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Age-specific effectiveness following each dose of acellular pertussis vaccine among infants and children in New Zealand

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ABSTRACT

Background: Though it is believed the switch from whole cell to acellular pertussis vaccine has contributed to the resurgence of pertussis disease, few studies have evaluated vaccine effectiveness (VE) and duration of protection provided by an acellular vaccine schedule including three primary doses but no toddler-age dose. We assessed this schedule in New Zealand (NZ), a setting with historically high rates of pertussis disease, and low but recently improved immunisation coverage. We further evaluated protection following the preschool-age booster dose.

Methods: We performed a nested case-control study using national-level healthcare data. Hospitalised and non-hospitalised pertussis was detected among children 6 weeks to 7 years of age between January 2006 and December 2013. The NZ National Immunisation Register provided vaccination status for cases and controls. Conditional logistic regression was used to calculate dose-specific VE with duration of immunity examined by stratifying VE into ages aligned with the immunisation schedule.

Results: VE against pertussis hospitalisation was 93% (95% confidence interval [CI]: 87, 96) following three doses among infants aged 5–11 months who received three compared to zero doses. This protection was sustained through children's fourth birthdays (VE $\geqslant$ 91%). VE against non-hospitalised pertussis was also sustained after three doses, from 86% (95% CI: 80, 90) among 5–11 month olds to 84% (95% CI: 80, 88) among 3-year-olds. Following the first booster dose at 4 years of age, the protective VE of 93% (95% CI: 90, 95) among 4-year-olds continued through 7 years of age (VE $\geqslant$ 91%).

Conclusions: We found a high level of protection with no reduction in VE following both the primary course and the first booster dose. These findings support a 3-dose primary course of acellular vaccine with no booster dose until 4 years of age.

1. Introduction

Vaccination has made a substantial impact on the pertussis burden; however, there is still significant morbidity and infant mortality worldwide. Many countries that shifted from the more reactogenic whole cell to acellular pertussis vaccine have seen a resurgence of pertussis disease [1], a phenomenon also observed in countries still using the whole cell vaccines [2]. A range of explanations have been offered, including lower initial efficacy and more rapid waning for acellular vaccines. A lack of effect on carriage and transmission is also likely to play a major role [2,3].

Questions around acellular vaccine and pertussis re-emergence have prompted recent examination of the duration of protection that various schedules for acellular vaccines provide [4–22]. Most studies are based on schedules with a second year of life booster dose. Findings are mixed for the few studies based on schedules with three primary doses and no toddler-age dose. The majority of these studies showed sustained vaccine effectiveness (VE) up to age 3 years [8,10,21,22]. Conversely, an Australian study that demonstrated waning protection, from 79% in 1-year-olds to 59% in 3-year-olds [9], motivated the re-instatement of a toddler-age dose 11 years after it was discontinued from the Australian schedule. No previous studies based on schedules without a toddler-age dose have followed children past the age of 4 years.

Unlike other settings without a toddler dose, New Zealand (NZ) has historically high rates of pertussis disease [23,24], and low but recently improved immunisation coverage [25–27]. Acellular vac-

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cine replaced whole cell vaccine in 2000, and since 2006 when the 15-month-old dose was discontinued, the immunisation schedule has remained a primary diphtheria-tetanus-acellular pertussis (DTaP) course recommended at 6 weeks, 3 months and 5 months of age followed by a DTaP booster at 4 years and a reduced antigen diphtheria–tetanus–acellular pertussis vaccine (Tdap) booster at age 11 years [23].

To inform decision makers about the effectiveness of this schedule, we assessed the duration of protection following the current 3-dose primary series by measuring age-dose-specific VE against hospitalised and notified pertussis. We similarly assessed the duration of protection following the 4-year-old booster dose, through to children's eighth birthdays.

2. Methods

The vaccine used throughout this study period was Infanrix® hexa, a combined diphtheria-tetanus-acellular pertussis, hepatitis B, enhanced inactivated polio vaccine and *Haemophilus influenzae* type b vaccine.

Vaccination data were obtained from the National Immunisation Register (NIR). Routine NIR enrolment began with children born in 2005 and has continued for subsequent birth cohorts. Parents can opt to have some or all of their child's information excluded from the register. The cohort of children born January 1, 2006 through December 31, 2013 who were enrolled and never had information opted-off the NIR formed the eligible study population. The study cohort was followed for pertussis from birth to December 31, 2013.

To report on hospitalisations and notifications separately, two sources of data were used to detect pertussis disease: the National Minimum Data Set (NMDS), a collection of administrative and clinical information about all publicly funded hospitalisations; and EpiSurv, NZ's passive surveillance notifiable disease database. Healthcare providers are required by law to report all clinically suspect pertussis to public health [28]. Automatic electronic reporting of positive specimens from laboratories has also been required since 2007. Hospitalised pertussis cases were selected from NMDS records with an International Classification of Diseases, Tenth Revision, Australian Modification (ICD-10-AM) discharge diagnosis code of A37 (A37.0–A37.9) in the primary or any of the 99 available secondary diagnosis fields. Non-hospitalised notified cases were sourced from EpiSurv records, restricted to individuals who had no hospitalisation record for the same episode of pertussis in the NMDS. Where an individual child had multiple hospitalisations and/or notifications, only the first was considered.

