

# Pneumococcal disease in Australia: current status and future challenges

A report of the workshop held at the National Centre for Immunisation Research and Surveillance, 8–9 November, 2002

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## Introduction

In March 1999, a workshop titled 'Pneumococcal disease in Australia' was held at the National Centre for Immunisation Research and Surveillance of Vaccine Preventable Disease in Sydney. A summary of the workshop<sup>1</sup> and recommendations for surveillance<sup>2</sup> were subsequently published in *Communicable Diseases Intelligence* in April 2000. More detailed papers arising from presentations by a wide range of Australian experts appeared later that year as a supplement of the *Medical Journal of Australia*. The papers in the supplement described the epidemiology of invasive pneumococcal disease (IPD) in areas of Australia with a relatively low proportion (metropolitan New South Wales, Victoria) and a relatively high proportion (Northern Territory and Western Australia) of the population who are Aborigines or Torres Strait Islanders. The most prominent issues identified were the high incidence of IPD among Aboriginal children, particularly in Central Australia, associated with a more diverse range of serotypes than non-Indigenous children; the morbidity and mortality of IPD, particularly meningitis; and increasing levels of antibiotic resistance among strains of *Streptococcus pneumoniae*.

At the time of the first meeting, pneumococcal disease in young children was not vaccine-preventable as the only vaccine then available, the 23-valent polysaccharide vaccine, (23vPPV) is poorly immunogenic under the age of 2 years. Subsequently, the seven-valent conjugate pneumococcal vaccine (7vPCV) was approved for use in Australia by the Therapeutic Goods Administration in December 2000. A Pneumococcal Working Party, jointly chaired by the Australian Technical Advisory Group on Immunisation and the Communicable Diseases Network Australia had been established earlier in 2000. The Pneumococcal Working Party recommended urgent implementation of a publicly funded vaccination program with 7vPCV for children at highest risk of IPD, primarily those with predisposing medical conditions aged under 5 years and all Indigenous children aged under 2 years. The program commenced in July 2001 in Central Australia and was progressively implemented in other states and territories over the next 6 months. At the time of the

first workshop, invasive pneumococcal disease was notifiable only in the Northern Territory (since 1995) and Queensland (since 1996).<sup>2</sup> In January 2001, the Communicable Diseases Network Australia agreed to make IPD a notifiable disease in all Australian jurisdictions, with enhanced surveillance systems implemented and funded by the end of 2001. The second national workshop in November 2002 provided an opportunity to evaluate the first year of enhanced surveillance and the 7vPCV vaccination program and to learn from the experience following the introduction of universal 7vPCV vaccination of children under 2 years of age in the United States of America at the end of 2000.

## Day 1. Surveillance of invasive pneumococcal disease

### Long term population-based surveillance in the United States of America and Australia

#### United States of America

Cynthia Whitney, a medical epidemiologist from the Centers for Disease Control and Prevention Atlanta, reviewed the current epidemiology of pneumococcal disease in the USA and the impact of the conjugate vaccine. Surveillance of IPD is based on 10 sentinel areas (counties, cities or states) with a total population of 20 to 24 million people. Cases of IPD occurring in these sentinel areas are actively followed up and isolates are collected and analysed for serotype and antimicrobial resistance at the Centers for Disease Control and Prevention or reference laboratories. Surveillance is aimed at assessing vaccine effectiveness. Early assessments indicate a reduction of the order of 70 per cent in the incidence of IPD in children aged less than 2 years. Vaccine failures have been documented in 129 cases of which 47 per cent were cases with non-vaccine serotypes, 37 per cent with vaccine serotypes and 17 per cent with vaccine-related serotypes. Among the 48 cases with vaccine serotypes, only 11 were fully vaccinated and the most common serotype isolated was 6B (n=6). The majority of children who were vaccine failures had other underlying conditions predisposing to pneumococcal infection.

