk of bias: Reporting bias (Cohen, Hoberman), industry funding (Hoberman 1997)
e. Imprecision: Optimal information size not met
f. Studies taken from: (1) Cochrane Review, Kozyrskyj 2010 (Adam 1996, 2000, Block 2000, 2004, Boulesteix 1995, Catania 2004, Cohen 1997, 1998, Gooch 1996, Hendrickse 1988, Hoberman 1997, Kafetzis 1997, Ploussard 1984), (2) Hoberman 2016
g. Inconsistency: High heterogeneity

References

1. Hoberman A, Paradise JL, Rockette HE, Kearney DH, Bhatnagar S, Shope TR, et al. Shortened Antimicrobial Treatment for Acute Otitis Media in Young Children. The New England journal of medicine. 2016;375(25):2446-56. Epub 2016/12/22. doi: 10.1056/NEJMoa1606043. PubMed PMID: 28002709; PubMed Central PMCID: PMCPMC5319589.
2. Kozyrskyj A, Klassen TP, Moffatt M, Harvey K. Short-course antibiotics for acute otitis media. The Cochrane database of systematic reviews. 2010(9):Cd001095. Epub 2010/09/09. doi: 10.1002/14651858.CD001095.pub2. PubMed PMID: 20824827.

Summary of findings:

27. Azithromycin compared to Amoxicillin with or without clavulanate for acute otitis media

Patient or population: Children aged 3 months to 15 years old with acute otitis media.

Setting: Primary health care.

Intervention: Azithromycin (Studies used: 30-60mg/kg (60mg/kg extended release tablet)) Duration was a single stat dose or daily for 3-6 days.

Comparison: Amoxicillin with or without clavulanate (Studies used: 40-90mg/kg/day two to three divided doses daily.) Duration was for 7-10 days.

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Azithromycin	**With Azithromycin**	**Difference**		
Treatment failure assessed by: clinical and otoscopic assessment. follow up: ≤1 months № of participants: 5150 (19 RCTs) [1,2,3,4,a]	**RR 0.99** (0.89 to 1.11)	22.0%	**21.8%** (19.6 to 24.4)	0.2% fewer (NS) (2.4 fewer to 2.4 more)	⨁⨁⨁◯ MODERATE [b]	In children with AOM treated with Azithromycin compared to Amoxicillin+/- clavulanate there is probably no reduction in treatment failure during 1 month follow-up. NNT Not Applicable
Treatment failure assessed by: clinical and otoscopic assessment. follow up: range 8 to 19 days № of participants: 5274 (19 RCTs) [1,2,3,4,a]	**RR 1.18** (0.98 to 1.43)	12.5%	**14.8%** (12.3 to 17.9)	2.3% more(NS) (0.3 fewer to 5.4 more)	⨁⨁⨁◯ MODERATE [b]	In children with AOM treated with Azithromycin compared to Amoxicillin+/- clavulanate there is probably no reduction in treatment failure during 8-19 days follow-up. NNT Not Applicable
Treatment failure (Single dose Azithromycin compared to longer course Amoxicillin+/- clavulanate) assessed by: clinical and otoscopic assessment. follow up: ≤1 months № of participants: 1320 (4 RCTs) [2,3,4,c]	**RR 0.95** (0.80 to 1.12)	26.9%	**25.6%** (21.5 to 30.2)	1.3% fewer(NS) (5.4 fewer to 3.2 more)	⨁⨁⨁◯ MODERATE [d]	In children with AOM treated with single dose Azithromycin compared to Amoxicillin+/- clavulanate there is probably no reduction in treatment failure during 1 month follow-up. NNT Not Applicable
Treatment failure by end of therapy in remote Aboriginal children assessed by: video pneumatic otoscopy, tympanometry follow up: range 6 to 11 days № of participants: 320 (1 RCT) [3,e]	**RR 0.93** (0.75 to 1.15)	53.5%	**49.8%** (40.2 to 61.6)	3.7% fewer(NS) (13.4 fewer to 8 more)	⨁⨁⨁◯ MODERATE [f]	In remote Australian Aboriginal Children with AOM treated with single dose Azithromycin compared to Amoxicillin there is probably no reduction in treatment failure at 6-11 days follow-up. NNT Not Applicable.

Summary of findings:

27. Azithromycin compared to Amoxicillin with or without clavulanate for acute otitis media

Patient or population: Children aged 3 months to 15 years old with acute otitis media.

Setting: Primary health care.

Intervention: Azithromycin (Studies used: 30-60mg/kg (60mg/kg extended release tablet)) Duration was a single stat dose or daily for 3-6 days.

Comparison: Amoxicillin with or without clavulanate (Studies used: 40-90mg/kg/day two to three divided doses daily.) Duration was for 7-10 days.

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Azithromycin	**With Azithromycin**	**Difference**		
Adverse effects (gastrointestinal) assessed by: parental report follow up: median 1 months № of participants: 5269 (16 RCTs) [2,3,4,g]	**RR 0.59** (0.52 to 0.68)	17.9%	**10.5%** (9.3 to 12.1)	**7.3% fewer** (8.6 fewer to 5.7 fewer)	⨁⨁◯◯ LOW [b,h]	In children with AOM treated with Azithromycin compared to Amoxicillin+/- clavulanate there are possibly fewer gastrointestinal adverse effects during 1 month follow-up. NNT ~14

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: (1) Cochrane Review, Kozyrskyj 2010 (Arguedas 1996, 2005, Aronovitz 1996, Arrieta 2003, Block 2003, Dagan 2000, Daniel 1993, de Jose 1998, Dunne 2003, Guven 2006, Hoberman 2005, Khurana 1996, McLinn 1996, Mohs 1993, Petalozza 1992, Principi 1995, Schaad 1993); (2) Courter Meta-Analysis 2010 (McLinn 1996, Block 2003, Dagan 2000, Dunne 2003, Guven 2006, Hoberman 2005, Arguedas 2005); (3) Morris 2010, (4) Arguedas 2011
b. Risk of bias: selection and performance bias (several studies)
c. Studies taken from: (1) Cochrane Review, Kozyrskyj 2010 (Arguedas 2005, Block 2003); (2) Morris 2010, (3) Arguedas 2011
d. Risk of Bias: Interin analysis (selective reporting bias) (Arguedas 2005)
e. Study: Morris 2010
f. Imprecision: Small study, not powered to detect equivalence
g. Studies taken from: (1) Cochrane Review, Kozyrskyj 2010 (Arguedas 1996, 2005, Arrieta 2003, Block 2003, Dagan 2000, Daniel 1993, de Jose 1998, Guven 2006, Khurana 1996, McLinn 1996, Mohs 1993, Petalozza 1992, Principi 1995, Schaad 1993); (2) Morris 2010, (3) Arguedas 2011
h. Inconsistency: High heterogeneity

References

1. Courter JD, Baker WL, Nowak KS, Smogowicz LA, Desjardins LL, Coleman CI, et al. Increased clinical failures when treating acute otitis media with macrolides: a meta-analysis. The Annals of pharmacotherapy. 2010;44(3):471-8. Epub 2010/02/13. doi: 10.1345/aph.1M344. PubMed PMID: 20150506.
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3. Morris PS, Gadil G, McCallum GB, Wilson CA, Smith-Vaughan HC, Torzillo P, et al. Single-dose azithromycin versus seven days of amoxycillin in the treatment of acute otitis media in Aboriginal children (AATAAC): a double blind, randomised controlled trial. The Medical journal of Australia. 2010;192(1):24-9. Epub 2010/01/06. PubMed PMID: 20047544.
4. Arguedas A, Soley C, Kamicker BJ, Jorgensen DM. Single-dose extended-release azithromycin versus a 10-day regimen of amoxicillin/clavulanate for the treatment of children with acute otitis media. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2011;15(4):e240-8. Epub 2011/01/29. doi: 10.1016/j.ijid.2010.12.003. PubMed PMID: 21269858.

Summary of findings:

28. Immediate antibiotics compared to watchful waiting for acute otitis media

Patient or population: Children aged 6 months to 16 years with acute otitis media

Setting: Primary health care

Intervention: Immediate antibiotics (Studies used: Amoxycillin 90mg/kg/day twice daily for 7 to 10 days and Phenoxymethylpenecillin 50mg/kg/day twice daily for 5 days)

Comparison: Watchful waiting

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Immediate antibiotics	**With Immediate antibiotics**	**Difference**		
Pain assessed: parental report follow up: range 3 to 7 days № of participants: 959 (4 RCTs) [1,a]	**RR 0.75** (0.50 to 1.12)	35.6%	**26.7%** (17.8 to 39.8)	8.9% fewer (NS) (17.8 fewer to 4.3 more)	⨁⨁⨁◯ MODERATE [b]	In children with AOM treated with immediate antibiotics compared to watchful waiting there is probably no less pain at 3-7 days. NNT Not Applicable.
Pain assessed: parental report follow up: range 11 to 14 days № of participants: 247 (1 RCT) [1,c]	**RR 0.91** (0.75 to 1.10)	66.9%	**60.9%** (50.2 to 73.6)	6.0% fewer(NS) (16.7 fewer to 6.7 more)	⨁⨁◯◯ LOW [b,d,e]	In children with AOM treated with immediate antibiotics compared to watchful waiting there is possibly no less pain at 11-14 days. NNT Not Applicable.
Adverse effects (vomiting, diarrhoea or rash) assessed: parental report follow up: range 7 to 40 days № of participants: 550 (2 RCTs) [1,f]	**RR 1.71** (1.24 to 2.36)	16.7%	**28.5%** (20.7 to 39.3)	**11.8% more** (4 more to 22.7 more)	⨁⨁⨁◯ MODERATE [e]	In children with AOM treated with immediate antibiotics compared to watchful waiting there is probably more adverse events at 7-40 days follow-up. NNH ~ 9
Abnormal tympanometry assessed: tympanometry follow up: median 4 weeks № of participants: 207 (1 RCT) [1,g]	**RR 1.03** (0.78 to 1.35)	49.5%	**51.0%** (38.6 to 66.8)	1.5% more(NS) (10.9 fewer to 17.3 more)	⨁⨁◯◯ LOW [d,e]	In children with AOM treated with immediate antibiotics compared to watchful waiting there is probably no difference to report a difference in tympanometry findings. NNT Not Applicable.

