**Appendix 3 (as supplied by the authors): Summary of meta-analyses of the effectiveness of pneumococcal polysaccharide vaccines (in order of publication year)**

| No. | Year | Author | Target group | Included RCTs | Outcomes (No. of studies) | Results ( OR or RR <1 favours vaccine) | Vaccine type valency (No. of studies) |
|---|---|---|---|---|---|---|---|
| 1 | 2008 | Moberley[1] | Adults | Alfageme 2006<br>Örtqvist 1998<br>Koivula 1997<br>Davis 1987<br>Leech 1987<br>Klastersky 1986<br>Simberkoff 1986<br>Galliat 1985<br>Austrian 1980<br>Riley 1977<br>Smit 1977<br>Austrian 1976<br>Kaufman 1947 | Invasive pneumococcal disease<br>- all types (10)<br>- vaccine types (5)<br><br>Pneumonia, all cause (13)<br><br>Definitive pneumococcal pneumonia<br>- all types (10)<br>- vaccine types (4)<br><br>Presumptive pneumococcal pneumonia<br>- all types (8)<br><br>- vaccine types (5)<br><br>Mortality<br>- all cause (11)<br>- due to pneumonia (7)<br>- due to pneumococcal disease (3) | <br>OR 0.26 (0.15-0.46)<br>OR 0.18 (0.10-0.31)<br><br>OR 0.71 (0.52-0.97)<br><br><br>OR 0.26(0.15-0.46)<br>OR 0.13(0.05-0.38)<br><br><br>OR 0.47(0.23-0.99)<br><br>OR 0.27 (0.08-0.87)<br><br><br>OR 0.87(0.69-1.10)<br>OR 0.75 (0.39-1.43)<br><br>OR 2.51 (0.45-14.13) | <br>2/3 (1), 12(1), 14(5), 17(1), 23(2)<br>2/3 (1), 13(1), 14(2), 23(1)<br><br>2/3(1), 6(1), 12(3), 13(1), 14(4), 17(1), 23(2)<br><br><br>2/3 (1), 12(1), 14(5), 17(1), 23(2)<br>2/3 (1), 12(1), 14(1), 23(1)<br><br><br>2/3 (1), 6(1), 12(1), 14(2), 17(1), 23(2)<br>2/3 (1), 6(1), 12(1), 14(1), 23(1)<br><br><br>2/3 (1), 12(2), 14(6), 17(1), 23(1)<br>2/3 (1), 12(2), 14(2), 17(1), 23(1)<br><br>14(2), 17(1) |
| | | | Conclusions summarized in abstract | This meta-analysis provides evidence supporting the recommendation for PPV to prevent IPD in adults. The evidence from RCTs is less clear with respect to adults with chronic illness. This might be because of lack of effect or lack of power in the studies. The metaanalysis does not provide compelling evidence to support the routine use of PPV to prevent all-cause pneumonia or mortality. | | | |
| 2 | 2007 | Chang[2] | Children and adults with bronchiectasis | None (3 excluded) | Reduction of the severity and frequency of respiratory exacerbations and pulmonary decline | - | - |
| | | | Conclusions summarized in abstract | At present, there is a lack of reliable evidence to support or refute the routine use of pneumococcal vaccine as routine management in children and adults with bronchiectasis. Randomised controlled trials examining the efficacy of this intervention using various vaccine types in different age groups are needed. Until further evidence is available, it is recommended that health providers adhere to national guidelines. | | | |

