Pneumococcal disease in Australia

Summary of the Pneumococcal Disease in Australia: Epidemiology, Surveillance and Immunisation Workshop, convened by the National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, Royal Alexandra Hospital for Children, Sydney, 26-27 March 1999

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Abstract

The proceedings of the Pneumococcal Disease in Australia Workshop, held on 26-27 March 1999 are presented in this report. The world-wide epidemiology of the pneumococcus, with its predilection for the very young and the very old, differs between the developing and the developed world, and between indigenous and non-indigenous populations. Sources of data on pneumococcal disease in each of the Australian States, clinical aspects of invasive and non-invasive disease, and the role of the public health laboratory in surveillance of serotypes and antimicrobial sensitivity, both nationally and over time, were discussed at the Workshop. Polysaccharide pneumococcal vaccines are recommended for those over 65 years of age and for at-risk groups, but are supplied free of charge only in Victoria and for indigenous Australians over 50 years of age. Children will require conjugate vaccines, which are likely to be licensed in the United States of America early in 2000. In Australia indigenous children, especially in rural areas, will be the priority group for conjugate vaccines. *Commun Dis Intell*2000;24:89-92.

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World-wide epidemiology

Streptococcus pneumoniae (pneumococcus) is responsible for more deaths world-wide than any other single pathogen.[1] It causes meningitis, bacteraemia, pneumonia and otitis media, particularly affecting infants and children under 5 years of age, adults over 60 years of age, and

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those with chronic underlying medical conditions or immunosuppression.

Invasive pneumococcal disease (associated with a sterile site isolate) in infants differs between industrialised countries, where it is mostly bacteraemia and meningitis, and developing countries, where it is mostly pneumonia.[2] Indigenous populations in Australia and North America have very high rates of invasive disease, with those in Australian Aboriginal children the highest recorded in the world.[3] In adults over 65 years of age in Europe and the United States of America, the reported incidence ranges from 24–80/100,000 population; Australian rates are similar, with 17-30/100,000 population. It is also considered a huge problem in developing countries.

Non-invasive pneumococcal disease is much more common than invasive disease and also causes significant morbidity. In children otitis media predominates and in adults pneumonia predominates. The frequent use of antibiotics to treat respiratory tract infections, only a fraction of which are pneumonia or otitis media, is an important driving force in the world-wide development of pneumococcal resistance to penicillin, because of selection pressure on pneumococci colonising the upper respiratory tract.

There are over 90 known pneumococcal serotypes. Fortunately, 85-90% of adult infections are caused by one of the 23 serotypes whose purified capsular polysaccharide antigens are included in current vaccines. In children, because the number of serotypes causing disease is much less than in adults, conjugate vaccines containing 7-11 serotypes show great promise for preventing pneumococcal infection. These insights were amongst those shared by Dr Kim Mulholland, from the World Health Organization (WHO) in Geneva.

Epidemiology of pneumococcal disease in Australia

Data on the epidemiology of pneumococcal disease in indigenous and non-indigenous adults and children in various areas of Australia were presented by a number of speakers.

Non-indigenous populations

For non-indigenous adults, data from hospital discharges and laboratory data confirm that invasive pneumococcal infection primarily manifests as pneumonia and mainly affects adults over 60 years of age. Predisposing factors include malignancy and other causes of immunosuppression, diabetes, alcohol abuse, asplenia and chronic renal disease.

In non-indigenous children the incidence of invasive infection (mostly bacteraemia and meningitis) is highest in the first 2 years of life. Significant risk factors in these young children include attendance at child-care centres, parental smoking and recent otitis media. Pneumococcal meningitis causes significant morbidity, death (case-fatality rate, 10%) and long-term neurological sequelae.

Indigenous populations

In all age groups, indigenous rates of invasive pneumococcal infection are up to 75 times higher than in non-indigenous groups, and are caused by a broader range of serotypes. In Queensland, meningitis occurs earlier than in non-indigenous children (6 versus 12 months). Across northern Australia a striking difference is the high incidence of infection in younger indigenous adults (aged 15–50 years), as well as at the extremes of age, especially in those who have chronic lung, liver and kidney disease, with or without alcohol abuse. Roughly one-quarter of the serotypes involved are not covered by the 7-valent conjugate vaccine. As with Hib disease, the incidence of invasive pneumococcal disease in indigenous children is not uniform. Attack rates in northern Australia are lower than in Central Australia, and lower in urban regions than in rural/remote regions. Ear disease starts early and its pattern around the country varies; in remote areas otitis media is more likely to be associated with perforated tympanic membranes with purulent discharge.[4]

Sources of data on pneumococcal disease

The available sources of data differ widely among jurisdictions. These were outlined in presentations from each State and Territory.

