Clinical Infectious Diseases

MAJOR ARTICLE

Effectiveness of Acellular Pertussis Vaccine in Older Adults: Nested Matched Case-control Study

Bette C. Liu,[1,©] Wen-Qiang He,[1] Anthony T. Newall,[1] Helen E. Quinn,[2,3] Mark Bartlett,[4] Andrew Hayen,[5] Vicky Sheppeard,[6] Nectarios Rose,[6] C Raina MacIntyre,[7] and Peter McIntyre[2,8]

[1]School of Public Health and Community Medicine, University of New South Wales, Sydney, Australia; [2]National Centre for Immunisation Research and Surveillance and University of Sydney, Australia; [3]Discipline of Child and Adolescent Health, Faculty of Medicine and Health, University of Sydney, Sydney, New South Wales, Australia; [4]Sax Institute, Sydney, Australia; [5]University of Technology, Sydney, Australia; [6]Health Protection, New South Wales Ministry of Health, Sydney, New South Wales, Australia; [7]Kirby Institute, University of New South Wales, Sydney New South Wales,, Australia; and [8]Department of Women's and Children's Health, University of Otago, Dunedin, New Zealand

Background. Despite recommendations that older adults receive acellular pertussis vaccines, data on direct effectiveness in adults aged over 50 years are sparse.

Methods. A case-control study nested within an adult cohort. Cases were identified from linked pertussis notifications and each matched to 3 controls on age, sex, and cohort recruitment date. Cases and controls were invited to complete a questionnaire, with verification of vaccination status by their primary care provider. Vaccine effectiveness (VE) was estimated by conditional logistic regression, with adjustment for reported contact with children and area of residence.

Results. Of 1112 notified cases in the cohort, we had complete data for 333 cases and 506 controls. Among 172 PCR-diagnosed cases (mean age, 61 years), 11.2% versus 19.5% of controls had provider-verified pertussis vaccination, on average, 3.2 years earlier. Adjusted VE against PCR-diagnosed pertussis was 52% (95% CI, 15–73%), nonsignificantly higher if vaccinated within 2 years (63%; −5–87%). Adjusted VE was similar in adults born before 1950, presumed primed by natural infection (51%; −8–77%) versus those born 1950 or later who may have received whole-cell pertussis vaccine (53%; −11–80%) (*P*-heterogeneity = 0.9). Among 156 cases identified by single-point serology, adjusted VE was −55% (−177–13%).

Conclusions. We found modest protection against PCR-confirmed pertussis among older adults (mean age, 61 years; range, 46–81 years) within 5 years after acellular vaccine. The most likely explanation for the markedly divergent VE estimate from cases identified by single-titer serology is misclassification arising from limited diagnostic specificity in our setting.

Keywords. pertussis; whooping cough; vaccine effectiveness; adult.

Despite widespread vaccination in high-income countries, pertussis remains one of the most poorly controlled vaccine-preventable diseases, with outbreaks continuing to occur every few years [1–3]. Although severe morbidity is highest in the youngest, adults can suffer serious complications [4, 5], with reports suggesting 5–12% of those aged over 65 with pertussis are hospitalized [4, 6, 7] and about 8% develop radiologically confirmed pneumonia [7].

Formulations of acellular pertussis vaccine suitable for adults with reduced amounts of diphtheria and tetanus toxoid (Tdap) have been available since 2000. The only randomized controlled trial in adults reported vaccine efficacy of 92% (95% confidence interval [CI], 32–99%) but was based on 10 cases and excluded those aged more than 65 years [8]. More recent studies reported satisfactory immunogenicity of Tdap in adults aged more than 55 [9] and 65 [10] years; however, data on the effectiveness of acellular pertussis vaccine in older adults are limited to a single case-control study that reported low but imprecise vaccine effectiveness (VE) (24%; 95% CI, −59–64%) in a subgroup of adults (mean age, 69 years) [11]. Waning effectiveness of acellular vaccine has been demonstrated in children primed with acellular vaccines [12], but no data are available for adults primed with whole-cell vaccine and/or prior infection.

From 2009 to 2012, the largest Australian state, New South Wales (NSW; population 7 million), implemented a cocooning vaccination program, which provided free Tdap vaccine to adults caring for infants, with vaccine coverage of about 20% in a cohort of older adults [13]. We conducted a case-control study nested within this cohort, which, based on coverage and expected numbers of pertussis cases, had 90% power to estimate a minimum VE of 40%, with an $\alpha = .05$. Although recommendations to vaccinate older adults have been in place for some years [3, 14], this study is the first to specifically evaluate the magnitude and duration of direct protection in older adults.

METHODS

We used an established cohort, the Sax Institute's 45 and Up Study [15]. Briefly, between 2006 and 2008, adults aged 45 years

Received 4 June 2019; editorial decision 12 July 2019; accepted 19 August 2019; published online August 26, 2019.

Correspondence: B. C. Liu, School of Public Health and Community Medicine, Samuels Building, UNSW Kensington, NSW 2052, Australia (bette.liu@unsw.edu.au).

Clinical Infectious Diseases® 2019;XX(XX):1–11

DOI: 10.1093/cid/ciz821

and over residing in NSW were invited from Australia's national health insurance database, the Department of Human Services (formerly Medicare Australia) enrollment database, to participate. There was oversampling of those living in rural regions and those aged more than 80 years. Overall, 267 153 participants (average age, 62 years) completed a questionnaire and consented to be followed up through surveys and linkage to health records. The cohort represented 10% of the eligible population in the study age range resident in NSW.

