Polysaccharide pneumococcal vaccination

Polysaccharide pneumococcal vaccination: new evidence

A J Hall

Efficacy of anti-pneumococcal vaccination in patients with COPD

The use of polysaccharide pneumococcal vaccination in elderly or high risk populations remains controversial. Evidence from less developed countries is the most persuasive in the absence of HIV, but in more developed countries the nine randomised controlled trials to date are inconclusive. They have now been the subject of some five meta-analyses[1–5] and to this can be added a recent meta-analysis of both the randomised controlled trials and observational studies.[6] There has even been a review of the meta-analyses![7]

The most recent review is helpful because it compares the trials and the observational studies using similar quality criteria and methods of pooling results. The strongest evidence is based on pneumococcal bacteraemia as the end point. Here studies of all types—case-control, cohort and randomised controlled trials—show consistent evidence of around 50% protection. However, it remains unclear whether this represents true protection or a suppression of bacteraemia without affecting the underlying disease (pneumonia). When it comes to pneumonia, the picture is much more confusing—and here we mean all cause pneumonia. Both observational studies and randomised controlled studies show significant heterogeneity between studies. If an estimate of protection is made despite this heterogeneity, then the trials show a tiny harmful effect compared with a beneficial 35% in observational studies (although the confidence interval included no protection).

In this situation it is very good to see some new primary data—especially from a trial. In this issue of *Thorax* a study by Alfageme *et al*[8] examines whether the vaccine would prevent community acquired pneumonia in individuals with chronic obstructive airways disease. The study was relatively small and so, although the overall efficacy was 24%, this did not reach statistical significance. However, they did find statistically significant evidence of protection in two subgroup analyses—namely, in individuals aged less than 65 years and in those with severe disease. It was not clear if these subgroups were specified a priori. The authors conclude by recommending vaccination in these groups. Given that these are a relatively small population at high risk, this would seem reasonable. Assuming the vaccine does no harm—on which point the evidence is reasonably strong—then the cost will be modest for the potential benefit.

In contrast, the UK has adopted a policy of vaccinating all individuals aged over 65 years—at considerable cost. This programme is being evaluated, although currently only by pneumococcal bacteraemia. As the introduction was phased in—beginning with those aged over 80 years in August 2003, followed by those over 75 years from April 2004, and finally those aged 65 and older from April 2005—the results are currently only robust for those older than 80. These were presented at the HPA conference in Warwick this September. They show a 9% decline in the rate of bacteraemia with no effect on case fatality. A particular problem with using surveillance data for estimating effects in this programme are that the coverage rate was only estimated at 26% in 2003/4. There is therefore a large potential for confounding by selection of those in contact with health services and with differing levels of health from the whole population. It is to be hoped that pneumonia can be included as an end point in this surveillance but, even then, confounding will remain an issue unless risk factors are collected on both those affected and on the vaccinated population.

One concern with all of these studies has been the misclassification inherent in using all cause pneumonia as an outcome—an effect on pneumococcal pneumonia could be diluted. Methods of diagnosing pneumococcal disease have improved markedly in recent years. The time has surely come to apply these to this issue, with adequate numbers and in a carefully designed study that can cope with confounding.

This issue has become more complex with the advent of pneumococcal conjugate vaccines. The USA introduced a 7-valent vaccine into the routine childhood programme in 2000. Although this vaccine was designed for the common pneumococcal serotypes affecting children, an effect has been seen on adult disease.[9] Rates of invasive pneumococcal disease have declined in all age groups from 50 years upwards with the greatest decline (a remarkable 35%) seen in those aged over 84 years. This is likely to be causal since an effect on adult pneumonia was seen in the original US trial of childhood pneumococcal conjugate vaccine. It is presumed that this represents an effect on transmission from young children since it is known that carriage of the pneumococcus is reduced by the conjugate vaccine. Any future evaluation will therefore need to take account of any concurrent pneumococcal conjugate vaccination in the population.

It has also been proposed that the conjugate vaccines—possibly with more serotypes added—might be used directly in the elderly. The rationale here would be to induce better immune memory with a priming dose of conjugate followed by a booster dose of the 23-valent polysaccharide. Clearly trials of this approach are warranted but, as Conaty and colleagues point out,[6] we must not allow the same situation to arise in the high risk and elderly as has happened with polysaccharide vaccine. We need carefully designed clinical trials of adequate size using the best modern methods of diagnosing pneumococcal pneumonia to determine the end point.

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REFERENCES

1 **Fine MJ**, Smith MA, Carson CA, *et al*. Efficacy of pneumococcal vaccination in adults. A meta-analysis of randomized controlled trials. *Arch Intern Med* 1994;**154**:2666–7.
2 **Hutchison BG**, Oxman AD, Shannon HS, *et al*. Clinical effectiveness of pneumococcal vaccine. Meta-analysis. *Can Fam Physician* 1999;**45**:2381–93.
3 **Moore R**, Wiffen P, Lloyd S. Are the pneumococcal polysaccharide vaccines effective? Meta-analysis of the prospective trials. *BMC Fam Pract*, 2000;**1**(1).Available from http://www.biomedcentral.com/1471-2296/1/1.
4 **Cornu C**, Yzebe D, Leophonte P, *et al*. Efficacy of pneumococcal polysaccharide vaccine in immunocompetent adults: a meta-analysis of randomized trials. *Vaccine* 2001;**19**:4780–90.
5 **Watson L**, Wilson BJ, Waugh N. A systematic review of pneumococcal polysaccharide vaccine adults. *Vaccine* 2002;**20**:2166–73.
6 **Conaty S**, Watson L, Dinnes J, *et al*. The effectiveness of pneumococcal polysaccharide vaccines in adults: a systematic review of observational studies and comparison with results from randomized controlled trials. *Vaccine* 2004;**22**:3214–24.

