Invasive pneumococcal disease in non-Indigenous people in north Queensland, 2001–2009

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ABSTRACT

Objective: To compare trends in invasive pneumococcal disease (IPD) in non-Indigenous people in north Queensland before and after the introduction of funded pneumococcal vaccines, and to examine the proportion of cases that occurred after vaccine roll-out that could be vaccine-preventable.

Design, setting and participants: In 2005, a 7-valent pneumococcal conjugate vaccine (7vPCV) for non-Indigenous children and a 23-valent pneumococcal polysaccharide vaccine (23vPPV) for non-Indigenous adults aged ⩾ 65 years were made freely available. Trends in IPD in the non-Indigenous estimated resident population in north Queensland (about 581 850 in 2006) were compared between the 4 years before (2001–2004) and after (2006–2009) the vaccines were rolled out.

Main outcome measures: Incidences and serotypes of IPD in non-Indigenous people.

Results: After the introduction of the vaccines, there were significant declines for all ages in the average annual incidence of IPD (–34%; $P < 0.05$) and 7vPCV serotype IPD (–77%; $P < 0.05$). In children aged < 5 years, there was a 91% decline in the incidence of 7vPCV serotype IPD ($P < 0.05$); in adults aged 15–64 years and ⩾ 65 years there were 62% and 77% declines, respectively, in 7vPCV and 23vPPV common-serotype IPD ($P < 0.05$). There was a 188% increase in 23vPPV-only serotype IPD in adults aged 15–64 years ($P < 0.05$), whereas there was no significant change in adults aged ⩾ 65 years. Serotype 19A was the most frequently identified serotype in 2006–2009, causing 19% of all IPD in those 4 years.

Conclusions: There is circumstantial evidence that 7vPCV has had a powerful indirect effect in preventing IPD in adults in north Queensland; 23vPPV may have had a direct effect in adults aged ⩾ 65 years. It is likely that with combined direct and indirect effects, newer conjugate vaccines could prevent more IPD than could be prevented with the two current vaccines.

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Although pneumococcal vaccines had been available for Indigenous people for several years beforehand, they became freely available for non-Indigenous Australian people in 2005. From the beginning of 2005, the 7-valent pneumococcal conjugate vaccine (7vPCV) became available for non-Indigenous children in a three-dose (at 2, 4 and 6 months of age) primary vaccination schedule, with catch-up vaccination (with fewer doses, depending on age) up to the child's second birthday.[1] 7vPCV was already funded for children with certain underlying medical conditions up to 59 months of age, with a "booster" dose of the 23-valent pneumococcal polysaccharide vaccine (23vPPV) at 4–5 years of age.[1]

At the same time, 23vPPV was made freely available for all non-Indigenous adults ⩾ 65 years of age. Although 23vPPV was also recommended for those aged < 65 years with certain underlying diseases and conditions (including tobacco smoking),[1] 23vPPV is not funded for these "at-risk" non-Indigenous people (unless they are < 5 years of age).

It is now well recognised that 7vPCV has the potential to protect unvaccinated individuals from the serotypes included in the vaccine via herd, or indirect, effects.[2] However, the vaccine may also allow the emergence of invasive pneumococcal disease (IPD) caused by non-7vPCV serotypes — so-called replacement disease.[2]

Our objectives were to examine trends in the epidemiology of IPD in non-Indigenous people in north Queensland between the 4 years before the vaccines were made freely available (2001–2004) and the 4 years (2006–2009) after the transitional introductory year (2005), and to examine the proportion of cases that occurred in 2006–2009 that could be vaccine-preventable, considering current and forthcoming vaccines.

METHODS

IPD is defined by the isolation of *Streptococcus pneumoniae* from a usually sterile body site. It is a notifiable disease in Queensland, and diagnostic laboratories are required to notify local public health units of each case. Data on all cases are collected using a standardised questionnaire that records demographic and clinical features, and this information is linked with the pneumococcal vaccination status of each patient and with the infecting pneumococcus serotype.