The NIR and two disease data sets were linked using National Health Index (NHI) numbers, unique person identifiers assigned at birth or at first healthcare contact for those born outside the country. Cases with missing NHI numbers and any children with inexplicable vaccination records (e.g., a child with vaccination date prior to birth date) were excluded.

Dose-specific immunisation coverage was measured using pertussis immunisation event information for the children in the eligible NIR cohort. Age specific pertussis rates were calculated using population estimates from the census. VE was estimated using a nested case-control design.

Controls were children randomly selected via incidence density sampling from the eligible NIR cohort. To maximise precision, 20 controls were selected per case, matched on date of birth and area of residence. The age matching requirement was relaxed progressively by day, either side of the case birthdate, until 20 controls were selected. Controls were assigned an index date equal to the pertussis date (admission date for hospitalisations or report date for notifications) for their matched case.

The exposure of interest was the number of pertussis vaccine doses received prior to the pertussis date (cases) or index date (controls). A wash-out period was applied, with a dose considered received if it was administered at least 14 days prior to the pertussis/index date.

Demographic characteristics were compared between cases and controls using Pearson's chi-square test. We used conditional logistic regression to estimate odds ratios (OR). VE, as a percentage, and associated 95% confidence intervals (CIs) were estimated using the formula $VE = (1 - OR) \times 100$. Separate models were fit with pertussis hospitalisations and non-hospitalised notifications as the dependent variable and number of pertussis vaccine doses as the independent variable. Duration of immunity was examined by stratifying VE into ages aligned with the immunisation schedule (age 6 weeks–2 months for dose 1; age 3–4 months for dose 2; age 5–11 months, 1, 2 and 3 years for dose 3; and age 4, 5, 6 and 7 years for dose 4). Potential confounders (sex, ethnicity and socioeconomic status based on the NZ Deprivation Index [29]) were included in models if they changed the vaccine-outcome measure by at least 10% or if inclusion did not affect precision of the VE estimate.

We performed multiple sensitivity analyses to check the robustness of our findings. For hospitalisations and non-hospitalised notifications we first restricted cases to those with laboratory confirmation, either by isolation or PCR DNA detection of B. pertussis, to examine possible misclassification bias. Separately, we then examined our choice of a 14-day wash-out period by reducing it to 7 days and again to 0 days, then stratified VE estimates by birth year to assess the impact of recently improved vaccination coverage and timeliness. For case-control studies to produce unbiased results, controls need to be selected from the same population that gives rise to cases. For non-hospitalised notifications in our study, this source population is made up of the individuals who, had they become ill, would have sought healthcare and been notified. To account for variability in healthcare seeking behaviour and practitioner reporting inherent in passive surveillance systems, and to validate using the eligible NIR cohort to sample controls in our main analysis, we used electronic primary care patient management system records to sample controls from individuals enrolled at the same general practice as a case and who had a non-cough related visit on the index date.

All data management and analyses were performed using SAS® version 9.4 (SAS Institute Inc., Cary, NC). Ethics permission was granted from the NZ Health and Disability Ethics Committee.

3. Results

There were 531,640 children born between 2006 and 2013 enrolled on the NIR. Of these, 11,457 (2%) had their immunisation event details opted off the NIR, leaving 520,183 children eligible to be included in the study.

3.1. Vaccine coverage

Among eligible children, timely pertussis vaccination coverage was highest for dose 1, with 87% percent of children receiving their first dose of pertussis vaccine by age 8 weeks (Fig. 1). Seventy-six percent received their third dose before 6 months of age. By their first birthdays, 1% and 6% of children remained unvaccinated or undervaccinated (received only 1–2 doses), respectively. Age appropriate coverage for the primary series improved in more recent birth cohorts - 66% of children born in 2006–2007 compared to 86% of those born in 2012–2013 received their third dose prior

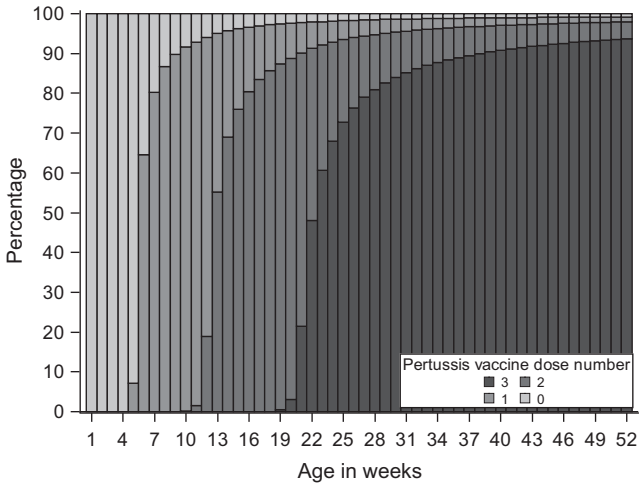

Fig. 1. Pertussis vaccination coverage for doses 1–3 by age, New Zealand, 2006–2013.

to age 6 months (Fig. 2). Of children born before 2009, 82% received their first booster dose before turning 5 years of age.