*continued*

| Ref. | Year | Author | Target group | Included RCTs | Outcomes (No. of studies) | Results ( OR or RR <1 favours vaccine) | Vaccine type valency (No. of studies) |
|---|---|---|---|---|---|---|---|
| 3 | 2006 | Granger [3] | COPD patients | Alfageme 2006<br>Steentoft 2006 | Acute exacerbations (1) | OR 1.43 (0.31-6.69) | 23 |
| | | | | Davis 1987 | Pneumonia (3) | | |
| | | | | Leech 1987 | - all | OR 0.89 (0.58-1.37) | 23(2), 14(1) |
| | | | | | - 23 valent | OR 0.97 (0.61-1.53) | |
| | | | | | - 14 valent | OR 0.42 (0.10-1.72) | |
| | | | | | Emergency department visits (1) | | |
| | | | | | pneumonia | RR 0.99 (0.52-1.88) | 14 (1) |
| | | | | | LRTI | RR 1.00 (0.75-1.33) | 14 (1) |
| | | | | | URTI | RR 1.29 (0.68-2.47) | 14 (1) |
| | | | | | Mortality, cardiorespiratory (3) | | |
| | | | | | - all | OR 1.07 (0.69-1.66) | 23(1), 14(2) |
| | | | | | - 23 valent | OR 1.11 (0.66-1.88) | |
| | | | | | - 14 valent | OR 0.98 (0.44-2.18) | |
| | | | Conclusions summarized in abstract | There is no evidence from randomised controlled trials that injectable pneumococcal vaccination in persons with COPD has a significant impact on morbidity or mortality. Further large randomised controlled trials would be needed to ascertain if the small benefits suggested by individual studies are real. | | | |
| 4 | 2005 | Chaithong-wongwatt-hana[4] | Pregnant women (to prevent infant infection) | Munoz 2001 | Neonatal infections | | |
| | | | | O'Dempsey 1996 | - pneumonia (1) | RR 0.58 (0.18-1.90) | 23(1) |
| | | | | Shahid 1995 | - meningitis (1) | RR 3.04 (0.13-73.44) | 23(1) |
| | | | | | - otitis media (1) | RR 0.14 (0.01-2.75) | 23(1) |
| | | | | | - all infection (1) | RR 0.51 (0.18-1.41) | 23(1) |
| | | | Conclusions summarized in abstract | There is insufficient evidence to support whether pneumococcal vaccination during pregnancy could reduce infant infections. | | | |
| 5 | 2004 | Melegaro[5] | Elderly: low risk groups (LRG) and high risk groups (HRG) | Honkanen 1999 | Pneumococcal pneumonia | | |
| | | | | Örtqvist 1998 | - LRG (3) | OR 0.84 (0.47-1.50) | 14(2),23(1) |
| | | | | Koivula 1997 | - HRG (4) | OR 1.20 (0.75-1.92) | 14(2),17(1), 23(1) |
| | | | | Davis 1987 | | | |
| | | | | Leech 1987 | | | |
| | | | | Simberkoff 1986 | Invasive pneumococcal disease | | |
| | | | | Klastersky 1986 | - LRG (2) | OR 0.35 (0.08-1.49) | 14(1),23(1) |
| | | | | Gaillat 1985 | - HRG (4) | OR 0.80 (0.80-2.88) | 14(2),17(1), 23(1) |
| | | | Conclusions summarized in abstract (abbrev.) | When taken with the results of other metaanalyses and observational studies, it appears that PPV offers protection against IPD in the general elderly population whereas it has a moderate effect in the high-risk elderly. The vaccine has little or no effect against pneumonia. | | | |