For IPD in children, the seven serotypes that are included in 7vPCV were defined as "7vPCV serotypes" and the remainder as "non-7vPCV serotypes". In adults, the seven serotypes common to both vaccines were defined as "7vPCV and 23vPPV common-serotypes", the other 16 serotypes included in 23vPPV as "23vPPV-only serotypes", and the remainder as "non-vaccine serotypes". All invasive serotype 6A pneumococci isolated before mid 2009 were re-examined to determine if any should be reclassified as the more recently recognised serotype 6C; from mid 2009, all serogroup 6 IPD isolates were routinely examined for serotype 6C.[3]

Average annual IPD incidence rates during the two 4-year periods were calculated using the 2006 experimental estimated resident populations (ERPs) derived by the Queensland Treasury's Office of Economic and Statistical Research. These ERPs, based on 2006 national census data,[4] have been specifically developed to define Queensland health service district populations. The non-Indigenous ERP in north Queensland in 2006 was about 581 850. Confidence intervals for the incidences were calculated from tabulated 95% significance factors.[5]

Ethics approval was not necessary for this study, as surveillance and notification of IPD are required by law.

RESULTS

There were 216 cases of IPD in non-Indigenous people in north Queensland in 2001–2004, and 142 in 2006–2009. For all ages, the average annual IPD incidence declined significantly after the introduction of the vaccines ($P < 0.05$), as did the incidence of 7vPCV serotype IPD ($P < 0.05$) (Box 1).

Children aged < 5 years

In children aged < 5 years, there were 66% and 91% declines in the incidences of all IPD and 7vPCV serotype IPD, respectively ($P < 0.05$) (Box 1). In 2006–2009, children aged < 5 years accounted for 17% of all IPD cases, compared with 32% in 2001–2004. 7vPCV serotypes accounted for 21% of all IPD cases in these children in 2006–2009, compared with 83% in 2001–2004 (Box 2). Of the five young children with 7vPCV serotype IPD in 2006–2009, two were very young and had only just received a first dose of vaccine, an older child had not received the recommended third dose, one child was just too old to be eligible for the vaccine, and the remaining child represented a (serotype 6B) three-dose primary schedule vaccine failure.

Children aged 5–14 years

There were eight cases of IPD in children aged 5–14 years in 2001–2004, and only four in 2006–2009. Three of these 12 children had leukaemia; none had received any pneumococcal vaccination. Four of the cases in 2001–2004 and two in 2006–2009 were caused by 7vPCV serotype pneumococci.

Adults aged 15–64 years

There were no appreciable changes in the incidences of all IPD or 23vPPV serotype IPD in adults aged 15–64 years over the two 4-year periods (Box 1). However, there was a 62% decrease in 7vPCV and 23vPPV common-serotype IPD ($P < 0.05$), but this was countered by a 188% increase in 23vPPV-only serotype IPD ($P < 0.05$); the latter serotypes accounted for 62% of all IPD in this age group in 2006–2009 compared with 21% in 2001–2004 (Box 3). Although there was a decline in almost every 7vPCV serotype, increases in 23vPPV-only serotypes 19A, 22F, 1 and 3 were particularly evident, collectively accounting for 71% of the 23vPPV-only serotype IPD in adults aged 15–64 years in 2006–2009.

Of the 68 adults aged 15–64 years with IPD in 2006–2009 caused by any of the 23 serotypes included in 23vPPV, 10 did not have any apparent risk factor (ie, an underlying disease or condition) for IPD. Of the remaining 58, 27 had a single risk factor, 18 had two, eight had three and five had four risk factors. Tobacco smoking (present in 37) was the most frequent risk factor in this age group; 13 smokers had at least one other risk factor. Other predominant risk factors included alcohol misuse (15), chronic respiratory disease (9), cardiac disease (8) and diabetes (6); three people were asplenic. Only three of the 58 at-risk adults were known to have been appropriately vaccinated with 23vPPV, and 51 had never been vaccinated.

Adults aged ⩾ 65 years

The incidence of all IPD in adults aged ⩾ 65 years did not change significantly between the two 4-year periods (Box 1). However, there was a 54% decrease in 23vPPV serotype IPD in 2006–2009 ($P < 0.05$), which was a consequence of a significant 77% decline in 7vPCV and 23vPPV common-serotype IPD ($P < 0.05$), as there was no

1 Changes in incidence of invasive pneumococcal disease in non-Indigenous people in north Queensland, by age group and serotype, 2001–2004 v 2006–2009

