Effectiveness versus efficacy of conjugated pneumococcal vaccine:
a systematic review of randomised, controlled trials
with meta-analysis examining absolute risk reduction and
relative risk

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Plain English Summary

Numbers Needed to Treat (NNT) is a measure of the effectiveness. In the context of newer vaccines it is good to ask how many children need to be vaccinated so that one life is saved - the NNT of the vaccine. This is sometimes called the Numbers Needed to Vaccinate (NNV) The next question is related to the cost: How much does it cost to vaccinate one child with this new vaccine. Once we have these 2 figures we can easily calculate the cost per life saved. We did a meta analysis (a study of all the studies available) to look at Pneumococcal vaccine. The vaccine has very poor efficacy that the NNT to save one life could not be calculated. Instead we calculated the NNT to prevent one case of clinical pneumonia - (a condition that is usually easily treated with very inexpensive medicines). This allows the cost of prevention with vaccine to be compared to the cost of treatment with simple antibiotics. There was a small but statistically significant benefit of vaccination on clinical pneumonia (OR=0.927, 95%CI 0.885-0.971, NNT=200), radiological pneumonia (OR=0.749; 95%CI 0.682-0.822, NNT=143) and invasive disease caused by vaccine serotypes (OR=0.215, 95%CI 0.149-0.311, NNV=500). The small benefit in terms of reduction of clinical pneumonia is also offset by an increase in Asthma (0.001, 95% CI 0.000 to 0.002, p=0.007, NNT=1000)

Abstract

Objectives
Use of the 7-valent pneumococcal conjugate vaccine (PCV7) resulted in reduction in vaccine serotypes invasive pneumococcal disease (IPD). However, IPD due to serotypes not included in the PCV7 increased in frequency. This prompted the introduction of a 13 valent vaccine. Previous systematic reviews have examined vaccine efficacy (odds ratio and relative risk). However, effectiveness of PCV in reducing childhood morbidity and mortality (in terms of absolute risk reduction (ARR) and numbers needed to treat (NNT)) has not been published. At the threshold of introducing the PCV13, such an assessment of the old vaccine is useful for comparison. The objective here was to evaluate the effectiveness of PCV through a systematic review of literature.

Methods
Systematic literature search for randomized controlled trials reporting on measures of vaccine effectiveness (invasive Pneumococcal disease, pneumonia, meningitis, allcause mortality, Pneumococcal disease specific mortality, and systemic adverse events/effects) was undertaken and data extracted based on a priori criteria. Data were analysed to calculate odds ratio, relative risk and absolute risk reduction (ARR); and pooled through meta-analysis. Number needed to treat (vaccinate) was calculated for effectiveness.

Results
There were five methodologically good trials presenting data through 11 publications. There was a small but statistically significant benefit of vaccination on clinical pneumonia (OR=0.927, 95%CI 0.885-0.971, NNT=200), radiological pneumonia (OR=0.749; 95%CI 0.682-0.822, NNT=143) and invasive disease caused by vaccine serotypes (OR=0.215, 95%CI 0.149-0.311, NNV=500). The effect on all-cause mortality was OR and RR=0.88, 95%CI 0.78 to 0.99, and RD 0.00, 95%CI -0.01 to 0.00 (NNT cannot be calculated). There was no difference in invasive Pneumococcal disease caused by vaccine-related and vaccine-unrelated serotypes. There was no data on meningitis and Pneumococcal disease-specific mortality. Examination of multiple adverse events did not show a difference in risk compared to control, except for a small but statistically significant increase in risk of asthma.

Conclusion
PCV7 appears to have limited effectiveness against pneumonia; but does not reduce all-cause mortality. There is significant reduction in vaccine serotype IPD. There is no data to draw conclusions for other clinical problems of public health significance such as meningitis, and Pneumococcal disease-specific mortality.
Introduction

