The 1996 pertussis epidemic in New Zealand: vaccine effectiveness

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Abstract

Aim. To assess if reduced vaccine effectiveness may have accounted for increased hospitalisations in the 1996 pertussis epidemic.

Methods. Vaccine effectiveness was estimated by comparing vaccine coverage of the population (derived from a literature review) with that of cases (from notification data available from 1 June 1996) - the screening method. Only three doses of pertussis vaccine were in the immunisation schedule until 1996, so vaccine effectiveness was calculated for three or more doses.

Results. Most likely estimates of vaccine effectiveness for Europeans were 88% (95% confidence interval 71 to 95%) for 5- to 14-month-olds, 80% for 15-month to 4-year-olds (66 to 88%) but lower for children aged 5 years and older with confidence limits including zero. Vaccine effectiveness estimates for Maori were less for each age group but based on few observations.

Conclusions. The increase in hospitalisations for young children in the 1996 epidemic cannot be directly attributed to a reduced vaccine effectiveness, as vaccine effectiveness estimates for preschool Europeans are in line with international evidence. Additionally, the vaccine effectiveness estimates in this study are likely to be underestimates due to bias. The lower estimates for vaccine effectiveness among Maori are likely to reflect increased pressure of these biases, although a biological basis for the difference or clustering of factors that cause failure are also possible. The vaccine effectiveness estimates decrease with age, a likely combination of waning vaccine immunity and the cross-sectional nature of the screening method itself for determining vaccine effectiveness.

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The 1996 pertussis epidemic resulted in about 50% more hospitalisations than the 1986 or 1991 epidemics, particularly for under one-year-olds.[1] As coverage is likely to have increased during this period, this paper explores reduced pertussis vaccine effectiveness (VE) as the cause of the increase. VE includes the actual vaccine efficacy and components of effectiveness of vaccine administration (for example, cold chain and timing of pertussis vaccine doses).

Notified cases are probably not representative of all community cases and have incomplete (sometimes inaccurate) ethnicity and immunisation data. Furthermore, we do not have reliable population immunisation coverage data. Yet, policy formulation requires the best use of available information. Our analysis and presentation of data try to take into account the potential biases and include some sensitivity analyses to test the assumptions used.

Methods

We use the screening method to determine VE:[2]

$$VE = 1 - \frac{PCV}{1 - PCV} * \frac{1 - PPV}{PPV}$$

where PPV is the proportion of the population vaccinated and PCV is the proportion of cases vaccinated. The screening method formula is one minus the odds ratio for disease in vaccinated compared to unvaccinated people. An odds ratio of 0.1 (i.e. disease ten times less likely in vaccinated) equates to a VE of 90% (i.e. vaccine preventing 90% of cases). A negative VE means that the vaccine is actually associated with a risk of disease at the particular age considered (e.g. if odds ratio = 3, VE= -200%). With this method, a negative vaccine effectiveness may arise for older children if the vaccine protection decays with time,[3] i.e. the vaccine has delayed onset of disease to an older age. For pertussis, delayed onset is not just an idle epidemiological curiosity - it is an important clinical benefit as pertussis at a young age is more likely to cause serious complications.

The screening method is prone to confounding,[2] so the VE was determined by strata of ethnicity and age, two factors likely to be associated with both vaccine coverage and pertussis incidence. (This stratification may also control for bias in notifications by ethnicity and age). The PPV (proportion of population vaccinated, or vaccine coverage) was derived from all available published coverage data (as per Table 1), by convergence of estimates of the authors and an expert (Anne McNicholas) on immunisation coverage. In deriving the estimates of vaccine coverage, likely biases were considered in each study select cohort of children with available records is likely to overestimate the vaccine coverage for the population at large). The estimation of coverage was conducted before VE calculations to prevent retrospective observer bias.

Notification data for pertussis were available for the 12 months from 1 June 1996, the date pertussis became a notifiable disease. Age was categorised as: 5-14 months; 15 months to 4 years; 5-9 years; 10-14 years; and 15+ years. These age groups are in line with the recommended immunisation schedule of the third dose of pertussis vaccine at 5 months and the fourth at 15 months. However, very few notified cases were eligible for the fourth dose of pertussis introduced in 1996, making this study an assessment of VE for three doses of vaccine. Only cases of European or Maori ethnic group (as recorded on the notification data) were considered due to insufficient numbers for other ethnic groups.

The PCV (proportion of cases vaccinated) was obtained from notification data, limited to *probable* or *confirmed* pertussis cases. A confirmed pertussis case was one that was laboratory-confirmed, or epidemiologically linked (i.e. in contact during the incubation period) to a laboratory-confirmed case. Probable cases were those recorded as having a cough lasting longer than two weeks and any one of the following additional symptoms: paroxysmal cough, cough ending in vomiting or apnoea, or inspiratory whoop. The vaccine status was classified as *vaccinated* if recorded as 'fully vaccinated' or in receipt of three or more doses of pertussis vaccine. Cases not *not vaccinated* were those recorded as 'not vaccinated', 'partially vaccinated' or with clear documentation that less than three doses of pertussis vaccine had been received. All other cases were assigned as unknown, excluded from baseline VE calculations, but included in a sensitivity analysis as vaccinated. Vaccine status was based either on parental recall or from documentation available to the notifier.