	Incidence (95% CI) per 100 000 population			
Age group, serotype	2001–2004	2006–2009	Percentage change	*P*
All ages				
All serotypes	9.3 (8.1–10.6)	6.1 (5.1–7.2)	–34%	< 0.05
7vPCV serotypes	6.1 (5.2–7.2)	1.4 (1.0–2.0)	–77%	< 0.05
< 5 years				
All serotypes	46.3 (36.2–58.6)	15.9 (10.1–23.6)	–66%	< 0.05
7vPCV serotypes	38.3 (29.2–49.6)	3.3 (1.1–7.7)	–91%	< 0.05
5–14 years				
All serotypes	2.5 (1.1–4.9)	1.2 (0.3–3.2)	–50%	ns
7vPCV serotypes	1.2 (0.3–3.2)	0.6 (0.1–2.2)	–50%	ns
15–64 years				
All serotypes	5.0 (4.0–6.3)	4.9 (3.9–6.1)	–2.6%	ns
23vPPV serotypes	4.2 (3.2–5.3)	4.2 (3.3–5.4)	+1%	ns
7vPCV and 23vPPV common-serotypes	3.1 (2.3–4.1)	1.2 (0.7–1.8)	–62%	< 0.05
23vPPV-only serotypes	1.1 (0.6–1.7)	3.0 (2.3–4.0)	+188%	< 0.05
⩾ 65 years				
All serotypes	23.0 (17.4–29.8)	14.1 (9.8–19.6)	–39%	ns
23vPPV serotypes	19.4 (14.2–25.7)	8.9 (5.5–13.4)	–54%	< 0.05
7vPCV and 23vPPV common-serotypes	12.5 (8.5–17.8)	2.8 (1.1–5.8)	–77%	< 0.05
23vPPV-only serotypes	6.9 (4.0–11.0)	6.0 (3.4–10.0)	–12%	ns

7vPCV = 7-valent pneumococcal conjugate vaccine. 23vPPV = 23-valent pneumococcal polysaccharide vaccine. ns = not significant ($P > 0.05$). ◆

2 Distribution of invasive pneumococcal serotypes isolated from non-Indigenous children aged < 5 years in north Queensland, 2001–2004 and 2006–2009

Serotype	2001–2004	2006–2009
7vPCV serotypes		
4	3	0
6B	8	1
9V	4	0
14	29	0
18C	8	2
19F	4	2
23F	2	0
Total	*58*	*5*
Non-7vPCV serotypes		
3	0	1
6A	5	1
8	0	1
15C	0	1
16F	0	1
19A	4	8
22F	1	1
38	0	3
Total	*10*	*17*
Unknown serotype	2	2
Total	70	24

7vPCV = 7-valent pneumococcal conjugate vaccine. 23vPPV = 23-valent pneumococcal polysaccharide vaccine. ◆

significant change in 23vPPV-only serotype IPD ($P > 0.05$). 7vPCV and 23vPPV common-serotypes accounted for 20% of all IPD in this age group in 2006–2009 compared with 54% in 2001–2004 (Box 3). Declines in serotypes 14 and 4 were particularly evident.

Of the 22 adults aged ⩾ 65 years with IPD caused by any of the 23vPPV serotypes in 2006–2009, 19 had at least one risk factor for the disease. The most prevalent underlying diseases were cardiac (9) and chronic respiratory (6) diseases and malignancy (6). Eight of the 22 were appropriately vaccinated (and therefore represented vaccine failures), two had been offered but refused 23vPPV, and one had not been revaccinated; 11 had never been vaccinated.

Frequency of serotypes

Thirteen (3.6%) of the 358 total isolates were not available for serotyping; 10 in 2001–2004 and three in 2006–2009. The 139 serotyped isolates that occurred in all ages in 2006–2009 belonged to 30 different serotypes. The most frequently identified serotype was 19A, causing 27 (19%) of the episodes. The 11 most frequently occurring isolates in 2006–2009 caused 94 (68%) of the episodes of IPD (Box 4).

DISCUSSION

Australia's funding of two large population-based pneumococcal vaccination programs simultaneously allows an assessment of the concurrent impacts of the two vaccines. The marked decline (34%) in overall IPD incidence in 2006–2009 can be attributed to pneumococcal vaccination, as it occurred so soon after the introduction of the vaccines.

Particularly impressive was the 77% decline, across all ages, of IPD caused by 7vPCV serotypes. The decline in children was clearly a direct effect of 7vPCV, whereas that in adults was probably an indirect effect of 7vPCV in young children rather than a direct effect of 23vPPV in adults. The latter conclusion is based on the absence of any decline in 23vPPV-only serotype IPD in adults and on the apparently low uptake of 23vPPV in at-risk adults.

