Laboratory Surveillance of Invasive Pneumococcal Disease in Australia, 2003 — predicting the future impact of the universal childhood conjugate vaccine program

Michael Watson,[1] Paul Roche,[2] Kathy Bayley,[5] Jan M Bell,[3] Peter Collignon,[4] Gwendolyn L Gilbert,[5] Geoff Hogg,[6] Anthony D Keil,[7] Vicki Krause,[8] Denise Murphy,[9] Helen V Smith,[9] Mitchell Brown,[1] Joanne Stylianopoulos,[6] John Turnidge[3]

Abstract

A comprehensive invasive pneumococcal disease (IPD) laboratory surveillance program was carried out in Australia in 2003. This program provided data on the prevalence of pneumococcal serotypes and antimicrobial resistance. There were 1,995 isolates tested with 34 per cent (683) from children aged less than five years and 27 per cent (535) from the elderly aged more than 65 years. One thousand eight hundred and sixty were isolates from blood, 79 from CSF and 56 from other sterile sites. In young children, 84 per cent of isolates were a serotype and 92 per cent a serogroup in the 7-valent pneumococcal conjugate vaccine (7vPCV). Of penicillin resistant isolates in children less than five years of age 85 per cent and 98 per cent were a serotype and serogroup in the 7vPCV respectively. When the universal 7vPCV vaccine program in young children is introduced in 2005, a proportion of cases of IPD should also be prevented in young adults (estimated reduction of 54 cases annually) and elderly Australians (an estimated reduction of 110 cases annually) as a result of improved herd immunity. Pneumococcal serotypes with higher rates of penicillin resistance (19F, 14 and 6B) were more prevalent in the elderly than in young children. In contrast, erythromycin resistance was more common in children less than five years of age (24%) compared to the elderly (15%). The predominant serotype with erythromycin resistance in Australia was serotype 14 and thus there is likely to be a major reduction in erythromycin resistance as a result of 7vPCV vaccination. Continued surveillance of pneumococcal serotype distribution and antibiotic susceptibility will be essential in order to identify serotype replacement by non-vaccine serotypes and to monitor the overall impact of current and future vaccine programs on invasive pneumococcal disease in Australia, not only in young children but also in other age groups. ***Commun Dis Intell*** **2004;28:455–464.**

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1. The NSW Pneumococcal Reference Laboratory, Department of Microbiology, The Children's Hospital at Westmead, Westmead, New South Wales
2. Surveillance Section, Australian Government Department of Health and Ageing, Canberra, Australian Capital Territory
3. The Department of Microbiology and Infectious Diseases, Adelaide Women's and Children's Hospital, Adelaide, South Australia
4. Infectious Diseases Unit and Microbiology Department, The Canberra Hospital, Garran, Australian Capital Territory
5. Centre for Infectious Diseases & Microbiology, Institute of Clinical Pathology and Medical Research, Westmead Hospital, Westmead, New South Wales
6. Microbiological Diagnostic Unit, Public Health Laboratory, Microbiology and Immunology Department, The University of Melbourne, Melbourne, Victoria
7. The Department of Microbiology, Women's and Children's Health Service, Western Australia.
8. Centre for Disease Control, Department of Health and Community Services, Casuarina, Northern Territory
9. Pneumococcal Reference Laboratory, Queensland Health Scientific Services, Queensland

Corresponding author: Dr Michael Watson, Clinical Microbiologist and Infectious Disease Physician, St John of God Pathology, Hollywood Hospital, Monash Avenue, Nedlands, Western Australia 6009. Telephone : +61 8 9284 8181. Facsimile: +61 8 9386 9852. Email: michael.watson@sjog.org.au

Introduction

Streptococcus pneumoniae is a major cause of morbidity and mortality worldwide.[1–4] It is a common cause of life threatening invasive disease (e.g. bactaeremia and meningitis) as well as non invasive disease (e.g. otitis media). It is important that comprehensive laboratory surveillance of invasive pneumococcal disease (IPD) is undertaken to assess the success of universal childhood 7-valent conjugate pneumococcal (7vPCV) vaccination which will be implemented in Australia in 2005. Laboratory surveillance of IPD has been conducted in various Australian states and territories prior to 2002.[5–9] This report summarises the results of laboratory surveillance for all Australian jurisdictions in 2003 and includes comprehensive pneumococcal serotyping of these isolates and antimicrobial resistance data.