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### North Queensland

Jeffrey Hanna, Director of the Tropical Public Health Unit based in Cairns, reported on enhanced surveillance of IPD in Far North Queensland since 1992, subsequently expanded to include the whole of north Queensland.<sup>3</sup> The incidence of IPD in Indigenous children under 2 years of age (297 cases per 100,000 population) is similar to that reported from the Top End of the Northern Territory (326 cases per 100,000 population) but dwarfed by the incidence among Aboriginal children in Central Australia (1,534 cases per 100,000 population). Importantly, the incidence in Far North Queensland of pneumococcal meningitis among Indigenous children (56 cases per 100,000 population) was higher than in non-Indigenous children (17 cases per 100,000 population) and occurred at a significantly younger age (median 0.5 years) than non-Indigenous children (1.0 years). In Indigenous children, only 62 per cent of isolates had serotypes contained in the 7vPCV, compared with 88 per cent among non-Indigenous children.

### Metropolitan New South Wales

Peter McIntyre, Deputy Director of the National Centre for Immunisation Research and Surveillance, updated to 2001 the earlier report to 1999 of enhanced surveillance of IPD in metropolitan New South Wales by a laboratory network.<sup>4</sup> The overall incidence of IPD in children aged under 2 years (100 cases per 100,000 population) and pneumococcal meningitis (10 cases per 100,000 population) and the serotype distribution (90 per cent included in 7vPCV) were unchanged. In children less than 5 years of age, additional medical risk factors (extreme prematurity, all premature infants with chronic lung disease and all children with Downs syndrome, diabetes mellitus and cystic fibrosis) were associated with increased numbers of cases. A case-control study in this population has shown that attending child care is most important as a risk factor for IPD in the first 3 months after commencement. Only 15 IPD cases were identified as Indigenous during the study period, giving a very similar incidence to non-Indigenous children. This may suggest that the incidence of IPD in Indigenous children living in an urban setting is lower than in rural and remote settings, but is limited by deficiencies in identifying Indigenous children in urban areas and needs further investigation.

### Enhanced surveillance of notifiable invasive pneumococcal disease in states and territories since 2001

Short presentations were made on national data collected from enhanced surveillance for IPD in 2001 and reports of IPD surveillance activities in 2002 in each state and territory. The national report for 2001

has recently been published<sup>5</sup> and the abstracts of each state and territory's presentation are included in the appendix to this report.

### Laboratory issues

Lyn Gilbert, Chair of the Laboratory Sub-group of the Pneumococcal Working Party, reviewed the contribution of laboratories to the surveillance of IPD, particularly in measuring the impact of vaccination on serotype distribution and the prevalence of antibiotic resistance. Maintenance of laboratory networks for forwarding IPD isolates and for serotyping and reporting is resource intensive. Current resources will not be sufficient for expanded antimicrobial susceptibility testing. There are a number of more sophisticated methods for serotyping and molecular typing of pneumococcal strains under development. The potential for molecular serotyping of *S. pneumoniae* was discussed in the context of a pilot project which has shown these new techniques correlate well with traditional serological typing, with the potential for micro-array technology to automate typing and antimicrobial susceptibility. In addition, multi-locus sequence-typing based on variations in seven *S. pneumoniae* genes, provides a tool for measuring the molecular epidemiology of antimicrobial resistance and serotype dynamics.

### Surveillance of pneumococcal vaccine coverage

While childhood immunisation coverage rates are now monitored in the Australian Childhood Immunisation Register (ACIR), no national register exists for adult vaccines. Hence, there is considerable uncertainty about the proportion of older Australians receiving the pneumococcal polysaccharide vaccine.

### Coverage estimates for 23vPPV — Victoria and Australia

Ross Andrews, who is currently evaluating the Victorian funded 23vPPV program, described survey methods aimed at estimating pneumococcal polysaccharide vaccine coverage. In Victoria, vaccine has been offered free of charge to all residents aged 65 years or more since 1997.<sup>6</sup> There are methodological problems in measuring pneumococcal vaccine coverage in older persons by telephone survey. A computer-assisted telephone interview validated against physician records in Victoria has estimated coverage for over 65 year olds receiving the vaccine within the past 5 years, to be between 47 and 51 per cent. Coverage increased over the 5 years 1996 to 2000. By contrast, using Pharmaceutical Benefits Scheme data the coverage in the rest of Australia was estimated to be 25 to 28 per cent, but is also a significant increase over estimates from 1996. In Victoria, preliminary data from a National Health and Medical Research Council funded hospital-based case-cohort study suggest that 23vPPV has an

effectiveness of 80 per cent when measured against an outcome of hospitalisation for pneumonia.