*continued*

| Ref. | Year | Author | Target group | Included RCTs | Outcomes (No. of studies) | Results ( OR or RR <1 favours vaccine) | Vaccine type valency (No. of studies) |
|---|---|---|---|---|---|---|---|
| 6 | 2004 | Conaty[6] | Adults | French 2000 | Invasive pneumococcal disease | | |
| | | | | Honkanen 1999 | - all RCTs (9) | OR 0.62 (0.37-1.04) | 14(5), 17(1), 23(3) |
| | | | | Örtqvist 1998 | - elderly/chronic disease (7) | OR 0.51 (0.21-1.23) | 14(4), 17(1), 23(2) |
| | | | | Koivula 1997 | | | |
| | | | | Davis 1987 | All-cause pneumonia | | |
| | | | | Leech 1987 | - all RCTs (13) | *$R^2$ 0.97 (0.81-1.16) | 6(1), 12(3), 14(6), 23(3) |
| | | | | Simberkoff 1986 | - develop. (high incidence) (3) | *$R^2$ 0.66 (0.57-0.77) | 6(1), 12(1) 14(1) |
| | | | | Klatersky 1986 | - elderly/chronic disease (9) | *$R^2$ 1.03 (0.86-1.25) | 12F(2), 14(5), 23(2) |
| | | | | Gaillat 1985 | | | |
| | | | | Austrian 1980 | | | |
| | | | | Riley 1977 | | | |
| | | | | Smit 1977 | | | |
| | | | Conclusions summarized in abstract | From 13 observational studies the estimate of vaccine efficacy against invasive disease was 53% (46%–59%) compared with 38% (–4% to 63%) from nine RCTs. Estimates of protection against all-cause pneumonia were based on fewer, heterogeneous studies that were not consistent with the findings from RCTs for this outcome. From five studies combined efficacy was 32% (7%–50%) compared with 3% (–16% to 19%) from 13 RCTs. | | |
| 7 | 2004 | Davies[7] | Sickle cell patients | Goldblatt 2000 | Definitive pneumococcal | | |
| | | | | John 1985 | infection (1) | OR 3.01(0.65-13.91) | 14(1) |
| | | | | Rigau-Pirez 1983 | | | |
| | | | | Vernacchio 1998 | | | |
| | | | Conclusions summarized in abstract (abbrev.) | Only one trial reported incidence of pneumococcal infection, and this demonstrated that the polysaccharide pneumococcal vaccine used (PPV14) failed to reduce significantly the risk of infection in children under three years of age, but was associated with only minor adverse events. (…)We therefore recommend that conjugate pneumococcal vaccines are used in people with sickle cell disease. | | |
| 8 | 2003 | Straetemans[8] | Children, focus on AOM, PPV and PCV examined, only PPV reported here | Douglas 1986 | Proportion children with AOM | | |
| | | | | Karma 1985 | - all ages (7) | RR 0.94 (0.86-1.03) | 8(2), 14(2) |
| | | | | Douglas 1984 | - aged up to 24 months (4) | RR 0.98 (0.87-1.11) | 14 |
| | | | | Schuller 1983 | - older than 24 months (2) | RR 0.84 (0.65-1.09) | 14 |
| | | | | Makela 1981 | - 6–54 months (1) | RR 0.90 (0.77-1.06) | |
| | | | | Sloyer 1981 | | | |
| | | | | Teele 1981 | AOM episodes per person month | | |
| | | | | | - vaccine type (3) | RR 0.72 (0.43-1.21) | 8(1), 14(2) |
| | | | | | - all types, <24m (7) | RR 0.93 (0.84-1.04) | 8(2), 14(5) |
| | | | | | - all types, >24m (5) | RR 0.77(0.67-0.89) | 14(5) |
| | | | | | - all types(12) | RR 0.88(0.79-0.97) | 8(2),14(10) |
| | | | | | AOM episodes per person month in children with previous AOM | | |
| | | | | | - <24 months (3) | RR 0.80 (0.69-0.93) | 8(2), 14(1) |
| | | | | | - >24 months (3) | RR 0.85 (0.71-1.02) | 14 (3) |
| | | | | | - all ages (6) | RR 0.74 (0.59-0.93) | 8(2), 14(4) |
| | | | Conclusions summarized in abstract (abbrev.) | Based on the currently available results of the effectiveness of pneumococcal vaccination for the prevention of AOM, a large scale use of pneumococcal polysaccharide and conjugate vaccination for this specific indication is not yet recommended. | | | |