Antimicrobial resistance in invasive pneumococci is an emerging problem in Australia.[10] Laboratory data on resistance to penicillin and erythromycin and the key serotypes responsible for antimicrobial resistance in each state and territory are reported. The potential benefits of the universal childhood immunisation program for adults are discussed.

Methods and Materials

Case definition

For the purposes of laboratory surveillance, a case of IPD was included when *Streptococcus pneumoniae* was isolated by culture from a normally sterile body site (blood, cerebrospinal fluid (CSF), joint fluid etc). Only one isolate was tested from each patient episode. A new episode was deemed to occur if an isolate was cultured more than 14 days after a previous positive culture.

Data sources and collection

A network of laboratories in Australia (see list of participating laboratories) obtained pneumococcal isolates referred from all major private and public microbiology laboratories in Australia. Isolates were stored for later serotyping at one of the three designated pneumococcal typing laboratories. Indigenous status data was linked to laboratory data only in the Northern Territory in 2003 and detailed analysis by Indigenous status was not performed in this year's report in contrast to the 2002 report.[11] Enhanced data on IPD including information on pneumococcal serotypes in Indigenous people are collected as an extension of the National Notifiable Diseases Surveillance System (NNDSS) and the 2003 data are provided in the accompanying surveillance report.[12]

Serotyping

Pneumococcal serotyping was performed at the Pneumococcal Reference Laboratory of Queensland Health Scientific Services (for Western Australia, Northern Territory and Queensland), the Children's Hospital at Westmead's NSW Pneumococcal Reference Laboratory (for New South Wales and the Australian Capital Territory) and the Microbiological Diagnostic Unit (for Victoria, Tasmania and South Australia). Serotyping was performed by the Quellung reaction using antisera from the Statens Seruminstitut, Copenhagen, Denmark.[13]

Analysis of serotypes included the prevalence of vaccine serotypes and vaccine serogroups (that is, pneumococci with serotypes within the same serogroups as vaccine types).[14] The pneumococcal serotypes in the three vaccines referred to in this paper are shown in Table 1.

Susceptibility testing

Susceptibility testing was performed by a range of different methods. In New South Wales, Victoria, Tasmania, Australian Capital Territory and South Australia the available results were from routine diagnostic laboratories. These laboratories used National Committee for Clinical Laboratory Standards (NCCLS) disc diffusion,[15] Calibrated Dichotomous Susceptibility (CDS) disc diffusion[16] or agar dilution susceptibility testing methods. Most laboratories also confirmed penicillin resistance using the E test method.[17] Results from Queensland, Northern Territory and Western Australia were performed using NCCLS disc diffusion and E test methods in a reference laboratory.

Isolates were categorized as fully sensitive to penicillin or resistant (includes intermediate and high level resistance using NCCLS breakpoints (Minimum Inhibitory Concentration (MIC) ≥0.125mg/L). Erythromycin was categorized as either sensitive or resistant (MIC ≥1mg/L).

Table 1. Pneumococcal vaccines and constituent serotypes referred to in this report

Vaccine	7-valent conjugate vaccine (7vPCV)	11-valent conjugate vaccine (11vPCV)	23-valent polysaccharide vaccine (23vPPV)
Pneumococcal Serotypes	4, 6B, 9V, 14, 18C, 19F, 23F	1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F

Statistical analysis

Yates corrected Chi square test was used for univariate analysis using Epi info statistical software Version 6.02 (CDC, USA).