Pneumococcal conjugate vaccine (PCV) has been recommended by the World Health Organization for consideration in the routine immunization programme of developing countries (1,2) based on the impression that it is highly efficacious and thereby effective in reducing childhood morbidity and mortality attributable to pneumonia. However, recent correspondence suggests that the efficacy of PCV for clinically important outcomes may have been over-estimated (3). Most of the currently available data reflect vaccine efficacy in terms of sero-efficacy (immunogenicity), and to some extent protective efficacy against Pneumococcal serotypes contained in the vaccine. Previous systematic reviews have not examined the absolute reduction in risk (ARR) attributable to PCV, restricting the findings to efficacy expressed by relative risk reduction. ARR is an important outcome for policy-makers and health-care stakeholders to base decisions on (4, 5). This issue gains particular importance because when the baseline risk of an outcome is small (as appears to be the case with invasive pneumococcal disease, based on the control group event rate in trials on PCV), impressive vaccine efficacy (reduction in RR) may not directly translate to equivalent effectiveness (absolute risk reduction). In such a setting, the number needed to treat (vaccinate) would be very large, hence the cost considerations alone could constrain poorer economies from deciding in favour of an otherwise efficacious intervention. In other words, while OR and RR reflect efficacy in a research setting, ARR reflects the public health benefit (effectiveness) in a real-world setting.

A Cochrane systematic review published in 2004 examined efficacy of PCV (6), but the review was outdated at the time of initiating this review. The authors of the review presented outcomes as relative risk (RR), but not ‘absolute risk reduction’ (ARR). The Cochrane Review was recently updated (7), however since it appeared during the completion of this systematic review, we did not access it, in order to avoid bias. Upon competition of this review, we have studied the review and noted the same limitations as in the older version.

During the completion of this systematic review, yet another systematic review appeared in the literature again reporting efficacy measures (relative risk reduction for invasive Pneumococcal disease, otitis media, and pneumonia) (8). However, number needed to treat and effectiveness were not explored. These facts necessitate critical appraisal of available literature to derive best evidence on the effectiveness (or otherwise) of PCV, especially in the context of developing countries.

We therefore undertook a systematic review of literature examining randomized controlled trials reporting the effect of Pneumococcal conjugate vaccine (PCV) on clinically relevant outcomes (mortality, invasive pneumococcal disease, pneumonia, meningitis and systemic adverse effects/ events). We did not include otitis media since the burden of disease (incidence, morbidity and mortality) is currently not of public health significance to merit a prevention programme in most countries. We calculated ARR and NNT (numbers needed to harm for adverse events), to enable decision-making stakeholders to estimate the likely impact of PCV in their real-world scenario. Since reliable national data on the burden of Pneumococcal disease is lacking in most developing countries, we also tried to estimate the burden of disease by examining the event rates among control groups in the various RCTs.

Methods:

We undertook a systematic review of literature with the following characteristics:
Types of studies: Randomised clinical trials (RCT) comparing PCV versus placebo/another vaccine, irrespective of blinding, publication status, or language.
Types of participants: Participants of any age, gender, and socio-economic status who were either confirmed to be HIV negative or not tested for the same. RCT recruiting only HIV positive participants were excluded because testing is not usually performed prior to routine vaccination.
Types of interventions: We analysed PCV (intervention) versus placebo, or no intervention, or another vaccine (control). We considered PCV with any valency, any type of protein conjugate, any number of serotypes, administered by any route, using any schedule, with or without simultaneous administration of other vaccines, administered singly or as a combination vaccine. Trials that only compared different doses, schedules or types of PCV, without a comparator group who received placebo or another vaccine or no vaccination were excluded. As Pneumococcal polysaccharide vaccine is not recommended for use in young infants, it was not included in this systematic review.

Types of outcome measures:

Primary outcome: Incidence of pneumonia (defined by any standard definition).

Secondary outcomes: Incidence of invasive Pneumococcal disease (IPD), meningitis, all-cause mortality, Pneumococcal disease specific mortality and systemic adverse events/effects. Baseline Pneumococcal disease morbidity was evaluated through calculation of event rate among control group in RCTs for clinical pneumonia (of unspecified etiology), radiological pneumonia (consolidation of unspecified etiology) and invasive pneumococcal disease defined as Pneumococcus cultured from blood or cerebro-spinal fluid (CSF). Invasive pneumococcal disease event rate was grouped as follows: all serotypes, vaccine serotypes, vaccine-related serotypes and non-vaccine-related serotypes. Adverse events studied were (i) serious adverse events (reported by authors in their studies), (ii) death in the first week after administering the vaccine or placebo, (iii) evidence of serotype replacement (increase in incidence of Pneumococcal disease with strains not included in the vaccine) and (iv) incidence of other events reported by authors of individual trials. Non serious events including post-vaccination fever, pain and erythema were not considered. NNH was calculated for adverse events where data was available.