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7 **Mangtani P**, Cutts F, Hall AJ. Efficacy of polysaccharide pneumococcal vaccine adults in more developed countries: the state of the evidence. *Lancet Infect Dis* 2003;**3**:71–8.

8 **Alfageme I**, Vazquez R, Reyes N, *et al*. Clinical efficacy of anti-pneumococcal vaccination in patients with COPD. *Thorax* 2006;**61**:189–95.

9 **Lexau CA**, Lynfield R, Danila R, *et al*. Changing epidemiology of invasive pneumococcal disease among older adults in the era of pediatric pneumococcal conjugate vaccine. *JAMA* 2005;**294**:2043–51.

Air pollution and respiratory health of young children

Think globally, breathe locally

R J Delfino

Why the worldwide health impact of air pollution on young children begins in our neighbourhoods

To date, most epidemiological studies of paediatric pulmonary disease and air pollution have focused on the impacts of air pollutants that are both regulated and monitored on a daily basis by governments. This includes particle mass concentrations and gaseous air pollutants such as ozone and sulfur dioxide. In most studies this has led to the use of available regional air monitoring data. Generally, these approaches have resulted in important new information about ongoing health impacts in many nations or have confirmed previous findings of adverse associations with respiratory morbidity. This has justified calls for greater involvement by citizens, local community organisations, industry, and governments to curb air pollutant exposures.[1] However, there is increasing evidence that concentrations of air pollutants—especially particle components and size distributions not routinely monitored—have spatial distributions that can vary by neighbourhood. In urban areas the most prevalent determinant of sub-regional air pollutant concentrations is local traffic. Roadway traffic will continue to increase worldwide, as evidenced by projections that transportation energy consumption in emerging economies such as China will increase at an annual rate from 2002 to 2015 of 4.4 quadrillion Btu (1055.1 Joule/Btu).[2]

WHAT IS IMPORTANT ABOUT PROXIMITY TO TRAFFIC?

Concentrations of ultrafine particles <100 nm in diameter are influenced strongly and positively by distance from roadways.[3] There is also growing evidence that photochemically generated ultrafine particles are a potentially important regional exposure.[3] Ultrafine particles have low mass concentrations in air compared with regulated particulate matter <10 μm in diameter (PM_{10}). However, the large surface area per unit mass of ultrafine particles can carry to the lungs large quantities of toxic air pollutants including oxidant gases, organic compounds, and transition metals.[4] This toxicity of ultrafine particles is combined with their high pulmonary deposition efficiency and high particle number concentration which are magnitudes higher than larger particles. The traffic related increase in ultrafine particles is additional to a parallel increase in a plethora of pollutant gases and volatile and semi-volatile organic compounds that can undergo chemical transformations and can attach to the elemental carbon core of ultrafine particles.

Many organic compounds associated with vehicle emissions such as polycyclic aromatic hydrocarbons, along with transition metals, have been identified as having adjuvant effects on cytokine mediated airway inflammation, in part through oxidative stress mechanisms.[5–8] This process has been linked to the enhancement of allergic respiratory responses to airborne allergens and may be involved in the onset of atopy.[9] Evidence for this has come primarily from studies that have used diesel exhaust particles as a model exposure since this source is particularly rich in redox cycling compounds.[8]

The development of respiratory allergic phenotypes is thought to begin early in life through a failure of the T cell population to mature adequately from a Th2 to Th1 subtype, thus driving an imbalance toward Th2 immunity.[10] The adjuvant effects of air pollutants on this shift may begin in utero, as supported by evidence from a cohort study of an increased risk of childhood asthma and wheezing following in utero exposure to environmental tobacco smoke.[11] In addition to risks attributable to a developing immune system, young children are also susceptible to adverse health effects of air pollutants because they generally have higher levels of activity compared with adults, and have greater minute ventilation rates per body weight leading to higher doses of irritants. Submicron particle dose in the pulmonary region has been predicted to be particularly high among 3 month old children compared with adults.[12] These factors are coupled with the likelihood that young children often play outside near traffic sources.

THE RESPIRATORY HEALTH OF CHILDREN AND EXPOSURE TO TRAFFIC RELATED AIR POLLUTION

In this issue of *Thorax* Pierse *et al*[13] provide evidence for the importance of traffic related air pollutants near the home to the respiratory health of children aged 1–5 years surveyed in 1998 and again in 2001 when aged 4–8 years. The authors found that parent reported prevalence and incidence of cough without a cold and the incidence of wheeze were positively associated with an increase in the estimated concentration of PM_{10} from sources near the homes of children aged 1–5 years. The estimations of PM_{10} were based on a dispersion model that was tailored for the study area (Leicester) and was primarily based on traffic flow and wind speed and direction in relation to the home address. However, as discussed above, ultrafine particles and associated toxic air pollutants are more strongly influenced by proximity to traffic than larger particle size fractions included in PM_{10}.

The study by Pierse *et al*[13] adds to a growing trend in epidemiological studies of air pollution to reduce reliance on available regional air monitoring data by supplementing or supplanting it with data intended to estimate exposures closer to the individual participant. The goal of methods to estimate personal exposure is to reduce misclassification of air pollutant exposures. Exposure misclassification is expected to occur when the same regional exposure is applied to all study subjects regardless of distance to air monitors and of potentially important local pollutant sources. This can often limit studies to make cross sectional comparisons between cities rather than within cities, and opens the door for unmeasured confounding by factors that differ between regions. The ideal exposure measurement is to use personal air monitors, but this becomes impractical with a large study population such as the cohort of 4400 children studied by Pierse *et al*.[13] Methods to achieve a better estimation of personal exposures include local source dispersion models[14] and microenvironmental models that

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