

Duration of Protection After First Dose of Acellular Pertussis Vaccine in Infants

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KEY WORDS

pertussis, vaccine, effectiveness, waning, immunization

ABBREVIATIONS

ACIR—Australian Childhood Immunisation Register

CI—confidence interval

DTaP—diphtheria–tetanus–acellular pertussis vaccine

OR—odds ratio

PCR—polymerase chain reaction

Tdap—reduced antigen diphtheria–tetanus–acellular pertussis vaccine

VE—vaccine effectiveness

Dr Quinn designed the study, obtained the data, conducted the analysis, drafted the first version of the manuscript, and revised drafts; Dr Snelling designed the study, conducted the analysis, and revised drafts of the manuscript; Prof Macartney conceived the idea for the study and revised drafts of the manuscript; Prof McIntyre conceived the idea and designed the study, obtained the data, and revised drafts of the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Waning effectiveness of 5 doses of acellular pertussis vaccines is well documented after 6 years of age, but data are lacking for fewer doses in younger children.



WHAT THIS STUDY ADDS: In 2- to 3-month-old infants, 1 dose of the diphtheria–tetanus–acellular pertussis vaccine gave significant protection against hospitalized pertussis. The effectiveness of 3 doses decreased from 84% between 6 and 11 months to 59% after 3 years.

abstract



OBJECTIVE: Data on the effectiveness of the diphtheria–tetanus–acellular pertussis (DTaP) vaccine in the first 4 years of life are sparse. We evaluated the vaccine effectiveness (VE) of 1 and 2 doses of DTaP before 6 months of age and of 3 doses from 6 months of age in Australia, where, since 2003, a fourth dose is not given until 4 years.

METHODS: We matched reported pertussis cases aged 2 to 47 months between January 2005 and December 2009 to controls from a population-based immunization register by date of birth and region of residence. VE by number of doses and age group was calculated as $(1 - \text{odds ratio}) \times 100\%$.

RESULTS: VE against hospitalization increased from 55.3% (95% confidence interval [CI], 42.7%–65.1%) for 1 dose before 4 months of age to 83.0% (95% CI, 70.2%–90.3%) for 2 doses before 6 months. The VE of 3 doses of DTaP against all reported pertussis was 83.5% (95% CI, 79.1%–87.8%) between 6 and 11 months, declining to 70.7% (95% CI, 64.5%–75.8%) between 2 and 3 years of age and 59.2% (95% CI, 51.0%–66.0%) between 3 and 4 years of age.

CONCLUSIONS: DTaP provided good protection against pertussis in the first year of life from the first dose. Without a booster dose, the effectiveness of 3 doses waned more rapidly from 2 to 4 years of age than previously documented for children >6 years of age who had received 5 doses. *Pediatrics* 2014;133:e513–e519

Recently, evidence of progressive waning of vaccine effectiveness (VE) in children who have received 5 doses of diphtheria–tetanus–acellular pertussis (DTaP) vaccine at 2, 4, 6, and 18 months and 4 to 6 years of age has been reported from the United States.^{1,2} Postlicensure studies of the effectiveness of fewer doses of DTaP among younger children are limited,^{3–6} and schedule recommendations for acellular pertussis vaccines vary between countries.⁷ In addition, there are concerns that changes in the clonal composition of *Bordetella pertussis* strains, recently documented in Australia⁸ and elsewhere,⁹ may have resulted in declining vaccine effectiveness against, or increased severity of, pertussis in young children.