Results

Coverage data for three doses of pertussis vaccine suggest that coverage has been increasing in the 1990s (Table 1). From these results, PPV estimates were derived (Table 2).

Between 1 June 1996 and 31 May 1997, 717 cases of pertussis were notified, of which 551 were confirmed (n=425) or probable (n=126). (There were 627 of the 717 notified cases with a stated ethnicity (87.4%): 502 European, 98 Maori, 18 Pacific people, 9 Other.) Of the 551 confirmed or probable cases, 330 were stated as either Maori or European and aged five months to 14 years of age. Of these 330 cases, 221 were classified as vaccinated (67.0%), 67 not vaccinated (20.3%) and 42 were unknown (12.7%). The VE estimates varied by age and ethnic strata, being greater for Europeans and for younger children (Table 3).

Discussion

A 1987 review of pertussis vaccine effectiveness (VE) found a wide range of estimates depending on duration of follow-

Table 1. Results of literature review of coverage of three doses of pertussis vaccine in New Zealand.

Author (year)	Study method	Age of subject children in 1996-97	Likely bias in the PPV estimate	Estimate of PPV for three doses of pertussis vaccine, by strata
Bell et al (1997)[13]	Cohort of Christchurch children	1 to 2 years old	Overestimate	• 93% for all children (based on immunisations completed at 8 months of age)
Rainger et al (1997)[14]	Survey in Northern RHA	2 to 4 years old	Underestimate	• 86.0% overall • 77.6% for Maori • 90.6% for Other
McNicholas et al (1997)[15]	HBL Benefit claim data	6 months to 2 years old	-	• 91.0% across New Zealand
		18 months to 3 years old	-	• 90.6% across New Zealand • Also found higher rates for Southern and Central
McNicholas and Baker (1996)[16]	HBL Benefit claim data	1 to 3 years old	-	• 88.7% across New Zealand • 86.5%, 85.3, 93.0, and 91.3% respectively for Northern, Midland, Central and Southern RHAs respectively
McNicholas and Baker (1995)[17]	HBL Benefit claim data	2 to 4 years old	-	• 84.1% across New Zealand
Essex et al (1995)[18]	National Cohort	5 to 8 years old	Overestimate	• 95.6% vaccinated for pertussis at one year of age
Stehr-Green et al (1992)[19]	Survey in Hawkes Bay	6 to 9 years old	Underestimate	• 89%
Ramadas et al (1992)[20]	General practitioner note review in eastern BOP	6 to 9 years old	?	• 80.6%
1992 Immunisation Survey[21]	Survey, national	7 to 10 years old	Underestimate	• 79.4, 77.0, 80.3, and 85.7% for Northern, Midland, Central and Southern RHAs. • No ethnic specific estimates, but overall Maori about 10% less pertussis immunisation than European

Table 2. Estimates of vaccine coverage (PPV) for three doses of pertussis vaccine in 1996-97, by age and ethnicity.

		Age during 1996-97			
		5-14 months	15 months-4 years	5-9 years	10-14 years
Most likely estimates	Maori	73%	80%	74%	74%
	European	85%	92%	86%	86%
Low and high estimates for sensitivity analyses					
Low	Maori	65%	75%	70%	70%
	European	75%	85%	80%	80%
High	Maori	80%	85%	80%	80%
	European	90%	95%	90%	90%

Table 3. Vaccine effectiveness calculations by strata for confirmed or probable Maori and European notified cases of pertussis, 1 June 1996-31 May 1997.

Measure		Maori				European				Total
		5-14 m	15 m - 4 yrs	5-9 yrs	10-14 yrs	5-14 m	15 m - 4yrs	5-9 yrs	10-14 yrs	
Vaccinated cases		5	9	13	6	8	46	87	47	221
Non-vaccinated cases[1]		4	3	2	0	12	20	20	6	67
Total by strata[2]		10	16	18	9	24	75	117	61	330
PCV[3]		56%	75%	88%	86%	40%	70%	81%	89%	77%
VE: Most likely PPV estimates										
VE		54%	25%	-128%	-111%	88%	80%	29%	-28%	-
	Lower 95% CI	-72%	-177%	-912%	-1651%	71%	66%	-15%	-198%	-
	Upper 95% CI	88%	80%	48%	75%	95%	88%	56%	45%	-
VE: Sensitivity analysis										
VE: low PPV		33%	0%	-179%	-157%	78%	59%	-9%	-96%	-
VE: high PPV		69%	47%	-63%	-50%	93%	88%	52%	13%	-
VE: Unknown immunisation status = not vaccinated		63%	68%	9%	30%	91%	86%	53%	45%	-

PPV=proportion of population vaccinated; PCV=proportion of cases vaccinated; VE=vaccine effectiveness; CI=confidence interval.
[1]Values of zero were replaced by one in calculations of VE.
[2]Total by strata includes cases with unknown immunisation status.
[3]PCV equals vaccinated cases divided by the sum of vaccinated and non-vaccinated cases.

