Invasive pneumococcal disease in Indigenous people in north Queensland: an update, 2005–2007

Jeffrey N Hanna, Jan L Humphreys and Denise M Murphy

ABSTRACT

Objective: To examine trends in invasive pneumococcal disease (IPD) in Indigenous people in north Queensland following the introduction of the 7-valent pneumococcal conjugate vaccine (7vPCV).

Design: Trends in IPD were compared over three 3-year periods: before the introduction of 7vPCV for Indigenous children (1999–2001), and two consecutive periods after its introduction (2002–2004 and 2005–2007).

Main outcome measures: Incidences of IPD in Indigenous children and adults in 1999–2001 and 2005–2007; trends in IPD caused by 7vPCV and non-7vPCV serotypes; and trends in indirect protective effects and emergence of non-7vPCV serotype IPD.

Results: From 1999–2001 to 2005–2007, there was a 60% decline in IPD, with the virtual elimination of 7vPCV serotype IPD in young (< 5 years) Indigenous children. There is no evidence yet of an increase in non-7vPCV serotype IPD in these children. Although the annual incidence of IPD in Indigenous adults remained virtually unchanged, there was a 75% decline in 7vPCV serotype IPD in these adults ($\chi^2_{trend} = 11.65$, $P < 0.001$). However, the incidence of IPD caused by non-7vPCV serotypes more than tripled in adults ($\chi^2_{trend} = 7.58$, $P = 0.006$). Serotype 1 IPD has been prominent over the 9 years, but there is no evidence of a recent increase in serotype 19A IPD.

Conclusions: Vaccinating Indigenous children with 7vPCV has protected Indigenous adults in north Queensland through an indirect "herd immunity" effect. However, this benefit has been offset by a recent increase in non-7vPCV IPD in Indigenous adults. Newer pneumococcal conjugate vaccines could prevent, both directly and indirectly, a considerable amount of the persisting IPD in Indigenous people in the region.

MJA 2008; 189: 43–46

The 23-valent pneumococcal polysaccharide vaccine (23vPPV) was made available to eligible Indigenous adults in north Queensland from 1996, and the 7-valent pneumococcal conjugate vaccine (7vPCV) became freely available for Indigenous children aged under 2 years (with a dose of 23vPPV at age 24 months) from the latter part of 2001. This meant that, from 2001, invasive pneumococcal disease (IPD) became preventable not only in Indigenous adults, but also, for the first time, in Indigenous children.

In the 3 years after the introduction of 7vPCV (2002–2004), we documented a rapid decline in the annual incidence of IPD in Indigenous children in north Queensland.[1] Furthermore, it appeared that the use of 7vPCV in children was associated with an indirect protective effect in older Indigenous people, who were not eligible for this vaccine.[1] This indirect "herd immunity" effect is believed to occur because 7vPCV interrupts the transmission of vaccine-type pneumococci by reducing their acquisition in the nasopharynx of immunised children.[2]

However, initial enthusiasm about the capacity of 7vPCV to prevent IPD, both directly and indirectly, has recently been dampened:[3,4] 7vPCV is known to increase the prevalence of nasopharyngeal carriage of non-7vPCV serotype pneumococci in vaccinated children, and several recent studies from the United States have documented increases in the incidence of non-7vPCV serotype IPD in both children and adults.[5-7] These increases were not so apparent in the first few years after the introduction of 7vPCV, suggesting that the emergence of non-7vPCV serotype IPD is a gradual process.[5-7]

Before the introduction of pneumococcal vaccines, the incidences of IPD in Indigenous children[8] and adults were significantly greater than those documented in non-Indigenous people in north Queensland. Furthermore, a considerable proportion of cases in Indigenous children were caused by non-7vPCV serotype pneumococci.[1,8] For these reasons, it is essential to continue surveillance of IPD in Indigenous people to determine whether non-7vPCV serotype IPD emerges over time, and, if so, which serotypes are involved.

This study aimed to examine trends in the epidemiology of IPD in Indigenous people in north Queensland over another 3 years (2005–2007) after the introduction of 7vPCV, to determine trends in indirect effects, and to assess whether non-7vPCV serotype IPD is emerging in Indigenous people in north Queensland.

METHODS

We have used the same methods since our first study began in 1999.[1] Briefly, IPD is defined by the isolation of pneumococci from a usually sterile body site. Data on all IPD cases are collected with a standardised questionnaire that requests information on demographic and clinical features. This information is linked with the pneumococcal vaccination status of the patient and the serotype of the infecting pneumococcus. Definitions of "vaccine-preventable" and "vaccine failure" IPD were as used previously[1] (Box 1).

