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.