### Coverage estimates for 7vPCV

Peter McIntyre described the use of the ACIR to measure coverage of eligible children with the conjugate pneumococcal vaccine. ACIR data show that little vaccine was distributed outside the jurisdictions with the highest rural and remote Indigenous populations (the Northern Territory, Western Australia and Queensland) before 2002, with a progressive increase in 2002. Although the ACIR collects information on the Indigenous status of children, these data have not been available or have been poorly utilised until recently. If all doses recorded on the ACIR are assumed to have been given to Indigenous children, then of the estimated Indigenous birth cohort, over 90 per cent of the Northern Territory, 67 per cent of the Western Australian and Queensland and 44 per cent of other jurisdictions received 7vPCV in the first quarter of 2002. The availability of an Indigenous status indicator by state or territory on the ACIR will soon allow more accurate estimates. The currently available data from the ACIR, and other data presented at the meeting from the Northern Territory, Western Australia and Queensland, suggest that coverage of 7vPCV has been satisfactory in the highest risk populations.

### Surveillance of invasive pneumococcal disease — where to from here?

The first day concluded with an animated discussion on the needs of surveillance of IPD in the future. The present needs to improve the Commonwealth funded enhanced surveillance for IPD were described by Vicki Krause. These include capturing all incident cases; improving links with laboratories; collecting more complete data on Indigenous status; more broadly defining risk factors for pneumococcal disease; and measuring outcomes, including deaths, more accurately. Beyond these immediate needs, the groups discussed the sustainability of enhanced surveillance nationwide in the context of limited resources. Cynthia Whitney described the USA experience of using sentinel areas in place of nationwide surveillance and some of the limitations of this method. In most Australian states (except the Northern Territory and Western Australia and the far north of Queensland), there will be little measurable effect of the conjugate vaccine on rates of pneumococcal disease, since the majority of children in these regions are not eligible for free vaccine under the current schedule. The meeting concluded that high quality enhanced surveillance should be supported in the Northern Territory, rural Western Australia and Far North Queensland. Surveillance in

other areas should be reviewed in light of other priorities. Data from Victoria on the impact of the polysaccharide vaccine should continue to be collected to provide information relevant to the use of this vaccine in controlling pneumococcal disease in the elderly elsewhere in Australia. The costs of adding adult vaccine coverage data to the ACIR are probably prohibitive. Novel methods of increasing adult vaccine coverage, such as linking pneumococcal vaccination to annual influenza vaccinations, should be considered.

### *Day 2 – Pneumococcal vaccines and their impact*

The second day of the meeting focussed on the impact of pneumococcal vaccines on IPD. The coverage and impact of polysaccharide vaccines in the USA, and in non-Indigenous and Indigenous adults in regions of Australia, was reviewed first followed by similar data on 7vPCV.

### Pneumococcal polysaccharide vaccines

#### *Issues in the United States of America*

Cynthia Whitney reviewed data on the use of the polysaccharide vaccine in the USA, where the 23-valent vaccine has been in use since 1983. As in Australia, the vaccine is recommended for all persons aged 65 years or more and for at-risk groups aged 2 years or more. There have been concerns about an increase in pneumococcal disease following vaccination with 23vPPV in HIV-infected people with advanced disease.<sup>7,8</sup> In the USA, the 23-valent vaccine appears to protect HIV-infected people against pneumococcal disease without adverse effects, but efficacy is greatest when CD4+ cell counts are over 500. Therefore vaccination should be as early as possible after seroconversion or following immune-reconstitution with antiretroviral therapy. The question of re-vaccination of the elderly using 23-valent vaccine is being addressed. The duration of vaccine protection is difficult to measure in elderly populations who have a high prevalence of immunosuppressive disease and a high usage of medications. Currently, re-vaccination is recommended every 5 years; however, the safety of re-vaccination needs to be assessed since local reactions to the vaccine become more significant. Coverage in the USA in targeted populations is estimated to be 65 per cent and there are plans to increase this to 90 per cent in these groups. It is estimated that present levels of vaccination will reduce pneumococcal disease incidence in the elderly by 12 per cent and increasing the vaccine coverage could reduce this by as much as 25 per cent. Use of the 23-valent vaccine in the elderly is cost-effective.