Results

Cases under laboratory surveillance

There were 1,998 pneumococcal isolates forwarded to the three pneumococcal reference laboratories for serotyping and 1,995 were successfully serotyped. This represents 92 per cent of the 2,174 notified cases of invasive pneumococcal disease in Australia in 2003.[12] The number of isolates by state and territory and specimen type is shown in Table 2.

Figure 1. Pneumococcal isolates, Australia, 2003 by age and sex

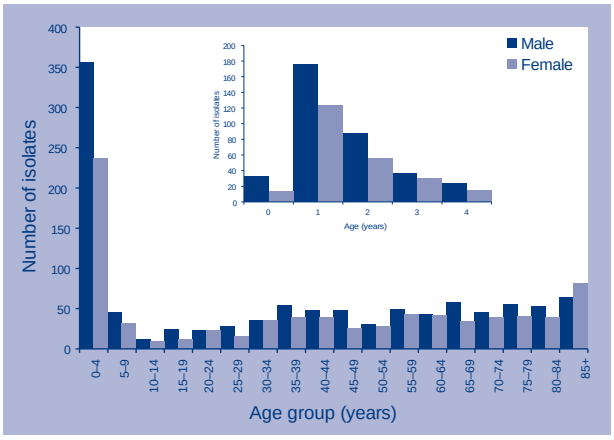


Table 2. Pneumococcal isolates analysed in this report, by reporting jurisdiction and specimen type

	Blood	Cerebrospinal fluid	Other sites*	Total
ACT	45	1	6	52
NSW	609	23	22	654
NT	66	2	1	69
Qld	412	24	5	441
SA	160	4	2	166
Tas	33	2	0	35
Vic	400	21	15	437
WA	135	2	5	142
Australia	1,860	79	56	1,995

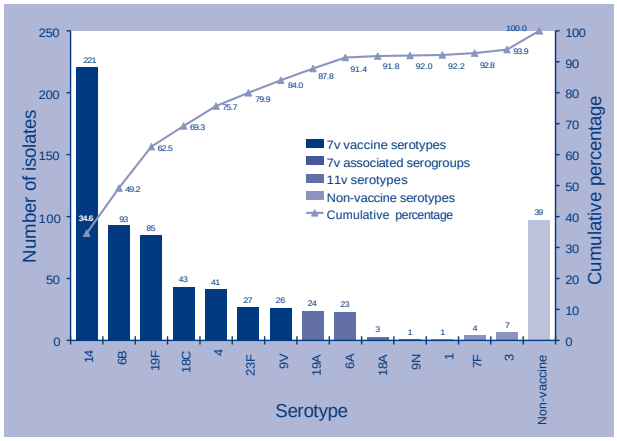
* Other sites includes joint, pleural, peritoneal and pericardial fluid.

The number of isolates by the age and sex of the patient is shown in Figure 1. There were more isolates from males than females (male to female ratio 1.3:1), which was the same sex ratio as seen in the notification data. The largest number of isolates were from children aged 1 year (Figure 1).

Serotypes responsible for invasive pneumococcal disease in Australian children less than five years of age and proportion represented in conjugate vaccines.

Six hundred and thirty-eight pneumococcal isolates from children less than five years of age were serotyped. The serotype distribution proportion of isolates from this age group represented in the 7vPCV and prototype 11vPCV conjugate pneumococcal vaccines are illustrated in Figure 2. Eighty-four percent of isolates were a serotype match for the 7vPCV vaccine and 92 per cent of isolates were a serogroup match. The future 11vPCV vaccine (addition of serotypes 1, 7F, 5 and 3) would add another 1.9 per cent of isolates belonging to vaccine serotypes.

Figure 2. Serotypes responsible for invasive pneumococcal disease in children less than five years, Australia, 2003



Pneumococcal serotypes with reduced susceptibility to penicillin and erythromycin in Australian children less than five years of age

Of the 638 isolates from children less than five years of age that were serotyped, 622 also had penicillin susceptibility results recorded. Overall, 71/622 (11%) had reduced susceptibility to penicillin. Sixty of these (85%) were serotypes and 70 (99%) were serogroups in the 7vPCV (Table 3).