3.2. Pertussis cases

From 2006 to 2013 there were 639 hospitalised pertussis cases and 2831 non-hospitalised cases among eligible children less than 8 years of age. Twenty-five (1%) notified cases were excluded because of missing NHI numbers. One (<1%) hospitalised case and three (<1%) notified cases were excluded because their vaccination records were inexplicable. Remaining in the analyses were 638 hospitalised and 2803 notified cases.

Across the study period the highest burden of both hospitalised and non-hospitalised pertussis was in the youngest infants (Fig. 3). Rates of pertussis hospitalisations for infants less than 6 months old increased continuously from 2006 until they peaked at 546 per 100,000 person-years in 2012. Rates of non-hospitalised notifications in this age group rose slightly in 2009 followed by a second, larger increase during the most recent epidemic, peaking in 2012 at 459 per 100,000 person-years. While non-hospitalised notification rates for those ⩾6 months old also increased across the study period, with the second highest rate at the 2012 peak in children aged 2–3 years (394 per 100,000 person-years), hospitalisation rates among these older infants and children remained relatively constant.

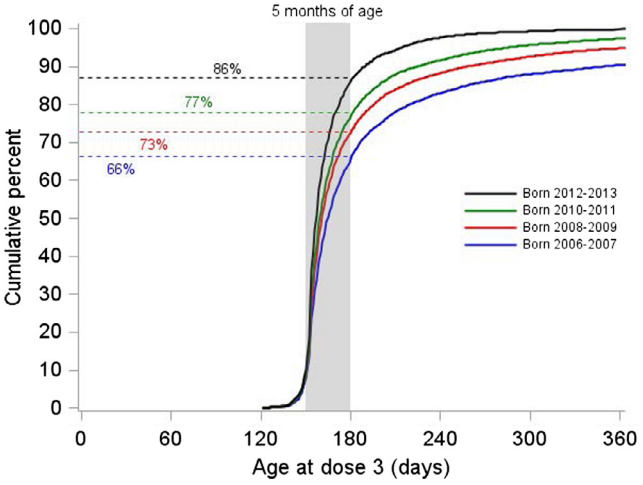

Fig. 2. Pertussis vaccination coverage for dose 3 by age and birth cohort, New Zealand, 2006–2013.

Among hospitalised cases, the median age at hospitalisation was 2 months (interquartile range [IQR]: 1, 6 months). Of the 625 (98%) children aged 6 weeks to 3 years, 576 (92%) had a primary diagnosis of pertussis and 29 (5%) were admitted to the intensive care unit (ICU). The median hospital stay was two days (IQR: 1, 5 days). Only 13 (2%) of the hospitalised cases were 4–7 years of age. Compared to the younger hospitalised cases, fewer had a primary diagnosis of pertussis (n = 10 [77%]) and only 23% had a hospital stay longer than one day. None were admitted to ICU. Non-hospitalised cases were significantly older than hospitalised cases (median 34 months [IQR: 16, 50 months], $P < 0.001$). Half (n = 1402) of the non-hospitalised cases had laboratory confirmation of pertussis.

Birthdates for controls ranged from 23 days before to 26 days after case birthdates, with 93% of controls born within two days of their matched case. Controls were significantly different from cases with respect to ethnicity (hospitalised and non-hospitalised) and socioeconomic status (hospitalised only) (all $P < 0.001$) (Table 1). Cases and controls were similar for all other measured characteristics.

3.3. Vaccine effectiveness

Matched VE against pertussis hospitalisation following the first dose was 43% (95% CI: 21, 58) among the youngest infants aged 6 weeks to 2 months (Table 2). VE increased significantly with each dose in the primary series - 84% (95% CI: 72, 91) for dose 2 and 93% (95% CI: 87, 96) for dose 3. This high level of effectiveness following three doses (⩾91%) was maintained through to children's fourth birthdays. The number of cases was too small to calculate VE against hospitalisation for older children.

Overall, VE for non-hospitalised notifications was lower than for hospitalisations (Table 2). There was no measurable effectiveness of one dose against pertussis notification in the youngest infants; however, moderate protection was established following the second dose (70%, 95% CI: 47, 83) with an additional, though non-significant, increase following the third dose (87%, 95% CI: 82, 91). VE was stable as children aged to their fourth birthdays. Following the first booster dose there was again an additional, though non-significant, increase in VE to 92% (95% CI: 89, 94) among 4-year-olds, which was sustained in children aged 5–7 years (87%, 95% CI: 66, 95).