Trends were compared over three 3-year periods: 1999–2001 (before the introduction of 7vPCV for Indigenous children), 2002–2004 and 2005–2007. Comparisons were made with the χ^2 test for trend.

The population estimates for north Queensland from the 2001 national census were used to determine the average annual incidences during 1999–2001, and similarly 2006 census estimates were used to determine incidences during 2005–2007. Confidence intervals for the incidences were calculated from tabulated 95% significance factors.[9]

RESULTS

Over the 9 years 1999–2007, there were 273 cases of IPD in Indigenous people in north Queensland (Box 2); the infecting serotype was determined in 264 (97%) of the cases.

Indigenous children

In Indigenous children less than 5 years of age, the average annual incidence of IPD fell

1 Definitions

A case of invasive pneumococcal disease (IPD) was defined as "vaccine-preventable" if:

- It was in an Indigenous child who was age-eligible for free vaccine, and was caused by a serotype in the 7-valent pneumococcal conjugate vaccine (7vPCV); or
- It was in an Indigenous adult and was caused by a serotype in the 23-valent pneumococcal polysaccharide vaccine (23vPPV), and the adult was eligible for free 23vPPV (smoking was included among eligibility criteria for Indigenous adults from 2001), or the case occurred 5 years or more after a scheduled dose of 23vPPV.

A case of IPD was defined as "vaccine failure" if:

- It was caused by a vaccine type, and the patient had documented evidence of having received a primary course of the relevant vaccine or the recommended booster (or revaccination) more than 2 weeks before the onset of illness. ◆

2 Cases of invasive pneumococcal disease among Indigenous people in north Queensland, 1999–2007

Age (years)	No. of cases		
	1999–2001	2002–2004	2005–2007
< 5	35	16	15
5–14	15	6	9
⩾ 15	58	50	69
Total	108	72	93

from 170 per 100 000 children in 1999–2001 (95% CI, 118–236 per 100 000) to 66 per 100 000 in 2005–2007 (95% CI, 37–109 per 100 000). The number of cases of 7vPCV serotype IPD also fell in this group, from 17 in 1999–2001, to two in 2002–2004 and none in 2005–2007 (χ^2_{trend} = 15.84, $P < 0.001$). In contrast, the number of cases of non-7vPCV serotype IPD remained virtually unchanged (Box 3A).

In Indigenous children aged 5–14 years, there were six cases of 7vPCV serotype IPD in 1999–2001, two in 2002–2004 and three in 2005–2007 ($\chi^2_{trend} = 0.06$, $P = 0.81$). The number of cases of non-7vPCV serotype IPD and distribution of serotypes are shown in Box 3B. There were no 7vPCV failures in this age group in 2005–2007. However, there were two cases of 23vPPV failure: two children developed serotype 1 IPD at ages 5.5 and 6.5 years despite having received 23vPPV at 24 and 26 months of age respectively.

Indigenous adults

In Indigenous adults aged ⩾ 15 years, the average annual incidence of IPD remained virtually unchanged: at 59 per 100 000 adults in 1999–2001 (95% CI, 44–76 per 100 000) and 63 per 100 000 in 2005–2007 (95% CI, 50–80 per 100 000).

There was a 75% decrease in 7vPCV serotype IPD cases in Indigenous adults, from 16 per 100 000 in 1999–2001 (95% CI, 9–26 per 100 000) to 4 per 100 000 in 2005–2007 (95% CI, 1–9 per 100 000; $\chi^2_{trend} = 11.65$, $P < 0.001$) (Box 4). In contrast, there was no change in the number of cases of IPD caused by serotypes present in the 23vPPV but not the 7vPCV (χ^2_{trend} = 0.007, $P = 0.93$). However, the number of cases of IPD caused by serotypes not present in either vaccine more than tripled (χ^2_{trend} = 7.58, $P = 0.006$), from 8 per 100 000 adults ⩾ 15 years in 1999–2001 (95% CI, 3–16 per 100 000) to 25 per 100 000 in 2005–2007 (95% CI, 15–34 per 100 000) (Box 4).

Among the cases of 23vPPV serotype IPD in Indigenous adults, 22 (46%) of the 48 in 1999–2001 were vaccine failures, as were 22 (54%) of the 41 in 2005–2007. Similarly, 20 (42%) and 17 (41%), respectively, were vaccine-preventable.