Of the 638 isolates from children less than five years of age that were serotyped, 567 also had susceptibility results for erythromycin recorded. Overall, 138/567 (24%) were resistant to erythromycin. One hundred and thirty-four of the 138 erythromycin resistant isolates were a serotype match for the 7vPCV and the remaining four isolates were a serogroup match (Table 4). The majority (70%) of erythromycin resistant isolates in children less than five years of age in Australia were serotype 14.

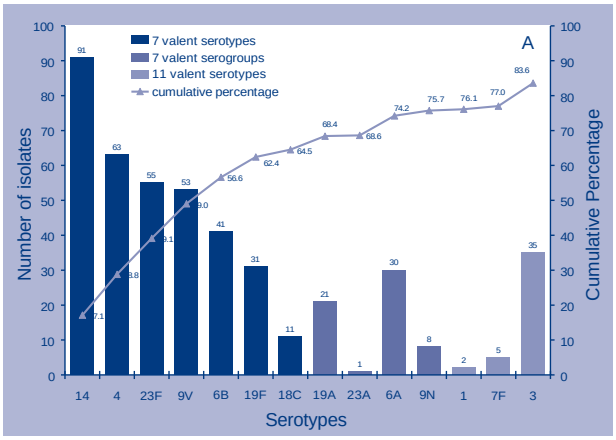
The rates of penicillin and erythromycin resistant pneumococci in children aged less than five years of age by state and territory are shown in Table 5. The overall rate of penicillin resistance and erythromycin resistance varied widely between states. There were no penicillin resistant isolates identified in the Northern Territory or Tasmania and rates ranged from five per cent in South Australia to 14 per cent in New South Wales. Erythromycin resistance was found in all states ranging from six per cent in the Northern Territory to 75 per cent in Tasmania, although the latter rate was based on only four isolates.

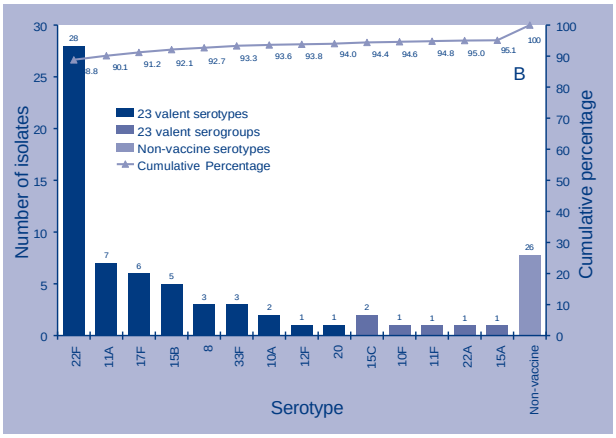
Differences in the prevalence of serotype 14—which accounted for 70 per cent of erythromycin resistance—largely reflected differences in erythromycin resistance rates between jurisdictions.

Serotypes responsible for IPD in Australian adults over 65 years of age.

Five hundred and thirty-five isolates from adults aged more than 65 years were analysed. Sixty-five percent of isolates were 7vPCV serotypes and 76 per cent 7vPCV serogroups (Figure 3, Panel A). 84 per cent of serotypes were in the 11vPCV conjugate vaccine and 94 per cent were serotypes in the 23vPPV polysaccharide vaccine (Panel B).

Figure 3. Serotypes responsible for invasive pneumococcal disease in adults aged more than 65 years, Australia, 2003. Panel A serotypes in 7- and 11vPCV vaccines; Panel B Serotypes in the 23vPPV vaccine





The likely impact (via herd immunity) on incidence of IPD in the adult population over 65 years of age following the introduction of the universal childhood immunisation program with the 7vPCV vaccine in Australia was assessed based on the reductions seen in the USA.[14] Based on the serotype distribution in the elderly in 2003 it was estimated that 110 cases of IPD would be prevented in adults over 65 years of age as a result of herd immunity associated with universal 7vPCV vaccination in Australian children (Table 6).

