

Are the pneumococcal polysaccharide vaccines effective? Meta-analysis of the prospective trials

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Peer reviewer's commentary

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The authors have now commented upon and discussed the pros and cons of quasi-randomised trials in an acceptable way. It's worth pointing out though, that Honkanen's study did show 2 cases of invasive disease among vaccinees and 5 among those receiving "placebo". Since the invasive cases were identified from positive blood cultures it is highly unlikely that this result would have been biased by the randomisation method. Further, I still object to the choice of papers for combining and to the conclusion that the vaccine – based on this meta-analysis – can be said to be without effect on invasive pneumococcal disease in the elderly.

Combination of papers: In their comment the authors argue that it is correct to combine AIDS patients (French's study) with e.g. immunocompetent persons >50 years of age (Ortvist's study) because they "represent the types of patients who are recommended to be vaccinated". In most countries recommendations for vaccination include all persons >2 years of age that have an increased risk for pneumococcal infections. That would absolutely apply also to the South African gold miners. This show how the authors mixes "circumstances" with "populations". In the discussion, p.14 last paragraph, the authors state, concerning the gold miners and the New Guinea highlanders, that "This set of circumstances is ideal for demonstrating the potential efficacy of the pneumococcal vaccine". On the next page (15), 2nd para, they state that "In more commonly encountered circumstances the vaccine is not effective". The conclusion from that reasoning would be that differences in living circumstances, not differences in immune status, is important for the outcome of vaccine studies.

Invasive pneumococcal disease: The authors conclude that the vaccine has no effect in prevention of invasive disease in the elderly. The incidence of invasive disease in this age group is about 50/100 000 (see below). The meta-analysis is based on 3 studies of only a total of 927 middle-aged and elderly persons. The relative risk was 0.53 but the confidence interval was wide (0.14 to 1.94). **What is the power of this meta-analysis to rule out a true effect against invasive disease?**

Four out of five case-control studies or indirect cohort studies show, and at least two prospective studies (Ortvist's and Honkanen's) indicate, that the vaccine does offer a 55-80% efficacy against invasive disease in the elderly.

The authors state on p.12 last lines and p.13 first line, that the incidence of invasive disease is about 7/100 000 in the general population, and implicate that even if the vaccine was efficacious against invasive disease, it would not be cost-effective. First, the incidence figure given is lower than the one reported from most countries (15-20 /100 000 in the general population), second, it is the incidence in the elderly, 30-100/100.000 in those over 65, that is of interest for this discussion. There are two recent cost-effectiveness studies based on efficacy rates found in Shapiro's case-control study (NEJM 1991) (which in fact is not far from the relative risk found in this paper), and an incidence of disease about 50/100 000. One found vaccination to cost-saving among elderly in the US (Sisk, JAMA 1997) and one showed it to be moderately to well cost-effective in 5 European countries (Ament et al, CID, in press).

Finally, the authors conclude that "prospective trials in the types of patients targeted in the Western world show the vaccine to be ineffective". However, although none of these studies were designed for studying invasive disease, the relative risk in vaccinated elderly for this end-point was 0.53. Thus, the authors final statement that "ten studies involving 24 000 high-risk individuals fail to show any benefits", is in my opinion, not quite correct.

Authors' response

Phil Wiffen, Andrew Moore and Benjamin Lipsky

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We understand the concerns that Dr Ortqvist has about combining papers. They were our concerns also. Our choice was simple, and driven by the fact that in developed countries we are not concerned with people in the same situations or conditions as those experienced by South African Gold Miners and New Guinea highlanders a quarter of a century ago. In using results from systematic reviews we are exhorted to ask whether the patients in a review are like the patients we are likely to treat. South African Gold Miners and New Guinea highlanders are not, those we chose to include are.

The difference between them is borne out by a convincing demonstration of efficacy for South African Gold Miners and New Guinea highlanders for four of five outcomes (Table 2). With generally similar incidence rates without vaccine there is no statistical benefit for any of the five outcomes with the populations more like those that we are urged to treat. To some extent this lack of efficacy on any outcome helps to answer the problem of missing an effective vaccine because of lack of power. It makes that contingency much less likely.

But even if the vaccine truly reduced the incidence of pneumococcal bacteraemia by 50%, then we would have to vaccinate 100,000 people to prevent 25 cases at a cost of £1,000,000 for the vaccine alone if the true incidence was 50 per 100,000. We are not sure that there is any benefit from pneumococcal vaccination. We are sure that some harm will accrue.