Search strategy: We searched the Cochrane Library using the term “Pneumococcal vaccine” in “Record Title”, on 15 March 2009, and updated it on 15 May 2009. Simultaneous Medline search for Randomized Controlled Trials, was conducted using the same term, without using any other filters. We also examined the lists of included and excluded trials in the Cochrane review and identified those meeting the inclusion and exclusion criteria of our systematic review.

Data extraction: Two reviewers (JLM and JP) independently extracted data from eligible trials. Disagreement was resolved through mutual discussion. Data on trial characteristics, design, participant characteristics, interventions, primary and secondary outcome measures, assessment of methodological quality (risk of bias), and sub-groups into which the trial could be included, were extracted.

Assessment of bias risk: The methodological quality (and hence risk of bias due to the methodology) of the trials was done using the Cochrane Risk of Bias Tool (9) by assessment of each trial for adequacy of allocation sequence generation, allocation concealment, blinding, addressing incomplete outcome data, freedom from selective outcome reporting and other sources of bias. Each trial was assessed against these parameters for each outcome and the risk of bias graded as Low or High within each study and across all studies.
Data analysis: Odds ratio (OR) was used as the primary reporting modality as it is the most robust statistical reporting format (10). However, it is reportedly difficult for clinicians and other decision-makers to understand its significance; hence Relative Risk and Absolute Risk Reduction are also reported here. NNT was calculated from the OR. Per protocol analysis was used and meta-analysis performed using Stata 9.1 (StataCorp 4905 Lakeway Drive, Special Edition College Station, Texas 77845 USA). Random effects model was used and heterogeneity explored when $I^2 >50\%$. For testing the difference between groups the Chi square test was performed.

Results:
Search results: The Cochrane Library search yielded 7 Cochrane reviews, 7 other systematic reviews and 255 methodologically appraised trials. Only one outdated Cochrane review (5) was relevant to this systematic review and was examined in detail to identify RCT relevant to this review. Medline search yielded 289 citations. Initial screening of titles and abstracts short-listed 45 papers, of which 34 were excluded for the following reasons: (i) not RCT comparing pneumococcal conjugate vaccine versus control (n=21), (ii) outcomes not relevant to this review (n=7), (iii) trials comparing alternate schedules/routes/doses (n=3), and (iv) effect of booster doses studied (n=3).

A total of 5 RCT reported through 11 publications were eligible for inclusion in this systematic review (11-21). Two trials were conducted in developing countries viz South Africa (17-19) and Gambia (20,21), and three in developed countries - one in USA (11-13), one in Finnish children (14,15) and one in American Indian children (16). All included healthy infants within a few weeks of birth. Three trials used a seven-valent PCV (11,14,16) while two used a 9-valent PCV (17,20). Two trials used Meningococcal conjugate vaccine as control (11,16), one used hepatitis-B vaccine (14) and two used placebo (17,20). Various outcomes relevant to this review were reported in the included RCT, however none of the trials reported meningitis, or Pneumococcal disease mortality as outcomes. Four trials were described as double-blind (14,16,17,20) and one was a cluster-randomized trial. A summary of the characteristics of these five trials is shown in Table 1. The five trials fulfilled the criteria for high methodological quality (low risk of bias) as shown in Table 2.

The South African trial (17-19) included infants from the population without pre-selection based on HIV status. However, the authors reported results separately in HIV positive and negative children by extrapolating pre-existing population prevalence to the recruited population. Thus the exact number of HIV positive and negative children is not known; however the authors provided an estimated number through personal communication to the authors of the 2004 Cochrane review (5). However, this “estimated number” is different from that in subsequent publications (18,19), suggesting that the data included in the 2004 Cochrane review may be erroneous. Therefore, given that HIV testing in not done routinely prior to immunization with PCV, in this review, the combined data of HIV positive and negative children has been used for analysis.

The Finland trial (14,15) was a three-arm trial with two arms comparing two different 7-valent PCV with a control (hepatitis B vaccine). The two PCV differed in the nature of the protein conjugate; but were otherwise similar in terms of antigen content and composition. For this review, the data of both PCV arms were added together and compared against the control.

The US (NCKP) trial reported the results in two separate publications (11,12) and these had to be considered separately as the denominator for different outcomes was different. Hansen et al (13) presented results of the same trial by retrospectively using WHO criteria for defining pneumonia radiologically. However they did not provide data that could be used in the meta-analysis.