From 2008 until 2011, Australia experienced a sustained pertussis epidemic, with differing timing by region.¹⁰ In contrast to the pattern in previous epidemics,¹¹ children <10 years of age, including (in contrast to the United States) preschool-aged children, had the highest incidence rates¹⁰ despite sustained high vaccine coverage (see Supplemental Figure 4). In September 2003, 4 years after the replacement of the locally manufactured whole cell pertussis vaccine by DTaP in the Australian National Immunization Program, the 18-month booster dose was discontinued, leaving a childhood schedule of 3 primary DTaP doses at 2, 4, and 6 months of age and a booster at 4 years of age. In 2004, a reduced antigen diphtheria–tetanus–acellular pertussis vaccine (Tdap) was introduced for adolescents, thus retaining a total of 5 doses before the age of 18 years.^{12,13} Adoption of this schedule change was supported by a modeling study¹⁴ based on a 6-year duration of protection after 3 doses of DTaP at 2, 4, and 6 months.¹⁵ In this national study we first examined secular trends in reported pertussis cases. We then assessed the effectiveness of 1 and 2 doses of DTaP before 6

months of age and the effectiveness of 3 doses from 6 months to 4 years of age using a matched case–control approach.

METHODS

Study Population and Case Definition

By law, all cases of pertussis must be reported to public health authorities in all Australian states and territories according to nationally uniform criteria. A confirmed case requires either definitive laboratory evidence (detection by polymerase chain reaction [PCR] test or isolation by culture) or suggestive laboratory evidence (single point serology) together with a compatible clinical illness (coughing illness lasting 2 weeks and either coughing paroxysms, inspiratory whoop, or posttussive vomiting). Diagnostic laboratories have been required to directly report all positive pertussis test results to public health authorities since 1993,¹⁶ and separate notification by clinicians is uncommon.¹⁷ During the period of the VE analysis, detection of *B pertussis* by PCR, using the IS481 target, accounted for the great majority of notifications.¹⁸

Secular Trends in Cases

Notification data were obtained from the National Notifiable Diseases Surveillance System. All pertussis notifications for children aged <4 years with a diagnosis date between January 1, 1995 and December 31, 2010 were included. Age group–specific rates were calculated using Australian Bureau of Statistics estimated resident population data.

Hospitalization data were obtained from the Australian Institute of Health and Welfare National Hospital Morbidity Database, which compiles administrative, demographic, and clinical information about patients admitted to public and private hospitals. All hospital admissions for children aged <4 years between January 1, 1995 and December 31, 2010 were included. Eligible admissions were

extracted based on the International Classification of Diseases, Ninth Revision, code 033 (whooping cough), and 10th Revision, Australian Modification (ICD-10-AM), code A37 (whooping cough), where the code of interest or a subcode was listed as the principal diagnosis or in any other diagnosis field. Age group–specific rates were calculated using Australian Bureau of Statistics estimated resident population data.

Case–Control Study

VE was estimated by using a matched case–control approach. The analysis was stratified by age group, and in infants aged <12 months a subanalysis was performed for notified pertussis cases also recorded as hospitalized. All pertussis cases in Australia with disease onset from January 1, 2005 (from January 1, 2006 only for Western Australia and from January 1, 2007 only for Tasmania) until December 31, 2009 were included. Additional fields were region of residence, date of birth, disease onset date, hospitalization status, and vaccination status. Eligible cases were patients aged 2 months to <4 years. Cases where immunization status was not recorded in the notification data set supplied by states and territories were excluded. During this period, DTaP combination vaccines from 1 manufacturer (Glaxo-SmithKline) were in almost exclusive use around Australia.

The National Centre for Immunization Research and Surveillance holds a deidentified data set for the Australian Childhood Immunization Register (ACIR). The ACIR is a population-based register, which includes all children of citizens and permanent residents enrolled in the national publicly funded health care system, regardless of vaccination status (99% enrollment by 12 months of age). The vaccination status of notified cases was almost always derived from the ACIR, although parents were also interviewed as part of public health follow-up. For

each case, controls were randomly sampled from the ACIR. They were matched to cases by date of birth and state or territory of residence. Because the analysis relies on discordance in vaccination status between cases and matched controls, and given the high vaccine coverage for 3 or more doses of DTaP-containing vaccines (92% at 12 months and 95% at 24 months)¹⁹ and the ready availability of controls from the ACIR, we sampled 20 age-matched controls for each case to maximize precision. We selected eligible controls born on the day before or the day after the birth date of the index case to ensure that cases were not matched to themselves. The vaccination status of controls was ascertained using the ACIR. Any doses received by a control after the date of disease onset in their matched case were not included in the total.