Adjusting for gender, ethnicity and socioeconomic status resulted in reduced VE following the first dose, from 43% (95% CI: 21, 58) to 28% (95% CI: 0, 48) for hospitalised and from 28% (95% CI: −23, 58) to 1% (95% CI: −73, 43) for non-hospitalised infants. Confounding of these estimates was predominantly driven by differences in ethnicity between the vaccinated and unvaccinated groups. No confounding was observed for other age-dose combinations, with fully adjusted estimates nearly identical to crude matched estimates and no appreciable loss to precision. No sensitivity analyses resulted in appreciably different VE estimates.

4. Discussion

Pertussis resurgences around the world are a major challenge for immunisation programmes. Populations using acellular pertussis regimes are acknowledged to need a high coverage (>95%) primary course followed by one or more booster doses to prevent clinical disease [1]. Most countries assume the need for a booster

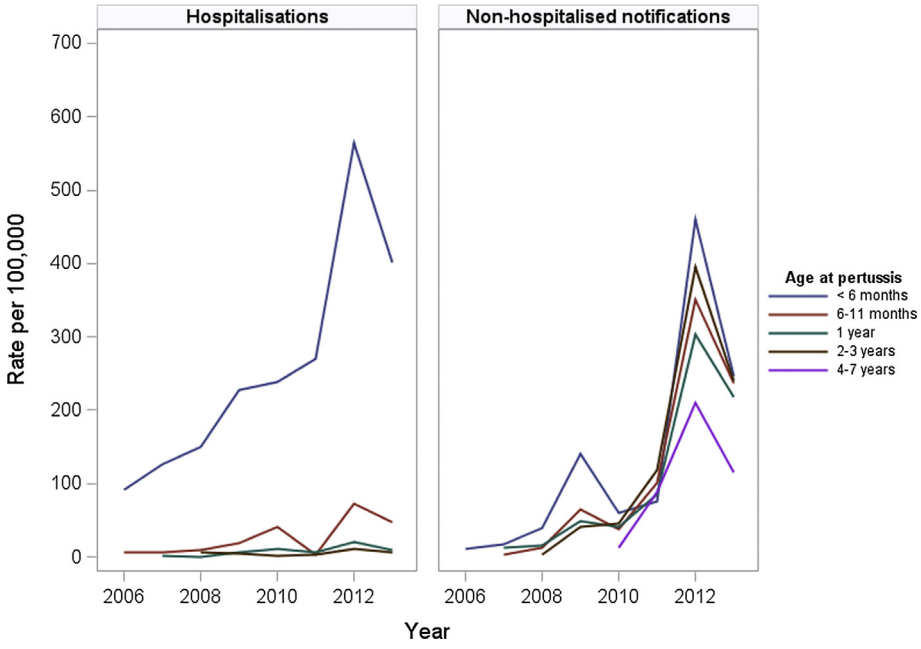

Fig. 3. Incidence of hospitalised and notified pertussis, children born 2006–2013, New Zealand.

Table 1
Characteristics of pertussis cases and controls matched on age and residential region, children age 6 weeks to 3 years and born 2006–2013, by type, New Zealand.

Characteristic	Hospitalisations					Non-hospitalised notifications				
	Cases		Controls		P-value	Cases		Controls		P-value
	N	(%)	N	(%)		N	(%)	N	(%)	
Total	N = 625		N = 12,428			N = 2028		N = 40,363		
Age at pertussis[a]										
6 w–2 m	322	(51.5)	6349	(51.1)	1.000	99	(4.9)	1972	(4.9)	1.000
3–4 m	122	(19.5)	2486	(20.0)		123	(6.1)	2479	(6.1)	
5–11 m	104	(16.6)	2060	(16.6)		294	(14.5)	5871	(14.6)	
1 y	36	(5.8)	717	(5.8)		545	(22.4)	9027	(22.4)	
2 y	24	(3.8)	484	(3.9)		491	(24.2)	9790	(24.3)	
3 y	17	(2.7)	332	(2.7)		567	(28.0)	11,224	(27.8)	
Gender										
Male	315	(50.4)	6343	(51.0)	0.756	1003	(49.5)	20,588	(51.0)	0.173
Female	310	(49.6)	6085	(49.0)		1025	(50.5)	19,775	(49.0)	
Ethnicity										
European	239	(38.2)	6232	(50.3)	<0.001	1383	(68.4)	23,647	(58.8)	<0.001
Māori	256	(41.0)	3207	(25.9)		418	(20.1)	8550	(21.3)	
Pacific Islander	109	(17.4)	1370	(11.1)		128	(6.3)	3274	(8.1)	
Asian	10	(1.6)	1382	(11.2)		65	(3.2)	3947	(9.8)	
Other[b]	11	(1.8)	196	(1.6)		28	(1.4)	808	(2.0)	
NZ Deprivation Index[c]										
1–2 (least deprived)	45	(7.2)	1704	(13.8)	<0.001	354	(17.5)	6749	(16.8)	0.134
3–4	60	(9.6)	1895	(15.3)		361	(17.9)	7296	(18.2)	
5–6	77	(12.4)	2150	(17.4)		429	(21.2)	7889	(19.6)	
7–8	152	(24.4)	2714	(21.9)		459	(22.7)	9115	(22.7)	
9–10 (most deprived)	289	(46.4)	3924	(31.7)		417	(20.6)	9148	(22.8)	
Region of residence[d]										
Northern	225	(36.0)	4472	(36.0)	1.000	395	(19.5)	7862	(19.5)	1.000
Midland	131	(21.0)	2639	(21.2)		285	(14.1)	5693	(14.1)	
Central	128	(20.5)	2524	(20.3)		552	(27.2)	10,985	(27.2)	
Southern	139	(22.2)	2753	(22.2)		788	(38.9)	15,667	(38.3)	