DISCUSSION

From 1999–2001 to 2005–2007, there was a 60% decline in IPD in young Indigenous children in north Queensland, which is consistent with predictions made before the introduction of 7vPCV.[8]

No 7vPCV failures have yet been documented in north Queensland. However, there have now been three 23vPPV failures in Indigenous children since it was introduced into the immunisation schedule in mid-2001: a serotype 12F vaccine failure occurred in 2003 in a 2.5-year-old child who had received 23vPPV at 21 months of age,[1] and two serotype 1 vaccine failures occurred more recently.

There is no evidence yet of an emergence of non-7vPCV serotype IPD in Indigenous children or (contrary to an initial impression[1]) an indirect protective effect in children aged 5–14 years. Nevertheless, there is now very strong evidence that Indigenous adults are benefiting indirectly from the use of 7vPCV in children. This was shown by a significant decline in 7vPCV serotype IPD in adults over the three periods, but no concurrent decline in IPD caused by serotypes present only in the 23vPPV; these observations are consistent with those from elsewhere.[7,10] Children are a significant reservoir of pneumococci, and contact with young children is a recognised risk factor for IPD in adults.[11] Because 7vPCV reduces nasopharyngeal carriage of vaccine serotypes, transmission of these pneumococci to close contacts is, in turn, also reduced.[11]

In contrast, the initial benefits of 23vPPV to Indigenous adults in north Queensland appear to have now plateaued.[1] Little is known about the longer-term protection afforded by that vaccine, particularly in pop-

3 Distribution of non-7vPCV serotype invasive pneumococci isolated from Indigenous children in north Queensland, 1999–2007

Serotype	1999–2001	2002–2004	2005–2007
A. Children aged < 5 years			
1	6	0	2
5	1	0	0
6A	1	3	3
7F	0	1	2
8	0	1	0
10A	0	1	1
10F	0	0	1
12F	0	1	0
13	1	0	0
16F	0	1	1
17F	1	0	0
18A	0	0	1
18B	1	0	0
19A	2	3	1
33F	1	2	3
Total	14	13	15
B. Children aged 5–14 years			
1	2	1	3
7F	2	1	2
10A	0	0	1
12F	2	0	0
18A	0	1	0
18B	1	0	0
19A	2	0	0
23B	0	1	0
Total	9	4	6

7vPCV = 7-valent pneumococcal conjugate vaccine ◆

ulations with a very high prevalence of comorbid conditions.

It is of considerable concern that there has been a significant increase in the number of IPD cases in Indigenous adults caused by serotypes not present in either vaccine. Similarly, the repertoire of serotypes not present in either vaccine that caused IPD in Indigenous adults has expanded from seven in 1999–2001 to 13 in 2002–2007 (Box 4).

Although these could be coincidental findings, an increase in the nasopharyngeal carriage of serotypes not present in either vaccine ("replacement colonisation"[12]) was seen in Native Alaskan adults after the introduction of childhood 7vPCV.[12] In addition, a 44% increase in IPD caused by non-vaccine serotypes was recently reported in HIV-infected adults in the US.[13] If we assume an association between the increase in IPD caused by non-vaccine serotypes and the introduction of 7vPCV, then this increase has offset the decrease in IPD caused by 7vPCV serotypes, as has also been seen in Native Alaskan adults.[12]

Although the relatively small numbers of cases in our study do not allow definitive conclusions about particular pneumococcal serotypes, some observations are nevertheless warranted. Serotype 1 has long been recognised as a cause of occasional outbreaks of IPD, but was recently suggested to cause an ongoing cyclical pattern of IPD in some settings.[14] "Outbreaks" of serotype 1 IPD occurred in Indigenous populations in north Queensland in 1992–1995, 1999–2001 and 2005–2007, supporting the hypothesis that serotype 1 is endemic in the region and causes a cyclical pattern of IPD.