For this nested case-control study, in 2016 the cohort was linked to pertussis notifications, hospitalizations, and death records by the NSW Centre for Health Record Linkage [16]. Pertussis notifications are recorded in the NSW Notifiable Conditions Information Management System (NCIMS), which is a statutory database of all notifiable conditions required to be reported by health practitioners and laboratories under the NSW Public Health Act [17]. Cases of pertussis that meet case definitions [18] are recorded. Confirmed cases had either definitive laboratory evidence {culture or nucleic acid testing (polymerase chain reaction [PCR]) or seroconversion in the absence of recent vaccination} or both a clinical history consistent with pertussis and suggestive laboratory evidence (single high titer of immunoglobulin [Ig] A or IgG antibody to Bordetella pertussis or significant change in IgA or IgG, in the absence of vaccination) (see Appendix) [18]. Thus, cases notified by laboratories based on high single-point serology require active clinical follow-up to be considered confirmed, but not if pertussis is detected by PCR, which is considered definitive. Data in the NCIMS include the notified condition, date of onset, and test type. The NSW Admitted Patient Data Collection records all inpatient hospital admissions in NSW. For each hospitalization the primary diagnosis is coded to the International Classification of Diseases, 10th revision, Australian Modification (ICD-10-AM) [19]; data also include the admission date. Death data are available from the NSW Registry of Births, Deaths, and Marriages and include the date of death. All databases include identifying details enabling linkage to the 45 and Up Study cohort, and at the time of linkage complete data were available until 31 December 2015.

Prior to case and control selection, we excluded cohort participants with a linked record of pertussis (either a notification or a hospitalization where the primary diagnosis was coded as ICD-10-AM A37 Whooping cough) prior to recruitment. We also excluded any participants who linked to a death record.

Cases were defined as cohort participants who, following cohort recruitment, had a first linked record of pertussis (either statutory notification of confirmed pertussis or a hospitalization with a primary ICD-10-AM diagnosis code on admission of A37 Whooping cough). For each case, up to 3 matched controls were selected from the cohort. Controls were matched to cases on age (in 5-year age groups from 45 years), sex, and date of cohort recruitment (4 intervals from before 1 July 2007, 1 July–31 December 2007, 1 January–30 June 2008, after 30 June 2008) and assigned an index date equivalent to the pertussis onset date for their matched case. We invited all cases and matched controls by post and included a questionnaire asking about their vaccination status, their contact with children in the 3 weeks prior to illness or index date, and their healthcare provider details to verify their vaccination status. We also asked cases to provide information about the impact of their pertussis diagnosis on their health and work. For those agreeing to participate we contacted their healthcare provider to verify their pertussis vaccination status. The 45 and Up Study received ethics approval from the University of New South Wales' human research ethics committee (HREC) and this specific study received approval from the NSW Population and Health Services HREC (HREC/10/CIPHS/97). All study participants provided written consent to be included.

Statistical Analysis

For our main prespecified analyses, we included only respondent cases and their matched controls, for whom we had validated vaccination status from their healthcare provider. Participants were classified as vaccinated if they had a healthcare provider–verified pertussis vaccine administered at least 1 month prior [20] to the pertussis notification or index date (for controls). We estimated the odds ratio (OR) of pertussis infection using conditional logistic regression and examined the effect of adjusting for area of residence, educational level, household income, smoking status, asthma, body mass index (BMI), attending routine cancer screening, and contact with children based on questionnaire responses. Where adjustment variables had missing data, in analyses we included those with missing data in a separate category. We calculated pertussis VE as (1-adjusted OR) × 100%. We estimated VE overall and by the pertussis identification method (PCR, serology). For PCR-confirmed pertussis cases we estimated VE according to time since vaccine receipt (<2, 2 to <5, 5+ years compared with no vaccination) and by age (<65 vs ≥65 years).

To maximize our analysis population we conducted additional analyses. For PCR-confirmed cases who had validated vaccination records but no respondent matched control with a validated vaccination record and who were therefore excluded from our main analysis, we selected new matched controls (on age group, sex, cohort recruitment date) from the pool of controls with a validated vaccination record but who had no respondent matching case with a validated vaccination record.

All analyses were conducted using R version 3.5.1 [21].

RESULTS

We identified and invited 1112 confirmed cases: 527 (47.4%) were based on PCR, 566 (50.9%) on single-titer serology, whereas 19 had no laboratory diagnostic information. We invited 3291 corresponding matched controls. Of those invited, 60% (671 of 1112) of cases and 49% (1610 of 3291) of controls

agreed to participate, and in participants we obtained validated vaccination status for 69% (463 of 671) of cases and 67% (1080 of 1610) of controls (Figure 1).

Compared with nonparticipating cases, participants were more likely to be younger, women, and have higher incomes and educational levels and less likely to be current smokers. Such differences were less apparent for controls (Table A1). Of participants, the proportion of their health practitioners who also responded did not vary substantially by a range of characteristics, although practitioner response rates for cases were slightly greater for older participants and for never smokers (Table A2).

In analyses restricted to cases and their corresponding controls with validated vaccination data (prespecified analysis population), we had 333 cases and 506 controls (Figure 1); 130 cases with validated vaccination status lacked a matched control with