up, study design and case definition.[4] In recent studies using a moderate to severe disease case definition of pertussis, VE for three doses of vaccine ranged from 86% to 98% for whole cell vaccine (excluding the Connaught product) and 59% to 89% for acellular vaccines.[5] Only whole cell pertussis vaccines have been routinely used on the New Zealand national immunisation schedule: Wyeth Lederle vaccine (January 1994 to present); Swiss Serum (September 1993 to January 1994 and also prior to January 1988); Pasteur Merieux (May 1989 to September 1993); and CSL (January 1988 to May 1989). Both the Wyeth Lederle vaccine (VE 86% for three doses, 99% for four doses) and Pasteur Merieux vaccine (VE 96%) had higher VE than acellular vaccines in recent randomised trials[5,6]

The VE estimates in this study (Table 3) for European children aged five to 14 months (88%), and 15 months to

four years (80%), are in line with estimates for similar aged children in the UK and US using the screening method.[7,8] Application of the screening method to Wellington cases during the 1991 epidemic also provided similar VE for the youngest children.[9] The VE estimates for European pre-school children therefore do not support reduced vaccine effectiveness as a direct explanation for the increase in pertussis hospitalisations in the 1996 epidemic compared to previous epidemics.

The lower VE for Maori is cause for concern but is based on small numbers. Both Maori and European VE estimates are likely to be underestimated due to cumulative biases and these may be greater for Maori given that a lower percentage of Maori cases are suspected to be notified compared to European cases.[1] Specifically, residual misclassification of either pertussis disease status or immunisation status, is likely to lower the VE estimates. Second, cases with unknown vaccine status are more likely to be unvaccinated and, excluding them from the analysis (as we did for most estimates), would result in lower VE; the final row of Table 3 assumes they are all unvaccinated, resulting in improved VE estimates. Third, immunised cases may be more likely to be notified for two reasons: people with pertussis who present to their general practitioner are probably also more likely to have presented for immunisation in the past; and general practitioners who are more likely to notify a case of pertussis are also probably more likely to achieve higher immunisation coverage. The effect of this third bias is perhaps crudely corrected by assuming that the cases used to estimate the VE actually come from a subgroup of the population with a higher PPV (see second to last row of Table 3). However, a counteracting diagnostic bias may be increasing VE estimates if the diagnosis is less likely to be made in children known to be fully immunised. Finally, small cell sizes may have caused a low VE estimate by chance alone but it is unlikely that chance would consistently cause most VE estimates by strata to be low.

The VE estimates decreased with increasing age for both Europeans and Maori, as expected. The decreasing VE observed with increasing age, even to negative estimates, may be due to a combination of waning immunity, the screening method itself and an accumulation of the biases discussed in the previous paragraph. The pertussis vaccine may be effective in the short term, but having waning immunity[10] such that for older children and adults, previous vaccination offers less protection against pertussis infection than a previous natural pertussis infection - although the assumed superiority of naturally acquired immunity to vaccine acquired immunity has been challenged.[11,12] Any resultant increased community incidence of pertussis in older children and adults may in turn increase the exposure of young children to pertussis infection. Whether increased community incidence due to waning immunity is an explanation for the apparent increase in hospitalisations in the 1996 epidemic is uncertain. Alternative explanations include an increase in hospitalisations purely due to an increased case-hospitalisation rate, or possibly clustering of disease among socioeconomic groups more likely to be admitted.

Conclusion

The acceptable VE estimates for European children aged 5-14 months (88%) and 15 months to four years (80%) suggest that low VE, for preschoolers at least, is not a direct cause of the increase in pertussis hospitalisations in the 1996 epidemic compared to the previous two epidemics. Increased community incidence remains possible even though immunisation coverage has been increasing and the vaccine appears effective, because of the waning vaccine immunity and the possibility that older children and adults are in fact the major sources of infection. The fourth dose of pertussis vaccine introduced in 1996 should lower community incidence. Booster doses of pertussis vaccine, perhaps throughout life as currently recommended for tetanus and diphtheria, also deserve consideration both to protect older children and adults, and to increase community immunity. But a substantial effect of community immunity is not certain as all vaccines, acellular and cellular, have reduced VE for milder disease (e.g. subclinical infection) that may be important for transmission in the population.[5]

The VE estimates in this study are likely to be underestimates due to bias. The lower estimates for VE among Maori are likely to reflect increased pressure of biases, although a biological basis for the difference or clustering of factors that cause failure are also possible. The screening method presented in this paper could be used to estimate the VE for other vaccine preventable diseases using notification data. However, care must be taken in interpretation due to the biases described here, particularly for older children and a vaccine with waning immunity. Increased representativeness and accuracy of notification data is required for more robust analysis.

Disclaimer. Dr Mansoor is an employee of the Ministry of Health. However, the views expressed in the article are those of the authors and do not necessarily reflect those of the Ministry.

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