Statistical Analysis

Comparisons of demographic characteristics between cases and controls were performed using the Pearson χ^2 test and a significance level of $P < .05$. For the categorical analysis of VE by age group, a conditional logistic regression model was generated in SAS version 9.3 (SAS Institute, Inc, Cary, NC) using the PHREG procedure. The model was stratified by the age groups 2 to 3 months, 4 to 5 months, 6 to 11 months, and 1, 2, and 3 years, to estimate the odds ratio (OR) for receipt of 1, 2, or 3 vaccine doses for notified pertussis cases compared with their matched controls. VE estimates and 95% CIs were based on the OR using the formula $VE = 1 - OR \times 100\%$.

To more precisely measure changes in the VE of 3 doses against all notified pertussis cases from 6 months to 4 years of age, a separate conditional logistic model was constructed in Stata version 12.1 (Stata Corp, College Station, TX), which included an age–vaccine status interaction variable fitted with fractional

polynomials.²⁰ For all comparisons, $P < .05$ was considered evidence of statistical significance.

Sensitivity analyses were conducted to evaluate the potential impact of differential immunization status among excluded cases with unrecorded vaccination status, where such cases were reclassified under the alternate extreme assumptions that they were all unvaccinated or all fully vaccinated for age.

RESULTS

Secular Trends

Figure 1 shows age-specific pertussis notification rates from 1995 to 2010. After the introduction of DTaP vaccine for all doses in 1999, notification rates were consistently low in children aged ≥ 6 months and eligible for 3 doses of vaccine. Notification rates for all age groups increased steeply from 2007. This was particularly notable for children aged 2 to 3 years, who had the second highest notification rate in 2008 to 2010 but typically had the lowest notification rates in previous peak periods. As with notification rates, hospitalization rates for all age groups rose from 2007, although they did not surpass those of the 1997 epidemic (Fig 2).

Vaccine Effectiveness

Of 5226 notified cases in the available data sets for the VE analysis, 642 (12%) were excluded because vaccination status was not recorded, leaving 4584 cases for the matched analysis (see Supplemental Figure 5). Cases for whom no record of vaccination status was available were significantly older (10% aged < 12 months versus 13% aged ≥ 12 months; $P < .001$) and more likely to be from the state of New South Wales (15% versus 6% elsewhere; $P < .001$). The total number of notified cases increased progressively from the second to the fourth year of life, whereas the absolute number of hospitalized cases decreased substantially after 12 months of age (see Supplemental Figure 6). The proportion of cases who had received no vaccine doses decreased progressively with age, from 6 to 11 months (22%) to 3 years (11%). The majority of cases (92%) were diagnosed by PCR, with another 6% diagnosed by serology.

National data from the ACIR between 2000 and 2010 showed that after 2 months of age, the proportion of children aged up to 12 months recorded as having received no doses of DTaP remained nearly constant, with the first