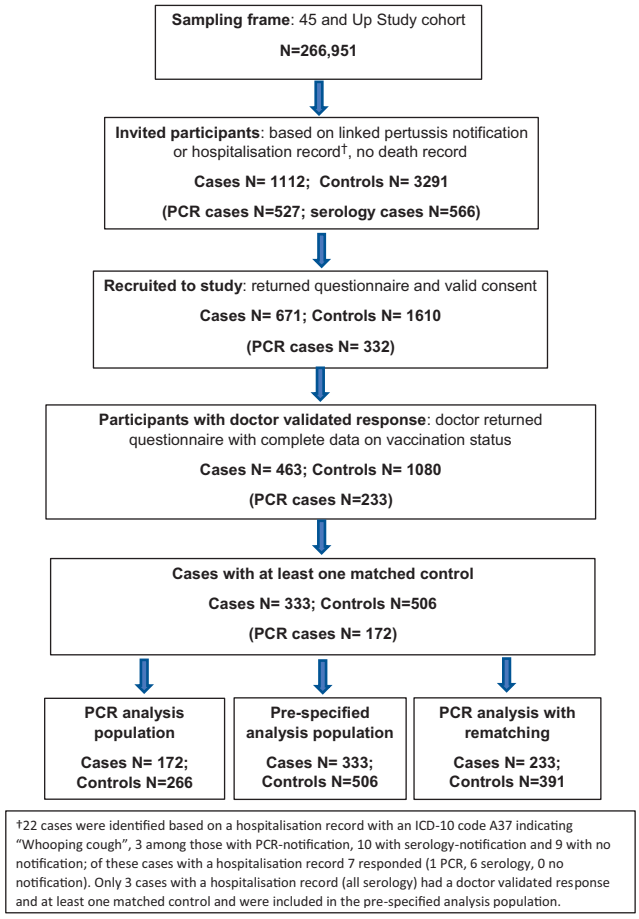


Figure 1. Study sampling frame, recruitment, and analysis population: flow chart. †22 cases were identified based on a hospitalization record with an ICD-10 code A37 indicating "Whooping cough": 3 among those with polymerase chain reaction (PCR) notification, 10 with serology notification, and 9 with no notification; of these cases with a hospitalization record, 7 responded (1 PCR, 6 serology, 0 no notification). Only 3 cases with a hospitalization record (all serology) had a doctor-validated response and at least 1 matched control and were included in the prespecified analysis population. Abbreviations: ICD-10, International Classification of Diseases, 10th revision; PCR, polymerase chain reaction.

validated vaccination status. The mean age of participants at diagnosis/index date was 62 years. Characteristics of the included cases and controls were similar except for the proportion reporting contact with children in the 3 weeks prior to the onset/index date (36% of cases vs 23% of controls; see Table 1). In analyses confined to the subset of cases with a PCR pertussis diagnosis (and their matching controls) we had 172 cases and 266 controls, with a mean age at diagnosis/index date of 61 years (range, 46–81 years). Similar to the prespecified analysis group, the only significant difference between cases and controls was a higher proportion of cases reporting contact with children (Table 2).

In prespecified analyses, the proportions of cases and controls vaccinated were, respectively, 17% (53 of 333) and 16% (82 of 506); the average time between vaccination and diagnosis/index date overall was 3.0 years (range, 0.8–8.8 years) and for cases and controls, respectively, was 3.0 and 2.9 years. For the PCR-only analysis, the proportions of cases and controls vaccinated were 12% (20 of 172) and 20% (52 of 266), respectively, and the mean time since vaccination was 3.2 years. In the prespecified population (333 cases, 506 controls) there was no evidence of VE (adjusted VE, 8%; 95% CI, −36–37%) (see Figure 2). However, VE estimates differed substantially by diagnostic method. Among the PCR-only population, adjusted VE was 52% (95% CI, 15–73%; P = .01), whereas in the serology-only population, adjusted VE was −55% (95% CI, −177–13%; P = .14; P-heterogeneity = .005). In addition to matching on age, sex, and recruitment date, in the final models the ORs (and VE estimates) were adjusted for reported contact with children and region of residence. Adjustment for education, income, smoking, asthma, BMI, and routine cancer screening did not materially change the estimates and were therefore not included in the final model.

Among the PCR-only population (N = 438), Figure 3 shows VE overall and by time since vaccination and age group. We found no trend towards declining VE with greater time since vaccination in the PCR-only population, although the category "≥5 years since vaccination" had a narrow range (mean, 5.9 years; range, 5.0–6.7 years). When stratified by age, VE in those aged younger than 65 years (mean age, 57.6 years) was similar to those aged 65 and over (mean age, 70.0 years) (55% [95% CI, 7–78%] vs 49% [95% CI, −32–80%]; P-heterogeneity = 0.8). As a post hoc analysis we also estimated VE by birth year (<1950/1950+) to correspond to prevaccine and whole-cell pertussis vaccine eras [11]. We found no difference in VE: those with birth year before 1950 (mean age, 67.5 years; case N = 77) had a VE of 51% (95% CI, −8–77%) and those born in 1950 or later (mean age, 55.8 years; case N = 85) had a VE of 53% (95% CI, −11–80%; P-heterogeneity = 0.9).

There were 61 PCR cases who had no matched controls with validated vaccination data and were excluded from the main analysis reported in Figure 3. When we included alternate

Table 1. Characteristics of Cases and Controls in the Prespecified Analysis Population

	Cases, N (%)	Controls, N (%)	*P*
Total	333 (100.0)	506 (100.0)	
Recruitment date			
Before 1 July 2007	64 (19.2)	92 (18.2)	.97
1 July–31 December 2007	20 (6.0)	29 (5.7)	
1 January–30 June 2008	87 (26.1)	131 (25.9)	
After 30 June 2008	162 (48.6)	254 (50.2)	
Mean (SD) age at diagnosis/index, years	61.8 (8.0)	61.7 (7.8)	.85
Age at diagnosis/index date (years)			
45–49	18 (5.4)	33 (6.5)	.66
50–54	63 (18.9)	81 (16.0)	
55–59	63 (18.9)	95 (18.8)	
60–64	74 (22.2)	134 (26.5)	
65–69	58 (17.4)	85 (16.8)	
≥70	57 (17.1)	78 (15.4)	
Sex			
Male	106 (31.8)	156 (30.8)	.76
Female	227 (68.2)	350 (69.2)	
Body mass index (kg/m^2)			
<25	103 (30.9)	178 (35.2)	.64
25–30	124 (37.2)	179 (35.4)	
≥30	70 (21.0)	100 (19.8)	
Unknown	36 (10.8)	49 (9.7)	
Highest educational level			
Certificate or lower	229 (68.8)	326 (64.4)	.22
University or higher	88 (26.4)	161 (31.8)	
Unknown	16 (4.8)	19 (3.8)	
Residence			
Major city	150 (45.0)	256 (50.6)	.39
Inner regional	131 (39.3)	174 (34.4)	
Outer regional or remote or very remote	38 (11.4)	59 (11.7)	
Unknown	14 (4.2)	17 (3.4)	
Annual household income (AUD)			
<70 000	165 (49.5)	238 (47.0)	.77
≥70 000	145 (43.5)	230 (45.5)	
Unknown	23 (6.9)	38 (7.5)	
Smoking status			
Never	208 (62.5)	304 (60.1)	.16
Past	98 (29.4)	152 (30.0)	
Current	11 (3.3)	33 (6.5)	
Unknown	16 (4.8)	17 (3.4)	
Asthma			
No	264 (79.3)	422 (83.4)	.32
Yes	55 (16.5)	67 (13.2)	
Unknown	14 (4.2)	17 (3.4)	
Contact with children			
No	176 (52.9)	246 (48.6)	<.001
Yes	119 (35.7)	115 (22.7)	
Unknown	38 (11.4)	145 (28.7)	
Attended routine cancer screening program			
No	38 (11.4)	51 (10.1)	.51
Yes	277 (83.2)	432 (85.4)	
Unknown	18 (5.4)	23 (4.5)	

Percentages are column percentages. Abbreviation: AUD, Australian dollars.

matched controls with validated vaccination data but lacking a matched case with validated vaccination data, the number of PCR cases increased to 233 with 391 controls. Adjusted VE did not change significantly (40%; 95% CI, 4–63%) nor did it differ by time since vaccination or by age group (Appendix Figure 1).

