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Relative effectiveness of revaccination with 23-valent pneumococcal polysaccharide vaccine in preventing invasive pneumococcal disease in adult Aboriginal and Torres Strait Islander people, Australia

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ABSTRACT

Background: Aboriginal and Torres Strait Islander (Indigenous) Australians have high rates of invasive pneumococcal disease (IPD), with repeat doses of 23-valent polysaccharide pneumococcal vaccine (PPV23) recommended. We report the relative effectiveness of revaccination using a cohort from linked administrative data.

Methods: All resident North Queensland Indigenous adults who received any PPV23 vaccination between 2000 and 2012 were identified and linked with IPD cases. IPD rates were compared for individuals revaccinated >five years after initial PPV23 dose against individuals not revaccinated.

Results: Analysed data included 12,809 individuals and 89,612 person-years. Revaccinated adults had similar rates of IPD as non-revaccinated adults, after adjusting for potential confounders (HR = 0.92; 95%CI: 0.35–2.42). Findings were similar for vaccine-specific serotypes (HR = 1.32; 95%CI: 0.32–5.43).

Conclusions: Benefits of PPV23 revaccination against IPD in this high-risk population were not demonstrated, although estimates were imprecise. Findings should be validated in other high-risk cohorts, and against all-cause pneumonia as an outcome.

1. Introduction

Aboriginal and Torres Strait Islander Australians, hereafter respectfully referred to as Indigenous Australians, have consistently higher rates of invasive pneumococcal disease (IPD) across all ages compared to non-Indigenous Australians [1]. A specific schedule of repeat doses of 23-valent polysaccharide pneumococcal vaccine (PPV23) is recommended for Indigenous adults due to their elevated disease rates. A 2013 Cochrane Review reported PPV23 has vaccine efficacy (VE) of 74% (95%CI: 55%–86%) against IPD in adults [2]. In 1999, PPV23 for Indigenous Australians ≥ 50 years of age was added to the Australian national immunisation program schedule. This introduction, in combination with indirect protection due to the introduction of a 7-valent pneumococcal conjugate vaccine to the childhood schedule in 2000, led to the annual incidence of PPV23-related IPD declining more than 80% in far North Queensland between 1996 and 2004 [3].

From 2000, single revaccination was recommended five-years after the first dose for Indigenous peoples ≥ 50 years of age. From 2003, this revaccination recommendation was extended to Indigenous adults aged 15–49 years with underlying medical conditions or who were smokers [4]. These recommendations were based on immunogenicity studies, which suggested antibodies will have fallen significantly in the five years following the first dose, and that revaccination can boost values to match post-first dose levels [11]. Although serum antibody response studies have assessed immune response to revaccination in this population [5], studies detailing the relative effectiveness of PPV23 revaccination in preventing clinical endpoints are lacking [6].

Australian revaccination recommendations currently include single PPV23 revaccination for Indigenous Australians, at least five years after the initial dose, with no more than three lifetime adult doses. This study aims to evaluate the relative effectiveness of PPV23 revaccination, compared to no revaccination, in preventing IPD in the Indigenous Australian adult population in North Queensland, Australia.

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2. Methods

A retrospective study using data linked from the Queensland vaccination register (Vaccination Information and Vaccination Administration System), notifiable diseases database (Notifiable Conditions System), and death registry was conducted.

Invasive pneumococcal disease is a notifiable condition in Queensland under public health legislation, requiring reporting to the state health department. All resident North Queensland Indigenous adults (≥16 years), who received any PPV23 vaccination between 01 January 2000 and 31 December 2012, were identified and included in the study. North Queensland was defined as the areas covered by previous health administration units: the Cairns and Hinterland, Cape York, Mackay, Northwest (formerly Mount Isa), Torres Strait Northern Peninsula, and Townsville Health Service Districts. The University of Queensland School of Population Health Ethics Committee approved the study.

IPD incidence rates were compared between three groups: adults who received only a first dose of PPV23; adults eligible for revaccination who were not revaccinated (that is, received first vaccination more than five years earlier); and adults who were revaccinated. The Queensland vaccination register is not a population-based register so we could not construct a group of wholly unvaccinated adults for comparison. Each individual's analysis-time was restricted to the first five-years they spent in each group in order to ensure individuals in each of the groups had similar follow-up times (information on external migration was not available). Individuals could move between groups according to vaccination status, and could potentially contribute analysis-time to all three vaccination groups over the life of the study. Individuals left the study at IPD diagnosis, through censoring at death, or study completion. Supplementary Fig. 1 displays information on group membership for a series of example individuals.