Summary of findings:

28. Immediate antibiotics compared to watchful waiting for acute otitis media

Patient or population: Children aged 6 months to 16 years with acute otitis media

Setting: Primary health care

Intervention: Immediate antibiotics (Studies used: Amoxycillin 90mg/kg/day twice daily for 7 to 10 days and Phenoxymethylpenecillin 50mg/kg/day twice daily for 5 days)

Comparison: Watchful waiting

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Immediate antibiotics	**With Immediate antibiotics**	**Difference**		
Tympanic membrane perforation assessed: otoscopy follow up: median 3 months № of participants: 179 (1 RCT) [1,h]	not estimable	0.0%	**0.0%** (0.0 to 0.0)	0.0% fewer (0 fewer to 0 fewer)	⨁⨁⨁◯ MODERATE [e,i]	In children with AOM treated with immediate antibiotics compared to watchful waiting there is probably no difference to report on TM perforation as sequelae of AOM.
AOM recurrences assessed: acute ear symptoms / abnormal tympanic membrane / AOM severity score higher than that at enrolment follow up: range 13 to 30 days № of participants: 209 (1 RCT) [1,g]	**RR 1.41** (0.74 to 2.69)	13.0%	**18.3%** (9.6 to 35.0)	5.3% more(NS) (3.4 fewer to 22 more)	⨁⨁◯◯ LOW [d,e,i]	In children with AOM treated with immediate antibiotics compared to watchful waiting there is probably no difference to report on AOM recurrences. NNT Not Applicable.
Outpatient antibiotic prescriptions № of participants: 313932 (1 observational study) [2,j]	Large Israeli observational study. Guidelines introduced in 2004 which recommended watchful waiting. Pre-guideline prescription rates for first episode AOM in children >24 months was 56%. From 2004 to 2007, rate decreased to 47%.				⨁◯◯◯ VERY LOW [k]	In children with AOM treated with immediate antibiotics compared to watchful waiting there is possibly a reduction of antibiotic prescriptions.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: Cochrane Review, Venekamp 2015 (Little 2001, McCormick 2005, Spiro 2006, Neumark 2007)
b. Imprecision: Confidence interval for estimate of effect covers both benefit and harm.
c. Studies taken from: Cochrane Review, Venekamp 2015 (Spiro 2006)
d. Risk of bias: Attrition bias
e. Imprecision: Optimal information size not reached
f. Studies taken from: Cochrane Review, Venekamp 2015 (Little 2001, Spiro 2006)
g. Studies taken from: Cochrane Review, Venekamp 2015 (McCormick 2005)
h. Studies taken from: Cochrane Review, Venekamp 2015 (Neumark 2007)
i. Imprecision: Low event rate
j. Grossman 2010
k. Script rates are a surrogate for overall antibiotic consumption, itself only important insofar as it promotes resistance, which was not measured here

References

1. Venekamp RP, Sanders SL, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. The Cochrane database of systematic reviews. 2015(6):Cd000219. Epub 2015/06/24. doi: 10.1002/14651858.CD000219.pub4. PubMed PMID: 26099233.
2. Grossman Z, Silverman BG, Porter B, Miron D. Implementing the delayed antibiotic therapy approach significantly reduced antibiotics consumption in Israeli children with first documented Acute otitis media. The Pediatric infectious disease journal. 2010;29(7):595-9. Epub 2010/07/01. PubMed PMID: 20589979.

Summary of findings:

29 Prophylactic antibiotics compared to placebo / no treatment for prevention of recurrent acute otitis media

Patient or population: Prevention of recurrent acute otitis media in children aged 0 to 14 years.

Setting: Primary health care.

Intervention: Prophylactic antibiotics (Studies used Amoxycillin 20-50mg/kg daily, Ampicillin 125-250mg/day (dose age dependant), Trimethoprim/sulfamethoxazole 4-8/12-40 mg/kg/day twice daily, Sulfisoxazole 75 mg/kg/day or 500-1000mg (dose age dependant) twice daily and Phenoxymethyl penicillin V 25 mg/kg/day). Duration was 6.5 weeks to 2 years.

Comparison: Placebo / no treatment

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Prophylactic antibiotics	**With Prophylactic antibiotics**	**Difference**		
Prevention - any AOM or CSOM during treatment assessed by: clinical assessment, pneumatic otoscope / otoscope +/- tympanostomy. follow up: range 10 weeks to 24 months № of participants: 1461 (14 RCTs) [1,a]	**RR 0.65** (0.53 to 0.79)	55.7%	**36.2%** (29.5 to 44.0)	**19.5% fewer** (26.2 fewer to 11.7 fewer)	⨁⨁⨁◯ MODERATE [b]	In children with rAOM treated with prophylactic antibiotics compared to placebo/no treatment there are probably fewer AOM episodes during treatment at 2-24 months. NNT ~5
Prevention - episodes of AOM or CSOM during treatment assessed by: clinical assessment, pneumatic otoscope / otoscope +/- tympanostomy. follow up: range 10 weeks to 24 months № of participants: 1327 (13 RCTs) [1,c]	**Incidence Rate Ratio 0.51** (0.39 to 0.66)				⨁⨁⨁◯ MODERATE [b]	In children with rAOM treated with prophylactic antibiotics compared to placebo/no treatment there are probably fewer episodes of AOM during Rx. Prevents ~1.5 episodes per year of treatment, per child.
Adverse effects (any clinical side effects during intervention) assessed by: parental report follow up: range 10 weeks to 24 months № of participants: 817 (12 RCTs) [1,d]	**RR 1.99** (0.25 to 15.89)	0.8%	**1.7%** (0.2 to 13.2)	0.8% more (NS) (0.6 fewer to 12.4 more)	⨁◯◯◯ VERY LOW [b,e]	In children with rAOM treated with prophylactic antibiotics compared to placebo/no treatment there is possibly no difference to report on adverse effects during 24 months follow-up. NNH Not Applicable

Summary of findings:

29 Prophylactic antibiotics compared to placebo / no treatment for prevention of recurrent acute otitis media

Patient or population: Prevention of recurrent acute otitis media in children aged 0 to 14 years.

Setting: Primary health care.

Intervention: Prophylactic antibiotics (Studies used Amoxycillin 20-50mg/kg daily, Ampicillin 125-250mg/day (dose age dependant), Trimethoprim/sulfamethoxazole 4-8/12-40 mg/kg/day twice daily, Sulfisoxazole 75 mg/kg/day or 500-1000mg (dose age dependant) twice daily and Phenoxymethyl penicillin V 25 mg/kg/day). Duration was 6.5 weeks to 2 years.

Comparison: Placebo / no treatment

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Prophylactic antibiotics	**With Prophylactic antibiotics**	**Difference**		
Antibiotic resistance during intervention assessed by: nasopharyngeal swabs follow up: range 12 to 24 months № of participants: 181 (2 RCTs) [1,f]	**RR 1.37** (0.83 to 2.26)	22.5%	**30.8%** (18.7 to 50.8)	8.3% more(NS) (3.8 fewer to 28.3 more)	⨁⨁◯◯ LOW [g,h]	In children with rAOM treated with prophylactic antibiotics compared to placebo there is possibly no difference to report on antibiotic resistance. NNT Not applicable. NNH Not Applicable

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: (1) Cochrane Review, Leach 2006 updated 2011 (Casselbrant 1992 Gaskins 1982, Gonzalez 1986, Liston 1983, Leach 2008, Mandel 1996, Maynard 1972, Perrin 1974, Persico 1985, Principi 1989, Roark 1997, Sih 1993, Teele 2000, Varsano 1985)
b. Inconsistency: High heterogeneity
c. Studies taken from: (1) Cochrane Review, Leach 2006 updated 2011 (Casselbrant 1992, Gray 1981, Gaskins 1982, Gonzalez 1986, Liston 1983, Leach 2008, Mandel 1996, Maynard 1972, Principi 1989, Roark 1997, Sih 1993, Schuller 1983a, Varsano 1985)
d. Studies taken from: (1) Cochrane Review, Leach 2006 updated 2011 (Casslebrant 1992, Gaskins 1982a, Gonzales 1986, Gray 1981, Leech 2008, Perrin 1974, Principi 1989a, Sih 1993a, Schuller 1983a, Teele 2000a, Versano 1985)
e. Imprecision: Low event rate. Optimal information size not reached. Confidence interval covers benefit and harm.
f. Studies taken from: Cochrane Review, Leach 2006 (Casslebrant 1992, Mandel 1996)
g. Indirectness: Nasopharyngeal carriage of only a small number of specific bacteria reported. Surrogate marker for clinically important resistant disease.
h. Imprecision: Optimal information size not reached

References

1. Leach AJ, Morris PS. Antibiotics for the prevention of acute and chronic suppurative otitis media in children. The Cochrane database of systematic reviews. 2006(4):Cd004401. Epub 2006/10/21. doi: 10.1002/14651858.CD004401.pub2. PubMed PMID: 17054203.

Summary of findings:

30. Tympanostomy tubes compared to no surgery for recurrent acute otitis media

Patient or population: Children aged 0 to 3 years with recurrent acute otitis media (rAOM).

Setting: Hospital.

Intervention: Tympanostomy tubes (TTs)

Comparison: No surgery.

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Tympanostomy tubes	**With Tympanostomy tubes**	**Difference**		
Hearing loss - Difference in mean decibel hearing. Ears with TTs compared to contralateral ears used as controls assessed with: Pure tone audiometry follow up: median 2 years № of participants: 44 (1 RCT) [1,a]	At 6 months post TT insertion a small but significant difference is found between TT and non-TT ears; better hearing in TT ears (-3.7dB [-7 to 0 dB]). At 12 months post insertion there is no significant difference (-0.8dB [-4.0 to +2.0 dB]). At 24 months, a small but significant difference is found; better hearing in non-TT ears (1.7dB [0 to +4.0dB]).				⨁⨁◯◯ LOW [b,c]	In children with rAOM receiving TTs compared to no surgery there is possibly an improvement in hearing at 6 months, which is not sustained at 12 months follow-up. NNT not evaluable
Incident rate of AOM episodes/child/year assessed with: parental report + pneumatic otoscopy +/- tympanometry +/- otomicroscopy +/- otorrhea. follow up: range 6 to 12 months № of participants: 385 (3 RCTs) [2,3,4,d]	-	The mean incident rate of AOM episodes/child/year was **1.29** episodes/patient/year [e]	-	rate ratio **0.8 episodes/patient/year fewer** (0.45 more to 1.43 more)	⨁◯◯◯ VERY LOW [b,f,g]	In children with rAOM receiving TTs compared to no surgery there are possibly fewer AOM episodes/child/year.
Proportion of children otitis free follow up: range 6 months to 2 years № of participants: 511 (5 RCTs) [2,3,4,5,h]	**RR 1.81** (1.44 to 2.27)	28.6%	**51.8%** (41.2 to 65.0)	**23.2% more** (12.6 more to 36.4 more)	⨁⨁◯◯ LOW [b,g]	Children with rAOM receiving TTs compared to no surgery are possibly more likely to remain free of otitis media at 6-24 months follow-up. NNT ~4

Summary of findings:

30. Tympanostomy tubes compared to no surgery for recurrent acute otitis media

Patient or population: Children aged 0 to 3 years with recurrent acute otitis media (rAOM).

