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Failure to vaccinate or failure of vaccine? Effectiveness of the 23-valent pneumococcal polysaccharide vaccine program in Indigenous adults in the Northern Territory of Australia

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ABSTRACT

Over the last decade, there has been no discernible reduction in Invasive Pneumococcal Disease (IPD) amongst Indigenous adults in the Northern Territory (NT) of Australia, despite increasing vaccination coverage. We examined the utility of two common methods, the screening method and the indirect method, to determine the 23-valent pneumococcal polysaccharide vaccine effectiveness (VE) in prevention of IPD amongst Indigenous adults in this setting. VE was calculated for the period 2001–2005 across two distinct geographical areas where the disease burden was known to differ. VE against vaccine-type IPD was 3.4% (95% CI −43, 35) for the NT. However, population vaccination coverage varied widely according to geographical region and where this was within the range appropriate for the use of the screening method, VE was within the expected range (67.2%, 95% CI 47, 80). VE according to the indirect cohort appeared unreliable in this setting due to the analysis being based on a very limited number of non-vaccine-type IPD cases. Surveillance based estimates of VE such as these need to be considered with caution, but the results suggest failure to vaccinate is the most likely reason vaccine-type IPD has not reduced in this setting.

1. Introduction

In common with other economically developed countries, age-specific rates of Invasive Pneumococcal Disease (IPD) in Australia are highest in the very young and the elderly. There is a marked disparity for Indigenous Australian adults residing in the Central region of the Northern Territory (NT), first recognised more than a decade ago [1], where age-specific rates for Indigenous adults aged 20–49 years were over 20 times those of their non-Indigenous counterparts—178/100,000 population (95% CI 132–235) compared to 8/100,000 (95% CI 3–16).

Indigenous Australians experience high rates of conditions that have not only been associated with increased risk of IPD, but also with reduced vaccine effectiveness (VE). Such conditions include high rates of alcohol abuse and associated malnutrition, smoking, diabetes mellitus, chronic renal failure and cardiac disease [2].

In light of this high disease burden, since 1995 the 23-valent pneumococcal polysaccharide vaccine (23vPPV) has been recommended for all Indigenous Australian adults aged ≥50 years and for those aged 15–49 years with medical risk factors [3]. As a regional initiative, this was expanded in 2000 to include all Indigenous adults in the NT aged ≥15 years [4]. Re-vaccination was recommended every 5 years, but since 2003, a maximum of three lifetime doses is now recommended for Indigenous adults—a second dose 5 years after the first dose and then a third dose 10 years after the second, or at age 50 years, whichever is later [3].

Data on the effectiveness of pneumococcal polysaccharide vaccine continues to remain controversial [5–8]. A Cochrane Review [5] provided supportive evidence for the prevention of IPD in adults with a pooled odds ratio (OR) from randomised controlled trials of 0.26 (95% CI 0.15–0.46), supported by pooled data from non-randomised studies (OR 0.48 95% CI 0.37–0.61). The protective value of vaccination in adults with chronic illness was less clear, with data from randomised controlled trials failing to demonstrate protective efficacy for this group [5,9]. Although this may be due to inadequate sample size and lack of power, it is of concern given

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that adults with chronic illness are a primary target for vaccination. A subsequent review has raised further questions about the quality of clinical trials and has led to calls for withdrawal of recommendations for the use of 23vPPV in high risk groups [6,10].

Within the NT, surveillance of IPD has been conducted since 1994 with laboratories required to report all cases to the NT public health authority. As the only licensed vaccine for adolescents and adults, the 23vPPV is the current standard for IPD prevention in these ages. Monitoring vaccine effectiveness in the field is essential, particularly so in the NT where there is high lifetime exposure to pneumococci [11], increased susceptibility to disease, repeated vaccination and the continued high burden of IPD amongst Indigenous adults. We aimed to describe IPD incidence over time and determine the effectiveness of the 23vPPV in this population group.

2. Methods

2.1. Enhanced surveillance

IPD was defined as a pneumococcal infection with *Streptococcus pneumoniae* isolated from a usually sterile body fluid. Cases occurring between 1 January 1994 and 31 December 2005 were identified from the NT notifiable diseases database. Enhanced surveillance for each notified case was conducted routinely by the NT public health authority. Enhanced surveillance included medical record review, search of the regional immunisation database and patient interview (where possible) to collect clinical and risk factor data and details of vaccination history. Isolates were submitted to the Pneumococcal Reference Laboratory of Queensland Health Scientific Services for serotyping. Serotyping was performed by the Quellung reaction using antisera from the Statens Seruminstitut, Copenhagen, Denmark. No further investigations beyond enhanced surveillance were conducted.