[a] Age at index date for controls.
[b] Other ethnicities not listed including Middle Eastern, Latin American and African.
[c] New Zealand Deprivation Index measures socioeconomic status. It is a relative measure of deprivation applied to small geographic areas and is based on nine questions from the 2006 census [40].
[d] Regions defined by standard groupings of New Zealand's 20 District Health Boards.

dose in the second year of life; however, the present investigation, employing a large study population for whom we could link data from multiple sources, does not support that assumption.

During an interval dominated by a prolonged pertussis epidemic we observed no reduction in VE between 6 months and 3 years of age following the 3-dose primary acellular pertussis vac-

Table 2
Estimated age and dose-specific vaccine effectiveness (VE) against hospitalised and notified pertussis, children born 2006–2013, New Zealand.

Age	Doses	Hospitalisations						Non-hospitalised notifications					
		Cases		Controls		VE (95% CI)		Cases		Controls		VE (95% CI)	
		N	(%)	N	(%)	Matched[a]	Adjusted[b]	N	(%)	N	(%)	Matched[a]	Adjusted[b]
Total		N = 638		N = 12,682				N = 2803		N = 55,662			
6 w–2 m		N = 322		N = 6329				N = 99		N = 1972			
	0	195	(60.6)	3420	(53.9)	Ref	Ref	45	(45.5)	804	(40.8)	Ref	Ref
	1	127	(39.4)	2925	(46.1)	43 (21, 58)	28 (0, 48)	54	(54.4)	1166	(59.1)	28 (−23, 58)	1 (−73, 43)
3 m–4 m		N = 122		N = 2486				N = 123		N = 2479			
	0	30	(24.6)	218	(8.8)	Ref	Ref	19	(15.5)	184	(7.4)	Ref	Ref
	2	32	(26.3)	1165	(46.9)	84 (72, 91)	82 (68, 90)	48	(39.0)	1339	(54.0)	70 (47, 83)	68 (43, 82)
5 m–11 m		N = 104		N = 2060				N = 294		N = 5871			
	0	36	(34.6)	97	(4.7)	Ref	Ref	66	(22.5)	240	(4.1)	Ref	Ref
	3	39	(37.5)	1243	(60.3)	93 (87, 96)	93 (87, 96)	168	(57.1)	4451	(75.8)	87 (82, 91)	86 (80, 90)
1 y		N = 36		N = 717				N = 454		N = 9027			
	0	15	(41.7)	32	(4.5)	Ref	Ref	124	(27.3)	372	(4.1)	Ref	Ref
	3	18	(50.0)	642	(89.5)	94 (87, 97)	94 (86, 97)	315	(69.4)	8204	(90.9)	89 (86, 91)	89 (86, 91)
2 y		N = 24		N = 484				N = 491		N = 9790			
	0	10	(41.7)	29	(6.0)	Ref	Ref	110	(22.4)	364	(3.7)	Ref	Ref
	3	14	(58.3)	434	(89.7)	92 (79, 97)	91 (73, 97)	373	(76.0)	8980	(91.7)	86 (83, 89)	86 (83, 89)
3 y		N = 17		N = 332				N = 567		N = 11,224			
	0	8	(47.1)	29	(6.0)	Ref	Ref	118	(20.8)	431	(3.8)	Ref	Ref
	3	9	(52.9)	434	(89.7)	97 (90, 99)	98 (91, 99)	428	(75.5)	10,267	(91.5)	85 (82, 88)	84 (80, 88)
4 y		N = 1		N = 19				N = 334		N = 6643			
	0	0	(0.0)	0	(0.0)	Ref	Ref	107	(32.0)	273	(4.1)	Ref	Ref
	3 + 1	0	(0.0)	17	(89.5)	–	–	127	(38.0)	3840	(57.8)	92 (89, 94)	93 (90, 95)
5 y		N = 7		N = 135				N = 253		N = 4979			
	0	2	(28.6)	3	(2.2)	Ref	Ref	85	(33.6)	211	(4.2)	Ref	Ref
	3 + 1	5	(71.4)	114	(84.4)	–	–	139	(54.9)	4030	(80.9)	92 (88, 94)	93 (90, 95)
6 y		N = 3		N = 60				N = 159		N = 3111			
	0	0	(0.0)	2	(3.3)	Ref	Ref	43	(27.0)	132	(4.2)	Ref	Ref
	3 + 1	2	(66.7)	45	(75.0)	–	–	102	(64.2)	2494	(80.2)	87 (81, 91)	88 (82, 92)
7 y		N = 2		N = 40				N = 29		N = 568			
	0	1	(50.0)	2	(5.0)	Ref	Ref	8	(27.6)	28	(4.9)	Ref	Ref
	3 + 1	1	(50.0)	30	(75.0)	–	–	19	(65.5)	461	(81.2)	87 (66, 95)	91 (73, 97)