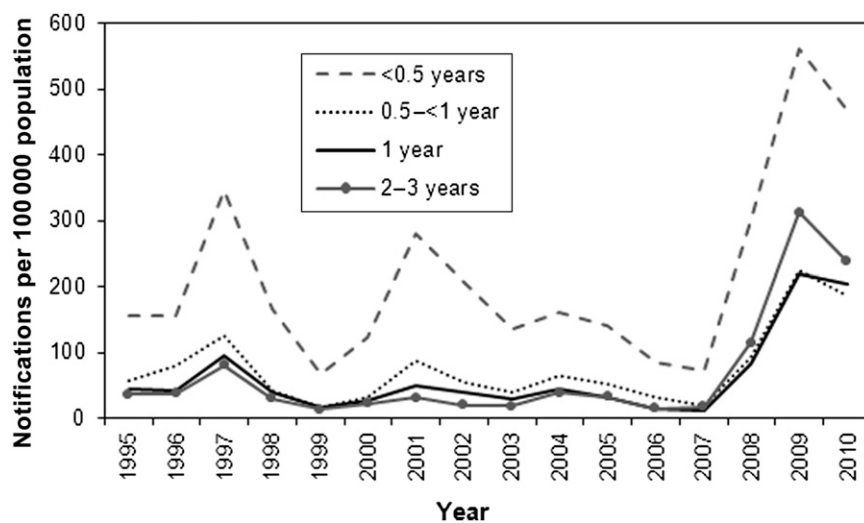


FIGURE 1 Pertussis notification rates in children aged < 4 years, 1995–2010, Australia.

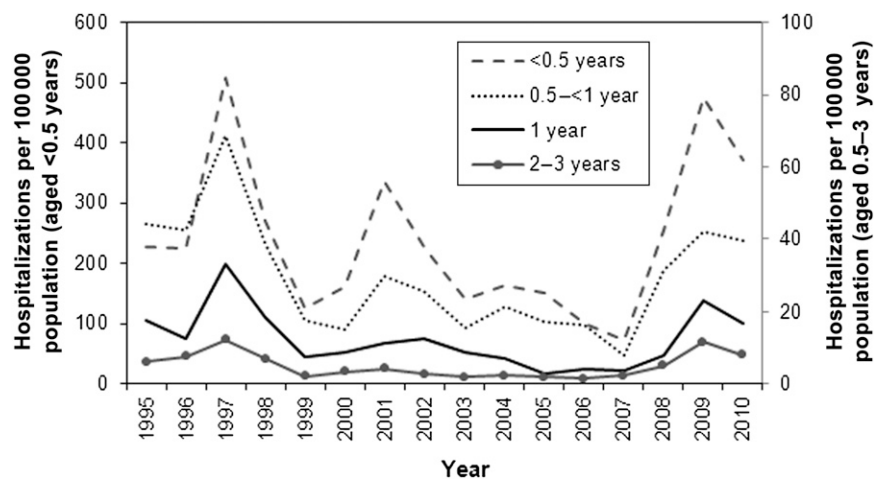


FIGURE 2 Pertussis hospitalization rates in children aged <4 years, 1995–2010, Australia.

TABLE 1 Estimated VE in Reported Pertussis Cases 2 to 11 mo of Age, by Hospitalization Status, 2005–2009

Age (mo)	Doses	Cases (%)	Controls (%)	OR (95% CI)	Estimated VE (95% CI)
All reported cases ^a					
2–3		<i>N</i> = 1446	<i>N</i> = 28 828		
		<i>N</i> = 601	<i>N</i> = 11 952		
	0	175 (29.1)	2081 (17.4)	Reference	Reference
	1	401 (66.7)	9634 (80.6)	0.46 (0.38–0.56)	53.7 (43.8–61.9)
4–5		<i>N</i> = 317	<i>N</i> = 6397		
	0	55 (17.4)	436 (6.8)	Reference	Reference
	2	138 (43.5)	4311 (67.4)	0.25 (0.18–0.34)	75.3 (65.7–82.3)
6–11		<i>N</i> = 528	<i>N</i> = 10479		
	0	110 (20.8)	493 (4.7)	Reference	Reference
	2	70 (13.3)	1698 (16.2)	0.19 (0.14–0.27)	80.8 (73.5–86.1)
	3	295 (55.9)	7991 (76.3)	0.17 (0.13–0.21)	83.5 (79.1–87.0)
Hospitalized cases					
2–3		<i>N</i> = 589	<i>N</i> = 11 721		
		<i>N</i> = 353	<i>N</i> = 7031		
	0	111 (31.4)	1293 (18.4)	Reference	Reference
	1	234 (66.3)	5633 (80.1)	0.45 (0.35–0.57)	55.3 (42.7–65.1)
4–5		<i>N</i> = 119	<i>N</i> = 2353		
	0	20 (16.8)	143 (6.1)	Reference	Reference
	2	40 (33.6)	1615 (68.6)	0.17 (0.10–0.30)	83.0 (70.2–90.3)
6–11		<i>N</i> = 117	<i>N</i> = 2337		
	0	25 (21.4)	115 (4.9)	Reference	Reference
	2	16 (13.7)	416 (17.8)	0.19 (0.10–0.37)	81.3 (63.4–90.5)
	3	59 (50.4)	1734 (74.2)	0.15 (0.09–0.25)	85.0 (75.0–91.0)