Following the introduction of 7vPCV, serotypes 6A and 33F have become prominent causes of IPD in Indigenous children less than 5 years of age in north Queensland (Box 3). The former is surprising, as a case–control study in the US showed that 7vPCV was 76% effective (95% CI, 39%–90%) in preventing serotype 6A IPD in children,[15] leading to a comment that the vaccine was effectively an "eight-valent" product.[16] Certainly, serotype 6A IPD declined significantly in most children in the US after the introduction of 7vPCV,[7] but the nasopharyngeal carriage of this serotype increased in vaccinated Native American children,[2] and it has emerged as a prominent cause of IPD in Native Alaskan children.[5] A recent increase in serotype 33F IPD among children in the US has also been documented.[10,17]

Serotypes 22F, 10F and 18A appear to have become more prominent causes of IPD in Indigenous adults in north Queensland following the vaccination of children with 7vPCV (Box 4). For this to have occurred, the nasopharyngeal carriage of these non-7vPCV serotypes would have had to increase in adults.[11] A recent non-significant increase in the carriage of serotype 22F has been noted among Native Alaskan adults.[12] Increases in IPD in adults caused by these serotypes do not appear to have been described elsewhere.

There is no clear evidence yet that serotype 19A IPD has recently increased in either Indigenous children or adults in north Queensland since the introduction of 7vPCV. The US case–control study showed that 7vPCV was not effective in protecting children against serotype 19A IPD,[15] and there has been a recent marked increase in IPD caused by this non-7vPCV serotype in children[6,7] and adults[7,10,13] elsewhere, including Native Alaskan children and adults.[5] Of note, 36% of the cases of IPD that occurred in children less than 5 years of age in the US in 2005 were caused by serotype 19A.[18]

Several mechanisms for the emergence of serotype 19A IPD have been proposed,[18] but it is unclear why this serotype has not become a more prominent cause of IPD among Indigenous people in north Queensland, as it was present in the region before the introduction of 7vPCV.[1,8] It is unlikely that 23vPPV has played a significant role in preventing the emergence of this serotype, as this vaccine is not scheduled for Indigenous children in Queensland until they reach 24 months of age. All six cases of serotype 19A IPD that occurred between 1999 and 2007 in children less than 5 years of age occurred before 24 months; presumably any recent emergence of this serotype would be apparent before this age, as seen in Native Alaskan children.[5]

Newer conjugate vaccines, including a 13-valent vaccine (which includes serotypes 1, 3, 5, 6A, 7F and 19A) are under clinical development.[19] Such vaccines will be necessary to eradicate apparently endemic serotype 1 IPD in Indigenous people in north Queensland, and could prevent a considerable amount of the persisting IPD caused by other serotypes, both directly and indirectly. Continued surveillance will be essential.

ACKNOWLEDGEMENTS

We wish to thank all laboratory and clinical staff involved in the diagnosis and management of the patients with IPD included in this report, and the

4 Distribution of cases and serotypes of invasive pneumococci isolated from Indigenous adults ⩾ 15 years of age in north Queensland, 1999–2007

Serotype	1999–2001	2002–2004	2005–2007
Serotypes in both 7vPCV and 23vPPV			
4	4	1	2
6B	1	0	0
9V	3	2	1
14	2	2	0
18C	2	1	0
19F	3	0	0
23F	1	0	1
Total	*16*	*6*	*4*
23vPPV-only serotypes			
1	7	1	11
3	3	3	4
5	3	0	0
7F	7	7	7
8	2	5	3
10A	1	1	1
11A	2	1	4
12F	2	2	0
19A	4	2	4
22F	0	3	3
33F	1	0	0
Total	*32*	*25*	*37*
Non-vaccine serotypes			
6A	1	2	2
7C	1	1	0
10F	0	9	4
13	0	0	4
16F	2	0	2
18A	1	1	6
23A	1	0	2
23B	1	0	0
31	0	1	0
34	0	0	2
35B	0	1	3
35F	0	1	0
38	1	1	0
48	0	2	0
Total	*8*	*19*	*25*
Unknown serotype	2	0	3
Total	58	50	69

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

members of the Tropical Population Health Unit Network who followed up and collected information.

COMPETING INTERESTS

Jeffrey Hanna has received honoraria and travel grants from vaccine companies, including the manufacturer and distributor of the 7-valent pneumococcal conjugate vaccine (Wyeth). Jan Humphreys received a travel grant from a vaccine company to attend a vaccine forum in 2007.

