

Pneumococcal polysaccharide vaccines do not protect the elderly from pneumococcal infections

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The decision by the United States Food and Drug Administration (FDA) in 1977 to license a pneumococcal vaccine containing 14 of the 90 known serotypes of *Streptococcus pneumoniae* was based on little evidence.¹ The only published trials of this product then available involved healthy people with unusual risks of pneumococcal infection: South African gold miners and people living in the New Guinea highlands. In more industrialised countries, however, individuals at highest risk of pneumococcal infection are the elderly and those with certain chronic illnesses. Although the vaccine had not been studied in these populations, the government-sponsored group that formulates national immunisation guidelines in the United States, the Advisory Committee on Immunisation Practices (ACIP), recommended that they be vaccinated to prevent pneumococcal pneumonia. In doing so, they committed the grave scientific error of taking information obtained from certain populations and applying it to other, very different ones.

Subsequent prospective controlled and *blinded* trials of the 14-valent vaccine, or a later one containing 23 serotypes, included more than 100,000 patient-years of observation in trials in the USA, Finland and Sweden.²⁻⁸ These investigations demonstrated that the ACIP's recommendations were unjustified: whether examined individually or in aggregate, these studies showed that the vaccine did not reduce pneumococcal pneumonias specifically, pneumonias from any cause, or overall mortality in the elderly or the chronically ill. In fact, combining the results of these trials shows that the frequency of each of these adverse outcomes was actually *higher* in those receiving the vaccine. At least seven meta-analyses (including two not cited by Assendelft *et al.*) in this issue have been published that collectively reviewed at least 16 randomised controlled trials – both

blinded and unblinded – comprising almost 50,000 patients. The analyses have differed in their methods, the kinds of studies included, and their classification of the information.⁹⁻¹⁵ Nevertheless, they agree in concluding that in industrialised nations the pneumococcal vaccine is ineffective in the elderly and the chronically ill. A recent large *retrospective* cohort study of the vaccine in the elderly in the USA (not available to Assendelft *et al.*) that evaluated 47,365 patients 65 years of age or older for three years also showed that it was ineffectual.^{16,17} As with several other studies, the authors dwelled on the nonsignificant reduction in pneumococcal bacteraemias in the vaccine group, while downplaying the larger failure of the vaccine to prevent pneumonia or deaths.

The reasons that the polyvalent polysaccharide vaccine has failed to provide protection to those at greatest risk for pneumococcal pneumonia in industrialised countries are uncertain. They may relate to the inability of chronically ill or elderly patients to generate an adequate immunological response to the pneumococcal antigens, infection from serotypes not included in the vaccine, or a lower frequency of pneumococci as the cause of pneumonias in these populations than previously believed.¹⁸ The most reasonable conclusion from the available evidence is that the vaccine may reduce the incidence of pneumococcal pneumonia among young, immunocompetent people in certain *epidemic* circumstances, such as gold miners in South Africa and New Guinea highlanders, or perhaps in military recruits, based on older studies with a different preparation. These groups have a high risk of acquiring infection because of close group living arrangements, and in some instances exposure to respiratory irritants, but because they are otherwise healthy they have a low risk of dying from it. The evidence is persuasive, however, that the vaccine lacks

effectiveness against *endemic* pneumococcal pneumonia, which tends to occur in the elderly and infirm. Unfortunately, it is among these persons that the mortality rate is substantial. Thus, the polysaccharide vaccine does not work in those who need it most. Perhaps the newer protein conjugated pneumococcal vaccine that has been effective in children¹⁹ will be more immunogenic in high-risk adults, but only randomised controlled trials will provide this information.

Despite the disappointing studies of the polysaccharide vaccine, the ACIP (USA) continues to advise vaccination of the elderly and infirm, and is being urged to extend vaccination recommendations for those aged 50 to 64²⁰ and to smokers and Native and African Americans.²¹ These recommendations are based on several retrospective studies using both standard and novel methods that suggested that the vaccine might be effective in preventing *invasive* pneumococcal disease (infections with positive cultures from normally sterile sites, primarily bacteraemia associated with pneumonia).²² Retrospective case-control studies are inherently weaker forms of evidence than prospective controlled trials. Nevertheless, because these investigations suggest that immunisation *may* reduce the frequency of pneumococcal bacteraemia, the ACIP has shifted the justification for vaccination from preventing pneumococcal *pneumonia* to preventing *bacteraemia* from this organism.²² Thus, what has been called the 'pneumonia shot' is no longer even recommended to prevent pneumonia! No evidence from prospective studies, however, indicates that a reduction in bacteraemia in patients with pneumococcal pneumonia will result in less frequent or shorter hospitalisations, decreased mortality, or reduced medical expenses. Moreover, studies suggesting that immunising the elderly is cost-effective for preventing bacteraemia depend on unreasonably high estimates of vaccine efficacy. The most widely cited cost-effectiveness analyses pertaining to American populations base their assumptions on a single retrospective study,²³ ignore the information from the prospective trials, and fail to acknowledge that the vaccine is ineffective in reducing the incidence of pneumococcal pneumonia.^{20,24-26} A cost-benefit analysis from the Netherlands suggested that in the base case analysis the cost of preventing invasive pneumococcal disease ranged from 11,000-33,000 euros per quality-adjusted life year, but again used unreasonably high estimates of vaccine efficacy.²⁷

The initially premature, and repeatedly promulgated recommendation by the ACIP and other authoritative agencies for the use of the polysaccharide pneumococcal vaccine among the elderly and the chronically ill thus rests on weak evidence based on retrospective studies. Their arguments do not adequately acknowledge the information from prospective, randomised, and blinded trials, nor do they address the concerns about the scientific validity of

their recommendations that we first raised over 20 years ago.⁸ It is therefore highly appropriate and admirable that authors from the Netherlands reviewed the available information to determine whether or not to recommend pneumococcal vaccination in the elderly in their country. Their careful and thoughtful analysis demonstrates the remarkable weakness of the information supporting vaccination and highlights the problem that the decision to encourage vaccination was formed before adequate studies became available. The authors are right to conclude that there is insufficient evidence to introduce pneumococcal vaccination of the elderly in the Netherlands. Rejecting the pressure to do so will ensure that at least the Netherlands will not contribute to 'the apparent conflict between evidence of effectiveness of pneumococcal polysaccharide vaccines and existing recommendations for their use'.²⁸

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