Notes: Age-specific VE estimates were not viable for hospitalisations among children 4–7 years of age due to small case numbers.
[a] Cases and controls were matched on age at pertussis index date and District Health Board area of residence.
[b] Matched model was adjusted by sex, ethnicity and socioeconomic deprivation index.

cination series, nor between 4 and 7 years of age following a booster dose at age 4 years. As expected, the VE estimates were high against hospitalised, more severe pertussis [1] and lower against non-hospitalised pertussis; however, the trajectories of the VE estimates were similar for both severe and less severe pertussis outcomes. Results from various sensitivity analyses did not change our primary finding that there was no evidence of reducing VE following the primary 3-dose series through to age 3 years, or following the first preschool-age booster dose through to age 7 years.

Our findings align with two recently published studies [8,10] and two older studies [21,22], but conflict with a national-level Australian study [9] and a meta-analysis [4]. The meta-analysis suggested that the odds of pertussis increased by a multiple of 1.33 for every year since the last dose of acellular pertussis-containing vaccine; however, the observed increase between intervals of the time since last dose was not linear. Rather, the increase was negligible 2–4 years after last dose and larger as time since last dose grew to 6 years. Further, the meta-analysis was based on studies with 3- and 5-dose schedules [30–34]. Results for 3-dose schedules were not presented separately, making comparison to our results challenging.

Our discordant findings with the national-level Australian study likely depend on a number of factors. Australia has a history of sustained high immunisation coverage and lower overall disease in comparison to NZ where frequent exposure may lead to natural boosting of wild and vaccine-derived immunity. Vaccination timeliness has also been historically better in Australia than in NZ. Differences in disease surveillance practices may also play an important role. Australia had high levels of PCR testing among pertussis notifications during the study period, ranging from nearly 60% in 2005 to over 90% in 2009 among children aged 1–4 years, with even higher levels for infants aged under 1 year [35]. In our study, a total of only 47% of notifications were PCR tested. Without widespread testing, New Zealand's notification criteria based on clinical symptoms may under ascertain less overt pertussis cases. The characterisation of pertussis strains in each country, given that genetic adaptation of the pathogen and waning of vaccine-induced immunity are inter-related [36–39], may also play a role in explaining the discrepancies. While a single VE study documented a high rate of pertactin deficiency among the small portion of isolates that were tested [20], no VE studies to date have directly incorporated relevant strain data. It has been documented in Australia that increases in the prevalence of ptxP3 strains are associated with increased pertussis notification [40]. Additionally, Australia has reported high frequency of B. pertussis isolates lacking pertactin production [41]. Strain adaptations from NZ have not been reported or published to date. A differential landscape of genetic adaptations between the two settings could further explain why an Australian study found significant waning immunity following a primary 3-dose schedule with no toddler booster.

A major strength of our study is NZ's unique healthcare structure and linkable national data collections. We were able to deter-

mine immunisation status for all but four of the total 3470 hospitalised and notified cases by linking directly to individuals' NIR records. We were also able to link hospital and notification data so we could report on these outcomes separately. Results from sensitivity analyses leant further weight to our findings.

Use of existing data meant we were restricted to covariable information that was part of routine administrative and clinical data collection. Though we were able to address more potential confounders than previous studies, our results may still be subject to unmeasured residual confounding. The structure of the NIR as a birth cohort register is another potential limitation of our study because it restricted the number of children who could be observed in later childhood. In other words, during the 2006–2013 observation period, all eight birth cohorts were observed during their first year of life whereas only one birth cohort (infants born in 2006) could be observed during their seventh year of life. Together with the declining incidence of pertussis as children aged, the constrained birth cohort structure of our study population resulted in diminishing precision of the VE estimate for older age groups. Still, the effect estimates for older age groups are steady with heavily overlapping confidence intervals, meaning it is unlikely that there was any true but undetected decrease in VE as children aged.

Adults and older siblings are the most important reservoir for transmission of pertussis to infants and young children [18,42,43]. Because whole-cell vaccine was discontinued only 6 years prior to the beginning of our study period, residual population immunity among adolescents who received whole-cell vaccine in the 1990s may have provided indirect protection for infants and children during our study period. Even though vaccination coverage in NZ was low in the 1990s – only 60–80% of children received the full primary course of whole-cell pertussis vaccines [27,44–46] – it is possible that retained protection from the whole-cell vaccine era may have influenced our findings.