There was near total agreement between the data extraction of both reviewers; the single discordance was in the trial reporting different numbers in the text and
Meta-analysis shows that both the odds and risk of developing clinical pneumonia are marginally reduced with Pneumococcal vaccination; number needed to treat is 200. The vaccine appears to be more beneficial in preventing radiological pneumonia, judged by lower odds and risk; NNT is 143.

As expected the odds and risk of invasive Pneumococcal disease (any serotype) were dramatically lower with vaccination; however the absolute risk difference was very small, yielding a NNT of 500. This was similar to the NNT for IPD caused by vaccine-serotypes. Vaccination did not have any effect on invasive Pneumococcal disease caused by vaccine related or unrelated serotypes.

Three trials included all-cause mortality as an outcome, however one did not report data (11). Meta-analysis showed that the odds and risk were similar with PCV (0.88, 95% CI 0.78 to 0.99), but RD was 0.00 (95%CI -0.00 to 0.00), making it impossible to calculate NNT. The

There is no data available on meningitis, or Pneumococcal disease specific mortality.

In terms of adverse effects, odds of post-vaccination mortality was lower with vaccination, although the risk was similar; likewise the risk difference was not statistically significant. A similar trend was observed for post-vaccination hospitalization. Serious adverse events and seizures appeared to be evenly distributed among those who did and did not receive PCV. An interesting but potentially disturbing finding was that asthma was more common following vaccination, although data is limited in terms of quality and quantity to definitely prove or disprove this issue.

Discussion

This is the first systematic review on PCV reporting measures of vaccine effectiveness. It shows that despite reduction in the odds and risk of developing pneumonia, invasive pneumococcal disease by vaccine serotypes and all-cause mortality (efficacy), vaccine effectiveness represented by absolute risk reduction is much lower.

At first glance, the results of this systematic review are surprising, in the sense that effectiveness of PCV appears to be much lower than that anticipated. This result is robust through all outcome reporting formats. Intention-to-treat analysis is likely to show even less benefit as compared to the per protocol analysis used here.

The poor effectiveness calls for explanation. It could be related to two phenomena viz over-estimation of the burden of childhood pneumonia (owing to non-specific definition) and over-estimation of the burden of Pneumococcal disease in particular (owing to extrapolation from limited data and/or assumptions when organisms are not isolated). The former tends to inflate the baseline risk; while the latter provides a large multiplication factor that could erroneously suggest greater benefit. A recent publication (22) cautioned against both tendencies—It is important to recognize this because trials calculate vaccine efficacy on the basis of a relatively specific definition of Pneumococcal disease, and try to derive population estimates of benefit using less specific definitions. For example, while this review shows nearly 25% reduced risk of pneumonia defined radiologically using stringent WHO criteria, it cannot be taken to mean that pneumonia is reduced by the same factor in the population.

These findings again highlight the dichotomy between efficacy and effectiveness. In the context of PCV, the former is measured either as seroefficacy (antibody levels after vaccination) or protective-efficacy (reduction in disease caused by vaccine serotypes), whereas effectiveness ought to be evaluated (by measuring reduction in disease burden, mortality etc) to facilitate informed decision-making by stakeholders (4). This is why measures of effectiveness were chosen in this systematic review.
On the brighter side, barring asthma, no major safety concerns are evident with PCV. If the prevalence of asthma is really higher, then it would raise serious concerns. This issue can be resolved through a larger trial, especially when newer PCV become available.

Therefore, the importance of this systematic review cannot be over-emphasized, as pneumococcal vaccine has become available in many developing countries with resultant pressure on health-care professionals, policy-makers and people in general; to prescribe/recommend/use the vaccine liberally. For these reasons, despite the demonstration of vaccine efficacy (albeit limited) through randomized controlled trials and recent systematic reviews (7,8); it was felt necessary to undertake a fresh systematic review to estimate the effectiveness of PCV.

It must be noted that the difficult issue of serotype replacement following vaccination has not been addressed here; this phenomenon is increasingly noted in many developed countries in recent years (23,24). This gains importance when vaccine effectiveness is high and large scale immunization programme are instituted.

It is also recognized that no trials examining the recently licensed 13-valent PCV were available for inclusion in this systematic review, hence the findings are not directly applicable to this newer vaccine.