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| Ref. | Year | Author | Target group | Included RCTs | Outcomes (No. of studies) | Results ( OR or RR <1 favours vaccine) | Vaccine type valency (No. of studies) |
|---|---|---|---|---|---|---|---|
| 9 | 2003 | Dear[9] | Adults, includes observational studies | Honkanen 1999<br>Örtqvist 1998<br>Koivula 1997<br>Davis 1987<br>Leech 1987<br>Klastersky 1986<br>Simberkoff 1986<br>Galliat 1985<br>Austrian 1980<br>Riley 1977<br>Smit 1977<br>Austrian 1976<br>Kaufman 1947 | Definitive pneumococcal pneumonia<br>- all (8)<br>- vaccine types only (4)<br><br>Pneumonia, all cause (14)<br><br>Pneumonia, presumptive pneumococcal<br>- all((7)<br><br>- vaccine types only (5)<br><br>Mortality<br>- all cause (11)<br><br>- pneumonia (8)<br>- pneumococcal infection(2) | <br>OR 0.28 (0.15-0.52)<br>OR 0.18 (0.05-0.58)<br><br>OR 0.77(0.58-1.02)<br><br><br>OR 0.52 (0.31-0.87)<br><br>0.23 (0.14-0.36)<br><br><br>OR 0.90(0.76-1.07)<br><br>OR 0.72(0.44-1.19)<br>OR 1.47 (0.18-12.37) | <br>2/3(1), 14(5), 17(1), 23(1)<br>2/3(1), 12(1), 14(1), 23(1)<br><br>2/3(1), 6(1), 12(3), 13(1), 14(5), 17(1), 23(2)<br><br><br>2/3(1), 6(1), 12(1), 14(2), 17(1), 23(1)<br>2/3(1), 6(1), 12(1), 14(), 23(1)<br><br><br>2/3(1), 12(2) 14(5), 17(1), 23(2)<br><br>2/3(1), 12(2), 14(4), 23(1)<br>12(1), 14(1) |
| | | | Conclusions summarized in abstract (abbrev.) | While polysaccharide pneumococcal vaccines do not appear to reduce the incidence of pneumonia or death in adults with or without chronic illness, or in the elderly (55 years and above), the evidence from non-randomised studies suggests that the vaccines are effective in reducing the incidence of the more specific outcome, invasive pneumococcal disease, among adults and the immunocompetent elderly (55 years and above). | | | |
| 10 | 2002 | Puig-Barbera[10] | Elderly | Honkanen 1999<br>Örtqvist 1998<br>Davis 1987<br>Simberkoff 1986<br>Galliat 1985<br>Bently 1981<br>Austrian 1980<br>Kaufman 1947 | Pneumococcal pneumonia (3)<br><br>Invasive pneumococcal disease | RR 1.15(0.66-1.99)<br><br>Includes non-RCTs | 14(2), 23(1) |
| | | | Conclusions summarized in abstract | No evidence was found supporting pneumococcal vaccine effectiveness to reduce or avoid S. pneumoniae disease in the elderly. | | | |