### **Vaccination programs with 23vPPV in north Queensland and Victoria**

Jeffrey Hanna reviewed the impact of the 23-valent polysaccharide vaccine on IPD in Far North Queensland. Over a seven year period, the incidence of IPD in Indigenous adults (eligible for vaccination at 50 years of age) has been reduced from 110 to 28 cases per 100,000 population.<sup>9</sup> This rate is approximately the same as that seen in the non-Indigenous population. A vaccine effectiveness of 50 to 80 per cent has been estimated from these data.

Ross Andrews provided evidence of the impact of the 23-valent vaccine on IPD in Victoria. From the examination of IPD surveillance data and estimated 23vPPV coverage, it is estimated that the funded vaccine program for the elderly in Victoria has prevented 109 cases and 20 deaths since the program was started.

### **Impact of pneumococcal conjugate vaccine programs**

In this session, there were presentations on the impact of 7vPCV from the sentinel surveillance sites in the USA and from three states with significant populations of Indigenous children living in rural and remote areas of northern Australia within the tropics (the Northern Territory, North Queensland and Western Australia). All these regions have demonstrated both significantly higher incidence and serotype diversity among Indigenous children.

### **Impact of 7vPCV on invasive pneumococcal disease in the United States of America**

Cynthia Whitney presented exciting data on the impact of conjugate pneumococcal vaccines in the USA. The 7 valent conjugate vaccine was licensed for use in February 2000 and recommended for use in all children aged less than 2 years and in children aged between 2 and 4 years with risk factors for pneumococcal disease, from June 2000. In some states, vaccine is provided free of charge only to children who fulfil stringent means test requirements, while in other states, vaccine is provided free of charge to all children. Therefore vaccine coverage varies by area.

A comparison of age-specific rates of pneumococcal disease in 2001 in the USA with baseline levels in the pre-vaccine years, 1998-99, shows an overall decline of 69 per cent in the age group 0-12 months and a decline of 44 per cent in one to two-year-olds. Disease caused by vaccine serotypes has declined overall from 156 to 34 cases per 100,000 population and for vaccine serotype-related disease from 20 to 10 cases per 100,000 population. Disease caused by non-vaccine serotypes has increased from 12 to 16 cases per 100,000 population, but this change is not statistically significant. The decline in the incidence

of vaccine serotypes range from 62 per cent for serotype 6B to 83 per cent for serotypes 14 and 19F. An interesting correlation between the declining incidence in children and an unexpected decline in adults has been observed — the first evidence of a herd effect of conjugate vaccines. There has been little change in the proportion of isolates resistant to penicillin seen following the introduction of 7vPCV, but to date there is also no evidence of serotype replacement in IPD cases.

### **Impact of 7vPCV on Invasive Pneumococcal Disease in northern Australia**

#### *Northern Territory*

Christine Selvey, Director of Immunisation in the Northern Territory Centre of Disease Control, presented data on the impact of 7vPCV in the Northern Territory, adding to data presented the previous day. In the Northern Territory, 50 per cent of the annual birth cohort (all children born in Central Australia and Indigenous children in the rest of the Northern Territory) are eligible for the 7vPCV. Vaccination was implemented from 1 June 2001 (starting with those born after 1 April 2001) and the 'catch-up' program was initiated in September 2001. As at August 2002, 96 per cent of eligible children had received the first dose of vaccine at 2 months of age, 74 per cent of older children had started the 'catch-up' vaccine schedule and 64 per cent of these had completed the vaccine course. Only three mild to moderate adverse events after conjugate vaccination were recorded. A few cases of IPD in children who have received one or more doses of 7vPCV have occurred, mostly among the 'catch-up' group. It is still too early to evaluate the impact of the conjugate vaccine on IPD in the Northern Territory, given the expected small numbers of cases. In Central Australia, evaluation is complicated by the decrease in incidence of IPD among Aboriginal children aged under 2 years, from 1,500 cases per 100,000 population from 1994 to 1998, to 700 cases per 100,000 population from 1999 to 2001, prior to commencement of the 7vPCV program. No change was seen in the incidence of IPD among Aboriginal children in the Top End.