Further, based on the serotype prevalence in the 20 to 39 year age group (n=263), approximately 54 cases in this age group should be prevented by the 7vPCV vaccination of Australian children (data not shown).

Table 3. Serotypes of isolates with reduced susceptibility to penicillin in children aged less than five years, Australia, 2003 (N = 71)

Serotype	19F*	9V*	14*	6B*	23F*	19A†	6A†	33F‡	Total
Number of isolates	19	16	16	8	1	6	4	1	71/622
Cumulative %	27%	49%	72%	83%	85%	93%	99%	100%	11%

* 7vPCV conjugate vaccine serotype.

† 7vPCV conjugate vaccine serogroup.

‡ 23vPPV polysaccharide vaccine serogroup.

Table 4. Serotypes with reduced susceptibility to erythromycin in children aged less than five years, Australia, 2003 (n=138)

Serotype	14*	19F*	6B*	18C*	23F*	4*	19A†	6A†	Total
Number of isolates	97	17	16	1	2	1	1	3	138/567
Cumulative %	70%	83%	94%	95%	96%	97%	98%	100%	24%

* 7vPCV conjugate vaccine serotype.

† 7vPCV conjugate vaccine serogroup.

‡ 23vPPV polysaccharide vaccine serogroup.

Table 5. Penicillin and erythromycin resistance in children aged less than five years, Australia, 2003, by state and territory

State	ACT	NSW	NT	Qld	SA	Tas	Vic	WA	Australia
Penicillin									
Proportion of isolates tested	11/11	211/212	18/19	159/160	65/66	5/5	116/128	37/37	622/638
Number (%) Penicillin reduced susceptibility	1 (9%)	30 (14%)	0 (0%)	22 (14%)	3 (5%)	0 (0%)	12 (10%)	3 (8%)	71 (11%)
Erythromycin									
Proportion of isolates tested	11/11	201/212	18/19	158/160	63/66	4/5	75/128	37/37	567/638
Number (%) Erythromycin resistant	3 (27%)	57 (28%)	1 (6%)	49 (31%)	15 (24%)	3 (75%)	5 (7%)	5 (14%)	138 (24%)

Table 6. Predicted number of cases of invasive pneumococcal disease in adults aged more than 65 years that could be prevented as a result of introduction of 7vPCV vaccine in children in Australia

Serotype	Number of isolates	Per cent change post vaccine*	Number of cases prevented
14	91	-36%	33
4	63	-26%	16
23F	55	-31%	17
9V	53	-36%	19
6B	41	-16%	7
19F	31	-4%	1
18C	11	-31%	3
19A	21	-22%	5
23A	1	-22%	<1
6A	30	-22%	7
9N	8	-22%	2
Overall	535	-20%	110

* Based on data from Reference 14.

Differences in penicillin and erythromycin resistance rates by age and serotype

The proportion of penicillin resistant pneumococci in Australians over 65 years of age was significantly higher (17%) than the proportion in children less than five years of age (11% Table 7).

The converse was true for erythromycin resistance with a significantly higher proportion of resistant isolates (24%) in children less than five years of age compared to adults over 65 years of age (15%, Table 8). This difference was contributed to by the larger proportion of erythromycin-resistant serotype 14 isolates in children.

Differences in serotype distribution and penicillin resistance of CSF isolates in patients less than five years of age compared those over five years of age

Pneumococcal isolates from the CSF of patients over five years of age were more likely to be resistant to penicillin than those from patients less than five years of age, but this difference did not reach statistical significance. Serotypes 6B and 14 accounted for a significantly higher proportion of pneumococcal isolates from the CSF of patients under five years of age than those over five years of age. Serotype 19F was more common in patient aged five years or more but the difference in proportion was not significant (Table 9).