In Victoria, the Victorian Hospital Pathogens Surveillance System, hospital discharge data, Australian Bureau of Statistics death data and annual surveys of vaccination coverage in adults over 65 years of age give a reasonably complete picture. In Western Australia specific studies by the Vaccine Impact Surveillance Network (Invasive Pneumococcal Study Group), which commenced in 1996, assessed the incidence, risk factors and serotypes responsible for invasive pneumococcal disease in Aboriginal and non-Aboriginal people. In Central Australia surveillance and monitoring of pneumococcal serotypes in Aboriginal people commenced in 1985. Fifty per cent of invasive disease occurs in children, much of it in the first year of life; the serotype data from these children show a pattern more like developed than developing countries.[5]

Invasive disease is notifiable in the Northern Territory where, prompted by high disease rates, an adult immunisation campaign was implemented in 1994. Although vaccination registers are patchy and incomplete, data are available on the distribution of free vaccine to at-risk indigenous groups. By 1998 about 50% of the older at-risk group had been covered. There was some impact on the incidence and mortality of invasive disease, though this was not evident in young adults. Of the 426 invasive pneumococcal cases in the period 1994-1998, 69% presented with pneumonia. Invasive pneumococcal disease is also notifiable in Queensland (since 1996), but not in any other State.

Overall in Australia, pneumococcal vaccine coverage is low, as measured by telephone surveys in Western Australia, South Australia, and Victoria. In 2000 data will be available from New South Wales.

Laboratory issues

The epidemiology of antimicrobial resistance

Antimicrobial resistance in pneumococci world-wide was reviewed by Associate Professor John Turnidge and in Australia by Associate Professor Peter Collignon.

World-wide, pneumococcal resistance to penicillin and to other antibiotics has been increasing since the 1960s.[6,7] The Surveillance Network in the United States of America in the period 1997–1998, showed that invasive isolates tended to

be less resistant than respiratory or superficial isolates, but multi-resistance is now common. The Alexander Project in Europe has shown rapid evolution and increasing levels of resistance to penicillin and other antibiotics.[8] There is a consistent relationship in studies world-wide between high usage of antibiotics and high levels of resistance, especially in isolates from respiratory tract infections.[9]

Any degree of resistance to penicillin is of clinical importance in central nervous system infections, but may be significant at other sites when high level resistance occurs. Resistance is serotype specific. The latest Australian data show 25% resistance (intermediate plus high level) to penicillin,[7] 16% to erythromycin (used for people allergic to penicillin) and varying levels to other antibiotics. Ongoing accurate surveillance with data on MICs (minimum inhibitory concentrations) and cephalosporins are important to monitor this. Prophylactic antibiotic use (as was seen when erythromycin was used for pertussis in Aboriginal communities) may increase resistance levels.

Resistance is particularly important for meningitis and otitis media in many developing countries, which have restricted access to antibiotics and poorly developed surveillance systems.

The role of public health laboratories

The role of public health laboratories in surveillance of serotypes and antimicrobial sensitivity, both nationally and over time, for different age groups and different disease patterns, was discussed by Professor Lyn Gilbert. Collaborative laboratory networks will be crucial in the monitoring of antibiotic susceptibility, and the spread of resistance genes between serotypes. Newer molecular methods for subtyping (such as multilocus sequence typing) will help define the distribution of serotypes, both before and after introduction of conjugate vaccines, so that vaccine efficacy can be assessed. The importance of using the information obtained through this surveillance to inform the prescribing patterns of doctors and medical students (future prescribers) was emphasised.

Pneumococcal vaccines

Polysaccharide vaccines

In Australia, 85% of pneumococcal disease is caused by serotypes contained in the current 23-valent unconjugated pneumococcal vaccine, which has been shown to protect against invasive disease in populations of adults with high attack rates (American recruits, Papua New Guineans). Trials in other countries, such as France, Finland and Sweden, have shown varying effectiveness in adults; estimates of effectiveness from case-control studies are in the order of 60% for prevention of invasive pneumococcal disease. In young children in Papua New Guinea the vaccine protected against bacteraemia, severe disease and mortality.

Pneumococcal vaccine is recommended for indigenous minorities, residents of institutions, at-risk immunocompetent people and the elderly, with revaccination every 5 years.[10] An as yet unpublished study of vaccine efficacy among HIV infected women in Uganda, showed lack of protection against disease.[11] These data have limited relevance for communities such as the Australian population, where highly active antiretroviral therapy is available. The WHO is seeking to coordinate results of all the unpublished studies of pneumococcal vaccination around the world.

