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Evidence Summaries

Vaccines for preventing pneumococcal infection in adults. Summary of the evidence and implications for public health programmes

Thambu David Sudarsanam^{a,*}, Prathap Tharyan^b^a Professor of Medicine, Christian Medical College, Vellore, Tamil Nadu 632002, India^b Professor of Psychiatry, Director, South Asian Cochrane Centre, Prof BV Moses & ICMR Centre for Research and Training in Evidence-Informed Healthcare and Health Policy, Christian Medical College, Vellore, Tamil Nadu 632002, India

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ABSTRACT

An update of a Cochrane systematic review summarised the evidence for the efficacy of pneumococcal polysaccharide vaccines (PPVs) from randomized controlled trials (RCTs) or quasi-RCTs that compared PPV with placebo, control vaccines or no intervention; and from non-RCTs that assessed pneumococcal vaccine effectiveness against sterile site, culture confirmed IPD where the trial design allowed for the control of important confounding factors (case–control and cohort studies). Of 25 included studies, 18 were RCTs including 64,852 participants and seven were non-RCTs – five case–control studies and two cohort studies including 62,294 participants; the non-RCTs contributing outcomes for culture-confirmed invasive pneumococcal disease (IPD) only.

The review found consistently strong evidence that the vaccine is effective in preventing the rarer outcome of invasive pneumococcal disease. Evidence from the included studies indicates vaccination might not afford as much protection in adults with chronic illness as it does for healthy adults. The available evidence did not demonstrate that pneumococcal polysaccharide vaccines prevent pneumonia (of all causes) or mortality in adults. This review did not consider adverse events.

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1. The evidence

An updated Cochrane systematic review identified 25 studies that gave pneumococcal polysaccharide vaccines (PPVs) to adults in different settings. Of the 25 studies, 18 were randomized controlled trials (RCTs) involving 64,852 participants and seven were non-RCTs involving 62,294 participants; the

non-RCTs contributing outcomes for culture-confirmed invasive pneumococcal disease (IPD) only.

2. Meta-analysis of the RCTs found

- Consistently strong evidence of the efficacy of pneumococcal polysaccharide vaccines against IPD (Protective

* Corresponding author.

E-mail address: thambu@cmcvellore.ac.in (T.D. Sudarsanam).
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vaccine efficacy of 74%, 95% CI 55%–86%; 11 trials, 36,489 participants). This efficacy for PPVs against IPD was seen in subgroups of trials done in adults from low-income countries (one trial, 5373 participants), and in trials done on otherwise healthy adults in high-income countries (five trials, 27,886 participants); but not in trials done on adults with chronic illnesses in high-income countries (five trials, 3230 participants), possibly because of inadequate numbers included in these trials in adults with chronic illnesses.

- Consistent evidence of protective efficacy against pneumonia due to all causes in adults from low-income countries (vaccine efficacy 46%, 95% CI 33%–57%; four trials, 14,562 participants); but not in adults with chronic illness in high-income countries (six trials, 4010 participants), or in adults from high-income countries without chronic illnesses (six trials, 29,186 participants).
- No evidence of protective efficacy against all-cause mortality (14 trials, 47,560 participants).
- Non-RCTs provided evidence for protection against IPD in populations for whom the vaccine is currently utilized (vaccine effectiveness of 52%, 95% CI 37%–61% for all serotypes; and 55%, 95% CI 38%–54% for vaccine-type disease; seven studies – five case–control studies, and two cohorts, 62,294 participants).
- The review however did not consider adverse events.
- The review concluded that pneumococcal vaccine is effective in preventing IPD in adults. The evidence for those with chronic illness was less clear. The review also concluded that the evidence does not support the routine use of PPV to prevent all-cause pneumonia or mortality.