Setting: Hospital.

Intervention: Tympanostomy tubes (TTs)

Comparison: No surgery.

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Tympanostomy tubes	**With Tympanostomy tubes**	**Difference**		
Change in Quality of Life from baseline assessed with: QOL-OM-6 tool follow up: range 4 to 12 months № of participants: 77 (1 RCT) [6,i]	OM-6 QOL questionnaire at base line, 4 months and 12 months post-surgery showed increase in QOL for both TTs (n=42) and no surgery (n=35) groups, with no difference between groups in mean improvement.				⨁⨁◯◯ LOW [g,j]	In children with rAOM treated with TTs compared to no surgery there is possibly no difference in QOL scores at 4-12 months follow-up.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm; **MD:** Mean difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Study: Le 1991
b. Risk of Bias: Selection and performance bias
c. Imprecision: Estimate of effect covers harm and benefit at different time points
d. Studies taken from: (1) Cochrane Review: McDonald 2008 updated 2011(Gebhart 1981), (2) Kujala 2012, (3) Gonzales 1986
e. Mean incident rate calculated with an unweighted mean.
f. Inconsistency: High heterogeneity
g. Imprecision: Optimal information size not reached / small study
h. Studies taken from: (1) Cochrane Review: McDonald 2008 updated 2011(Gebhart 1981 El Sayed 1996), (2) Kujala 2012, (3) Casselbrant 1992, (4) Gonzales 1986
i. Study: Kujala 2014
j. Risk of Bias: Attrition bias, raw QOL data not available

References

1. Le CT, Freeman DW, Fireman BH. Evaluation of ventilating tubes and myringotomy in the treatment of recurrent or persistent otitis media. The Pediatric infectious disease journal. 1991;10(1):2-11. Epub 1991/01/01. PubMed PMID: 2003051.
2. Gonzalez C, Arnold JE, Woody EA, Erhardt JB, Pratt SR, Getts A, et al. Prevention of recurrent acute otitis media: chemoprophylaxis versus tympanostomy tubes. The Laryngoscope. 1986;96(12):1330-4. Epub 1986/12/01. PubMed PMID: 3537596.

3. Kujala T, Alho OP, Luotonen J, Kristo A, Uhari M, Renko M, et al. Tympanostomy with and without adenoidectomy for the prevention of recurrences of acute otitis media: a randomized controlled trial. The Pediatric infectious disease journal. 2012;31(6):565-9. Epub 2012/04/03. doi: 10.1097/INF.0b013e318255ddde. PubMed PMID: 22466327.
4. McDonald S, Langton Hewer CD, Nunez DA. Grommets (ventilation tubes) for recurrent acute otitis media in children. The Cochrane database of systematic reviews. 2008(4):Cd004741. Epub 2008/10/10. doi: 10.1002/14651858.CD004741.pub2. PubMed PMID: 18843668.
5. Casselbrant ML, Kaleida PH, Rockette HE, Paradise JL, Bluestone CD, Kurs-Lasky M, et al. Efficacy of antimicrobial prophylaxis and of tympanostomy tube insertion for prevention of recurrent acute otitis media: results of a randomized clinical trial. The Pediatric infectious disease journal. 1992;11(4):278-86. Epub 1992/04/01. PubMed PMID: 1565551.
6. Kujala T, Alho OP, Kristo A, Uhari M, Renko M, Pokka T, et al. Quality of life after surgery for recurrent otitis media in a randomized controlled trial. The Pediatric infectious disease journal. 2014;33(7):715-9. Epub 2014/01/22. doi: 10.1097/inf.0000000000000265. PubMed PMID: 24445832.

Summary of findings:

31. Adenoidectomy +/- tympanostomy tubes compared to no surgery / tympanostomy tubes alone for recurrent acute otitis media

Patient or population: Children aged 10 months to 18 years with recurrent acute otitis media.

Setting: Hospital

Intervention: Adenoidectomy +/- Tympanostomy tubes

Comparison: No surgery / Tympanostomy tubes alone

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Adenoidectomy +/- tympanostomy tubes	**With Adenoidectomy +/- tympanostomy tubes**	**Difference**		
Treatment failure (classified as: ≥4 episodes AOM per year, presence effusion for >50% of time (>6 months), need for additional surgery, hearing improvement <10dB) follow up: 12 months № of participants: 610 (3 RCTs) [1,a]	**RR 0.58** (0.36 to 0.94)	28.2%	**16.4%** (10.1 to 26.5)	**11.8% fewer** (18 fewer to 1.7 fewer)	⨁⨁◯◯ LOW [b,c]	In children with rAOM undergoing adenoidectomy +/- TTs compared to no surgery/TTs alone there are possibly fewer treatment failures at 12 months follow-up. NNT ~9
Subgroup analysis - Patients <2 years old: Treatment failure (classified as: ≥4 episodes AOM per year, presence effusion for >50% of time (>6 months), need for additional surgery, hearing improvement <10dB) follow up: 12 months № of participants: 719 (5 RCTs) [1,d]	**RR 0.57** (0.42 to 0.78)	27.4%	**15.6%** (11.5 to 21.4)	**11.8% fewer** (15.9 fewer to 6 fewer)	⨁⨁◯◯ LOW [b,c]	In children <2 years old with rAOM undergoing adenoidectomy +/- TTs compared to no surgery/TTs alone, there are possibly fewer treatment failures at 12 months follow-up. NNT ~ 9

Summary of findings:

31. Adenoidectomy +/- tympanostomy tubes compared to no surgery / tympanostomy tubes alone for recurrent acute otitis media

Patient or population: Children aged 10 months to 18 years with recurrent acute otitis media.

Setting: Hospital

Intervention: Adenoidectomy +/- Tympanostomy tubes

Comparison: No surgery / Tympanostomy tubes alone

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Adenoidectomy +/- tympanostomy tubes	**With Adenoidectomy +/- tympanostomy tubes**	**Difference**		
Subgroup analysis - Patients >2 years old: Treatment failure (classified as: ≥4 episodes AOM per year, presence effusion for >50% of time (>6 months), need for additional surgery, hearing improvement <10dB) follow up: 12 months № of participants: 84 (5 RCTs) [1,d]	**RR 7.27** (0.95 to 55.60)	2.5%	**18.2%** (2.4 to 100.0)	15.7% more (NS) (0.1 fewer to 136.5 more)	⨁⨁◯◯ LOW [b,c,e]	In children > 2 years old with rAOM undergoing adenoidectomy +/- TTs compared to no surgery/TTs alone there is possibly no difference in treatment failures. NNT Not Applicable.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: Boonacker Meta-Analysis (Mattila 2003, Koivunen 2004, Kujala 2012)
b. Risk of Bias: Attrition bias, selection bias (Mattila 2003)
c. Imprecision: Optimal information size not reached
d. Studies taken from: Boonacker Meta-Analysis (Hammarén-Malmi 2005, Koivunen 2004, Kujala 2012, Mattila 2003, Nguyen 2004)
e. Imprecision: Broad estimate of effect

References

1. Boonacker CW, Rovers MM, Browning GG, Hoes AW, Schilder AG, Burton MJ. Adenoidectomy with or without grommets for children with otitis media: an individual patient data meta-analysis. Health technology assessment (Winchester, England). 2014;18(5):1-118. Epub 2014/01/21. doi: 10.3310/hta18050. PubMed PMID: 24438691; PubMed Central PMCID: PMCPMC4780935.

Summary of findings:

32. Adenoidectomy compared to no adenoidectomy as an adjunct to tympanostomy tube placement for recurrent acute otitis media

Patient or population: Children aged Recurrent acute otitis media in children aged

Setting: Hospital

Intervention: Adenoidectomy and tympanostomy tubes.

Comparison: No adenoidectomy / Tympanostomy tubes alone.

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Adenoidectomy / TT alone	**With Adenoidectomy + TT**	**Difference**		
Treatment failure (classified as: ≥4 episodes of AOM per year, presence effusion for >50% of time (>6 months), need for additional surgery, hearing improvement <10dB) follow up: 12 months № of participants: 329 (2 RCTs) [1,a]	**RR 0.81** (0.27 to 2.40)	12.3%	**9.9%** (3.3 to 29.5)	2.3% fewer (NS) (9 fewer to 17.2 more)	⨁⨁◯◯ LOW [b,c,d]	In children with rAOM undergoing TTs placement and adjunct adenoidectomy compared to no adenoidectomy, there is possibly no reduction in treatment failures at 12 months follow-up. NNT Not applicable
Subgroup analysis - Patients >2 years old: Treatment failure (classified as: ≥4 episodes of AOM per year, presence effusion for >50% of time (>6 months), need for additional surgery, hearing improvement <10dB) follow up: 12 months № of participants: 83 (2 RCTs) [1,a]	**RR 7.09** (0.93 to 54.20)	2.6%	**18.2%** (2.4 to 100.0)	15.6% more (NS) (0.2 fewer to 136.4 more)	⨁⨁◯◯ LOW [b,d,e,f]	In children >2 years old with rAOM undergoing TTs placement and adjunct adenoidectomy compared to no adenoidectomy, there is possibly no reduction in treatment failures at 12 months follow-up. NNT Not Applicable

Summary of findings:

32. Adenoidectomy compared to no adenoidectomy as an adjunct to tympanostomy tube placement for recurrent acute otitis media

Patient or population: Children aged Recurrent acute otitis media in children aged

Setting: Hospital

Intervention: Adenoidectomy and tympanostomy tubes.

Comparison: No adenoidectomy / Tympanostomy tubes alone.

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Adenoidectomy / TT alone	**With Adenoidectomy + TT**	**Difference**		
Subgroup analysis - Patients <2 years old: Treatment failure (classified as: ≥4 episodes of AOM per year, presence effusion for >50% of time (>6 months), need for additional surgery, hearing improvement <10dB) follow up: 12 months № of participants: 439 (2 RCTs) [1,a]	**RR 0.66** (0.41 to 1.06)	16.5%	**10.9%** (6.8 to 17.5)	5.6% fewer (NS) (9.7 fewer to 1 more)	⨁⨁◯◯ LOW [b,d]	In children <2 years old with rAOM undergoing TTs placement and adjunct adenoidectomy compared to no adenoidectomy, there is possibly no reduction in treatment failure at 12 months follow-up. NNT Not Applicable

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: Boonacker Meta-Analysis (Mattila 2003, Kujala 2012)
b. Risk of Bias: Attrition bias, selection bias (Mattila 2003)
c. Inconsistency: noted to have borderline heterogeneity. Not rated down.
d. Imprecision: Optimal information size not reached
e. Imprecision: Wide confidence interval
f. Strong association however only rated up one level given small numbers and low event rates.