This powerful indirect effect of 7vPCV has been documented elsewhere.[2,6] Although two young infants developed 7vPCV serotype IPD in 2006–2009, it is likely that many more cases in infants too young to have been fully vaccinated were also prevented via this indirect effect.[6,7]

Many countries recommend a fourth (booster) dose of 7vPCV in the second year of life.[2] As a three-dose primary vaccination schedule is used in Australia, it is reassuring that there was only one (serotype 6B) vaccine failure. Serotype 6B appears to be the most frequently identified serotype in children who represented vaccine failures in the United States.[8]

The lack of any discernible decline in 23vPPV-only serotype IPD in adults might suggest that the 23vPPV has not had any direct effect. However, although there was virtually no change in 23vPPV-only serotype IPD in adults ⩾ 65 years of age, there was a marked increase in adults aged 15–64 years, for whom the vaccine is not freely available. Therefore it is plausible that 23vPPV has had a direct effect in adults aged ⩾ 65 years, and without the vaccine this group may also have seen a marked increase in 23vPPV-only serotype IPD.

A marked increase in 23vPPV-only serotype IPD in adults has also been seen elsewhere, but has been documented in both adult age groups in the US.[2,7] The most plausible explanation for our observations in north Queensland is increased nasopharyngeal carriage of these serotypes in children given 7vPCV, and increased exposure of adult contacts via these children. The many at-risk adults aged 15–64 years who have not been vaccinated with 23vPPV are susceptible to disease from these serotypes, whereas the vaccine has presumably provided some degree of protection to older adults.

The increase in replacement serotype 19A IPD (now the most common across all age groups) is striking. Although this serotype has emerged markedly elsewhere following the introduction of 7vPCV,[2,6] it has not yet shown any apparent increase in IPD in Indigenous people in north

3 Distribution of invasive pneumococcal serotypes isolated from non-Indigenous adults in north Queensland, 2001–2004 and 2006–2009, by age group

	Age 15–64 years		Age ⩾ 65 years	
Serotype	2001–2004	2006–2009	2001–2004	2006–2009
7vPCV and 23vPPV common-serotypes				
4	13	4	8	1
6B	3	2	2	0
9V	6	4	3	2
14	16	2	15	2
18C	5	1	1	1
19F	2	2	0	0
23F	5	4	2	1
Total	*50*	*19*	*31*	*7*
23vPPV-only serotypes				
1	3	7	0	0
3	4	7	6	3
7F	2	4	1	1
8	2	2	0	1
9N	2	3	1	0
10A	0	2	1	1
11A	1	1	0	2
15B	1	0	1	0
17F	0	0	1	0
19A	0	13	2	5
22F	2	8	3	2
33F	0	2	1	0
Total	*17*	*49*	*17*	*15*
Non-vaccine serotypes				
6A	2	1	1	3
6C	0	2	0	1
7C	0	0	0	1
10F	1	0	1	0
16F	1	1	1	1
18A	0	0	1	0
18B	3	1	0	0
22A	1	0	0	1
23A	0	2	1	1
25	1	0	0	0
31	0	0	0	1
34	1	1	0	2
35B	0	0	1	2
38	0	2	0	0
Total	*10*	*10*	*6*	*13*
Unknown serotype	4	1	3	0
Total	81	79	57	35

7vPCV = 7-valent pneumococcal conjugate vaccine.
23vPPV = 23-valent pneumococcal polysaccharide vaccine. ◆

4 The 11 most frequent invasive pneumococcal serotypes isolated from non-Indigenous people of all ages in north Queensland, 2006–2009

Serotype	No. of isolates in 2006–2009	Change from 2001–2004
19A	27	+ 21
3	11	+ 1
22F	11	+ 5
1	8	+ 4
9V	6	–8
23F	6	–3
4	5	–20
6A	5	–3
7F	5	+ 2
14	5	–54
38	5	+ 5

Queensland.[9] Molecular studies of serotype 19A isolates indicate that the emergence of this serotype in children in the US was a consequence not only of a pre-existing 19A clone becoming more prevalent following the introduction of 7vPCV, but also of the emergence of new 19A clones.[10] These new clones have apparently emerged through capsular switching, whereby a non-19A clone acquired the genes expressing the 19A capsule.[10] It has been suggested that switching a 7vPCV to a non-7vPCV capsule has enabled some pneumococci to "evade the immune pressures evoked by the vaccine".[11] If this is correct, serotype 19A could become even more dominant in north Queensland, and might eventually gain dominance in Indigenous people in the region.