3. Why is this question important?

- Pneumococcal pneumonia and other diseases caused by *Streptococcus pneumoniae* (*S. pneumoniae*) continue to cause substantial morbidity and mortality throughout the world. Pneumonia is the most common presentation of pneumococcal disease in adults. Bacteraemic pneumonia is the most common cause of invasive pneumococcal disease (IPD), accounting for 90% of all cases. Mortality associated with invasive pneumococcal pneumonia in adults has remained unchanged at about 20% over the past 60 years.
- The continuing burden of pneumococcal disease is worsened by increasing numbers of people with chronic disease or HIV infection and an ageing population in many high-income countries.
- Antibiotic resistance continues to present a major threat to the successful treatment of infections.¹
- In low-income countries large numbers of people lack access to basic curative health care but might be reached by vaccination programmes.
- The 23-valent PPV has been utilized internationally to varying extents but mainly limited to older adults and adults with medical risk factors for IPD in high-income countries.²
- This review updates a previous Cochrane Review of the same topic published in 2008,³ and addressed whether PPV is effective in all adult populations or whether only some groups benefit.

Review on which this evidence summary is based: Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database of Systematic Reviews 2013, Issue 1. Art. No.: CD000422. <http://dx.doi.org/10.1002/14651858.CD000422.pub3>.

This evidence summary presents an overview of the findings and the implications for developed and developing countries. For further details, please read the full review that can be downloaded, free of charge (through various funded provisions) in most parts of the world, from The Cochrane Library (www.thecochranelibrary.com).

4. What did the systematic review seek and what did they find?

Review objectives: To assess the efficacy and effectiveness of PPVs in preventing pneumococcal disease or death in adults. The review did not assess adverse events.

Types of studies

What did the review authors search for?

1. Prospective, randomized controlled trials (RCTs) or quasi-RCTs that compared PPV with placebo, control vaccines or no intervention.
2. Non-RCTs that assessed pneumococcal vaccine effectiveness against sterile site, culture confirmed IPD where the trial design allowed for the control of important confounding factors (case–control and cohort studies)

What did the review find?

Twenty-five studies met inclusion criteria (18 RCTs involving 64,852 participants and seven non-RCTs – five case–control studies and two cohort studies involving 62,294 participants).

This review update excluded three RCTs (in two only the abstract was available, and in the third, the effects of steroids could not be separated); and 13 non-RCTs (due to not considering culture-confirmed IPD as an outcome in 12, and one study which used ICD codes to diagnose IPD).

Setting	<p>Excluded were studies reporting outcomes according to International Classification of diseases codes.</p> <p>The authors looked for interventions from countries irrespective of economic strata and irrespective of the patients' clinical setting.</p>	<p>The RCTs included healthy adults from low-income countries, populations that were considered to be at elevated risk of pneumococcal disease from developed country settings, USA, Canada, Belgium, Japan and Denmark and participants in high-income countries who were not recruited on the basis of underlying disease. The observational studies were from USA and Spain. The participants were in three distinct groups.</p>
Participants	<p>Adults of either sex, aged 16 years and above. The review excluded studies limited to HIV-positive participants as this was part of another review.</p>	<ol style="list-style-type: none"> 1. Firstly, otherwise healthy adults from low-income countries this group consisted of African mine workers and community-dwelling adults residing in the highlands of Papua New Guinea, considered to have been at elevated risk of disease due to overcrowding and environmental factors. 2. The second group were those populations that were considered to be at elevated risk of pneumococcal disease due to underlying medical illnesses such as chronic obstructive pulmonary disease or patients with bronchogenic carcinoma recruited participants on the basis of age (>55 years) and the presence of underlying chronic illness 3. The third population groups of the included RCTs were participants in high-income countries who were not recruited on the basis of underlying disease.
Interventions	<p>Vaccination with any PPV. The review included studies making the following comparisons:</p> <ul style="list-style-type: none"> • vaccine compared with placebo; • vaccine compared with no intervention; and • combination of pneumococcal vaccine with a non-pneumococcal vaccine compared with the other vaccine given alone. 	<p>Three case–control studies included participants aged from 18 years with medical conditions that placed them at higher risk of pneumococcal disease, or participants who were above 65 years of age; Two case–control studies related only to older adults: United States and Spain. The two cohort studies had mostly >65 year olds in the United States and Spain</p> <p>One group of vaccine RCTs conducted on African mine workers and community-dwelling adults residing in the highlands of Papua New Guinea used vaccines containing six to 14 pneumococcal polysaccharide serotypes</p> <p>The second group of RCTs in populations that were considered to be at elevated risk of pneumococcal disease due to underlying medical illnesses, used 14-valent or 23-valent PPVs</p> <p>The third in participants at elevated risk of pneumococcal disease due to their age and place of residence used vaccines containing two to 23-valent pneumococcal polysaccharide serotypes.</p>
Outcomes	<p>Disease outcomes were limited to those occurring 14 days or more after vaccination.</p> <p>For RCTs:</p> <p>Primary outcomes</p> <ul style="list-style-type: none"> • Invasive pneumococcal disease (IPD) • Pneumonia (all-cause) and • Mortality (all-cause). <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • IPD of a pneumococcal serotype included in the vaccine administered, • Definitive pneumococcal pneumonia, Definitive pneumococcal pneumonia with 	<p>The non-RCTs were mostly with the 23-valent vaccine while some were 14 valent vaccine trials</p> <p>IPD: a pneumococcal infection with <i>S. pneumonia</i> isolated from a usually sterile body fluid.</p> <p>Pneumonia (all-cause): clinically and radiographically confirmed pneumonia, independent of the cause of pneumonia.</p> <p>Definitive pneumococcal pneumonia: clinically and radiographically confirmed pneumonia with <i>S. pneumonia</i> isolated from a usually sterile site.</p> <p>Presumptive pneumococcal pneumonia: clinically and radiographically confirmed pneumonia with <i>S. pneumonia</i> isolated from a culture of sputum or a nasal swab.</p>