References

1. Boonacker CW, Rovers MM, Browning GG, Hoes AW, Schilder AG, Burton MJ. Adenoidectomy with or without grommets for children with otitis media: an individual patient data meta-analysis. Health technology assessment (Winchester, England). 2014;18(5):1-118. Epub 2014/01/21. doi: 10.3310/hta18050. PubMed PMID: 24438691; PubMed Central PMCID: PMCPMC4780935.

Summary of findings:

33. Topical antibiotics compared to ear toilet alone for chronic suppurative otitis media

Patient or population: Children and adults with chronic suppurative otitis media

Setting: Primary health care

Intervention: Topical antibiotics (Studies used: Oxfloxacin single dose and Ciprofloxacin three times daily for 7 days.)

Comparison: Ear toilet alone

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Topical antibiotics	**With Topical antibiotics**	**Difference**		
Persistent discharge assessed with: otoscopy follow up: 1 week № of participants: 197 (2 RCTs) [1,a]	**RR 0.45** (0.34 to 0.59)	80.8%	**36.4%** (27.5 to 47.7)	**44.4% fewer** (53.3 fewer to 33.1 fewer)	⨁⨁◯◯ LOW [b,c,d]	In patients with CSOM treated with topical antibiotics compared to ear toilet alone there are possibly fewer children with persistent ear discharge at 1 week follow-up. NNT ~3

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: Cochrane Review, Macfadyen 2005 (van Hesselt 2002, Kasemsuwan 1997)
b. Risk of Bias: Attrition bias noted (Kasemsuwan) but not rated down
c. Inconsistency: High heterogeneity
d. Imprecision: Small studies / optimal information size not reached.

References

1. Macfadyen CA, Acuin JM, Gamble C. Topical antibiotics without steroids for chronically discharging ears with underlying eardrum perforations. The Cochrane database of systematic reviews. 2005(4):Cd004618. Epub 2005/10/20. doi: 10.1002/14651858.CD004618.pub2. PubMed PMID: 16235370.

Summary of findings:

34. Topical quinolone antibiotic compared to topical antiseptic for chronic suppurative otitis media

Patient or population: Children and adults with chronic suppurative otitis media.

Setting: Primary health care

Intervention: Topical quinolone antibiotic (Studies used: Ofloxacin 3 drops, three times daily and Ciprofloxacin 3-6 drops twice to three times daily.) Duration varied from 10 days to 4 weeks.

Comparison: Topical antiseptic (Studies used: 1 to 5% Povidone iodine, 2% Acetic acid, 2% Boric acid and 1% Aluminium acetate). Duration varied from 10 days to 4 weeks

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Topical quinolone antibiotic	**With Topical quinolone antibiotic**	**Difference**		
Persistent discharge assessed with: otoscopy follow up: range 2 to 4 weeks № of participants: 702 (5 RCTs) [1,2,a]	**RR 0.56** (0.46 to 0.67)	57.0%	**31.9%** (26.2 to 38.2)	**25.1% fewer** (30.8 fewer to 18.8 fewer)	⨁⨁⨁◯ MODERATE [b,c]	In patients with CSOM treated with topical quinolone compared to topical antiseptic there are probably fewer patients with persistent discharge at 2-4 weeks follow-up. NNT ~ 4.
Healing of the tympanic membrane assessed with: otoscopy follow up: median 4 weeks № of participants: 399 (1 RCT) [2,d]	**RR 1.54** (0.91 to 2.61)	10.1%	**15.5%** (9.1 to 26.2)	5.4% more (NS) (0.9 fewer to 16.2 more)	⨁⨁◯◯ LOW [e,f]	In patients with CSOM treated with topical quinolone compared to topical antiseptic there is possibly no difference in healing of the tympanic membrane at 4 weeks. NNT Not Applicable

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: (1) Cochrane review, Macfadyen 2005 (van Hasselt 1997, Fradis 1997, Jaya 2003, Macfadyen 2005) and (2) Loock 2012
b. Risk of Bias: Attrition bias (van Hasselt 1997) noted however only small number in meta-analysis and removal does not affect overall result of data. Not rated down.
c. Indirectness: various antiseptic solutions used
d. Studies taken from: Cochrane review, Macfadyen 2005 (Macfayden 2005)
e. Imprecision: Small studies / optimal information size not reached
f. Imprecision: Single study

References

1. Loock JW. A randomised controlled trial of active chronic otitis media comparing courses of eardrops versus one-off topical treatments suitable for primary, secondary and tertiary healthcare settings. Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery. 2012;37(4):261-70. Epub 2012/07/19. doi: 10.1111/j.1749-4486.2012.02532.x. PubMed PMID: 22804826.
2. Macfadyen CA, Acuin JM, Gamble C. Topical antibiotics without steroids for chronically discharging ears with underlying eardrum perforations. The Cochrane database of systematic reviews. 2005(4):Cd004618. Epub 2005/10/20. doi: 10.1002/14651858.CD004618.pub2. PubMed PMID: 16235370.

Summary of findings:

35. Topical quinolone compared to topical non-quinolone antibiotic for chronic suppurative otitis media

Patient or population: Children and adults with chronic suppurative otitis media.

Setting: Primary health care.

Intervention: Topical quinolone antibiotic. (Studies used: Ciprofloxacin 0.3% 2-5 drops, three times daily, Ofloxacin 0.3% 3 - 6 drops, twice to three times daily or 6 drops once weekly.) Duration varied from 8 days to 3 weeks

Comparison: Topical non-quinolone antibiotic (Studies used: Tobramycin 0.3% 2-5 drops, three times daily, Gentamicin 0.3% 5 drops, three times daily, 0. 5% Neomycin, 0.1% polymyxin B 3-6 drops, twice to three times daily or 6 drops weekly.) Duration varied from 8 days to 3 weeks

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Topical quinolone	**With Topical quinolone**	**Difference**		
Persistent discharge assessed with: otoscopy follow up: 2 weeks № of participants: 276 (5 RCTs) [1,a]	**RR 0.65** (0.46 to 0.92)	37.4%	**24.3%** (17.2 to 34.4)	**13.1% fewer** (20.2 fewer to 3 fewer)	⨁⨁◯◯ LOW [b,c]	In patients with CSOM treated with topical quinolone antibiotics compared to topical non-quinolone antibiotics there are possibly fewer patients with persistent discharge at 2 weeks follow-up. NNT ~8
Persistent discharge assessed with: otoscopy follow up: range 2 to 3 weeks № of participants: 313 (6 RCTs) [1,d]	**RR 0.76** (0.55 to 1.04)	36.4%	**27.6%** (20.0 to 37.8)	8.7% fewer (NS) (16.4 fewer to 1.5 more)	⨁⨁⨁◯ MODERATE [c]	In patients with CSOM treated with topical quinolone antibiotics compared to topical non-quinolone antibiotics there is probably no difference in persistent discharge at 2-3 weeks follow-up. NNT Not applicable.
Persistent discharge - Topical quinolone vs topical non-quinolone with steroid assessed with: otoscopy follow up: median 14 days № of participants: 395 (3 RCTs) [1,e]	**RR 0.97** (0.57 to 1.64)	70.5%	**68.4%** (40.2 to 100.0)	2.1% fewer (NS) (30.3 fewer to 45.1 more)	⨁◯◯◯ VERY LOW [b,c,f]	In patients with CSOM treated with topical quinolone antibiotics compared to topical non-quinolone antibiotics with steroid there is insufficient evidence to report on persistent discharge at 14 days follow-up. NNT Not Applicable

Summary of findings:

35. Topical quinolone compared to topical non-quinolone antibiotic for chronic suppurative otitis media

Patient or population: Children and adults with chronic suppurative otitis media.

Setting: Primary health care.

Intervention: Topical quinolone antibiotic. (Studies used: Ciprofloxacin 0.3% 2-5 drops, three times daily, Ofloxacin 0.3% 3 - 6 drops, twice to three times daily or 6 drops once weekly.) Duration varied from 8 days to 3 weeks

Comparison: Topical non-quinolone antibiotic (Studies used: Tobramycin 0.3% 2-5 drops, three times daily, Gentamicin 0.3% 5 drops, three times daily, 0. 5% Neomycin, 0.1% polymyxin B 3-6 drops, twice to three times daily or 6 drops weekly.) Duration varied from 8 days to 3 weeks

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Topical quinolone	**With Topical quinolone**	**Difference**		
Persistent discharge - Topical quinolone vs topical non-quinolone with steroid. Remote Aboriginal children. assessed with: otoscopy follow up: range 6 to 8 weeks № of participants: 97 (1 RCT) [1,g]	**RR 0.97** (0.75 to 1.25)	72.3%	**70.2%** (54.3 to 90.4)	2.2% fewer (NS) (18.1 fewer to 18.1 more)	⊕⊕◯◯ LOW [c]	In remote Aboriginal children with CSOM treated with topical Ciprofloxacin compared to topical Framycetin-Gramicidin-Dexamethasone there is possibly no difference in persistent discharge at 6-8 weeks NNT Not Applicable

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: Cochrane Review, Macfadyen 2005 (Tutkun 1995, van Hasselt 1997, van Hasselt 1998 daily, van Hasselt 1998 weekly, Kaygusuz 2002)
b. Inconsistency: High heterogeneity
c. Imprecision: Small studies / optimal information size not reached
d. Studies taken from: Cochrane Review, Macfadyen 2005 (Tutkun 1995, van Hasselt 1997, van Hasselt 1998 daily, van Hasselt 1998 weekly, Kaygusuz 2002, Fradis 1997)
e. Studies taken from: Cochrane Review, Macfadyen 2005 (Miro 2000, Tong 1996, Couzos 2003)
f. Risk of Bias: Performance bias (no blinding - Miro 2000), early termination of study noted (Couzos 2003) due to poor recruitment.
g. Study taken from: Leach 2008
h. Studies taken from: Cochrane Review, Macfadyen 2005 (van Hasselt 1997, Kaygusuz 2002, Lorente 1995)
i. Studies taken from: Cochrane Review, Macfadyen 2005 (Fradis 1997, Kaygusuz 2002)

References

1. Macfadyen CA, Acuin JM, Gamble C. Topical antibiotics without steroids for chronically discharging ears with underlying eardrum perforations. The Cochrane database of systematic reviews. 2005(4):Cd004618. Epub 2005/10/20. doi: 10.1002/14651858.CD004618.pub2. PubMed PMID: 16235370.