The incidence of pertussis increased across our study period; however, this increase cannot be directly attributed to the removal of the toddler booster dose in 2006. The static rates of hospitalisations we saw among older infants and toddlers suggests that increased awareness during epidemics likely leads to increased reporting of mild illness in these age groups. Also, both overall and among toddlers, peak incidence during the 2011–2013 epidemic was similar to that observed in earlier epidemics during 1999–2000 and 2004–2005, prior to the 2006 removal of the acellular toddler booster dose [41,47]. Importantly, the comparative question of waning immunity cannot be addressed via absolute measures of disease incidence. The consistency of our dose- specific VE measures across increasing age groups supports that removal of the booster dose did not disproportionately affect disease incidence among toddlers.

5. Conclusions

This study has shown sustained protection against both hospitalised and non-hospitalised presentations for pertussis through to children's fourth birthdays following a 3-dose primary course of acellular pertussis-containing vaccine with no toddler dose. After a booster dose at age 4 years VE was also sustained, with no sign of waning over a further 3 years. Our investigation offers diversity to previously studied settings, with an immunisation schedule that starts earlier at age 6 weeks and a background of historically low vaccine coverage and high burden of disease.

Our results suggest that a primary course alone sustains vaccine-derived protection through to the fourth year of life, and a booster dose at that time continues effective protection in the context of high circulating wild disease, particularly for the prevention of more severe pertussis disease.

To consider whether genetic adaptation of the pertussis organism may be affecting the longevity of VE from acellular vaccines, future studies should incorporate characterisation of pertussis strains.

This study supports the NZ immunisation strategy of a primary course starting at age 6 weeks and a booster dose in the fourth year of life.

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Conflict of interest

Conectus at the University of Auckland has received various unrestricted grants from GlaxoSmithKline Biologicals, manufacturer of Boostrix®. None of the authors have received any direct funding. H.P-H. has served on advisory panels for GlaxoSmithKline, Merck Sharp and Dohme, and Pfizer, but has not personally received honoraria. S.R., D.W., D.G. and N.T.: No conflict.

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References

[1] World Health Organisation. Pertussis vaccines: WHO position paper. Wkly Epidemiol Rec 2015;85:433–60.
[2] Falleiros Arlant LH et al. Pertussis in Latin America: epidemiology and control strategies. Expert Rev Anti-infective Ther 2014;12(10):1265–75.
[3] Warfel JM, Zimmerman LI, Merkel TJ. Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model. Proc Natl Acad Sci 2014;111(2):787–92.
[4] McGirr A, Fisman DN. Duration of pertussis immunity after DTaP immunization: a meta-analysis. Pediatrics 2015;135(2):331–43.
[5] Worby CJ et al. Examining the role of different age groups, and of vaccination during the 2012 Minnesota pertussis outbreak. Sci Rep 2015;5.
[6] Haller S et al. Effectiveness of routine and booster pertussis vaccination in children and adolescents, Federal State of Brandenburg, Germany, 2002–2012. Pediatr Infect Dis J 2015;34(5):513–9.
[7] Gambhir M et al. A change in vaccine efficacy and duration of protection explains recent rises in pertussis incidence in the United States. PLoS Comput Biol 2015;11(4):e1004138.
[8] Sheridan SL et al. Acellular pertussis vaccine effectiveness for children during the 2009–2010 pertussis epidemic in Queensland. Med J Aust 2014;200(6):334–8.
[9] Quinn HE et al. Duration of protection after first dose of acellular pertussis vaccine in infants. Pediatrics 2014;133(3):e513–9.
[10] Campbell H et al. Accelerating control of pertussis in England and Wales. Emerg Infect Dis 2012;18(1):38–47.
[11] Klein NP et al. Waning protection after fifth dose of acellular pertussis vaccine in children. N Engl J Med 2012;367(11):1012–9.
[12] Ohfuji S et al. Effectiveness of acellular pertussis vaccine in a routine immunization program: a multicenter, case-control study in Japan. Vaccine 2015;33(8):1027–32.
[13] Magpantay F et al. Pertussis immunity and epidemiology: mode and duration of vaccine-induced immunity. Parasitology 2015:1–15.
[14] Tartof SY et al. Waning immunity to pertussis following 5 doses of DTaP. Pediatrics 2013;131(4):e1047–52.
[15] Witt MA, Katz PH, Witt DJ. Unexpectedly limited durability of immunity following acellular pertussis vaccination in preadolescents in a North American outbreak. Clin Infect Dis 2012;54(12):1730–5.