#### *Western Australia*

Carolein Giele, epidemiologist in the Communicable Disease Control Branch of the Health Department of Western Australia, presented data on the coverage of 7vPCV and incidence of IPD among Aboriginal children in Western Australia. There was good correlation between data on doses distributed and doses reported to the ACIR, with estimated coverage being high in rural and remote areas and sub-optimal in the urban area of Perth and surrounds. The small numbers of IPD cases in Aboriginal children precluded conclusions about the significance of 3 cases to date in 2002 but 2 of the 3 cases were not serotypes

included in 7vPCV. Presumptive antibiotic treatment before sample collection is likely to reduce the identification of IPD cases in the north of the state.

#### *North Queensland*

In north Queensland, the uptake of IPD vaccination in the eligible birth cohort is estimated to be 70 per cent for the first dose, 60 per cent for the second and 50 per cent for the third (within one month of the scheduled age). The number of IPD cases in Indigenous children aged less than 15 years has fallen from 15 cases in 1999 to 6 cases to the end of September 2002. None of the cases in 2002 were caused by vaccine serotypes, while the prevalence of non-vaccine serotypes has shown little change. There is some evidence that the incidence of IPD in non-Indigenous children, who are not eligible for funded vaccination, has also declined in the same period. This, together with data suggestive of a fall in incidence of IPD in Indigenous adults since the introduction of 7vPCV, may be an early indication of herd immunity from the reduction in pneumococcal colonisation among vaccine-eligible children.

#### **Impact of 7vPCV on ear disease**

##### *Northern Territory*

Amanda Leach, Senior Scientist with the Menzies School of Health Research and the Cooperative Research Centre for Aboriginal and Tropical Health in Darwin, presented background data from her team's previous research into ear disease among Aboriginal children in the Northern Territory. She also discussed research in progress to monitor the future impact of 7vPCV on ear disease in a number of areas of the Northern Territory. Rates of tympanic membrane perforation among Aboriginal people from previous published studies range from 5 to 37 per cent, with the World Health Organization nominating 4 per cent or higher as a 'massive public health problem'.<sup>10</sup> The Prevention of Otitis Media with Prevenar and Training (PROMPT) study, funded by Wyeth-Lederle vaccines, has recruited 20 communities for follow-up, with many having perforation rates among children of more than 25 per cent. The Prevenar Immunisation for Otitis Media Reductions in the Tiwi Islands (PRIORITI) is a longitudinal study in the Tiwi community, with data on pneumococcal colonisation extending back for almost 10 years. Early results suggest that pneumococcal colonisation has decreased overall, with a decrease in 7vPCV serotypes counterbalanced to some degree by an increase in other serotypes. Clinical implications are unclear, but there appears to be some decrease in tympanic membrane perforations compared with historical data. Close follow-up in both study cohorts will continue. Given the early onset of colonisation previously found in these populations, indirect impacts via decrease in colonisation in older contacts

of young infants may turn out to be as important as individual vaccine response in reducing ear disease.

##### *Sydney*

Michael Watson, Microbiologist and Infectious Disease Physician at The Children's Hospital Westmead, presented early results of a baseline comparison of serotypes seen in pneumococcal isolates from swabs from ear discharge. The predominant serotypes were very different from those seen in IPD isolates from the same population, with a predominance of 19F, as opposed to serotype 14. This has potential implications for the impact of 7vPCV in non-Indigenous populations when funded vaccination at a population level is introduced.