^a Reported cases include those hospitalized, not hospitalized, and of unknown hospitalization status.

dose received before 3 months of age in 87% (see Supplemental Figure 4). Accordingly, we measured between-dose VE for 1 dose only among children aged <4 months. Table 1 shows estimated VE against all notified pertussis and hospitalized cases only for 1, 2, and 3 doses. In the first year of life, protection against all notified pertussis cases was demonstrated after the first dose (VE 53.7%; 95% CI, 43.8%–61.9%), increasing

substantially after the second dose (VE 75.3%; 95% CI, 65.7%–82.3%). The estimated VE of 2 doses was nonsignificantly higher against hospitalization (83.0%; 95% CI, 70.2%–90.3%) than for all notified cases after 2 doses, as indicated by nonoverlapping 95% CIs, but the estimated VE for 1 dose for these categories was almost identical (53.7% vs 55.3%). For both notified and hospitalized cases, there was a small increment in

the estimated VE for 3 compared with 2 doses among children aged 6–11 months for both notified and hospitalized cases (Table 1).

Table 2 shows estimated VE among children over the age of 12 months by 1-year age groups. In the second year of life, VE decreased to 79.2% from 83.5% among 6–11 month olds. However, among children aged 2 to 3 years, there was an additional decrease in estimated VE to 70.7%, and the 95% CI (64.5%–75.8%) no longer overlapped with that estimated for 6- to 11-month-olds (83.5%; 95% CI, 79.1%–87.0%). Among 3-year-olds, VE declined further to 59.2% (95% CI, 51.0%–66.0%), significantly lower than for 1-year-olds, as indicated by non-overlapping 95% CIs (Table 2). When VE was modeled with age as a continuous variable, we found evidence of a progressive decline in the VE of 3 doses of pertussis-containing vaccine (vaccination–age interaction, $P < .01$), with point estimates and 95% CIs shown by 6-month age groups in Fig 3. This model estimated that the VE of 3 doses at 2, 4, and 6 months of age had decreased to below 50% before the age of 4 years. We did not estimate the VE for cases recorded as hospitalized when aged ≥ 12 months, because this was only 7% of all notifications in this age group, and the proportion of missing data for hospitalization status increased with age (Fig 2).

The sensitivity analysis demonstrated that the progressive decrease in VE we found after 12 months of age was robust to the assignment of all those with missing data as vaccinated appropriately for age, but not to the assignment of all being unvaccinated. The relative VE of 1, 2, and 3 doses in infants <12 months of age remained unchanged under both extreme assumptions (see Supplemental Table 3).