The coverage of the pneumococcal vaccines in the age groups for whom they are freely provided is not yet known in north Queensland. However, as the coverage of three doses of 7vPCV was 91% by 12 months of age for all children in Queensland in 2007,[12] it can be assumed that uptake of three doses in these infants is probably greater than 90%. Our observations of vaccine failure and lack of vaccination in adults aged ⩾ 65 with 23vPPV serotype IPD suggest that coverage is not yet optimal and the vaccine has lesser effectiveness in this group, many of whom have significant comorbidities. A recent systematic review acknowledged there was still uncertainty about the effectiveness of the vaccine in adults with chronic illnesses.[13] There is also considerable uncertainty about the duration of protection afforded by the vaccine,[14] which creates uncertainty about revaccination policies. However, given that 23vPPV may have provided a direct protective effect, further efforts to improve vaccine uptake in adults aged ⩾ 65 years is warranted.

The marked increase in 23vPPV-only serotypes in adults aged 15–64 years with IPD is of concern. The uptake of (unfunded) 23vPPV in this age group appears to be very low, even though 85% of those with 23vPPV serotype IPD had an underlying disease or condition for which the vaccine is recommended.[1] The most common risk factor was tobacco smoking, which leads to adverse structural and immunological changes within the respiratory tract and also increases the adherence of pneumococci to epithelial surfaces.[15] Given that the vaccine is likely to be more effective in many non-Indigenous adults aged 15–64 years (eg, smokers with no other risk conditions) than in older adults, this raises the question of whether 23vPPV should be funded for people in this age group with underlying diseases or conditions. One option could be to lower the age for funded 23vPPV from ⩾ 65 to ⩾ 50 years of age. However, of the adults aged 15–64 years with 23vPPV serotype IPD in 2006–2009, only 44% were aged 50–64 years (data not shown). Cost–benefit studies that take into account the changing profile of IPD in adults aged 15–64 years should be considered.

Most of the serotyped isolates in 2006–2009 were 23vPPV serotypes. Because there is no recognised indirect protective effect from 23vPPV,[14] very high coverage with 23vPPV will be required if further substantial reductions in IPD are to be achieved. However, because 23vPPV is not funded for at-risk adults aged 15–64 years, and the vaccine uptake in adults aged ⩾ 65 years seems suboptimal despite free availability, it seems unlikely that high coverage will be readily achieved.

The significant declines in incidence of 7vPCV and 23vPPV common-serotype IPD in both adult age groups are indicative of the powerful impact of the 7vPCV indirect protective effect. It has been estimated that in the US twice as many cases of IPD have been prevented by indirect than by direct 7vPCV effects.[2,6] Capitalising on these indirect effects will be essential to gain further reductions in incidence. As more birth cohorts of children receive 7vPCV, the indirect effects may continue to increase. However, only 33 (23%) of the IPD cases that occurred in non-Indigenous people of all ages in 2006–2009 were 7vPCV serotypes, indicating that there will be limitations on how much more can be expected from this vaccine in the future.

A 10vPCV (containing the 7vPCV serotypes and serotypes 1, 5 and 7F) is now available in Australia and has been used in the Northern Territory childhood vaccination schedule since October 2009.[16] This vaccine would have the potential to prevent, via both direct and indirect effects, more IPD than 7vPCV, as 46 (32%) of the IPD cases that occurred in all ages in 2006–2009 were serotypes included in this vaccine.

A 13vPCV (containing the 10vPCV serotypes and serotypes 3, 6A and 19A) has recently replaced 7vPCV in the childhood immunisation programs in the United Kingdom[17] and the US.[18] This vaccine would have the potential to prevent, via both direct and indirect effects, up to 64% of the IPD that occurred in non-Indigenous people in north Queensland in 2006–2009. Serotypes 19A and 3 account for most (88%) of the extra potential benefit of 13vPCV over 10vPCV in preventing IPD in the region.

Continued surveillance will be essential to monitor further trends in IPD in north Queensland and elsewhere. For example, serotype 22F, which is not included in any conjugate vaccine, has emerged as a dominant serotype in adults, both Indigenous[9] and non-Indigenous, in the region. This serotype, or other non-vaccine serotypes, could exploit opportunities for serotype replacement should either 10vPCV or 13vPCV be introduced to replace 7vPCV in the childhood vaccination schedule in Queensland.

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COMPETING INTERESTS

Jeffrey Hanna has been a member of Wyeth and GlaxoSmithKline (GSK) pneumococcal advisory boards, and he has received travel grants from the Australian distributors of pneumococcal vaccines (Wyeth, CSL Biotherapies and GSK). Jan Humphreys received a travel grant from Novartis to attend a vaccine forum in 2007.

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