#### *Summary and conclusions*

In relation to surveillance, the predominant issue discussed was universal versus sentinel enhanced surveillance of IPD. In northern Australia, it will be important for enhanced surveillance to continue and to be as complete as possible. There are a number of reasons for this. First, the high incidence and high serotype diversity of IPD in Indigenous children in these areas has prompted the recommendation for boosters with 23vPPV to increase serotype coverage. This makes high quality, comprehensive surveillance essential for national policy. It is also important internationally as such a vaccine program has not been implemented anywhere else but is potentially applicable to other comparable populations. Secondly, the small absolute numbers of cases require data to be accumulated as comprehensively as possible.

In relation to vaccine issues, both 23vPPV and 7vPCV policy are important. There was strong support from the meeting for the recent recommendation from the Australian Technical Advisory Group on Immunisation that both 23vPPV (for those over 65 years) and 7vPCV (for those less than 2 years) be publicly funded as universal programs. With respect to the current programs, there were important issues for Aboriginal and Torres Strait Islander people for both 23vPPV and 7vPCV. For 23vPPV, research is required into both the utility and frequency of boosters in adults as well as any potential role for 7vPCV in adults. Improving the identification of Aboriginal and Torres Strait Islander children is important, especially in urban areas.

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## Appendix: Abstracts of presentations from states and territories on invasive pneumococcal disease surveillance in 2002

### Invasive pneumococcal disease surveillance in the Australian Capital Territory

Louise Carter, Communicable Disease Control Section, Australian Capital Territory Department of Health and Community Care

Invasive pneumococcal disease (IPD) was listed as a notifiable infection under the Australian Capital Territory *Public Health Act 1997* in September 1999. Public health legislation requires the condition to be notified to the Australian Capital Territory health department by hospitals, medical practitioners and pathology laboratories. The Australian Capital Territory has a passive system which relies on the assistance of hospital infection control practitioners to review medical records and in-patient notes for information on vaccination history and factors which may predispose people to the disease. Serotyping of isolates from the Australian Capital Territory is performed in batches and does provide some feedback on intervention activities pertaining to IPD being conducted locally.

The burden of IPD in the Australian Capital Territory is low (around 5 cases per 100,000 population per annum), however, information other than demographic details provided by the reporting laboratories are often missing and details regarding pneumococcal vaccines previously administered are rarely validated. This presentation supports a uniform national surveillance system for IPD, so that trends regarding the control of this condition and the impact of the National Childhood Pneumococcal Vaccination Program can be accurately monitored.

### Invasive pneumococcal disease New South Wales, 2002 — in the beginning

Robin Gilmour, NSW Health Department

Invasive pneumococcal disease became notifiable by all laboratories in New South Wales in 2001, and 2002 saw the commencement of enhanced surveillance for notified cases who were aged less than 5 years or 50 years or older. Surveillance of IPD in New South Wales is derived from three sources: the New South Wales Notifiable Disease Database; the New South Wales enhanced IPD surveillance database (for cases aged less than 5 years or 50 years or more); and typing and antibiotic sensitivity testing from the Children's Hospital at Westmead.

The overall incidence of IPD in New South Wales is 13.4 cases per 100,000 population for the nine-month period. From the enhanced data (n=497) children aged less than 2 years continue to have the highest rate of disease (98.5 cases per 100,000 population). Adults aged more than 65 years accounted for 68 per cent, adults aged more than 85 years have the next highest rate of disease (74.5 cases per 100,000 population). Bacteraemia is the most common infection in children and pneumonia is most common in adults. Meningitis is uncommon in both age groups (3 per cent in adults and 7 per cent in children). Underlying illness was reported in 16 per cent of children and 72 per cent in adults. There have been 3 deaths (1.6%) reported in children aged under 5 years and 73 (29.9%) deaths in adults. Only 9 cases were reported as being Aboriginal or/and Torres Strait Islander. Eighty-two per cent of isolates in the Greater Sydney Region have been serotyped for the period January to June 2002. Thirty-six possible vaccine failures were identified up to September 2002.