Summary of findings:

36. Systemic antibiotic compared to topical antibiotic for chronic suppurative otitis media

Patient or population: Children and adults with chronic suppurative otitis media.

Setting: Primary health care.

Intervention: Systemic antibiotic [oral amoxicillin-clavulanic acid (375mg) three times daily, for 7days; Ciprofloxacin (500mg) twice daily for 10 days; intramuscular Gentamicin sulfate (80mg) twice daily for 5-10 days].

Comparison: Topical quinolone antibiotic [Studies used: Ofloxacin eardrops 0.3% three times daily, for 7days; Ciprofloxacin eardrops (250 microgram/mL) twice daily for 5-10 days].

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens
		Without Oral antibiotic	**With Oral antibiotic**	**Difference**		
Treatment failure - Systemic non-quinolone vs topical quinolone assessed with: persistent discharge on otoscopy follow up: range 1 to 2 weeks № of participants: 116 (2 RCTs) [1,a]	**RR 3.21** (1.88 to 5.49)	20.3%	**65.3%** (38.2 to 100.0)	**44.9% more** (17.9 more to 91.3 more)	⨁⨁⨁◯ MODERATE [b,c]	In patients with CSOM treated with systemic antibiotics compared to topical antibiotics there are probably more treatment failures at 1-2 weeks follow-up. NNH ~3
Treatment failure - Systemic quinolone vs topical quinolone assessed with: persistent discharge on otoscopy follow up: range 1 to 2 weeks № of participants: 175 (3 RCTs) [1,d]	**RR 3.18** (1.87 to 5.43)	15.0%	**47.7%** (28.1 to 81.4)	**32.7% more** (13.1 more to 66.5 more)	⨁⨁⨁◯ MODERATE [b,c]	In patients with CSOM treated with oral quinolone comapred to topical quinolone there are probably more treatment failures at 1-2 weeks follow-up. NNH ~4

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: Cochrane Review, Macfadyen 2006 (Yuen 1994, Esposito 1992)

b. Risk of Bias: Performance bias (blinding not described and not likely - Esposito 1992).

c. Imprecision: Optimal information size not reached.

d. Studies taken from: Cochrane Review, Macfadyen 2006 (Esposito 1990, de Miguel 1999, Povedano 1995)

e. Study taken from: Browning 1983

References

1. Macfadyen CA, Acuin JM, Gamble C. Systemic antibiotics versus topical treatments for chronically discharging ears with underlying eardrum perforations. The Cochrane database of systematic reviews. 2006(1):Cd005608. Epub 2006/01/27. doi: 10.1002/14651858.Cd005608. PubMed PMID: 16437533.

Summary of findings:

37. Oral Trimethoprim/Sulfamethoxazole compared to placebo for adjunct treatment (with topical quinolones) for chronic suppurative otitis media.

Patient or population: Children aged 1 to 12 years with chronic suppurative otitis media (TMP).

Setting: Primary health care.

Intervention: Oral Trimethoprim/Sulfamethoxazole (18 mg/kg, administered orally, two times daily) adjunct treatment (with topical quinolones) for 6 to 12 weeks.

Comparison: Placebo adjunct treatment (with topical quinolones)

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Oral Trimethoprim/ Sulfamethoxazole	**With Oral Trimethoprim/ Sulfamethoxazole**	**Difference**		
Persistent otorrhoea assessed with: otoscopy follow up: mean 6 weeks № of participants: 98 (1 RCT) [1,a]	**RR 0.52** (0.31 to 0.89)	52.9%	**27.5%** (16.4 to 47.1)	**25.4% fewer** (36.5 fewer to 5.8 fewer)	⨁⨁⨁◯ MODERATE [b]	In children with CSOM treated with TMP-SMX as an adjunct to topical therapy compared to topical therapy alone there are probably fewer children with persistent otorrhoea at 6 weeks follow-up. NNT ~4
Persistent otorrhoea assessed with: otoscopy follow up: mean 12 weeks № of participants: 96 (1 RCT) [1,a]	**RR 0.68** (0.41 to 1.14)	46.9%	**31.9%** (19.2 to 53.5)	15.0% fewer (NS) (27.7 fewer to 6.6 more)	⨁⨁⨁◯ MODERATE [b]	In children with CSOM treated with TMP-SMX as an adjunct to topical therapy compared to topical therapy alone there is probably no difference in persistent otorrohoea at 12 weeks follow-up. NNT Not Applicable
Persistent otorrhoea assessed with: otoscopy follow up: mean 1 years № of participants: 90 (1 RCT) [1,a,c]	**RR 1.28** (0.59 to 2.78)	19.6%	**25.0%** (11.5 to 54.4)	5.5% more (NS) (8 fewer to 34.8 more)	⨁⨁◯◯ LOW [b,d]	In children with CSOM treated with TMP-SMX as an adjunct to topical therapy compared to topical therapy alone there is possibly no difference in persistent otorrhoea at 1 year follow-up. NNT Not Applicable
Adverse events (diarrhoea or vomiting) assessed with: parental report follow up: mean 6 weeks № of participants: 98 (1 RCT) [1,a]	**RR 4.34** (0.50 to 37.46)	2.0%	**8.5%** (1.0 to 73.5)	6.5% more (NS) (1 fewer to 71.5 more)	⨁⨁⨁◯ MODERATE [b]	Children with CSOM treated with TMP-SMX as adjunct to topical therapy versus topical therapy alone probably results in no difference in adverse effects. NNH Not Applicable

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm

Summary of findings:

37. Oral Trimethoprim/Sulfamethoxazole compared to placebo for adjunct treatment (with topical quinolones) for chronic suppurative otitis media.

Patient or population: Children aged 1 to 12 years with chronic suppurative otitis media (TMP).

Setting: Primary health care.

Intervention: Oral Trimethoprim/Sulfamethoxazole (18 mg/kg, administered orally, two times daily) adjunct treatment (with topical quinolones) for 6 to 12 weeks.

Comparison: Placebo adjunct treatment (with topical quinolones)

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Oral Trimethoprim/ Sulfamethoxazole	**With Oral Trimethoprim/ Sulfamethoxazole**	**Difference**		

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Study taken from: van der Veen 2007
b. Imprecision: Small study
c. After 12 weeks study medication discontinued and patients referred back to care provider. Treatment recommendation in case otorrhea was: trimethoprim/ sulfamethoxazole (18 mg/kg, 2 times per day, for 6–12 weeks) for the placebo group and azithromycin (5 mg/ kg, once per day, for 6–12 weeks) for the trimethoprim/ sulfamethoxazole group, however this was up to discretion of doctor and other treatment could be offered.
d. Risk of Bias: Performance bias (lack blinding)

References

1. van der Veen EL, Rovers MM, Albers FW, Sanders EA, Schilder AG. Effectiveness of trimethoprim/sulfamethoxazole for children with chronic active otitis media: a randomized, placebo-controlled trial. Pediatrics. 2007;119(5):897-904. Epub 2007/05/03. doi: 10.1542/peds.2006-2787. PubMed PMID: 17473089.

Summary of findings:

38. Topical quinolone with steroids compared to topical quinolone without steroids for chronic suppurative otitis media

Patient or population: Adults (>18 years) with chronic suppurative otitis media

Setting: Primary health care.

Intervention: Topical quinolone with steroids (Ofloxacin 0.3% and dexamethasone 0.1% combination, 12 drops, twice daily for 10 days).

Comparison: Topical quinolone without steroids (Ofloxacin 0.3%, 12 drops twice daily for 10 days).

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens
		Without Topical quinolone with steroids	**With Topical quinolone with steroids**	**Difference**		
Clinical cure assessed with: otoscopy follow up: mean 15 days № of participants: 105 (1 RCT) [1,a]	**RR 0.88** (0.67 to 1.15)	71.2%	**62.6%** (47.7 to 81.8)	8.5% fewer (NS) (23.5 fewer to 10.7 more)	⨁⨁◯◯ LOW [b]	In patients with CSOM treated with topical quinolones + steroids compared to topical quinolone only there is possibly no difference in clinical cure at 15 days follow-up. NNT Not Applicable

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Study: Panchasara 2015
b. Imprecision: Small, single study. Rated down by two.

References

1. Panchasara A, Singh A, Mandavia D, Jha S, Tripathi C. Efficacy and safety of ofloxacin and its combination with dexamethasone in chronic suppurative otitis media. A randomised, double blind, parallel group, comparative study. Acta otorhinolaryngologica Italica : organo ufficiale della Societa italiana di otorinolaringologia e chirurgia cervico-facciale. 2015;35(1):39-44. Epub 2015/05/28. PubMed PMID: 26015650; PubMed Central PMCID: PMCPMC4443576.

Summary of findings:

39 Swimming in a chlorinated pool compared to no swimming for treatment chronic suppurative otitis media

Patient or population: Remote Australian Aboriginal children aged 5 to 12 years with chronic suppurative otitis media

Setting: Primary care - remote Australian Aboriginal community.

Intervention: Swimming in a chlorinated pool daily for 4 weeks

Comparison: No swimming.

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without swimming in a chlorinated pool	**With swimming in a chlorinated pool**	**Difference**		
Ear discharge / CSOM assessed with: tympnaometry, pneumatic & video otoscope follow up: 4 weeks № of participants: 89 (1 RCT) [1,a]	**RR 0.88** (0.63 to 1.22)	66.7%	**58.7%** (42.0 to 81.3)	8.0% fewer (NS) (24.7 fewer to 14.7 more)	⨁⨁◯◯ LOW [b,c]	In remote Australian Aboriginal children with CSOM who swim daily compared to no swimming there is possibly no difference in ear discharge at 4 weeks follow-up. NNT Not Applicable

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Study taken from: Stephen 2013. Note: this data conflicts with observational studies showing significant benefit. Methodology is higher in this study.
b. Indirectness: Unique setting, data cannot be generalised to all children
c. Imprecision: Small study

References

1. Stephen AT, Leach AJ, Morris PS. Impact of swimming on chronic suppurative otitis media in Aboriginal children: a randomised controlled trial. The Medical journal of Australia. 2013;199(1):51-5. Epub 2013/07/09. PubMed PMID: 23829265.

Summary of findings:

40. Antiseptic irrigation of middle ear at time of surgery compared to no treatment for the prevention of post-operative tympanostomy tube otorrhoea

Patient or population: Children < 12 years with rAOM or OME undergoing tympanostomy tube (TTs) insertion.

Setting: Hospital.

Intervention: Single application of triple irrigation of the ear canal with 50% solution of povidone-iodine topical antiseptic (Betadine) and saline for one minute before insertion TTs.