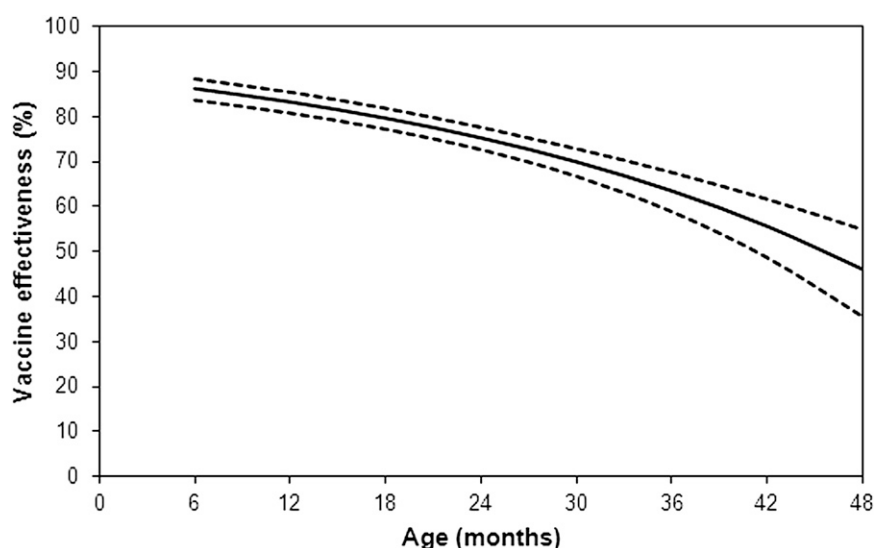
DISCUSSION

This is the largest reported observational study of acellular pertussis vaccine

TABLE 2 Estimated VE Among All Reported Pertussis Cases^a Aged 1 to 3 y, 2005–2009

Age (y)	Doses	Cases (%), N = 3123	Controls (%), N = 61 636	OR (95% CI)	Estimated VE (95% CI)
1		N = 870	N = 15 170		
	0	162 (18.6)	774 (4.5)	Reference	Reference
2	3	662 (76.1)	15 170 (87.6)	0.21 (0.17–0.25)	79.2 (75.0–82.8)
		N = 927	N = 18 438		
3	0	140 (15.1)	887 (4.8)	Reference	Reference
	3	754 (81.3)	16 354 (88.7)	0.29 (0.24–0.36)	70.7 (64.5–75.8)
3		N = 1326	N = 25 878		
	0	150 (11.3)	1186 (4.6)	Reference	Reference
	3	1141 (86.1)	23 031 (89.0)	0.41 (0.34–0.49)	59.2 (51.0–66.0)

^a Notified cases include those hospitalized, not hospitalized, and of unknown hospitalization status.

**FIGURE 3**

Modeled estimates of vaccine effectiveness for 3 doses of DTaP (versus no doses) against pertussis notification by age. Note: Effectiveness (solid line) and pointwise 95% confidence intervals (dotted lines) were estimated from the best fitting fractional polynomial transformation of the age⁶vaccine interaction, being a first degree cubic polynomial.

effectiveness in children aged <5 years, both against severe disease in infants and against all laboratory-confirmed pertussis. We had large numbers of cases because of a contemporaneous pertussis epidemic and widespread availability of PCR for diagnosis, with much greater sensitivity and ease of use compared with culture.²¹

In young infants, we found the VE of 1 dose of DTaP against hospitalization of 55.3% (95% CI, 42.7%–65.1%), consistent with previous estimates of 51% (95% CI, 41%–60%)⁵ and 68.0% (95% CI, 45.6%–81.1%).⁴ This supports the early administration of the first dose.^{22,23} This was recommended in successive

Australian states from 2009, and by 2011 50% of first doses were delivered before 8 weeks of age nationally.²⁴ There was a major increment in estimated VE to approximately 80% after the second dose but no detectable increase in VE after the third dose among children aged 6 to 11 months, despite large case numbers (Table 1). This finding supports the approach of a delayed third dose, as practiced in many Scandinavian countries⁷ and recently adopted by France.²⁵ High effectiveness in the first year is reassuring, because disease severity is highest in this age group. Despite pertussis strains with altered antigenic composition

being recently documented in young Australian infants,⁸ VE was high in the first year of life.