Conclusions:

PCV has limited effectiveness against pneumonia; but is not effective in reducing all-cause mortality. There is significant reduction in invasive Pneumococcal disease caused by vaccine serotypes. There is no data to draw conclusions for other clinical problems of public health significance such as meningitis, and Pneumococcal disease specific mortality. Thus this systematic review shows that although currently available PCV have fair efficacy, they have limited effectiveness, for clinically relevant outcomes of importance. Examination of multiple adverse events did not show a difference in risk compared to control, except for a small but statistically significant increase in risk of asthma.

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Authors’ Contributions:

JLM and NV undertook the literature search. JLM was responsible for data extraction, data analysis and manuscript preparation. VS undertook the statistical analysis and confirmation of results. JMP conceptualized the review, extracted data, assisted with analysis, and finalized the manuscript.

Conflicts of interest:

None of the authors has any conflict of interest.

Funding:

None
References


### Table 1: Characteristics of included trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Setting</th>
<th>Participants</th>
<th>Intervention</th>
<th>Control</th>
<th>Outcomes</th>
<th>Schedule</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>US (NCKP) trial</td>
<td>23 medical centres in Northern California Kaiser Permanente</td>
<td>Healthy infants</td>
<td>PCV-7* (n=18927)</td>
<td>Meningococcus C conjugate vaccine (n=18941)</td>
<td>IPD by vaccine serotypes, otitis media, pneumonia, mortality</td>
<td>2,4,6, 12-15 months.</td>
<td>11-13</td>
</tr>
<tr>
<td>Finland trial</td>
<td>Communities of Tampere, Kangasala and Nokia in Finland.</td>
<td>Healthy infants</td>
<td>PCV-7* (n=831), PCV-7** (n=835)</td>
<td>Hepatitis B vaccine (n=831)</td>
<td>mortality, IPD****, adverse events</td>
<td>2,4,6, 12 months</td>
<td>14,15</td>
</tr>
<tr>
<td>US (American Indian) trial</td>
<td>Navajo and White Mountain Apache tribes in USA</td>
<td>Healthy infants</td>
<td>PCV-7* (n=4165), PCV-7** (n=835)</td>
<td>Meningococcus C conjugate vaccine (n=3926)</td>
<td>mortality, IPD****, adverse events</td>
<td>2,4,6, 12-15 months</td>
<td>16</td>
</tr>
<tr>
<td>South African trial</td>
<td>Soweto, South Africa</td>
<td>Healthy infants</td>
<td>PCV-9*** (n=19914)</td>
<td>Placebo (n=19922)</td>
<td>mortality, IPD****, pneumonia, adverse events</td>
<td>6,10,14 weeks, Longest follow-up: 6.1 years 17-19</td>
<td>20,21</td>
</tr>
<tr>
<td>Gambian trial</td>
<td>Upper and Central River Division of the Gambia.</td>
<td>Healthy infants</td>
<td>PCV-9*** (n=8718)</td>
<td>Placebo (n=8719)</td>
<td>mortality, pneumonia (various definitions), IPD, adverse events</td>
<td>Schedule: not specified (3 doses given)</td>
<td></td>
</tr>
</tbody>
</table>

*Composition: 2mcg of saccharides of serotypes 4, 9V, 14, 18C, 19F, 23F and 4 mcg of 6B conjugated to CRM197
** Composition: 2mcg of saccharides of serotypes 4, 9V, 14, 18C, 19F, 23F and 4 mcg of 6B conjugated to meningococcal outer membrane protein complex.
*** Composition: 2mcg of capsular polysaccharide (serotypes 1,4,5,9V,14,19F,23F), 4mcg of 6B, 2mcg of oligosaccharide 18C, conjugated to CRM197.
**** Invasive pneumococcal disease by vaccine serotypes, non-vaccine serotypes ad vaccine related serotypes.
Table 2: Assessment of methodological quality and risk of bias

<table>
<thead>
<tr>
<th>Criteria</th>
<th>US (NCKP) trial</th>
<th>Finland trial</th>
<th>US (American Indian) trial</th>
<th>South African trial</th>
<th>Gambian trial</th>
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</thead>
<tbody>
<tr>
<td>Adequacy of allocation sequence generation</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
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<tr>
<td>Adequacy of allocation concealment</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
</tr>
<tr>
<td>Adequacy of blinding</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Adequacy of addressing incomplete outcome data</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Freedom from selective outcome reporting</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Freedom from other sources of bias</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Overall bias</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>
Table 3: Meta-analysis showing efficacy and safety data of Pneumococcal conjugate vaccine