Comparison: No treatment.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens
		Without antiseptic irrigation of middle ear at time of surgery	**With antiseptic irrigation of middle ear at time of surgery**	**Difference**		
Post-operative TTO (by child) follow up: 1 weeks № of participants: 100 (1 RCT) [1,a]	**RR 1.25** (0.36 to 4.38)	8.0%	**10.0%** (2.9 to 35.0)	2.0% more (NS) (5.1 fewer to 27 more)	⨁◯◯◯ VERY LOW [b,c]	In children with TTs who receive antiseptic irrigation at time of surgery compared to no treatment there is insufficient evidence to support prevention of TTO at 1 week follow-up. NNT Not Applicable

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm; **TTs:** Tympanostomy tubes; **TTO**: Tympanostomy tube otorrhoea

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Study from: Cochrane Review, Syed 2013 (Cannon 1997)
b. Risk of Bias: Selection bias, participants and outcome assessor not blinded.
c. Imprecision: Small, single study. Broad estimate of effect.

References

1. Syed MI, Suller S, Browning GG, Akeroyd MA. Interventions for the prevention of postoperative ear discharge after insertion of ventilation tubes (grommets) in children. The Cochrane database of systematic reviews. 2013(4):Cd008512. Epub 2013/05/02. doi: 10.1002/14651858.CD008512.pub2. PubMed PMID: 23633358.

Summary of findings:

41. Saline irrigation at time of surgery compared to topical antibiotics for the prevention of post-operative tympanostomy tube otorrhoea

Patient or population: Children 3-11 years with AOM or OME undergoing tympanostomy tube (TTs) insertion.

Setting: Hospital

Intervention: Saline irrigation of middle ear at time of surgery.

Comparison: Ofloxacin for 5 days post-operatively.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens
		5-day post-operative Ofloxacin	**With Saline irrigation of middle ear at time of surgery**	**Difference**		
Post-operative TTO follow up: 2 weeks № of participants: 140 (1 RCT) [1,a]	**RR 1.83** (0.72 to 4.68)	8.6%	**15.7%** (6.2 to 40.1)	7.1% more(NS) (2.4 fewer to 31.5 more)	⊕⊕◯◯ LOW [b,c]	In children undergoing TTs surgery, saline irrigation at time of surgery compared to 5-days post-surgery treatment with topical Ofloxacin there is possibly no difference in TTO at 2 weeks follow-up. NNT Not Applicable

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm; **TTs:** tympanostomy tubes; **TTO:** Tympanostomy tube otorrhoea

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Study taken from: Cochrane Review, Syed 2013 (Kocaturk 2005)
b. Risk of Bias: Participants not blinded, however outcome assessor blinded. Not rated down.
c. Imprecision: Single, small study

References

1. Syed MI, Suller S, Browning GG, Akeroyd MA. Interventions for the prevention of postoperative ear discharge after insertion of ventilation tubes (grommets) in children. The Cochrane database of systematic reviews. 2013(4):Cd008512. Epub 2013/05/02. doi: 10.1002/14651858.CD008512.pub2. PubMed PMID: 23633358.

Summary of findings:

42. Single dose Ciprofloxacin compared to prolonged application Ciprofloxacin for the prevention of post-operative tympanostomy tube otorrhoea

Patient or population: Children 3-14 years with rAOm or OME undergoing tympanostomy tube (TTs) insertion.

Setting: Hospital.

Intervention: Single dose Ciprofloxacin post-surgery.

Comparison: Prolonged application Ciprofloxacin for 5 days.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens
		Without single dose Ciprofloxacin	**With single dose Ciprofloxacin**	**Difference**		
Post-operative TTO follow up: 2 weeks № of participants: 35 (1 RCT) [1,a]	**RR 0.71** (0.13 to 3.72)	16.7%	**11.8%** (2.2 to 62.0)	4.8% fewer (NS) (14.5 fewer to 45.3 more)	⨁◯◯◯ VERY LOW [b,c]	In children with TTs treated with single dose Ciprofloxacin compared to Ciprofloxacin for 5 days post-surgery there is no difference in TTO at 2 weeks follow-up. NNT Not Applicable

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm; **TTs:** tympanostomy tubes; **TTO:** Tympanostomy tube otorrhoea

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Study taken from: Cochrane Review, Syed 2013 (Nawasreh 2004)
b. Risk of Bias: Participants not blinded and unclear if outcome assessor blinded.
c. Imprecision: Broad estimate of effect. Single, small study.

References

1. Syed MI, Suller S, Browning GG, Akeroyd MA. Interventions for the prevention of postoperative ear discharge after insertion of ventilation tubes (grommets) in children. The Cochrane database of systematic reviews. 2013(4):Cd008512. Epub 2013/05/02. doi: 10.1002/14651858.CD008512.pub2. PubMed PMID: 23633358.

Summary of findings:

43. Topical antibiotic ear-drops (with or without a corticosteroid) compared to no treatment for tympanostomy tube otorrhoea

Patient or population: Children aged 1 to 10 years with tympanostomy tube otorrhoea.

Setting: Primary health care.

Intervention: Antibiotic ear-drops (Study used: hydrocortisone–bacitracin–colistin ear-drops, five drops, three times daily, in the discharging ear or ears for 7 days).

Comparison: No treatment

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Antibiotic eardrops (with or without a corticosteroid)	**With Antibiotic eardrops (with or without a corticosteroid)**	**Difference**		
Resolution of ear discharge assessed with: otoscopy follow up: 2 weeks № of participants: 151 (1 RCT) [1,a]	**RR 2.09** (1.62 to 2.69)	45.3%	**94.7%** (73.4 to 100.0)	**49.4% more** (28.1 more to 76.6 more)	⨁⨁⨁◯ MODERATE [b,c]	In children with TTO treated with topical antibiotic+/-steroid eardrops compared to no treatment there is probably more resolution of ear discharge at 2 weeks follow-up. NNT ~3
Persistence of ear discharge assessed with: otoscopy follow up: >4 weeks № of participants: 147 (1 RCT) [1,a]	**RR 0.08** (0.01 to 0.62)	16.4%	**1.3%** (0.2 to 10.2)	**15.1% fewer** (16.3 fewer to 6.2 fewer)	⨁⨁⨁◯ MODERATE [b,c]	In children with TTO treated with topical antibiotic+/-steroid eardrops compared to no treatment there are probably fewer children with persistent ear discharge at >4weeks follow-up. NNT ~7

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: Cochrane Review, Venekamp 2016 (van Dongen 2014)
b. Risk of Bias: Open label trial
c. Imprecision: Small study, however trial stopped early due to recommendation by committee given results of interim analysis.

References

1. Venekamp RP, Javed F, van Dongen TM, Waddell A, Schilder AG. Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion. The Cochrane database of systematic reviews. 2016;11:Cd011684. Epub 2016/11/18. doi: 10.1002/14651858.CD011684.pub2. PubMed PMID: 27854381.

Summary of findings:

44. Antibiotic eardrops (without a corticosteroid) compared to saline rinsing of the ear canal for children with tympanostomy tube otorrhoea

Patient or population: Children aged 7 months to 9 years with tympanostomy tube otorrhoea.

Setting: Primary health care.

Intervention: Antibiotic eardrops (Study used: Ciprofloxacin 3 mg/mL otic drops, four drops, twice daily for 1 week. This was accompanied by massage of the tragus).

Comparison: Saline rinsing of the ear canal (Study used: 10 mL saline through a syringe, by the parents, three times daily for 1 week).

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Antibiotic eardrops (with or without a corticosteroid)	**With Antibiotic eardrops (with or without a corticosteroid)**	**Difference**		
Resolution of ear discharge assessed with: otoscopy follow up: 1 weeks № of participants: 48 (1 RCT) [1,a]	**RR 1.67** (1.04 to 2.69)	46.2%	**77.1%** (48.0 to 100.0)	**30.9% more** (1.8 more to 78 more)	⨁⨁⨁◯ MODERATE [b,c]	In children with TTO treated with topical Ciprofloxacin compared to saline rinsing there is probably more resolution of ear discharge at 1 week follow-up. NNT ~4
Tube blockage assessed with: otoscopy follow up: 1 weeks № of participants: 48 (1 RCT) [1,a]	**RR 1.77** (0.32 to 9.67)	7.7%	**13.6%** (2.5 to 74.4)	5.9% more(NS) (5.2 fewer to 66.7 more)	⨁⨁◯◯ LOW [b,c,d]	In children with TTO treated with topical Ciprofloxacin compared to saline rinsing there is possibly no difference in TT blockages. NNT Not Applicable

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: Cochrane Review, Venekamp 2016 (Heslop 2010)
b. Risk of bias: Risk of performance bias noted but outcome assessor blinded. Not rated down.
c. Imprecision: Small study
d. Imprecision: Low event rate

References

1. Venekamp RP, Javed F, van Dongen TM, Waddell A, Schilder AG. Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion. The Cochrane database of systematic reviews. 2016;11:Cd011684. Epub 2016/11/18. doi: 10.1002/14651858.CD011684.pub2. PubMed PMID: 27854381.

Summary of findings:

45. Antibiotic(s) + corticosteroid eardrops compared to antibiotic ear-drops for children with tympanostomy tube otorrhoea

Patient or population: Children aged 6 months to 12 years with tympanostomy tube otorrhoea (TTO)

Setting: Primary health care.

Intervention: Antibiotic(s) + corticosteroid ear-drops (Studies used: Ciprofloxacin 0.3% & fluocinolone acetonide 0.025% twice daily, Ciprofloxacin (0.3%) & dexamethasone (0.1%) 3-4 drops, twice daily.) Duration was for 7 days.