Potential confounding variables collected were age (in 10-year age groups), sex, socio-economic status, remoteness, and proximity to death. Socio-economic status was measured in thirds at the postcode level using the Australian Bureau of Statistics Socio-Economic Index for Areas, a measure of relative disadvantage [7]. Remoteness was categorised as regional, remote, or very remote, according to Australian Standard Geographical Classification Remoteness Structure [8]. We included the proximity to death variable as a proxy for general health status. Individuals were categorised as being either within two-years of death or not within two-years of death. If death occurred within four weeks of IPD notification, we categorised that individual as being not within two years of death at the time of notification. All variables, except sex, could potentially have varied with time.

To consider the association between vaccination group and first IPD notification, Cox proportional hazards models were used. First univariable and then multivariable (adjusted for age, sex, remoteness, social position, proximity to death, year of vaccination) analyses were undertaken. Separate models were run for all IPD cases, and then for PPV23-serotype IPD cases only. To assess the sensitivity of results to the extension of revaccination recommendations in 2003, a sensitivity analysis was conducted considering only data from 2004 onwards. Effect estimates are reported as hazard ratios (HR) with 95% confidence intervals. Analyses were conducted using Stata v14.0 (StataCorp, College Station, TX, USA).

3. Results

Over the thirteen-year study period, there were 256 IPD notifications in Indigenous Australian adults residing in North Queensland. There were 154 cases of PPV23-serotype IPD, 75 cases of non-PPV23 serotype IPD, and 27 cases with unknown serotypes. The adult Indigenous population in North Queensland in the 2006 Australian census was 40,583. There were 12,809 adults with pneumococcal vaccination records included in the analysis, contributing a total of 89,612 years of data: 9704 adults contributed analysis-time to the first-dose vaccination group (41,892 person-years), 6466 to the not-revaccinated group (16,963 person-years), and 7151 to the revaccinated group (30,757 person-years). Participants who entered the revaccination group were older (mean (SD) = 42.3 (14.3) years) and more likely to be within two years of death (6.3%), than those entering the no revaccination group (35.7 (12.1) years and 2.0%), respectively (Supplementary Table 1). Among participants with vaccination records, there were 752 deaths while participants were in the study, and IPD was notified for 79 adults (two adults were notified on two occasions); 47 of these cases were PPV23-serotype IPD. Five deaths among vaccinated adults occurred within four weeks of IPD notification.

Revaccination status was not associated with IPD notification, either in univariable or multivariable models (Table 1). After adjusting for potentially confounding variables, adults who were revaccinated had a similar rate of all-serotype IPD notification as adults who were not revaccinated despite being eligible (HR = 0.92; 95%CI: 0.35–2.42). Similarly, there was no difference observed in IPD rates in adults who had received only a first dose compared with adults who were not revaccinated (HR = 0.93; 95% CI: 0.31–2.80). Among other variables considered, increasing age, being male, and being within two-years of death were associated with higher notification rates (Table 1). When PPV23-serotype IPD was considered, there was no difference between adults who were revaccinated and those who were not (HR = 1.32; 95%CI: 0.32–5.43; Supplementary Table 2). Age, being male, and being within two-years of death were the variables associated with significantly higher IPD rates. When data collected after the last revaccination recommendation change (i.e. from 2004 onwards) were considered, results were similar (HR = 1.47; 95%CI: 0.65–3.34; Supplementary Table 3). Being male, age, and being within two-years of death were the only significant variables associated with higher IPD rates.

4. Comment

Whilst recommendations around revaccination using PPV23 are common, particularly for high-risk populations, data about its effectiveness in preventing clinical endpoints are not. Using a linked-data set with thirteen years coverage of Indigenous Australian adults in North Queensland, Australia, we were unable to demonstrate lower IPD rates in PPV23-revaccinated individuals, when compared with their vaccine-eligible but not revaccinated peers.

Our findings align with recent data on modest response to revaccination identified in Australia's Northern Territory [5]. This immunogenicity study demonstrated a significantly poorer response in Indigenous adults to some serotypes with a repeat dose of PPV23 compared to their non-Indigenous adult peers receiving the first dose, with lower immunoglobulin-G responses upon revaccination [risk difference −38% (95%CI: −60% to −16%; p = 0.006)] [5]. Indigenous Australians have multiple reasons for having poorer immune response to PPV23, including prior carriage of pneumococci, chronic illness, and environmental and genetic factors.

One strength of our study is that linking administrative datasets allowed us to examine IPD cases over a thirteen-year period in a high-risk population. A significant limitation is that due to the low incidence of IPD cases among adults who have been vaccinated, the absolute number of cases is small with only 42 IPD notifications counting toward the not revaccinated versus revaccinated

Table 1
Confirmed invasive pneumococcal disease cases (n = 79) among 12,809 vaccinated North Queensland Indigenous Australians 2001–2012.