a pneumococcal serotype included in the vaccine administered,

- Presumptive pneumococcal pneumonia,
- Mortality due to pneumonia,
- Mortality due to pneumococcal infection, and
- Pneumococcal nasopharyngeal colonization,

Pneumococcal nasopharyngeal colonisation: defined as the detection of *S. pneumoniae* isolated from a culture from a nose or nasopharyngeal swab.

B. Non-RCTs

- IPD and IPD of a pneumococcal serotype included in the vaccine administered.

Date of the last search: 22 June 2012

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What were the effects of the vaccine for invasive pneumococcal disease in the RCTs

In 11 studies involving 36,489 participants there were 15 events in the vaccinated group and 63 events in the control group. Pneumococcal polysaccharide vaccine (PPV) reduced the risk of all IPD with a pooled estimated odds ratio (OR) of 0.26 (95% confidence interval (CI) 0.14 to 0.45; random-effects model), that is, a protective vaccine efficacy of 74% (95% CI 55%–86%). Statistical heterogeneity was not present ($I^2 = 0\%$, $P = 0.56$).

What were the effects of the vaccine for all cause pneumonia in the RCTs

Among 16 studies involving 47,734 participants, there were 978 events in the vaccinated group and 1547 events in the control group. Pooled estimated OR was 0.72 (95% CI 0.56 to 0.93; random-effects model). However, there was a high level of statistical heterogeneity present amongst the included studies ($I^2 = 85\%$, $P < 0.00001$).

What were the effects of the vaccine for all-cause mortality in the RCTs

In 47,560 participants, 1018 events in the vaccinated group and 1039 in the control group. A pooled estimated OR of 0.90 (95% CI 0.74–1.09; random-effects model). A high level of statistical heterogeneity was present ($I^2 = 69\%$, $P < 0.0001$).

What were the effects of the vaccine for vaccine type IPD, definitive pneumococcal disease, presumed pneumococcal disease, mortality due to pneumonia and pneumococcal infection and nasopharyngeal colonization in the RCTs

For vaccine type IPD the vaccine was effective: OR 0.18, 95% CI 0.10–0.31). Statistical heterogeneity was absent ($I^2 = 0\%$, $P = 0.70$).

For definitive pneumococcal disease PPV reduced the risk of definitive pneumococcal pneumonia, with a pooled estimated OR of 0.26 (95% CI 0.15–0.46; random-effects model) with minimal heterogeneity with a similar result for the vaccine type definitive disease

For presumptive pneumococcal pneumonia the vaccine was effective: OR 0.46 (95% CI 0.25–0.84; random-effects model) with similar benefit for the vaccine type strains.

There was significant heterogeneity in both situations.

For mortality due to pneumonia, 30,723 participants, 135 events in the vaccinated group and 221 events in the control group. (OR 0.71, 95%CI 0.44–1.16; random-effects model) with a high level of statistical heterogeneity again present ($I^2 = 72\%$, $P = 0.0004$). This did not suggest benefit.