For cases notified based on single-point serology and their matched controls (N = 388) we conducted exploratory analyses to examine if there were differences in VE by time since vaccination and whether cases had presumptive evidence of active follow-up consistent with them qualifying as truly "confirmed" according to case definitions (as follow-up may have been incomplete; see "Methods"). We found no differences in ORs by time since vaccine receipt, but found that cases with no evidence of active follow-up were 5 times more likely to have been vaccinated (40.4%; 23 of 57) than those with evidence suggesting follow-up (9.1%; 9 of 99), resulting in substantially different ORs and VE estimates (Table A3).

DISCUSSION

Among older adults (mean age, 61 years), we found significant effectiveness of acellular pertussis vaccine against PCR-confirmed pertussis infection of approximately 50%. We did not find evidence of waning protection with increasing age or with time since vaccination, but these subanalyses lacked statistical power.

Our findings add substantially to current evidence on acellular pertussis VE in older adults. The only randomized trial estimating efficacy of the adult formulation of acellular pertussis vaccine had participants with a mean age of 35 years, excluded adults aged over 65, and had limited statistical power [8]. Of 11 other published studies estimating VE [22–30], all but one [11] included only adolescents, most of whom were primed with acellular vaccines. The earlier case-control study estimating VE in older adults was based on PCR-confirmed cases in a US health maintenance organization database. They found, in data restricted to cases born in the prevaccine era (before 1950; mean age, 69 years; case N = 61), that VE was low and nonsignificant (24%; 95% CI, −59–64%), but among those born in the whole-cell vaccine era (1950–1985; mean age, 43 years; case N = 129) VE was substantially higher (68%; 95% CI, 46–82%) [11]. Our findings contrast, as we found no significant differences in VE by age (<65 vs ≥65 years) nor by equivalent birth cohorts (born before 1950 vs 1950 or later).

One major methodological difference between the US study and ours is that we had population-based controls while the US study had both PCR-negative and population-based controls. While the US study found that the use of PCR-negative controls resulted in lower VE estimates overall, this difference was only observed among the younger subgroup of participants (mean age, 11 years), who had all been exposed to acellular vaccines, but not in the 2 older subgroups, suggesting this potential for

Table 2. Characteristics of Cases and Controls in Polymerase Chain Reaction–Analysis Population

	Cases, N (%)	Controls, N (%)	*P*
Total	172 (39.3)	266 (60.7)	
Recruitment date			
Before 1 July 2007	24 (14.0)	36 (13.5)	.99
1 July–31 December 2007	13 (7.6)	21 (7.9)	
1 January–30 June 2008	44 (25.6)	67 (25.2)	
After 30 June 2008	91 (52.9)	142 (53.4)	
Mean (SD) age at diagnosis/index, years	61.1 (7.7)	61.3 (7.4)	.75
Age at diagnosis/index date (years)			
45–49	11 (6.4)	19 (7.1)	.35
50–54	37 (21.5)	43 (16.2)	
55–59	31 (18.0)	45 (16.9)	
60–64	40 (23.3)	83 (31.2)	
65–69	29 (16.9)	49 (18.4)	
≥70	24 (14.0)	27 (10.2)	
Sex			
Male	54 (31.4)	83 (31.2)	.97
Female	118 (68.6)	183 (68.8)	
Body mass index (kg/m^2)			
<25	60 (34.9)	97 (36.5)	.58
25–30	66 (38.4)	87 (32.7)	
≥30	29 (16.9)	56 (21.1)	
Unknown	17 (9.9)	26 (9.8)	
Highest educational level			
Certificate or lower	111 (64.5)	171 (64.3)	.96
University or higher	56 (32.6)	86 (32.3)	
Unknown	5 (2.9)	9 (3.4)	
Residence			
Major city	88 (51.2)	121 (45.5)	.11
Inner regional	69 (40.1)	102 (38.3)	
Outer regional or remote or very remote	11 (6.4)	36 (13.5)	
Unknown	4 (2.3)	7 (2.6)	
Annual household income (AUD)			
<70 000	74 (43.0)	129 (48.5)	.44
≥70 000	89 (51.7)	121 (45.5)	
Unknown	9 (5.2)	16 (6.0)	
Smoking status			
Never	106 (61.6)	157 (59.0)	.19
Past	58 (33.7)	86 (32.3)	
Current	3 (1.7)	16 (6.0)	
Unknown	5 (2.9)	7 (2.6)	
Asthma			
No	144 (83.7)	222 (83.5)	.99
Yes	24 (14.0)	37 (13.9)	
Unknown	4 (2.3)	7 (2.6)	
Contact with children			
No	92 (53.5)	124 (46.6)	<.001
Yes	63 (36.6)	67 (25.2)	
Unknown	17 (9.9)	75 (28.2)	
Attended cancer screening program			
No	20 (11.6)	22 (8.3)	.24
Yes	146 (84.9)	235 (88.3)	
Unknown	6 (3.5)	9 (3.4)	

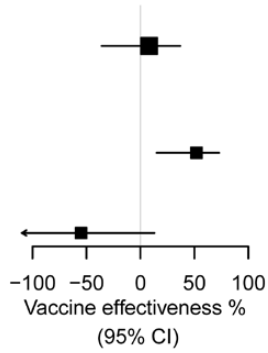
Percentages are column percentages. Abbreviation: AUD, Australian dollars.

bias may not be uniform across age groups. Differences in VE between test-negative and population-based controls are presumably due to test-negative controls being more similar to the cases (ie, having more risk factors leading to pertussis testing and subsequent diagnosis than population-based controls). In our analyses, to account for differences in the propensity for pertussis testing and diagnosis, we adjusted for characteristics including contact with children, comorbidities (asthma, smoking, BMI), and healthcare seeking (attending cancer screening). This adjustment led to an approximately 10% increase in the estimated VE rather than any decrease, and was primarily driven by adjustment for contact with children. The other factors did not materially change our estimates, suggesting that they were not major confounders of our results.