Discussion

The impact of a universal 7vPCV program for young children on invasive pneumococcal disease has now been clearly demonstrated in the United States of America (USA).[14] The vaccine program has benefited not only young children but it has also benefited their parent's age group (20 to 39 years) and the elderly in whom the rates of IPD have also decreased. Recently the National Health and Medical Research Council has recommended 7vPCV for all children in Australia as part of their primary immunisation series[18] and the Australian government has undertaken to fund this initiative from January 2005. Reliable baseline data on serotype prevalence in Australian children is essential to measure the impact of this new vaccine program. This study has examined serotype distribution and antimicrobial resistance in more than 90 per cent of the notified cases of IPD in Australia in 2003. These data allow us to predict the likely benefits which will be seen as a result of this new vaccine initiative.

A large proportion of young Australian children with IPD in 2003 were infected with pneumococcal serotypes (84%) or serogroups (92%) in the 7vPCV vaccine. While still not conclusive, some cross-protection for serogroups contained in the vaccine have been reported.[14] It is therefore reasonable to predict that Australia will see a significant decline in IPD in young children in the coming years when the new 7vPCV vaccination program is fully implemented. This could be of the order seen in the USA, where IPD declined by 69 per cent in the under 2-year olds in the first two years of a universal childhood vaccination program in this age group.[14]

The serotype distribution of penicillin resistant pneumococcal strains in young Australian children showed that 85 per cent of penicillin resistant isolates were a serotype and 99 per cent were a serogroup in 7vPCV. There is evidence from the USA that the rate of IPD due to penicillin resistant strains can be expected to fall by as much as 35 per cent with introduction of the 7vPCV.[14]

There are significant regional differences in penicillin and erythromycin resistance in Australia. Victoria in particular appears to have relatively low rates of erythromycin resistance and a low prevalence of serotype 14 which is frequently erythromycin resistant. A recent study by the NSW Pneumococcal Reference Laboratory has identified the predominant penicillin susceptible, erythromycin resistant clone of serotype 14 in NSW to be multi-locus sequence type (MLST) 9 (M. Watson, unpublished observations). The molecular mechanism of resistance to erythromycin in these MLST9 strains in New South Wales appears to be due to the macrolide efflux gene (*mef*) which does not confer cross resistance to the lincosamides such as clindamycin (M. Watson, unpublished observations). Serotype 14 erythromycin resistant isolates accounts for over 70 per cent of macrolide resistant isolates in children in Australia. By contrast the Northern Territory has a very low prevalence of macrolide resistance in children probably due to the virtual absence of serotype 14 following the introduction of the 7vPCV vaccination program in 2001 for all indigenous children in the NT and non-Indigenous children in Central Australia. Variations in rates of antibiotic prescribing and consumption would also explain variation in the prevalence of antimicrobial resistance across Australia and between age groups.

In the first two years of the childhood 7vPCV vaccine program in the United States there were declines in IPD disease rates in adults (32% in the 20 to 39 year age group and 18% in the aged 65 years or older).[14] Extrapolating the reductions in the prevalence of 7vPCV vaccine serotypes seen in the elderly population in the USA,[14] we predict that 110 (20%) episodes of IPD in adults over 65 years of age and 54 (20%) cases in the 20–39 year age group in Australia could be prevented as a result of the paediatric immunisation program. These calculations, based as they are on incomplete data, may under-estimate the eventual impact of universal 7vPCV vaccination

Table 7. Proportions of penicillin resistant pneumococcal isolates by age group and serotype, Australia, 2003

Serotype	Children aged less than five years		Adults aged over 65 years		Significance of difference
	Proportion	Percentage	Proportion	Percentage	
Total isolates tested	622/638	97	514/535	96	NS
Resistant serotypes	71/622	11	85/514	17	p<0.05
7v vaccine serotypes*	60/71	84	76/85	89	NS
Serotype 19F	19/85	22	15/31	48	p<0.05
Serotype 14	16/221	7	18/91	19	p<0.005
Serotype 6B	8/93	9	8/41	19	NS
Serotype 9V	16/26	61	31/53	58	NS
Serotype 23F	1/27	4	3/55	5	NS

* includes serotypes in the 7vPCV conjugate vaccine (14, 19F, 14, 6B, 23F, 18C, 4).