For mortality due to pneumococcal disease no benefit was seen but the sample size was small: 2445 participants (OR 2.51, 95% CI 0.45–14.13; random-effects model; $I^2 = 0\%$).

The data on nasopharyngeal carriage could not be included as the data were not in a form that could be analyzed.

What were the effects of the vaccine for Invasive pneumococcal disease together and vaccine strains among observational studies

For overall results from the seven studies included the OR was 0.48 (95% CI 0.37–0.61; random-effects model). Statistical heterogeneity was low ($I^2 = 31.4\%$, $P = 0.19$).

For vaccine-type IPD, three studies were included in this outcome, with an OR of 0.45 (95% CI 0.38–0.54; random-effects model; $I^2 = 0\%$)

What were the conclusions of the review?

The review concluded that it “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 meta-analysis does not provide evidence to support the routine use of PPV to prevent all-cause pneumonia or mortality.”

What were the assessments of the overall quality of the evidence?

The study quality was assessed using the Cochrane risk of bias tool which looks at the randomization process, allocation concealment, blinding, completeness of outcome data and possible selective reporting. Most RCTs scored poorly across the factors assessed and only four trials were deemed to have an overall low risk of bias. Thirty-nine per cent of trials described an adequate method of sequence generation and allocation concealment, 44% of trials reported adequate blinding of participants and personnel and 67% reported adequate blinding of outcome assessors, 22% scored low risk of bias for incomplete outcome data, and 17% scored low risk of bias on selective reporting. The poor scores were more common in the earlier trials and were largely due to inadequate reporting rather than known in adequate methods.

Non-RCTs

Non-RCTs scored low risk of bias against allocation concealment (as adequate control of confounding factors was a study inclusion criterion). The predetermined important confounding factors were age, chronic illness, smoking, influenza vaccination and

Strengths and limitations	<p>nursing home residency. The five case–control studies matched participants according to the presence of underlying disease (severity and number of conditions) and date of hospital admission. Most studies reported matching according to age.</p> <p>Both cohort studies followed participants for three years and controlled for age, sex and underlying medical conditions; they included compromised immune status, smoking status and influenza vaccination status in the model of effectiveness of PPV.</p> <p>Vaccination was a time variable factor and participants were considered to be vaccinated 14 days following vaccine administration.</p> <p>The strengths of the review include the standard Cochrane methods used and including both RCT as well as observational studies. The studies were from both developing as well as developed countries</p> <p>The limitations include the absence of a summary of findings table using the GRADE approach that would summarise absolute and relative effects for the key outcomes linked to the overall quality of evidence (or confidence in these estimates). The review did not assess vaccine safety, costs and any effectiveness issues to inform public health policy.</p>
Did the results and conclusions of the review differ from other reviews on this topic?	<p>Numerous systematic reviews and seven previous meta-analyses have looked at this important issue. The conclusions varied, depending on selection criteria, clinical settings and vaccine trials included. Overall, the findings from this study were similar to those presented in this updated Cochrane Review with respect to effectiveness against presumptive pneumonia, all cause pneumonia and death.</p>
What further research is required?	<p>The review suggested that the 23-valent PPV may have a place as a control treatment in RCTs of conjugate or potential protein vaccine candidates.</p> <p>It also suggested that given adults with chronic illness are the same population who are targeted for vaccination, further trials assessing vaccine efficacy against IPD amongst those with chronic disease appear warranted. However, such trials would need to be large given that the meta-analysis of five pooled studies in the review remained underpowered against the rare event of IPD (2/1619 participants in the control group developed IPD).</p>
What are the implications of the review for public health?	<p>This meta-analysis supports the use of pneumococcal polysaccharide vaccine (PPV) to prevent invasive pneumococcal disease (IPD) in adults, particularly otherwise healthy adults, in high-income and low-income countries. The evidence from randomized controlled trials (RCTs) does not support the routine use of PPV to prevent all-cause pneumonia or mortality in adults.</p>

Declaration of interest

TDS and PT are contributors to The Cochrane Collaboration. TDS is an editor with the Cochrane Infectious Diseases Group. PT is a programme partner of the Effective Healthcare Research Consortium.

Conflicts of interest

All authors have none to declare.

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