Among children from 1 to 3 years of age, not eligible for a booster dose, we found evidence that 3-dose VE declines progressively from 2 years of age (70.7%; 95% CI, 64.5%–75.8%), to <50% by 4 years of age. This is in contrast to the findings of a previous Australian study, conducted when the locally manufactured whole cell pertussis was in use, which estimated the VE of 3 or more doses (scheduled at 2, 4, and 6 months of age) among children aged 2 to 4 years to be 84.5% (95% CI, 78.3%–88.9%) against all reported pertussis.²⁶ Although pertussis infection among immunized children 2 to 3 years uncommonly results in hospitalization, those not hospitalized may have symptoms severe enough to lead to emergency department presentation, and both hospital and emergency department presentation are underestimated.²⁷ Importantly, children 2 to 3 years of age commonly have younger siblings and may play an important role in the transmission of infection to unimmunized infants, vulnerable to severe disease.^{28–30} Of the few studies of field effectiveness of acellular pertussis vaccines in children <5 years of age,^{3–6} none separately estimated VE for the first and second year of life or evaluated changes in VE after 2 years of age. The US study estimated that the effectiveness of 3 doses of pertussis-containing vaccine in children aged <2 years was 91.7% (95% CI, 74.5%–97.3%), but some 30% of cases had received whole cell vaccine.³ In Denmark, where an acellular pertussis vaccine containing only pertussis toxin is exclusively used, but with a later third dose, VE for 3 doses among children aged <2 years was estimated to be 78% (95% CI, 59%–88%) and 93% (95% CI, 78%–98%) for non-hospitalized and hospitalized cases, respectively.⁵ In contrast to our results,

a very high VE for 3 doses of acellular vaccine among children aged 12 to 39 months of 96.6% (95% CI, 90.2%–98.7%) was estimated for all reported cases from England and Wales, one of the few other countries where no booster is given in the second year of life.⁶ This higher estimate could be related to the study being conducted during a non-epidemic period or lower ascertainment of less severe cases, which tends to raise VE estimates³¹ Similarly, our estimates may have been reduced because we had a higher proportion of less severe cases, as would be expected with the substantial increases in PCR testing for pertussis identified during the period of the study.³² The lack of increase in coded hospitalizations during the 2008–2010 epidemic (Figs 1 and 2), despite greatly increased testing, would be in keeping with lower severity among reported cases. We found in sensitivity analysis that point estimates of VE increased under the extreme (and implausible) assumption that all children with unrecorded vaccination status were unvaccinated; because incomplete records occurred disproportionately among older children, evidence for waning VE was also sensitive to this assumption (see Supplemental Information). We believe that missing records were not related

to vaccination status per se but rather to less intense follow-up of large numbers of cases in older children, so VE estimates were not likely to be systematically biased. A limitation of this study was the lack of gender and socioeconomic data for cases and controls, which may have been confounders in the analysis, although the large numbers of controls used should have minimized this effect.

Our study is the first to examine trends in VE between 2 and 4 years of age after 3 primary doses of acellular vaccine. Waning immunity is a likely explanation for the progressive decline in estimated VE we found from 12 months of age in the absence of a booster dose. A number of lines of evidence support this explanation. First, although magnified by increased testing, the 10-fold increase in the incidence of notified pertussis infection in the 2- to 4-year age group in the current epidemic compared with the previous 3-year period is striking.¹⁰ Second, it is consistent with antibody persistence data showing that pertussis toxin immunoglobulin G antibody decreases to close to baseline levels by 18 months after the last dose at 6 months.^{33,34} Third, Australian population-based seroepidemiologic data have demonstrated similar findings, with a significant increase in the

prevalence of undetectable pertussis toxin immunoglobulin G antibody 3 years after discontinuation of the 18-month booster.³⁵

CONCLUSIONS

Our data have important implications for policy and practice in all countries using acellular vaccines. First, with respect to protection of young infants, our finding of robust protection after 1 or 2 doses argues for the first dose to be given as early as possible, with 6 weeks of age approved for the first dose by all major regulatory authorities. Second, they provide strong support for a booster dose in the second year of life, either as a delayed third dose after a 2-dose primary schedule or a fourth dose if 3 primary doses are given before 6 months of age. This an important consideration in the context of maternal Tdap immunization, because there may be a reduced immune response after the primary series of DTaP in infants born to mothers who have received Tdap in the third trimester of pregnancy.³⁶

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