[16] Misegades LK et al. Association of childhood pertussis with receipt of 5 doses of pertussis vaccine by time since last vaccine dose, California, 2010. JAMA 2012;308(20):2126–32.
[17] Wolff G et al. Estimates of pertussis vaccine effectiveness in United States air force pediatric dependents. Vaccine 2015;33(28):3228–33.
[18] Lavine JS et al. Short-lived immunity against pertussis, age-specific routes of transmission, and the utility of a teenage booster vaccine. Vaccine 2012;30 (3):544–51.
[19] Fulton TR et al. Protective effect of contemporary pertussis vaccines: a systematic review and meta-analysis. Clin Infect Dis 2016. ciw051.
[20] Breakwell L et al. Pertussis vaccine effectiveness in the setting of pertactin-deficient pertussis. Pediatrics 2016. e20153973.
[21] Simondon F et al. A randomized double-blind trial comparing a two-component acellular to a whole-cell pertussis vaccine in Senegal. Vaccine 1997;15(15):1606–12.
[22] Schmitt H-J et al. Efficacy of acellular pertussis vaccine in early childhood after household exposure. JAMA 1996;275(1):37–41.
[23] Ministry of Health, Immunisation Handbook. 2014. Wellington: Ministry of Health; 2014.
[24] Grant CC, Reid S. Pertussis continues to put New Zealand's immunisation strategy to the test. NZ Med J 2010;123(1313):46–61.
[25] Turner N. The challenge of improving immunization coverage: the New Zealand example. Expert Rev Vaccines 2012;11(1):09.
[26] Ministry of Health. National and DHB immunisation data; 2015. Available from: http://www.health.govt.nz/our-work/preventative-health-wellness/immunisation/immunisation-coverage/national-and-dhb-immunisation-data [cited 2015 20 June].
[27] Ministry of Health. The national childhood immunisation coverage survey 2005:2007. Available from: <http://www.health.govt.nz/publication/national-childhood-immunisation-coverage-survey-2005>.
[28] Ministry of Health, Communicable Disease Control Manual. 2012. Wellington: Ministry of Health; 2012.
[29] Salmond C, Crampton P, Atkinson J. NZDep2006 index of deprivation. Wellington: Department of Public Health, University of Otago; 2007.
[30] Gustafsson L et al. Long-term follow-up of Swedish children vaccinated with acellular pertussis vaccines at 3, 5, and 12 months of age indicates the need for a booster dose at 5–7 years of age. Pediatrics 2006;118(3):978–84.
[31] Lacombe K et al. Risk factors for acellular and whole-cell pertussis vaccine failure in Senegalese children. Vaccine 2004;23(5):623–8.
[32] Olin P et al. Declining pertussis incidence in Sweden following the introduction of acellular pertussis vaccine. Vaccine 2003;21(17):2015–21.
[33] Esposito S et al. Long-term pertussis-specific immune responses to a combined diphtheria, tetanus, tricomponent acellular pertussis and hepatitis B vaccine in pre-term infants. Vaccine 2002;20(23):2928–32.
[34] Salmaso S et al. Sustained efficacy during the first 6 years of life of 3-component acellular pertussis vaccines administered in infancy: the Italian experience. Pediatrics 2001;108(5). e81-e81.
[35] Kaczmarek M, Ware R, Lambert S. The contribution of PCR testing to influenza and pertussis notifications in Australia. Epidemiol Infect 2015:1–9.
[36] Mooi FR, Zeddeman A, van Gent M. The pertussis problem: classical epidemiology and strain characterization should go hand in hand. Jornal de pediatria 2015;9(4):315–7.
[37] Martin SW et al. Pertactin-negative *Bordetella pertussis* strains: evidence for a possible selective advantage. Clin Infect Dis 2015;60(2):223–7.
[38] Bouchez V et al. Genomic content of *Bordetella pertussis* clinical isolates circulating in areas of intensive children vaccination. PLoS One 2008;3(6): e2437.
[39] Mooi F, Van Der Maas N, De Melker H. Pertussis resurgence: waning immunity and pathogen adaptation–two sides of the same coin. Epidemiol Infect 2014;142(04):685–94.
[40] Octavia S et al. Newly emerging clones of *Bordetella pertussis* carrying prn2 and ptxP3 alleles implicated in Australian pertussis epidemic in 2008–2010. J Infect Dis 2012;205(8):1220–4.
[41] The Institute of Environmental Science and Research, L. Pertussis Report. January 2013–December 2013. Available from: <https://surv.esr.cri.nz/PDF_surveillance/PertussisRpt/2015/PertussisreportJan-Mar2015.pdf>.
[42] Skoff TH et al. Sources of infant pertussis infection in the United States. Pediatrics 2015;136(4):635–41.
[43] Lavine J et al. Imperfect vaccine-induced immunity and whooping cough transmission to infants. Vaccine 2010;29(1):11–6.
[44] Stehr-Green P et al. How well are we protecting our children? An immunisation coverage survey in Hawke's Bay. NZ Med J 1992;105 (938):277–9.
[45] Grant C. Controlling pertussis in New Zealand by improving our immunisation rate; 2000.
[46] Grant C. The epidemiology of pertussis in New Zealand and risk factors for pertussis in New Zealand infants. In: Pediatrics. University of Auckland; 2004.
[47] Grant C. Vaccinating adults and special groups: current issues in pertussis. In: 7th New Zealand national immunisation conference, Rotorua; 2011.