Comparison: Antibiotic ear-drops (Studies used: Ofloxacin 5 drops twice daily, Ciprofloxacin 3 drops twice daily) Duration was 7-10 days.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens
		Without Antibiotic(s) + corticosteroid eardrops	**With Antibiotic(s) + corticosteroid eardrops**	**Difference**		
Resolution of ear discharge assessed with: physician assessment / parental report follow up: <2 weeks № of participants: 590 (2 RCTs) [1,a]	**RR 1.76** (1.33 to 2.31)	19.9%	**35.1%** (26.5 to 46.0)	**15.1% more** (6.6 more to 26.1 more)	⨁⨁◯◯ LOW [b,c,d]	In children with TTO treated with topical antibiotic+steroid eardrops compared to topical antibiotic eardrops alone there are possibly fewer children with ear discharge at <2 weeks. NNT ~7
Adverse events assessed with: parental report follow up: <4 weeks № of participants: 1023 (3 RCTs) [1,e]	**RR 0.86** (0.55 to 1.32)	7.8%	**6.7%** (4.3 to 10.3)	1.1% fewer (NS) (3.5 fewer to 2.5 more)	⨁⨁◯◯ LOW [b,c,d]	In children with TTO treated with topical antibiotic+steroid eardrops compared to topical antibiotic eardrops alone there is possibly no difference in adverse events during 4 weeks follow-up. NNT Not Applicable
Resolution of ear discharge assessed with: physician assessment / parental report follow up: range 2 to 4 weeks № of participants: 590 (2 RCTs) [1,a]	**RR 1.09** (0.90 to 1.31)	76.0%	**82.9%** (68.4 to 99.6)	6.8% more (NS) (7.6 fewer to 23.6 more)	⨁⨁◯◯ LOW [b,d]	In children with TTO treated with topical antibiotic+steroid eardrops compared to topical antibiotic eardrops alone there is possibly no difference in children with ear discharge at 2-4 weeks follow-up. NNT Not Applicable

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: Cochrane Review, Venekamp 2016 (Roland 2003, Roland 2004)
b. Risk of Bias: Attrition bias (Roland 2003, Roland 2004) & Performance bias - lack of participant blinding (Roland 2004)
c. Imprecision: Optimal information size not reached. Not rated down
d. Risk publication bias: 2 studies not published and not included in meta-analysis.
e. Studies taken from: Cochrane Review, Venekamp 2016 (NCT01404611, Roland 2003, Roland 2004)

References

1. Venekamp RP, Javed F, van Dongen TM, Waddell A, Schilder AG. Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion. The Cochrane database of systematic reviews. 2016;11:Cd011684. Epub 2016/11/18. doi: 10.1002/14651858.CD011684.pub2. PubMed PMID: 27854381.

Summary of findings:

46. Ear plugs compared to no ear plugs when swimming or bathing for prevention of tympanostomy tube otorrhoea

Patient or population: Children aged 6 months to 6 years with tympanostomy tubes (TT).

Setting: Community.

Intervention: Ear plugs (Soft, plastic,prefabricated ear plug (Doc's Proplugs) or mouldable silicone ear plug (Insta-Putty, Insta-Mold Products) when swimming or bathing. Duration was 1 year.

Comparison: No ear plugs when swimming or bathing.

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without ear plugs	**With ear plugs**	**Difference**		
Rate of otorrhoea (annual) assessed with: physician diagnosed by otoscopy follow up: 1 years № of participants: 172 (1 RCT) [1,a]	-	The mean rate of otorrhoea (annual) was **1.2**	-	MD **0.36 lower** (0.45 lower to 0.27 lower)	⨁⨁◯◯ LOW [b,c]	In children with TTO who wear ear plugs compared to no ear plugs when swimming or bathing there are possibly fewer episodes of otorrhoea at 1 year follow-up.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm; **MD**: Mean difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: Cochrane review, Moualed 2016 (Goldstein 2005)
b. Risk of Bias: Performance bias and attrition bias
c. Imprecision: Small study

References

1. Moualed D, Masterson L, Kumar S, Donnelly N. Water precautions for prevention of infection in children with ventilation tubes (grommets). The Cochrane database of systematic reviews. 2016(1):Cd010375. Epub 2016/01/28. doi: 10.1002/14651858.CD010375.pub2. PubMed PMID: 26816299.

Summary of findings:

47. No swimming or head submersion during bathing compared to unrestricted swimming or head submersion during bathing for prevention of tympanostomy tube otorrhoea

Patient or population: Children aged 3 months to 12 years with tympanostomy tubes (TTs).

Setting: Community.

Intervention: No swimming or head submersion during bathing. Duration was for 1 year.

Comparison: Unrestricted swimming or head submersion during bathing.

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without No swimming or head submersion during bathing	**With No swimming or head submersion during bathing**	**Difference**		
Rate of otorrhoea (annual) assessed with: review of medical record and parental report follow up: 1 years № of participants: 92 (1 RCT) [1,a]	-	The mean rate of otorrhoea (annual) was **1.17** episodes otorrhoea / year	-	MD **0 episodes otorrhoea / year** (0.14 lower to 0.14 higher) [b]	⨁◯◯◯ VERY LOW [c,d]	In children with TTs advised to avoid swimming and head submersion during bathing compared to unrestricted swimming or head submersion during bathing there are possibly no fewer episodes of otorrhoea at 1 year follow-up.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT:** Number needed to treat; **NNH**: Number needed to harm; **MD**: Mean difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Study taken from: Cochrane Review, Moualed 2016 (Parker 1994)
b. Some caution must be taken with interpretation of the 95% confidence interval in this case as it was not possible to calculate standard deviations for the study data and Goldstein 2005 values have been used.
c. Risk of Bias: Performance bias, selection bias, attrition bias
d. Imprecision: Small study

References

1. Moualed D, Masterson L, Kumar S, Donnelly N. Water precautions for prevention of infection in children with ventilation tubes (grommets). The Cochrane database of systematic reviews. 2016(1):Cd010375. Epub 2016/01/28. doi: 10.1002/14651858.CD010375.pub2. PubMed PMID: 26816299.

Summary of findings:

48. Oral antibiotics compared to placebo or no treatment for children with tympanostomy tube otorrhoea

Patient or population: Children aged 6 months to 10 years with tympanostomy tube otorrhoea (TTO).

Setting: Primary health care.

Intervention: Oral antibiotics (Studies used: Amoxicillin+clavulanate 45 mg/kg/day divided into 2 doses or 30/7.5 mg/kg per day divided into 3 doses.) Duration was for 7 days.

Comparison: Placebo or no treatment.

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Oral antibiotics	**With Oral antibiotics**	**Difference**		
Resolution of ear discharge assessed with: physician assessment by otoscpy and suction. follow up: <2 weeks № of participants: 79 (1 RCT) [1,a]	**RR 2.21** (1.36 to 3.60)	32.5%	**71.8%** (44.2 to 100.0)	**39.3% more** (11.7 more to 84.5 more)	⨁⨁⨁◯ MODERATE [b,c]	In children with TTO treated with Amoxicillin+clavulanate compared with placebo there is probably more resolution of ear discharge at <2 weeks follow-up. NNT 3
Resolution of ear discharge assessed with: physician assessment by otoscopy follow up: 2 weeks № of participants: 152 (1 RCT) [1,d]	**RR 1.23** (0.90 to 1.69)	45.3%	**55.8%** (40.8 to 76.6)	10.4% more(NS) (4.5 fewer to 31.3 more)	⨁⨁◯◯ LOW [c,e]	In children with TTO treated with Amoxicillin+clavulanate compared to initial observation there is possibly no difference in ear discharge at 2 weeks follow-up. NNT Not Applicable
Adverse events (contralateral acute otitis media with perforation of the tympanic membrane, extrusion of tympanostomy tube, granulation, gastrointestinal and cutaneous) assessed with: parental report follow up: <2 weeks № of participants: 79 (1 RCT) [1,a]	**RR 1.71** (0.69 to 4.25)	15.0%	**25.7%** (10.3 to 63.7)	10.7% more(NS) (4.7 fewer to 48.8 more)	⨁⨁⨁◯ MODERATE [b,c,f]	In children with TTO treated with Amoxicillin-clavulanate compared with placebo there are probably no fewer adverse events during 2 weeks follow-up. NNH Not Applicable
Chronic ear discharge (>4 weeks) assessed with: parental report follow up: 6 months № of participants: 147 (1 RCT) [1,d]	**RR 0.41** (0.15 to 1.11)	16.4%	**6.7%** (2.5 to 18.2)	9.7% fewer (NS) (14 fewer to 1.8 more)	⨁⨁◯◯ LOW [c,e]	In children with TTO treated with Amoxicillin+clavulanate compared with placebo there is possibly no difference to report on chronic ear discharge at 6 months follow-up. NNT Not Applicable

Summary of findings:

48. Oral antibiotics compared to placebo or no treatment for children with tympanostomy tube otorrhoea

Patient or population: Children aged 6 months to 10 years with tympanostomy tube otorrhoea (TTO).

Setting: Primary health care.

Intervention: Oral antibiotics (Studies used: Amoxicillin+clavulanate 45 mg/kg/day divided into 2 doses or 30/7.5 mg/kg per day divided into 3 doses.) Duration was for 7 days.

Comparison: Placebo or no treatment.

Outcome № of participants (studies)	Relative effect (95% CI)	**Anticipated absolute effects (95% CI)**			Quality	What happens
		Without Oral antibiotics	**With Oral antibiotics**	**Difference**		
Tube extrusion assessed with: physician assessment and otoscopy follow up: <2 weeks № of participants: 79 (1 RCT) [1,a]	**RR 0.51** (0.05 to 5.43)	5.0%	**2.6%** (0.3 to 27.2)	2.5% fewer (NS) (4.8 fewer to 22.1 more)	⨁⨁◯◯ LOW [b,c,f,g]	In children with TTO treated with Amoxicilli+clavulanate compared with placebo there is possibly no difference to report on tube extrusion at <2 weeks follow-up. NNT Not Applicable

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: Cochrane Review, Venekamp 2016 (Ruohola 2003)
b. Risk of Bias: Attrition bias noted but not rated down (Ruohola 2003)
c. Imprecision: Small study
d. Studies taken from: Cochrane Review, Venekamp 2016 (van Dongen 2014)
e. Risk of bias: Open label study
f. Imprecision: Low event rate
g. Imprecision: Broad estimate of effect; confidence interval includes significant both significant benefit and harm.

References

1. Venekamp RP, Javed F, van Dongen TM, Waddell A, Schilder AG. Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion. The Cochrane database of systematic reviews. 2016;11:Cd011684. Epub 2016/11/18. doi: 10.1002/14651858.CD011684.pub2. PubMed PMID: 27854381.

Summary of findings:

49. Oral antibiotics compared to saline rinsing of the ear canal for children with tympanostomy tube otorrhoea

Patient or population: Children aged 7 months to 9 years with tympanostomy tube otorrhoea (TTO).

Setting: Primary health care.

Intervention: Oral antibiotics (Study used: Amoxicillin 25-50 mg/kg/day divided into three daily doses for one week. In case of penicillin allergy, erythromycin, 40 mg/kg/day divided into three doses daily for a week was chosen).

Comparison: Saline rinsing of the ear canal (Study used: 10 mL saline through a syringe, by the parents, three times daily for 1 week).