None of the earlier reports of VE/efficacy in older adults [8, 11] attempted to examine waning. Cost-effectiveness analyses of vaccination of older adults with acellular pertussis vaccine have assumed mean durations of protection of 8 years [31] based mostly on studies in children [32], although a much shorter duration of protection has been reported among those who received all primary doses as acellular vaccine in childhood [12]. While we had limited statistical power, we found that up to 6 years after vaccination, the point estimate for VE showed no declining trend. Based on their age, most adults in our study would have been primed, either by having pertussis infection or having been vaccinated with whole-cell vaccines as a child. Therefore, our findings regarding both the effectiveness and duration of protection must be interpreted in this context.

The finding of an association (although not significant) between pertussis vaccination and a pertussis notification on the basis of positive single-titer serology was surprising and inconsistent with our results for PCR-confirmed cases. In Australia, pertussis notification using single high-titer serology requires both clinical evidence and exclusion of recent vaccination (see Appendix). Potential flaws in this case reporting include, first, variations in the sensitivity and specificity of serological tests used by referring laboratories and, second, that public health unit workload may preclude active follow-up of notifications made directly from laboratories, which account for most pertussis notifications in NSW [33]. Our post hoc analyses comparing serology cases with and without proxy evidence of active follow-up (Table A3) support the likelihood of substantial misclassification among cases identified solely through serologic diagnosis. These findings have implications for pertussis surveillance in Australia, particularly in adults, a population for whom, historically, the majority of notifications were based on serological confirmation [2]. Indeed, as more adults are vaccinated as part of population-wide programs targeting pregnant women or older adults [13], diagnoses based primarily on pertussis serology may become more unreliable and

	Cases N	Controls* N	Unadjusted OR	Adjusted+ OR	Adjusted+ vaccine effectiveness (%) (95%CI)	P value
Overall						
Unvaccinated	280	424	Ref	Ref	Ref	
Vaccinated	53	82	0.98	0.92	8 (−36 to 37)	0.69
By case type						
PCR						
Unvaccinated	152	214	Ref	Ref	Ref	
Vaccinated	20	52	0.54	0.48	52 (15 to 73)	0.01
Serology						
Unvaccinated	124	202	Ref	Ref	Ref	
Vaccinated	32	30	1.74	1.55	−55 (−177 to 13)	0.14



* Matched on recruitment date, age and sex
+Adjusted for contact with children and region of residence

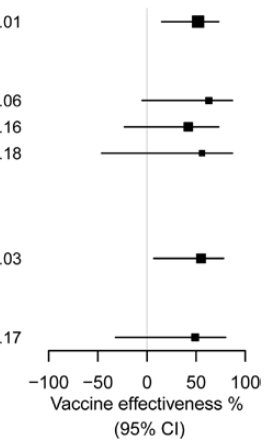
Figure 2. Odds ratios and vaccine effectiveness of acellular pertussis vaccine, prespecified population (N = 839). Abbreviations: CI, confidence interval; OR, odds ratio; PCR, polymerase chain reaction; Ref, reference.

routine surveillance systems will need to adapt to maintain case specificity.

Our study strengths include the relatively large sample size and nested matched design, which allowed us to select controls who were similar to cases in terms of not only age and sex but also characteristics such as health-seeking behavior, which has been shown to be higher overall in this cohort than in the general population [15]. We were also able to adjust our analyses for underlying factors that may be associated with pertussis incidence and severity [4, 6], as well as characteristics associated with greater likelihood to participate in the study. Limitations include that our response rate was less than anticipated, which meant that we had insufficient statistical power for robust VE estimates in subgroups including in those aged 65 years and older and according to time since vaccination. Also, response rates differed by case and control status and may bias our VE estimates away from the null if responding controls were more likely to be vaccinated, although this was not the case in the main prespecified analysis population (see Figure 2). As mentioned, we also lacked PCR-negative controls, with the majority of the controls' health practitioners responding that they had not been tested for pertussis. Finally, we lacked data on patient symptoms, which would have assisted in interpretation of the findings based on serological diagnoses.

Overall, we found in adults aged, on average, 61 years that acellular pertussis vaccine is approximately 50% effective in preventing PCR-confirmed pertussis infection. Together with findings from other studies [8, 11], we conclude that while

	Cases N	Controls* N	Unadjusted OR	Adjusted+ OR	Adjusted+ vaccine effectiveness (%) (95%CI)	P value
Overall						
Unvaccinated	152	214	Ref	Ref	Ref	
Vaccinated	20	52	0.54	0.48	52 (15 to 73)	0.01
By time since vaccination						
Unvaccinated	152	214	Ref	Ref	Ref	
<2 years	5	16	0.44	0.37	63 (−5 to 87)	0.06
2–5 years	11	26	0.60	0.58	42 (−23 to 73)	0.16
≥5 years	4	10	0.56	0.44	56 (−46 to 87)	0.18
By age at diagnosis/index date						
<65 years						
Unvaccinated	107	156	Ref	Ref	Ref	
Vaccinated	12	34	0.51	0.45	55 (7 to 78)	0.03
≥65 years						
Unvaccinated	45	58	Ref	Ref	Ref	
Vaccinated	8	18	0.57	0.51	49 (−32 to 80)	0.17



*Matched on recruitment date, age and sex
+Adjusted for contact with children and region of residence

Figure 3. Odds ratios and vaccine effectiveness of acellular pertussis vaccine, PCR-only population (N = 438). CI, confidence interval; OR, odds ratio; PCR, polymerase chain reaction; Ref, reference.

effectiveness of the adult acellular pertussis vaccine may decline in older age, it still confers a level of protection that is comparable to that often reported for vaccines such as influenza [34], which are routinely recommended for older adults. While a more effective vaccine would be ideal, Tdap should still be considered an important intervention among public health strategies to prevent infectious respiratory morbidity in older adults.