** NNT cannot be calculated

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RCT</th>
<th>Vaccinated (n)</th>
<th>Control (n)</th>
<th>OR (95% CI), I²</th>
<th>RR (95% CI), I²</th>
<th>RD (95% CI), I²</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Pneumonia</td>
<td>3</td>
<td>43335</td>
<td>43284</td>
<td>0.927 (0.885, 0.971), 0%</td>
<td>0.940 (0.905, 0.977), 0%</td>
<td>-0.005 (-0.010, 0.001), 41.1%</td>
<td>200 (100, 1000)</td>
</tr>
<tr>
<td>Radiological Pneumonia</td>
<td>3</td>
<td>43335</td>
<td>43284</td>
<td>0.749 (0.682, 0.822), 64.7%</td>
<td>0.744 (0.636, 0.870), 64.4%</td>
<td>-0.007 (-0.012, 0.002), 84.9%</td>
<td>143 (83, 500)</td>
</tr>
<tr>
<td>IPD (vaccine serotypes)</td>
<td>5</td>
<td>46998</td>
<td>45886</td>
<td>0.215 (0.149, 0.311), 0%</td>
<td>0.158 (0.075, 0.333), 24.0%</td>
<td>-0.002 (-0.004, -0.000), 90.6%</td>
<td>500 (250, ~)</td>
</tr>
<tr>
<td>IPD (all serotypes)</td>
<td>5</td>
<td>46998</td>
<td>45886</td>
<td>0.395 (0.297, 0.526), 57.7%</td>
<td>0.341 (0.180, 0.645), 62.2%</td>
<td>-0.002 (-0.004, -0.000), 85.7%</td>
<td>500 (250, ~)</td>
</tr>
<tr>
<td>IPD (Vaccine related serotype)</td>
<td>4</td>
<td>45407</td>
<td>45092</td>
<td>0.838 (0.376, 1.866), 35.8%</td>
<td>0.931 (0.286, 3.027), 25.8%</td>
<td>-0.000 (-0.001, 0.001), 59.1%</td>
<td>**</td>
</tr>
<tr>
<td>IPD (Vaccine unrelated serotype)</td>
<td>5</td>
<td>46998</td>
<td>45886</td>
<td>1.199 (0.667, 2.155), 10.3%</td>
<td>1.151 (0.599, 2.210), 5.2%</td>
<td>0.000 (-0.000, +0.000), 100.0%</td>
<td>**</td>
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<tr>
<td>Meningitis</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cause mortality</td>
<td>3</td>
<td>27411</td>
<td>28065</td>
<td>0.88 (0.78-0.99), 0%</td>
<td>0.88 (0.78-0.99), 0%</td>
<td>0.00 (-0.00, 0.00)</td>
<td>**</td>
</tr>
<tr>
<td>Pneumococcal disease specific mortality</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</table>

**ADVERSE EVENTS**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RCT</th>
<th>Vaccinated (n)</th>
<th>Control (n)</th>
<th>OR (95% CI), I²</th>
<th>RR (95% CI), I²</th>
<th>RD (95% CI), I²</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>4</td>
<td>28753</td>
<td>27618</td>
<td>1.02 (0.53, 1.96), 28.5%</td>
<td>1.02 (0.53, 1.96), 28.4%</td>
<td>0.00 (-0.002, 0.002), 14.8%</td>
<td></td>
</tr>
<tr>
<td>Hospitalization</td>
<td>3</td>
<td>27162</td>
<td>26824</td>
<td>0.910 (0.857, 0.965), 72.3%</td>
<td>0.925 (0.831, 1.031), 77.8%</td>
<td>-0.008 (-0.020, 0.005), 76.2%</td>
<td>125 (50, 200)</td>
</tr>
<tr>
<td>Serious adverse events as defined by authors</td>
<td>4</td>
<td>31745</td>
<td>30632</td>
<td>0.987 (0.785, 1.242), 69.9%</td>
<td>1.500 (0.748, 3.006), 67.8%</td>
<td>0.000 (-0.002, 0.003), 73.6%</td>
<td>***</td>
</tr>
<tr>
<td>Seizures</td>
<td>2</td>
<td>33810</td>
<td>33804</td>
<td>1.095 (0.721, 1.664), 88.7%</td>
<td>0.957 (0.90255, 3.598), 88.2%</td>
<td>0.000 (-0.002, 0.002), 89.2%</td>
<td>***</td>
</tr>
</tbody>
</table>
*** NNT result suggests that vaccination could benefit as well as harm