AUTHOR DETAILS

Jeffrey N Hanna, MPH, FAFPHM, Public Health Physician[1]
Jan L Humphreys, Public Health Nursing Officer[2]
Denise M Murphy, DipMedTech, Supervising Scientist[3]
1 Tropical Population Health Network, Queensland Health, Cairns, QLD.
2 Tropical Population Health Network, Queensland Health, Townsville, QLD.
3 Pneumococcal Reference Laboratory, Forensic and Scientific Services, Queensland Health, Brisbane, QLD.
Correspondence:
jeffrey_hanna@health.qld.gov.au

REFERENCES

1 Hanna JN, Humphreys JL, Murphy DM. Invasive pneumococcal disease in Indigenous people in north Queensland, 1999–2004. *Med J Aust* 2006; 184: 118-121.
2 Millar EV, O'Brien KL, Watt JP, et al. Effect of community-wide conjugate pneumococcal vaccine use in infancy on nasopharyngeal carriage through 3 years of age: a cross-sectional study in a high-risk population. *Clin Infect Dis* 2006; 43: 8-15.
3 Peters TR, Poehling KA. Invasive pneumococcal disease: the target is moving. *JAMA* 2007; 297: 1825-1826.
4 Hanage WP. Serotype replacement in invasive pneumococcal disease: where do we go from here? *J Infect Dis* 2007; 196: 1282-1284.
5 Singleton RJ, Hennessy TW, Bulkow LR, et al. Invasive pneumococcal disease caused by nonvaccine serotypes among Alaska Native children with high levels of 7-valent pneumococcal conjugate vaccine coverage. *JAMA* 2007; 297: 1784-1792.
6 Pelton SI, Huot H, Finklestein JA, et al. Emergence of 19A as a virulent and multidrug resistant pneumococcus in Massachusetts following universal immunization of infants with pneumococcal conjugate vaccine. *Pediatr Infect Dis J* 2007; 26: 468-472.
7 Hicks LA, Harrison LH, Flannery B, et al. Incidence of pneumococcal disease due to non-pneumococcal conjugate vaccine (PCV7) serotypes in the United States during the era of widespread PCV7 vaccination, 1998–2004. *J Infect Dis* 2007; 196: 1346-1354.
8 Fagan RL, Hanna JN, Messer RD, et al. The epidemiology of invasive pneumococcal disease in children in Far North Queensland. *J Paediatr Child Health* 2001; 37: 571-575.
9 Bailar JC, Ederer F. Significance factors for the ratio of a Poisson variable to its expectation. *Biometrics* 1964; 20: 639-643.
10 Lexau CA, Lynfield R, Danila R, et al. Changing epidemiology of invasive pneumococcal disease among older adults in the era of pediatric pneumococcal conjugate vaccine. *JAMA* 2005; 294: 2043-2051.
11 Bogaert D, de Groot R, Hermans PWM. *Streptococcus pneumoniae* colonisation: the key to pneumococcal disease. *Lancet Infect Dis* 2004; 4: 144-154.
12 Hammitt LL, Bruden DL, Butler JC, et al. Indirect effects of conjugate vaccine on adult carriage of *Streptococcus pneumoniae*: an explanation of trends in invasive disease. *J Infect Dis* 2006; 193: 1487-1494.
13 Flannery B, Heffernan RT, Harrison LH, et al. Changes in invasive pneumococcal disease among HIV-infected adults living in the era of childhood pneumococcal immunization. *Ann Intern Med* 2006; 144: 1-9.
14 Hausdorff WP. The roles of pneumococcal serotypes 1 and 5 in paediatric invasive disease. *Vaccine* 2007; 25: 2406-2412.
15 Whitney CG, Pilishvili T, Farley MM, et al. Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case-control study. *Lancet* 2006; 368: 1495-1502.
16 O'Brien KL, Levine OS. Effectiveness of pneumococcal conjugate vaccine. *Lancet* 2006; 368: 1469-1470.
17 Gonzalez BE, Hulten KG, Lamberth L, et al; the US Pediatric Multicenter Pneumococcal Surveillance Group. *Streptococcus pneumoniae* serogroups 15 and 33: an increasing cause of pneumococcal infections in children in the United States after the introduction of the pneumococcal 7-valent conjugate vaccine. *Pediatr Infect Dis J* 2006; 25: 301-305.
18 Moore MR, Gertz RE Jr, Woodbury RL, et al. Population snapshot of emergent *Streptococcus pneumoniae* serotype 19A in the United States, 2005. *J Infect Dis* 2008; 197: 1016-1027.
19 Scott DA, Komjathy SF, Hu BT, et al. Phase 1 trial of a 13-valent pneumococcal conjugate vaccine in healthy adults. *Vaccine* 2007; 25: 6164-6166.

(Received 20 Feb 2008, accepted 7 May 2008) ❑