NS = not significant.

Table 8. Proportion of erythromycin resistant pneumococcal isolates by age group and serotype, Australia, 2003

Serotype	Children aged less than five years		Adults aged over 65 years		Significance of difference
	Proportion	Percentage	Proportion	Percentage	
Total isolates tested	567/638	89	474/535	89	NS
Resistant serotypes	138/567	24	69/474	15	p<0.001
7v vaccine serotypes*	135/138	98	58/69	84	p<0.001
Serotype 19F	17/85	20	11/31	35	NS
Serotype 14	97/221	44	28/91	31	p<0.05
Serotype 6B	16/93	17	6/41	15	NS
Serotype 9V	0/26	0	1/53	2	NS
Serotype 23F	2/27	7	7/55	13	NS

* includes serotypes in the 7vPCV conjugate vaccine (14, 19F, 14, 6B, 23F, 18C, 4).

NS = not significant.

Table 9. Proportions of penicillin resistant isolates and common serotypes isolated from cerebrospinal fluid, by age group, Australia, 2003

Serotype in CSF	Cases aged less than 5 years (n=34)		Cases aged 5 years and above (n=45)		Significance of difference
	Proportion	Percentage	Proportion	Percentage	
Penicillin resistant isolates	3/32	9	11/41	27	NS
Serotype 19F	1/34	3	9/45	20	NS
Serotype 6B	9/34	26	2/45	4	p<0.05
Serotype 14	11/34	32	3/45	6	p<0.01
Serotype 9V	2/34	6	5/45	11	NS

There may also be additional benefits of 7vPCV vaccination by reductions in the prevalence of antibiotic resistant isolates in the elderly through improved herd immunity. However the prevalence of resistance varies significantly between children and adults. This appears to be associated with variations in the prevalence of penicillin and erythromycin resistant clones rather than existence of genetically distinct molecular clones in the two populations (M. Watson unpublished observations). The relatively higher prevalence of penicillin resistant serotypes in the elderly suggests that a reservoir of penicillin resistance exists in the elderly population in Australia with significant selective pressure towards acquisition of penicillin resistant strains of serotype 19F, 14 and 6B occurring in this age group. It is likely

that immunising children with the 7vPCV will reduce the incidence of penicillin resistant serotypes in the elderly since children would be less likely to pass on this serotype to their 'grandparents'. Reductions in IPD caused by serotype 19F and 6B have not been clearly demonstrated in the USA at this time, however a reduction of serotype 14 IPD in the elderly has been observed.[14] In 2003, serotype 19F in the elderly was a cause of meningitis in the older age group and three of the four penicillin resistant serotypes isolated in CSF from people over 65 years of age in Australia. The 23vPPV polysaccharide pneumococcal vaccine continues to provide good serotype coverage for adults, which supports the recent government decision to fully fund this vaccine for those at risk in Australia.

The continued laboratory surveillance of IPD is a vital component of the pneumococcal vaccine strategy for Australia. The funding of this surveillance has assisted a national approach to surveillance and reporting of this important reference laboratory work. Committed funding for serotype and uniform antibiotic susceptibility testing would assure appropriate monitoring of the impact of the new universal childhood 7vPCV program. Our surveillance to date suggests that introduction of the 7vPCV for all children and the 23vPPV vaccine for the 65 years and over in Australia in 2005 is likely to lead to major benefits for both children and the elderly.

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List of Contributors to Pneumococcal Laboratory Surveillance

ACT

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