In Victoria, free pneumococcal vaccine is provided for all adults over 65 years of age. In 3 years coverage has increased to 42%. Elsewhere vaccine is funded only for Aboriginal and Torres Strait Islanders over 50 years of age.

In Far North Queensland, vaccination of Aboriginal adults over 50 years and younger adults with risk factors has reduced the incidence of invasive disease from 120 to 75/100,000 (personal communication, Jeffrey Hanna). Further lowering the age of universal vaccination in Aboriginal adults in areas where incidence rates are high is being considered.

Conjugate vaccines

Because young children under 2 years of age do not respond well to polysaccharide vaccines, conjugate vaccines have been developed. Dr Dace Madore, from Lederle-Praxis Biologicals, New York, described the 7-valent pneumococcal CRM_{197} conjugate vaccine. Its first efficacy trial has been completed (but results are not yet published) in northern California, demonstrating 100% efficacy; serological correlates for protection are being studied. This vaccine is proving highly effective in preventing invasive disease due to the serotypes included in the vaccine, and its routine use should have a significant impact on childhood morbidity and mortality due to pneumococcal invasive disease. Kinetics of the immune response vary by serotype;[12] it does not interfere with other concomitantly administered childhood vaccines. Standardisation of serological methods is critical for comparing new vaccine formulations.

Will conjugate pneumococcal vaccines have a place in immunisation programs?

The results of the Californian trial suggest that the pneumococcal 7-valent conjugate vaccine will be highly effective in preventing invasive pneumococcal disease in children in the developed world. More recent results from this trial suggest important reductions in otitis media and pneumonia.[13]

Pneumococcal conjugate vaccines (7-valent, 9-valent and 11-valent) are in advanced stages of development, and are undergoing trials in different parts of the world. Determining endpoints of these pneumococcal trials is complicated by two factors. Firstly, the high carriage rates of the organism (in sub-Saharan Africa, ~90% of children carry pneumococci by 6 months of age frequently with multiple carriage of different types), and secondly, by the possibility of replacement (that is, reduction of carriage and disease by some serotypes resulting in replacement by other serotypes).[1] Phase III immunogenicity (as opposed to efficacy) trials, based on correlates of protective antibody levels, will be required to evaluate the efficacy of additional serotypes in pneumococcal conjugate vaccines. Accurate data about burden of disease, and careful regional and national economic analyses are essential for these expensive vaccines.

In the developing world issues of access and equity are particularly important.[14] Universal childhood immunisation narrowed the morbidity/mortality gap between children of rich and poor countries; the use of new expensive vaccines (for example, Hib) only in rich countries is again widening this gap. The arrival of effective pneumococcal conjugate

vaccines will directly challenge our existing concepts of new vaccine use. When 1-2 million children die each year in poor countries, having an effective vaccine that is not available because of cost, is intolerable. Pneumococcal vaccination regimens will need to be modified for developing countries, from the point of view of age, serotype coverage and affordability. One approach is maternal immunisation with a 23-valent unconjugated pneumococcal vaccine, to provide the neonate with passive protection from maternally transmitted antibodies. Another approach is neonatal vaccination with a conjugate vaccine. At present the pneumococcus remains a most significant cause of paediatric mortality in the world; the conjugate vaccine has not yet been extensively tested in children in the developing world, although the existing published data suggest it is protective.[15,16]

In Australia, conjugate vaccines are likely to be included in the infant schedule. Combination vaccines may impact on this, as may the need for boosting, either in childhood or adulthood. It is clear that there is an unequivocal need for conjugate pneumococcal vaccine to be delivered to remote communities where there are high attack rates of invasive disease and pneumonia. Indigenous Australians are the one population in the world who will most benefit from this scientific advance, because they have a lot of disease and we can afford the vaccine. Ear disease in indigenous children is more difficult; early colonisation and early onset of disease make it less likely that a vaccine started at 2 months of age will make a big difference. For otitis media, vaccination schedules starting at birth and maternal vaccination may need to be considered.

Conference speakers

Ross Andrews, Claire Caesar, Peter Collignon, Carolien Giele, Lyn Gilbert, Jag Gill, Robert Hall, Jeff Hanna, Geoff Hogg, Vicki Krause, Deborah Lehmann, Dace Madore, Peter McIntyre, Robert Menzies, Avner Misrachi, Kim Mulholland, Linda Selvey, Paul Torzillo, John Turnidge

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