Variables		Adults; n	Study-time; yrs	Cases; n	All cases					
					Univariable			Multivariable		
					HR	95% CI	P	HR	95% CI	P
Vaccination	No revaccination	6466	16,963	9	Ref.			Ref.		
	Revaccination	7151	30,757	33	1.09	0.42–2.86	0.86	0.92	0.35–2.42	0.86
	1-vaccination	9704	41,892	37	0.77	0.26–2.30	0.64	0.93	0.31–2.80	0.90
Age category	16–24	4176	22,998	10	Ref.			Ref.		
	25–34	4922	25,803	11	1.07	0.45–2.53	0.88	1.05	0.44–2.49	0.92
	35–44	3810	19,171	29	**3.75**	**1.82–7.74**	**<0.001**	**3.29**	**1.57–6.89**	**0.002**
	45–54	2546	12,735	16	**3.11**	**1.40–6.88**	**0.005**	**2.46**	**1.08–5.61**	**0.03**
	55–64	1273	5857	9	**3.86**	**1.56–9.54**	**0.004**	**2.66**	**1.02–6.90**	**0.05**
	65+	614	3048	4	**3.12**	**0.98–9.97**	**0.05**	1.76	0.51–6.04	0.37
Sex	Male	6017	41,874	53	Ref.			Ref.		
	Female	6792	47,738	26	**0.43**	**0.27–0.69**	**<0.001**	**0.47**	**0.30–0.75**	**0.002**
Socio-economic status	Lowest third	9287	66,037	49	Ref					
	Middle third	2785	18,658	22	1.58	0.96–2.62	0.07	1.24	0.70–2.18	0.46
	Highest third	737	4917	8	**2.18**	**1.03–4.60**	**0.04**	1.57	0.69–3.58	0.28
Remoteness	Regional	5404	36,651	42	Ref.			Ref.		
	Remote	3847	26,494	25	0.80	0.49–1.31	0.37	0.85	0.49–1.47	0.55
	Very Remote	3558	26,468	12	**0.39**	**0.20–0.74**	**0.004**	0.50	0.24–1.03	0.06
Proximity to death	Not within 2 years	12,664	88,403	66	Ref.			Ref.		
	Within 2 years	747	1209	13	**14.42**	**7.95–26.16**	**<0.001**	**10.38**	**5.52–19.54**	**<0.001**

Multivariable models adjusted for age, sex, social position, remoteness, proximity to death, and year of vaccination.
CI: Confidence Intervals; HR: Hazard Ratio.

comparison. Consequently, effect estimates are imprecise with wide confidence intervals. Given the VE for IPD prevention from first-dose PPV23 has been reported as 74% [2], and assuming the relative VE for revaccination is half of that (37%) compared to no revaccination, then, if revaccination was effective, we could expect to see a HR = 0.63, which is well within the 95%CI reported in Table 1. Consequently, we cannot rule out a positive effect of revaccination. To increase the precision of estimates in this population, future researchers could consider a more common, but also less specific, outcome, such as hospitalisation for pneumonia. A second limitation is that, due to the data source, we were unable to obtain detailed information on participants, including any comorbid conditions and their severity, which are highly prevalent in this population. We attempted to adjust for health status by constructing an indicator variable, proximity to death, based on being two-years from death – as expected this indicator was strongly associated with IPD notification. However, given the high rates of chronic disease in this population, many individuals with comorbid conditions will not have been identified. Individuals with chronic disease, and particularly with more severe chronic disease, may be more likely to be engaged in medical care – increasing the likelihood of both revaccination and IPD detection [9]. The magnitude of this bias is potentially large, and would bias the effect estimates for IPD prevention from revaccination towards the null hypothesis of no effect. Future researchers should, where possible, focus on using data sources that record the individual's high-risk chronic conditions, in order to better control for this potential health-care engagement bias.

The generalisability of these findings to other high-risk populations is unclear, and revaccination may offer benefit in these groups due to differing immunogenicity profiles. For example, Kawakami and colleagues found that in Japanese adults aged 70 years and older revaccination with PPV23 generated levels of serotype-specific IgG and opsonophagocytic antibodies that were similar to those recorded after primary vaccination [10].

In this linked cohort study, we have not been able to demonstrate a benefit from PPV23 revaccination in this high-risk population. However, the actual number of IPD cases was small, and effect estimates were imprecise, and we can not adequately control for the possible effects of health-care engagement bias. Consequently, these findings should be viewed cautiously when considering the benefits of PPV23 revaccination. Our findings need to be validated with work in other similarly high-risk cohorts. Future researchers in this, and other, populations should consider using more common outcomes, such as all-cause pneumonia, and ensure their data set includes possible confounding variables such as presence of high-risk chronic conditions.

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Conflict of interest

The authors have no conflict of interests, financial or otherwise, in the production of this manuscript.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.01.085.

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