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens
		Without Oral antibiotics	With Oral antibiotics	Difference		
Resolution of ear discharge assessed with: otoscopy follow up: 1 weeks № of participants: 46 (1 RCT) [1,a]	**RR 0.65** (0.30 to 1.43)	46.2%	**30.0%** (13.8 to 66.0)	16.2% fewer (NS) (32.3 fewer to 19.8 more)	⨁⨁◯◯ LOW [b]	In children with TTO treated with Amoxicillin compared to saline rinsing there is possibly no difference to support one treatment over the other for resolution of ear discharge at 1 week follow-up. NNT Not Applicable
Proportion of patients with tube blockage assessed with: otoscopy follow up: 1 weeks № of participants: 46 (1 RCT) [1,a]	**RR 1.95** (0.36 to 10.58)	7.7%	**15.0%** (2.8 to 81.4)	7.3% more (NS) (4.9 fewer to 73.7 more)	⨁⨁◯◯ LOW [b,c]	In children with TTO treated with Amoxicillin compared to saline rinsing there is possibly no difference to report on tube blockage at 1 week follow-up. NNH Not Applicable

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: Cochrane Review, Venekamp 2016 (Heslop 2010)
b. Imprecision: Small study
c. Imprecision: Low event rate

References

1. Venekamp RP, Javed F, van Dongen TM, Waddell A, Schilder AG. Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion. The Cochrane database of systematic reviews. 2016;11:Cd011684. Epub 2016/11/18. doi: 10.1002/14651858.CD011684.pub2. PubMed PMID: 27854381.

Summary of findings:

50. Antibiotic eardrops (with or without a corticosteroid) compared to Oral antibiotics for children with tympanostomy tube otorrhoea

Patient or population: Children aged 6 months to 12 years with tympanostomy tube otorrhoea (TTO).

Setting: Primary health care.

Intervention: Antibiotic ear-drops with or without a corticosteroid (Studies used: Ciprofloxacin 4 drops twice daily, Ofloxacin 0.25 ml twice daily, Ciprofloxacin + Hydrocortisone 4 drops twice daily, Hydrocortisone–Bacitracin–Colistin 5 drops three times daily). Duration was for 7-10 days.

Comparison: Oral antibiotics (Studies used: Amoxicillin+/-clavulanate 25-90 / 7.5 mg/kg per day divided into 2 to 3 doses.) Duration was for 7-10 days. In case of penicillin allergy, erythromycin, 40 mg/kg/day divided into 3 doses daily for 7 days was chosen.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
				Difference		
Resolution of ear discharge follow up: 1 weeks № of participants: 42 (1 RCT) [1,a]	**RR 2.58** (1.27 to 5.22)	30.0%	**77.4%** (38.1 to 100.0)	**47.4% more** (8.1 more to 126.6 more)	⨁⨁⨁◯ MODERATE [b,c]	In children with TTO treated with Ciprofloxacin compared to Amoxicillin there is probably more resolution of ear discharge at one week follow-up. NNT ~3
Resolution of ear discharge - Antibiotic-corticosteroid eardrops versus oral antibiotics follow up: range 2 to 4 weeks № of participants: 232 (2 RCTs) [1,d]	**RR 1.59** (1.35 to 1.88)	57.3%	**91.1%** (77.3 to 100.0)	**33.8% more** (20 more to 50.4 more)	⨁⨁◯◯ LOW [c,e]	In children with TTO treated with antibiotic+steroid eardrops compared to oral antibiotics there is possibly more resolution of ear discharge at two to four weeks follow-up. NNT ~3
Resolution of ear discharge - Antibiotic-corticosteroid eardrops versus oral antibiotics (Sensitivity analysis) follow up: median 2 weeks № of participants: 153 (1 RCT) [1,f]	**RR 1.70** (1.38 to 2.08)	55.8%	**94.9%** (77.1 to 100.0)	**39.1% more** (21.2 more to 60.3 more)	⨁⨁⨁◯ MODERATE [c]	In children with TTO treated with antibiotic+steroid eardrops compared to oral antibiotics there is possibly more resolution of ear discharge at two weeks follow-up. NNT ~3
Resolution of ear discharge - Antibiotic-only eardrops versus oral antibiotics follow up: range 2 to 4 weeks № of participants: 233 (1 RCT) [1,g]	**RR 1.00** (0.91 to 1.09)	89.4%	**89.4%** (81.3 to 97.4)	0.0% fewer (NS) (8 fewer to 8 more)	⨁⨁◯◯ LOW [c,e]	In children with TTO treated with Ofloxacin eardrops compared to Amoxicillin+clavulanate there is possibly no difference in ear discharge at 2-4 weeks follow-up. NNT Not applicable

Summary of findings:

50. Antibiotic eardrops (with or without a corticosteroid) compared to Oral antibiotics for children with tympanostomy tube otorrhoea

Patient or population: Children aged 6 months to 12 years with tympanostomy tube otorrhoea (TTO).

Setting: Primary health care.

Intervention: Antibiotic ear-drops with or without a corticosteroid (Studies used: Ciprofloxacin 4 drops twice daily, Ofloxacin 0.25 ml twice daily, Ciprofloxacin + Hydrocortisone 4 drops twice daily, Hydrocortisone–Bacitracin–Colistin 5 drops three times daily). Duration was for 7-10 days.

Comparison: Oral antibiotics (Studies used: Amoxicillin+/-clavulanate 25-90 / 7.5 mg/kg per day divided into 2 to 3 doses.) Duration was for 7-10 days. In case of penicillin allergy, erythromycin, 40 mg/kg/day divided into 3 doses daily for 7 days was chosen.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
				Difference		
Adverse events (ear pain, gastrointestinal) follow up: range 2 to 3 weeks № of participants: 705 (3 RCTs) [1,h]	**RR 0.37** (0.12 to 1.09)	31.7%	**11.7%** (3.8 to 34.5)	20.0% fewer (NS) (27.9 fewer to 2.9 more)	⨁⨁◯◯ LOW [c,e,i]	In children with TTO treated with antibiotic+/-steroid eardrops compared to oral antibiotics there is possibly no difference to report on adverse effects at 2-3 weeks follow-up. NNT Not Applicable
Proportion of patients with chronic ear discharge (>4 weeks) follow up: 6 months № of participants: 148 (1 RCT) [1,f]	**RR 0.20** (0.02 to 1.67)	6.8%	**1.4%** (0.1 to 11.3)	5.4% fewer (NS) (6.6 fewer to 4.5 more)	⨁⨁◯◯ LOW [c,e]	In children with TTO treated with hydrocortisone–bacitracin–colistin eardrops compared to amoxicillin+calvulanate there is possibly no difference to report ochronic ear discharge at 6 months follow-up. NNT Not Applicable
Proportion of patients with tube blockage follow up: range 1 to 3 weeks № of participants: 121 (2 RCTs) [j]	**RR 1.20** (0.33 to 4.45)	5.0%	**6.0%** (1.7 to 22.3)	1.0% more (NS) (3.3 fewer to 17.3 more)	⨁◯◯◯ VERY LOW [c,e]	In children with TTO treated with antibiotic+/-steroid ear drops compared to oral antibiotics there is possibly no difference to report on tube blockage. NNT Not Applicable
QOL scores - measured with otitis media-6 questionnaire assessed with: parental report follow up: 2 weeks № of participants: 153 (1 RCT) [1,f]	The changes in Otitis Media-6 total score (range 6 to 42) at two weeks were small, but favoured the antibiotic-corticosteroid eardrops group (difference in median change between treatment groups: -2, P < 0.01).				⨁⨁◯◯ LOW [c,e]	In children with TTO treated with hydrocortisone–bacitracin–colistin eardrops compared to amoxicillin+clavulanate there are possibly better QOL scores at 2 weeks follow-up.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: Cochrane Review, Venekamp 2016 (Heslop 2010)

b. Risk of bias: Lack of participant blinding however not rated down (outcome assessors blinded and adequate allocation concealment)
c. Imprecision: Small study / optimal information size not reahed
d. Studies taken from: Cochrane Review, Venekamp 2016 (Dohar 2006, van Dongen 2014)
e. Risk of bias: Open label trial, stopped early due to recommendation by committee given results of interim analysis - not rated down for this (van Dongen); attrition bias (Goldblatt); performance bias (Goldblatt and Dohar)
f. Studies taken from: Cochrane Review, Venekamp 2016 (van Dongen 2014)
g. Studies taken from: Cochrane Review, Venekamp 2016 (Goldblatt 1998)
h. Studies taken from: Cochrane Review, Venekamp 2016 (Dohar 2006, Goldblatt 1998, van Dongen 2014)
i. Inconsistency: High heterogeneity explained by excluding van Dongen. Not rated down.
j. Studies taken from: Cochrane Review, Venekamp 2016 (Dohar 2006, Heslop 2010)

References

1. Venekamp RP, Javed F, van Dongen TM, Waddell A, Schilder AG. Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion. The Cochrane database of systematic reviews. 2016;11:Cd011684. Epub 2016/11/18. doi: 10.1002/14651858.CD011684.pub2. PubMed PMID: 27854381.

Summary of findings:

51. Oral corticosteroids compared to placebo for children with tympanostomy tube otorrhoea

Patient or population: Children aged 6 months to 12 years with tympanostomy tube otorrhoea (TTO).

Setting: Primary health care.

Intervention: Oral corticosteroids (Studies used: Prednisolone 2 mg/kg/day divided into 3 equal doses for 3 days).

Comparison: Placebo.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality	What happens
		Without Oral corticosteroids	**With Oral corticosteroids**	**Difference**		
Resolution of ear discharge assessed with: physician assessment (when discharge could no longer be suctioned from ear canal) follow up: 2 weeks № of participants: 50 (1 RCT) [1,a]	**RR 1.08** (0.92 to 1.26)	88.9%	**96.0%** (81.8 to 100.0)	7.1% more (NS) (7.1 fewer to 23.1 more)	⨁⨁◯◯ LOW [b,c]	In children with TTO treated with Prednisolone compared to placebo there is possibly no difference in resolution of ear discharge at 2 weeks follow-up. NNT Not Applicable
Adverse events (gastrointestinal) assessed with: parental report follow up: 7 days № of participants: 50 (1 RCT) [1,a]	**RR 0.23** (0.01 to 4.63)	7.4%	**1.7%** (0.1 to 34.3)	5.7% fewer (NS) (7.3 fewer to 26.9 more)	⨁⨁◯◯ LOW [b,c]	In children with TTO treated with Prednisolone compared with placebo there possibly no difference in adverse events at 1 week follow-up. NNH Not Applicable.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **NS:** Not significant; **NNT**: Number needed to treat; **NNH**: Number needed to harm

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Studies taken from: Cochrane Review, Venekamp 2016 (Ruohola 1999)
b. Risk of bias: Attrition bias
c. Imprecision: Small study

References

1. Venekamp RP, Javed F, van Dongen TM, Waddell A, Schilder AG. Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion. The Cochrane database of systematic reviews. 2016;11:Cd011684. Epub 2016/11/18. doi: 10.1002/14651858.CD011684.pub2. PubMed PMID: 27854381.