Notes

Acknowledgments. The 45 and Up Study is managed by the Sax Institute in collaboration with major partner Cancer Council NSW and the following partners: the National Heart Foundation of Australia (NSW Division); NSW Ministry of Health; NSW Government Family and Community Services–Ageing, Carers and the Disability Council; and the Australian Red Cross Blood Service. The authors thank the many thousands of people participating in the 45 and Up Study and the Centre for Health Record Linkage and NSW Ministry of Health for providing the linked notification and Admitted Patient Data Collection and Register of Births Deaths and Marriages data. The authors thank Bruce Armstrong and Paula Spokes for their advice on study design, analysis, and interpretation.

Financial support. This project was supported by the Australian National Health and Medical Research Council (NHMRC) (grant number 1107008). B. C. L. and C. R. M. are supported by NHMRC fellowships.

Potential conflicts of interest. B. C. L. and A. H. hold grants from the Australian National Health and Medical Research Council during the conduct of the study. B. C. L. has held shares in CSL Limited and served once on an advisory board for Sanofi-Pasteur. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Cherry JD. Epidemic pertussis in 2012—the resurgence of a vaccine-preventable disease. N Engl J Med **2012**; 367:785–7.
2. Pillsbury A, Quinn HE, McIntyre PB. Australian vaccine preventable disease epidemiological review series: pertussis, 2006-2012. Commun Dis Intell Q Rep **2014**; 38:E179–94.
3. Liang JL, Tiwari T, Moro P, et al. Prevention of pertussis, tetanus, and diphtheria with vaccines in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep **2018**; 67:1–44.
4. De Serres G, Shadmani R, Duval B, et al. Morbidity of pertussis in adolescents and adults. J Infect Dis **2000**; 182:174–9.
5. Thomas PF, McIntyre PB, Jalaludin BB. Survey of pertussis morbidity in adults in western Sydney. Med J Aust **2000**; 173:74–6.
6. Liu BC, McIntyre P, Kaldor JM, Quinn HE, Ridda I, Banks E. Pertussis in older adults: prospective study of risk factors and morbidity. Clin Infect Dis **2012**; 55:1450–6.
7. Cortese MM, Baughman AL, Brown K, Srivastava P. A "new age" in pertussis prevention new opportunities through adult vaccination. Am J Prev Med **2007**; 32:177–85.
8. Ward JI, Cherry JD, Chang SJ, et al; APERT Study Group. Efficacy of an acellular pertussis vaccine among adolescents and adults. N Engl J Med **2005**; 353:1555–63.
9. Van Damme P, McIntyre P, Grimprel E, et al. Immunogenicity of the reduced-antigen-content dTpa vaccine (Boostrix(*)) in adults 55 years of age and over: a sub-analysis of four trials. Vaccine **2011**; 29:5932–9.
10. Weston WM, Friedland LR, Wu X, Howe B. Vaccination of adults 65 years of age and older with tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Boostrix(*)): results of two randomized trials. Vaccine **2012**; 30:1721–8.
11. Baxter R, Bartlett J, Rowhani-Rahbar A, Fireman B, Klein NP. Effectiveness of pertussis vaccines for adolescents and adults: case-control study. BMJ **2013**; 347:f4249.
12. Klein NP, Bartlett J, Rowhani-Rahbar A, Fireman B, Baxter R. Waning protection after fifth dose of acellular pertussis vaccine in children. N Engl J Med **2012**; 367:1012–9.
13. Dyda A, McIntyre P, Karki S, et al. Pertussis vaccination in a cohort of older Australian adults following a cocooning vaccination program. Vaccine **2018**; 36:4157–60.
14. Australian Immunisation Handbook. **2019**. Available at: https://immunisationhandbook.health.gov.au/recommendations?f%5B0%5D=field_related_diseases%3A3701. Accessed February 2019.
15. 45 and Up Study Collaborators; Banks E, Redman S, et al. Cohort profile: the 45 and Up Study. Int J Epidemiol **2008**; 37:941–7.
16. Title NSW Centre for Health Record Linkage. Available at: http://www.cherel.org.au/. Accessed February 2019.
17. New South Wales Government. Public Health Act 2010. Available at: https://www.legislation.nsw.gov.au/#/view/act/2010/127. Accessed February 2019.
18. Australian Government Department of Health. Australian national notifiable diseases and case definitions. Available at: http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd_pertus.htm. Accessed February 2019.
19. Innes K, Peasley K, Roberts R. Ten down under: implementing ICD-10 in Australia. J AHIMA **2000**; 71:52–6.
20. Halperin BA, Morris A, Mackinnon-Cameron D, et al. Kinetics of the antibody response to tetanus-diphtheria-acellular pertussis vaccine in women of childbearing age and postpartum women. Clin Infect Dis **2011**; 53:885–92.
21. The Comprehensive R Archive Network. Available at: https://cranr-projectorg/. Accessed April 2019.
22. Koepke R, Eickhoff JC, Ayele RA, et al. Estimating the effectiveness of tetanus-diphtheria-acellular pertussis vaccine (Tdap) for preventing pertussis: evidence of rapidly waning immunity and difference in effectiveness by Tdap brand. J Infect Dis **2014**; 210:942–53.
23. Klein NP, Bartlett J, Fireman B, Baxter R. Waning Tdap effectiveness in adolescents. Pediatrics **2016**; 137:e20153326.
24. Acosta AM, DeBolt C, Tasslimi A, et al. Tdap vaccine effectiveness in adolescents during the 2012 Washington State pertussis epidemic. Pediatrics **2015**; 135:981–9.
25. Breakwell L, Kelso P, Finley C, et al. Pertussis vaccine effectiveness in the setting of pertactin-deficient pertussis. Pediatrics **2016**; 137:05.
26. Wei SC, Tatti K, Cushing K, et al. Effectiveness of adolescent and adult tetanus, reduced-dose diphtheria, and acellular pertussis vaccine against pertussis. Clin Infect Dis **2010**; 51:315–21.
27. Rank C, Quinn HE, McIntyre PB. Pertussis vaccine effectiveness after mass immunization of high school students in Australia. Pediatr Infect Dis J **2009**; 28:152–3.
28. Haller S, Dehnert M, Karagiannis I, 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**; 34:513–9.
29. Terranella A, Rea V, Griffith M, et al. Vaccine effectiveness of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine during a pertussis outbreak in Maine. Vaccine **2016**; 34:2496–500.
30. Liko J, Robison SG, Cieslak PR. Pertussis vaccine performance in an epidemic year—Oregon, 2012. Clin Infect Dis **2014**; 59:261–3.
31. McGarry LJ, Krishnarajah G, Hill G, et al. Cost-effectiveness analysis of Tdap in the prevention of pertussis in the elderly. PLoS One **2013**; 8:e67260.
32. Wendelboe AM, Van Rie A, Salmaso S, Englund JA. Duration of immunity against pertussis after natural infection or vaccination. Pediatr Infect Dis J **2005**; 24:S58–61.
33. Allen CJ, Ferson MJ. Notification of infectious diseases by general practitioners: a quantitative and qualitative study. Med J Aust **2000**; 172:325–8.
34. Belongia EA, Simpson MD, King JP, et al. Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies. Lancet Infect Dis **2016**; 16:942–51.