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| Ref. | Year | Author | Target group | Included RCTs | Outcomes (No. of studies) | Results ( OR or RR <1 favours vaccine) | Vaccine type valency (No. of studies) |
|---|---|---|---|---|---|---|---|
| 11 | 2002 | Watson[11] | Adults | Honkanen 1999<br>Örtqvist 1998<br>Koivula 1997<br>Davis 1987<br>Leech 1987<br>Klastersky 1986<br>Simberkoff 1986<br>Galliat 1985<br>Austrian 1980<br>Riley 1977<br>Smit 1977<br>Austrian 1976 | Pneumococcal pneumonia<br>- industrialised (5)<br>- less industrialised (0)<br>- high risk (2)<br>- elderly (2)<br><br>Pneumonia, all cause<br>- industrialised (9)<br>- less industrialised (3)<br>- high risk (3)<br>- elderly (2)<br><br>Bacteraemia<br>- industrialised (6)<br>- less industrialised (1)<br>- high risk (1)<br>- elderly (1)<br><br>Mortality<br>-Industrialised (8)<br>-less industrialised (1)<br>-high risk (3)<br>-elderly (1) | <br>RR 1.06 (0.82-1.38)<br>-<br>RR 0.91 (0.33-2.53)<br>RR 1.01 (0.69-1.49)<br><br><br>RR 1.03 (0.86-1.25)<br>RR 0.67 (0.52-0.87)<br>RR 1.13 (0.79-1.62)<br>RR 1.15 (0.95-1.40)<br><br><br>RR 0.53 (0.20-1.43)<br>RR 0.14 (0.02-1.14)<br>RR0.81 (0.05-12.16)<br>RR 0.37 (0.07-1.91)<br><br><br>RR 1.07 (0.97-1.18)<br>RR 0.79 (0.63-0.99)<br>RR 1.15 (0.87-1.52)<br>RR 0.99 (0.80-1.22) | Unclear which study in which analyses |
| | | | Conclusions summarized in abstract | Benefit from pneumococcal vaccination depends on the baseline risk of infection and characteristics of a given population. Evidence from randomised trials for widespread adult vaccination in industrial countries is lacking. | | | |
| 12 | 2001 | Cornu[12] | Immunocompetent adults | Örtqvist 1998<br>Koivula 1997<br>Davis 1987<br>Leech 1987<br>Klastersky 1986<br>Simberkoff 1986<br>Galliat 1985<br>Austrian 1980<br>Riley 1977<br>Smit 1977<br>Austrian 1976 | Definitive pneumococcal pneumonia (6)<br><br>Presumptive pneumococcal pneumonia (8)<br><br>Pneumonia, all cause (11)<br><br>Mortality<br>- all cause (9)<br>- pneumonia (8) | OR 0.29(0.20-0.42)<br><br>OR 0.60 (0.37-0.96)<br><br>OR 0.80 (0.59-1.08)<br><br>OR 1.01 (0.91-1.12)<br>OR 0.69 (0.51-0.93) | 13(1), 14(3), 17(1), 23(1)<br><br>6(1), 12(3), 13(1), 14(1), 17(1), 23(1)<br><br>6(1)12(2), 13(1), 14(6), 23(1)<br><br>12(2), 14(6), 23(1)<br>12(2), 14(4), 17(1), 23(1) |
| | | | Conclusions summarized in abstract | In the fourteen trials totalling 48,837 patients retrieved, PPV prevents definite pneumococcal pneumonia by 71%, presumptive pneumococcal pneumonia by 40%, and mortality due to pneumonia by 32%, but not all-cause pneumonia or death. No preventive effect was seen in the subgroup of patients aged 55 years or more, possibly due to a lack of statistical power. | | |

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| Ref. | Year | Author | Target group | Included RCTs | Outcomes (No. of studies) | Results ( OR or RR <1 favours vaccine) | Vaccine type valency (No. of studies) |
|---|---|---|---|---|---|---|---|
| 13 | 2001 | Sheikh[13] | Asthma | Schuller 1983 | Excluded due to low quality (poor allocation concealment) | - | |
| | | | Conclusions summarized in abstract | This review found very limited evidence to support the routine use of pneumococcal vaccine in people with asthma. A randomised trial of vaccine efficacy in children and adults with asthma is needed. | | | |
| 14 | 2000 | Moore[14] | All | French 2000<br>Örtqvist 1998<br>Koivula 1997<br>Davis 1987<br>Leech 1987<br>Klastersky 1986<br>Simberkoff 1986<br>Galliat 1985<br>Austrian 1980<br>Riley 1977<br>Smit 1977<br>Austrian 1976 | Pneumococcal pneumonia<br>- healthy, immunocomp. (3)<br>- elderly, high risk (7)<br><br>Pneumonia, all cause<br>- healthy, immunocomp. (3)<br>- elderly, high risk (5)<br><br>Lower respiratory tract infection<br>- healthy, immunocomp. (2)<br>- elderly, high risk (3)<br><br>Mortality, pneumonia<br>- healthy, immunocomp. (1)<br>- elderly, high risk (8)<br><br>Pneumococcal bacteraemia<br>- healthy, immunocomp. (1)<br>- elderly, high risk ( 3) | <br>RR 0.16 (0.11-0.23)<br>RR 0.88 (0.72-1.07)<br><br><br>RR 0.56 (0.47-0.66)<br>RR 1.08 (0.92-1.27)<br><br><br>RR 0.85 (0.71-1.02)<br>RR 1.06 (0.97-1.16)<br><br><br>RR 0.70 (0.50-0.96)<br>RR 0.93 (0.72-1.20)<br><br><br>RR 0.18 (0.009-0.34)<br>RR 0.53 (0.14-1.94) | Unclear which study in which analyses |
| | | | Conclusions summarized in abstract | Present guidelines recommend pneumococcal vaccination for "high-risk" groups. There is no evidence from randomised trials that this is of any benefit. | | | |
| 15 | 1999 | Hutchison[15] | Adults | Davis 1987<br>Leech 1987<br>Klastersky 1986<br>Simberkoff 1986<br>Galliat 1985<br>Austrian 1980<br>Riley 1977<br>Smit 1977<br>Austrian 1976<br>Kaufman 1947<br>MacLeod 1945 | Pneumococcal pneumonia<br>- all types (7)<br>- vaccine types (9)<br><br>Systemic pneumococcal infection<br>- all types (6)<br>- vaccine types (4) | <br>OR 0.58 (0.47-0.72)<br>OR 0.25 (0.20-0.33)<br><br><br>OR 0.27 (0.13-0.49)<br>OR 0.17 (0.09-0.31) | <br>2/3(1), 4(1) 12(1), 14(3), 17(1)<br>2/3(1),4(1),6(2),12(2), 13(1) 14(2)<br><br><br>2/3(1),14(4),17(1)<br>2/3(1),6(1),13(1) 14(1) |
| | | | Conclusions summarized in abstract | Vaccination with pneumococcal polysaccharide vaccine can be expected to reduce the risk of systemic infection due to pneumococcal types included in the vaccine by 83% and systemic infection due to all pneumococci by 73%. We found no evidence that the vaccine was less efficacious for the elderly, institutionalized people, or those with chronic illness. | | | |