IPD rates per 100,000 population were calculated using the relevant age-specific Indigenous or non-Indigenous population for each year for the NT and also for the two distinct geographical regions created by dividing the NT into the arid Central and tropical Top End. Population data were obtained from the Health Gains Unit, Department of Health and Community Services, Darwin, and were based on Australian Bureau of Statistics resident population data for the relevant year.

We restricted our assessments of vaccine effectiveness (VE) to the period from 2001 to 2005 where vaccine coverage was relatively stable. We calculated VE using the screening method formula [12]:

$$\mathrm{VE} = 1 - \left[\left(\frac{\mathrm{Case_{vax}}}{1-\mathrm{Case_{vax}}}\right)\left(\frac{1-\mathrm{Pop_{vax}}}{\mathrm{Pop_{vax}}}\right)\right]$$

where $\mathrm{Case_{vax}}$ = proportion of cases vaccinated (average annual proportion, determined from enhanced surveillance); $\mathrm{Pop_{vax}}$ = proportion of population vaccinated (for the mid-time-point, determined from regional immunisation database).

Ninety-five percent confidence intervals (CI) for VE were calculated based on the odds ratio (OR). VE was calculated for two distinct geographical regions: the Top End and Central region. For the purposes of determining the proportion of cases vaccinated ($\mathrm{Case_{vax}}$), we limited cases to those individuals with IPD caused by a serotype contained in the 23vPPV (vaccine type, VT). These cases were considered "vaccinated" if they had received the vaccine from 14 days to 5 years prior to illness onset. Those whose vaccination occurred more than 5 years earlier were removed from the denominator for $\mathrm{Case_{vax}}$ and $\mathrm{Pop_{vax}}$ for the primary analysis as the previous vaccination could have afforded partial protection. A secondary analysis of VE was undertaken to assess receipt of at least one lifetime dose provided that dose had been received at least 14 days prior to illness onset.

VE was also estimated using the indirect cohort method [13]: VE = 1 − OR, where OR is the odds ratio of a person with vaccine serotype IPD being vaccinated, compared to that of a person with IPD caused by a non-vaccine serotype.

Definite vaccine failures (VT IPD in an individual vaccinated from 14 days to 5 years prior to illness onset) and all vaccine failures (VT IPD in an individual vaccinated any time before 14 days prior to illness onset) were described according to serotype, geographical region, risk factors, number of doses received and time since vaccination (for the same time period as VE was calculated, 2001–2005).

2.2. Ethics

Ethical approval (05/67) was granted by the Human Research Ethics Committee of the Northern Territory Department of Health and Community Services and Menzies School of Health Research, December 2005.

3. Results

From 1994 to 2005, there were 444 IPD cases aged 15–49 years, 87% of whom were Indigenous (Table 1). Rates of IPD amongst Indigenous adults in the NT were 110 per 100,000 population over this period, 18 times that of non-Indigenous adults. Indigenous adults in the Central region were four times more likely to develop IPD (222/100,000) than their counterparts residing in the Top End (56/100,000).

Of the 385 IPD cases in Indigenous adults, a serotype was available for 342 (89%). Of these cases, 253 were due to a serotype found in the 23vPPV, which was 66% all IPD and 74% of all known serotypes. There were 89 cases due to a serotype not found in the vaccine and 43 cases where the serotype was either not typeable/not typed ($n = 42$) or missing ($n = 1$) (Table 2).

Within the NT as a whole, the annual IPD rates for Indigenous adults remained high (in excess of 79/100,000 each year), with no apparent reduction over time in the rates of vaccine-type IPD (Table 2). Fig. 1 shows there was a substantial increase in vaccine coverage in the Central region over the last decade but no discernible impact on rates of vaccine-type IPD within the region. Population vaccine coverage in the Top End showed only a modest increase and, although vaccine-type IPD rates were much lower than the Central region, the rates in Top End do not appear to be reducing (Fig. 1).

Table 1
Average age-specific annual rate of IPD in adults aged 15–49 years/100,000 population according to geographical region and Indigenous status, 1994–2005, Northern Territory, Australia.

Population	Indigenous		Non-Indigenous		Incidence rate ratio
	IPD cases	Rate, 95% CI	IPD cases	Rate, 95% CI	
NT	385	110 (75–155)	59	6 (2–14)	18.3
Central region	253	222 (138–340)	21	12 (2–45)	18.5
Top End region	132	56 (28–100)	38	5 (1–13)	11.2