APPENDIX: NATIONAL NOTIFIABLE DISEASES CASE DEFINITION FOR PERTUSSIS REPORTING

Both confirmed cases and probable cases should be notified.

Confirmed case: A confirmed case requires either laboratory definitive evidence OR laboratory suggestive evidence AND clinical evidence.

Probable case: A probable case requires clinical evidence AND epidemiological evidence.

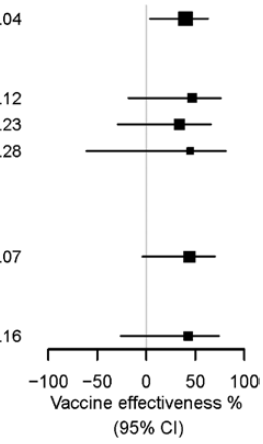
Laboratory definitive evidence: Isolation of *Bordetella pertussis* OR detection of *B. pertussis* by nucleic acid testing OR seroconversion in paired sera for *B. pertussis* using whole-cell or specific *B. pertussis* antigen(s) in the absence of recent pertussis vaccination.

Laboratory suggestive evidence: In the absence of recent vaccination, significant change (increase or decrease) in antibody level (IgG, IgA) to *B. pertussis* whole-cell or *B. pertussis*–specific antigen(s) OR single high IgG and/or IgA titer to pertussis toxin (PT) OR single high IgA titer to whole-cell *B. pertussis* antigen.

Clinical evidence: A coughing illness lasting 2 or more weeks OR paroxysms of coughing OR inspiratory whoop OR posttussive vomiting.

Epidemiological evidence: An epidemiological link is established when there is contact between 2 people involving a plausible mode of transmission at a time when one of them is likely to be infectious (from the catarrhal stage, approximately 1 week before, to 3 weeks after onset of cough) AND the other has an illness that starts within 6 to 20 days after this contact AND at least 1 case in the chain of epidemiologically linked cases (which may involve many cases) is a confirmed case with either laboratory definitive or laboratory suggestive evidence.

	Cases N	Controls* N	Unadjusted OR	Adjusted+ OR	Adjusted+ vaccine effectiveness (%) (95%CI)	P value
Overall						
Unvaccinated	205	321	Ref	Ref	Ref	
Vaccinated	28	70	0.63	0.60	40 (4 to 63)	0.04
By time since vaccination						
Unvaccinated	205	321	Ref	Ref	Ref	
<2 years	9	25	0.56	0.53	47 (−18 to 76)	0.12
2–5 years	14	32	0.69	0.66	34 (−29 to 66)	0.23
>=5 years	5	13	0.6	0.55	45 (−61 to 81)	0.28
By age at diagnosis/index date						
<65 years						
Unvaccinated	142	232	Ref	Ref	Ref	
Vaccinated	16	45	0.58	0.56	44 (−4 to 70)	0.07
>=65 years						
Unvaccinated	63	89	Ref	Ref	Ref	
Vaccinated	12	25	0.68	0.57	43 (−26 to 74)	0.16



*Matched on recruitment date, age and sex
+Adjusted for contact with children and region of residence

Appendix Figure A1. Odds ratios and vaccine effectiveness of acellular pertussis vaccine: PCR-only population, new matched controls (N = 624). Abbreviations: CI, confidence interval; OR, odds ratio; Ref, reference.

Table A1. Number and Percentage of Participants Responding Overall and According to Case and Control Status