*continued*

| Ref. | Year | Author | Target group | Included RCTs | Outcomes (No. of studies) | Results ( OR or RR <1 favours vaccine) | Vaccine type valency (No. of studies) |
|---|---|---|---|---|---|---|---|
| 16 | 1996 | Go | Normal subjects, antibody response only | | | | |
| | | | Conclusions summarized in abstract | Response to pneumococcal vaccine among normal subjects varies widely. Better designed and prospective studies are needed to define the parameters of a normal antibody response to pneumococcal vaccine so that uniform guidelines of interpretation can be formulated. | | | |
| 17 | 1994 | Fine[16] | Adults | Davis 1987<br>Leech 1987<br>Klastersky 1986<br>Simberkoff 1986<br>Galliat 1985<br>Austrian 1980<br>Riley 1977<br>Smit 1977<br>Austrian 1976 | Definitive pneumococcal pneumonia | | Unclear which study in which analyses |
| | | | | | - all types | OR 0.34 (0.24-0.48) | |
| | | | | | - vaccine types | OR 0.17 (0.09-0.33) | |
| | | | | | Presumptive pneumococcal pneumonia | | |
| | | | | | - all types | OR 0.47 (0.35-0.63) | |
| | | | | | - vaccine types | OR 0.39 (0.26-0.59) | |
| | | | | | Pneumonia, all cause | OR 0.90 (0.77-1.04) | |
| | | | | | Bronchitis | OR 0.84 (0.69-1.02) | |
| | | | | | Mortality | | |
| | | | | | - all cause | OR 1.02 (0.9-1.14) | |
| | | | | | - pneumonia | OR 0.78 (0.57-1.06) | |
| | | | | | - pneumococcal | OR 4.59 (0.54-38.81) | |
| | | | Conclusions summarized in abstract | Pneumococcal vaccination appears efficacious in reducing bacteremic pneumococcal pneumonia in low risk adults. However, evidence from randomized controlled trials fails to demonstrate vaccine efficacy for pneumococcal infection-related or other medical outcomes in the heterogeneous group of subjects currently labeled as high risk. | | |

RR = relative risk; OR = odds ratio; COPD = chronic obstructive pulmonary disease; NR = not reported; n/a = not applicable; LRTI = lower respiratory tract infection; URTI = upper respiratory tract infection; IPD = invasive pneumococcal disease; RCT = randomized controlled trial; AOM = acute otitis media; PPV / PPV14 = polysaccharide pneumococcal vaccine / 14-valent pneumococcal polysaccharide vaccine.
*Meaning unclear (reported as $R^2$ in tables, without explanation in text);

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