	Cases, n/N (% Responded)	Controls, n/N (% Responded)	Total, n/N (% Responded)
Total	671/1112 (60.3)	1610/3291 (48.9)	2281/4403 (51.8)
Age at diagnosis/index date (years)			
45–64	441/663 (66.5)	1056/1984 (53.2)	1497/2647 (56.6)
≥65	230/449 (51.2)	554/1307 (42.4)	784/1756 (44.6)
Sex			
Male	215/395 (54.4)	546/1184 (46.1)	761/1579 (48.2)
Female	456/717 (63.6)	1064/2107 (50.5)	1520/2824 (53.8)
Residence			
Major city	280/503 (55.7)	797/1698 (46.9)	1077/2201 (48.9)
Regional or remote	365/576 (63.4)	778/1534 (50.7)	1143/2110 (54.2)
Unknown	26/33 (78.8)	35/59 (59.3)	61/92 (66.3)
Annual household income (AUD)			
<70 000	339/596 (56.9)	825/1730 (47.7)	1164/2326 (50.0)
≥70 000	311/465 (66.9)	734/1413 (51.9)	1045/1878 (55.6)
Unknown	21/51 (41.2)	51/148 (34.5)	72/199 (36.2)
Highest educational level			
No university	477/815 (58.5)	1124/2436 (46.1)	1601/3251 (49.2)
University	186/278 (66.9)	474/821 (57.7)	660/1099 (60.1)
Unknown	8/19 (42.1)	12/34 (35.3)	20/53 (37.7)
Smoking status			
Never	417/665 (62.7)	968/1931 (50.1)	1385/2596 (53.4)
Past	220/380 (57.9)	543/1107 (49.1)	763/1487 (51.3)
Current	34/67 (50.7)	98/252 (38.9)	132/319 (41.4)
Unknown		1/1 (100.0)	1/1 (100.0)
Attended cancer screening program			
No	73/121 (60.3)	174/410 (42.4)	247/531 (46.5)
Yes	560/933 (60.0)	1381/2763 (50.0)	1941/3696 (52.5)
Unknown	38/58 (65.5)	55/118 (46.6)	93/176 (52.8)
Case diagnosis method			
PCR	332/528 (62.9)	…	…
Serology	330/565 (58.4)	…	…
Unknown	9/19 (47.4)	…	…
Diagnosis year			
<2009	96/167 (57.5)	…	…
2009	135/226 (59.7)	…	…
2010	89/153 (58.2)	…	…
2011	107/180 (59.4)	…	…
2012	66/110 (60.0)	…	…
2013	41/61 (67.2)	…	…
2014	48/71 (67.6)	…	…
2015	89/135 (65.9)	…	…

Abbreviations: AUD, Australian dollars; PCR, polymerase chain reaction.

Table A2. Number and Percentage of Responding Participants With Validated Vaccination Data From Their Health Care Provider Overall and According to Case and Control Status

	Cases, n/N (% Responded)	Controls, n/N (% Responded)	Total, n/N (% Responded)
Total	463/671 (69.0)	1080/1610 (67.1)	1543/2281 (67.6)
Age at diagnosis/index date (years)			
45–64	294/441 (66.7)	707/1056 (67)	1001/1497 (66.9)
≥65	169/230 (73.5)	373/554 (67.3)	542/784 (69.1)
Sex			
Male	148/215 (68.8)	348/546 (63.7)	496/761 (65.2)
Female	315/456 (69.1)	732/1064 (68.8)	1047/1520 (68.9)
Residence			
Major city	201/280 (71.8)	525/797 (65.9)	726/1077 (67.4)
Regional or remote	243/365 (66.6)	530/778 (68.1)	773/1143 (67.6)
Unknown	19/26 (73.1)	25/35 (71.4)	44/61 (72.1)
Annual household income (AUD)			
<70 000	236/339 (69.6)	545/825 (66.1)	781/1164 (67.1)
≥70 000	215/311 (69.1)	497/734 (67.7)	712/1045 (68.1)
Unknown	12/21 (57.1)	38/51 (74.5)	50/72 (69.4)
Highest educational level			
No university	329/477 (69.0)	736/1124 (65.5)	1065/1601 (66.5)
University	130/186 (69.9)	337/474 (71.1)	467/660 (70.8)
Unknown	4/8 (50.0)	7/12 (58.3)	11/20 (55.0)
Smoking status			
Never	305/417 (73.1)	665/968 (68.7)	970/1385 (70.0)
Past	144/220 (65.5)	349/543 (64.3)	493/763 (64.6)
Current	14/34 (41.2)	65/98 (66.3)	79/132 (59.8)
Unknown		1/1 (100.0)	1/1 (100.0)
Attended cancer screening program			
No	53/73 (72.6)	103/174 (59.2)	156/247 (63.2)
Yes	385/560 (68.8)	940/1381 (68.1)	1325/1941 (68.3)
Unknown	25/38 (65.8)	37/55 (67.3)	62/93 (66.7)
Case diagnosis method			
PCR	233/332 (70.2)	…	…
Serology	223/330 (67.6)	…	…
Unknown	7/9 (77.8)	…	…
Diagnosis year			
<2009	69/96 (71.9)	…	…
2009	83/135 (61.5)	…	…
2010	64/89 (71.9)	…	…
2011	78/107 (72.9)	…	…
2012	46/66 (69.7)	…	…
2013	30/41 (73.2)	…	…
2014	30/48 (62.5)	…	…
2015	63/89 (70.8)	…	…

Abbreviations: AUD, Australian dollars; PCR, polymerase chain reaction.

Table A3. Odds Ratios and Vaccine Effectiveness of Acellular Pertussis Vaccine, Serology-only Population (N = 388) Overall, by Time Since Vaccination, and According to Whether There Was a Record of Active Follow-up

	Cases	Controls[a]	Unadjusted OR	Adjusted OR[b]	Adjusted VE, % (95% CI)	*P*
Serology subgroup						
Unvaccinated	124	202	Ref	Ref	Ref	
Vaccinated	32	30	1.74	1.55	−55 (−177–13)	.14
By time since vaccination						
Unvaccinated	124	202	Ref	Ref	Ref	
Vaccinated ≤1 year prior	6	9	1.09	1.27	−27 (−281–60)	.68
Vaccinated >1 year prior	26	21	2.02	1.72	−72 (−241–12)	.11
Follow-up record						
Unvaccinated	90	132	Ref	Ref	Ref	
Vaccinated	9	13	1.02	0.83	17 (−128–69)	.72
No follow-up record						
Unvaccinated	34	70	Ref	Ref	Ref	
Vaccinated	23	17	2.79	2.57	−157 (−464 to −17)	.02

Serology cases were classified as having no record of active follow-up by the Public Health Unit if their notification record had missing data in the fields requesting information on hospitalization or death. Both are data fields that cannot be obtained through the routine laboratory notification. Abbreviations: CI, confidence interval; OR, odds ratio; Ref, reference.

[a]Matched on recruitment date, age, and sex.

[b]Adjusted for contact with children and region of residence.