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Pertussis vaccine effectiveness in a frequency matched population-based case-control Canadian Immunization Research Network study in Ontario, Canada 2009–2015 ☆

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ABSTRACT

Background: Resurgences of pertussis have occurred in several high-income countries, often linked to waning of immunity from acellular pertussis vaccines. The degree of waning observed has varied by study design and setting. In Ontario, pertussis has not shown a substantial resurgence in the past decade. The routine immunization schedule comprises three priming doses in infancy, toddler and pre-school doses, and an adolescent dose at 14–16 years of age.

Methods: We estimated pertussis vaccine effectiveness (VE) through a case-control study of 1335 cases statutorily reported to public health in Ontario and occurring between January 1, 2009 and March 31, 2015, compared with 5340 randomly selected population controls, frequency-matched by age, primary-care provider and year of diagnosis. Pertussis cases met provincial confirmed or probable case definitions. We used multivariable logistic regression to estimate crude and adjusted odds ratios (aOR).

Results: VE against pertussis was sustained between 92% (95% confidence interval (95%CI) 88–95%) in 2–3 year olds and 90% (95%CI: 80–95%) in 8–9 year olds, but fell rapidly to 49% (95%CI: 2–73%) in children 12–13 years of age. VE following the teenage booster given at 14–16 years in Ontario reached 76% (95%CI: 52–88%) in 14–16 year olds and 78% (95%CI: −31 to 96%) in those 16–22 years old. For children who were up-to-date with the immunization schedule, VE declined from 87% (95%CI: 84–90%) during the first year to 74% (95%CI: 63–82%) after 8 or more years following their last dose of immunization.

Conclusions: VE is high during the first decade of life but then falls rapidly. Protection is not fully restored by the teenage booster. Our findings are consistent with the localized outbreaks we observe in high school children and underline the importance of additional policies to protect infants.

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1. Introduction

Compared with some other vaccine preventable diseases, pertussis continues to challenge immunization programs. Globally, the World Health Organization estimated as many as 24.1 million cases and 160,700 deaths in children younger than 5 years in 2014 [1]. Despite this high burden and many decades of research, many uncertainties about how to improve pertussis control persist. Resolving these uncertainties requires a better understanding of how well pertussis vaccines work, and how they influence the epidemiology of the disease [2].

Pertussis epidemiology varies quite markedly from country to country, in part because of different historical epidemic patterns that have left different imprints on population immunity, as well as variation in vaccination coverage and schedules. In addition, pertussis epidemiology is influenced by the specific types of vaccine that have been used in a country. In the past two decades, almost all high-income countries switched from using whole cell pertussis vaccines to acellular vaccines because of concerns about the reactogenicity of whole cell vaccines. While less reactogenic, acellular vaccines have in general been found to have lower effectiveness than the vaccines they replaced [3]. Some high-income countries are now facing greater challenges controlling pertussis using acellular vaccines than faced by low- and middle-income countries, where whole cell vaccines continue to be recommended and used [4,5]. Where resurgences have been observed, they have predominantly affected secondary school aged children, reflecting rapidly waning protective immunity [6]. However, some large outbreaks including in the United Kingdom (UK) and United States (US) have led to severe cases and deaths in infants [7,8]. Since protection of infants is the primary goal of immunization programs, maternal immunization is being implemented in many jurisdictions and proving to be highly effective [9].

In Canada, pertussis has been relatively well-controlled in infants in recent decades since an acellular pertussis vaccine replaced a low-effectiveness whole cell vaccine in 1997. In Ontario, the most populous province of Canada, the publicly funded pertussis immunization program involves a primary series of diphtheria, tetanus, acellular pertussis, *Haemophilus influenza* type b vaccine (DTaP-Hib) at 2, 4, and 6 months, boosters at 18 months and 4–6 years, an adolescent Tdap booster at age 14–16 years, and a single adult booster. Incidence of pertussis in recent years has been low, varying between 0.9 and 10.0 per 100,000 population per year. We have not observed major province-wide outbreaks comparable to those seen in the US or UK, and no deaths from pertussis were reported during 2005–2016 [10]. However, a previous study using the test-negative design found that pertussis vaccine effectiveness (VE) had waned to almost nothing by 8 years post-immunization [3]. This finding raised concerns about whether the observation was consistent with the relatively low incidence of infection being observed in Ontario. If the findings are correct, they might indicate under-reporting, but otherwise the findings could be due to study methodology. Two other studies, both from the Kaiser Permanente Vaccine Study Center, have directly compared the test-negative design with the case-control design using population-matched controls, and concluded that these methods have different strengths and weaknesses [11,12]. In order to investigate further an apparent discordance between both incidence and VE being low, we sought to assess pertussis VE in Ontario using an alternative approach to control selection.

2. Methods

The study received Public Health Ontario ethics review board approval.

2.1. Study design and case selection

We conducted a frequency-matched case-control study. We identified probable and confirmed pertussis cases from Ontario's integrated Public Health Information System (iPHIS), the provincial reportable disease database, which captures cases of pertussis reported by laboratories and clinicians as mandated by the Health Protection and Promotion Act, 1990. We included cases occurring in Ontario residents born between April 1, 1992 and March 31, 2015 meeting either a confirmed or probable case definition [13], with date of onset of pertussis from January 1, 2009 to March 31, 2015 (Fig. 1). The Ontario Health Insurance Plan (OHIP) is a publicly funded healthcare system that includes virtually the entire population (excluding recent migrants within 3 months, military personnel, and indigenous persons living on a reserve). We excluded children <3 months old who are ineligible to receive pertussis vaccination, persons who first registered for OHIP coverage at ≥6 months of age as they may have received their primary vaccinations outside of Ontario, and those not rostered to a primary care physician. Rostering is a form of patient registration with a primary care physician that we used to make controls more comparable with cases. We linked cases to Ontario health administrative data held at ICES using a combination of deterministic (using the OHIP number) and probabilistic linkage (using a combination of first and last name, date of birth, sex, and postal code). The Ontario Registered Person's Database provided data on sex, socioeconomic status (approximated by neighbourhood income quintile using postal code) [14], and rural residence (defined as a community <10,000 persons using postal code). We used the Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD) to identify complex chronic conditions (any medical condition that would normally last at least 12 months and require specialist paediatric care) [15]. We identified physician office visits, emergency department use, and hospitalizations during the previous year from the OHIP database, the CIHI National Ambulatory Care Reporting System (NACRS), and the DAD, respectively. All datasets were linked using unique encoded patient identifiers and analyzed at ICES.

2.2. Control selection

Potential controls were selected from OHIP registrants (Fig. 1). In the first step, we created a pool of controls using the primary care providers of cases as the sampling frame, identifying all potential controls who were born after April 1, 1992 and placing them into 2-year age groups, with the exception of those <2 years old (grouped into 3–23 months), and those 18 years or older (18–22 years of age). As with the cases, we excluded children younger than 3 months and persons registered for OHIP coverage at 6 months of age or older as they may have received their primary vaccinations outside of Ontario. Controls were also required to be rostered and to have visited their primary care physician in the same year that the matched case was diagnosed with pertussis. Finally, we excluded controls that were identified in iPHIS to be a case, and selected controls from the potential pool in a 1:4 age group- and index year-stratified frequency match to cases using simple random sampling without replacement using Statistical Analysis System (SAS) version 9.3 (SAS Institute, Cary, North Carolina, United States).

2.3. Assessment of immunization status

Pertussis immunization status for both cases and controls was derived from a validated algorithm of immunization fee codes physicians billed to OHIP (Supplementary Table S1) [3]. Immunization status was classified as up-to-date for age, partially vaccinated

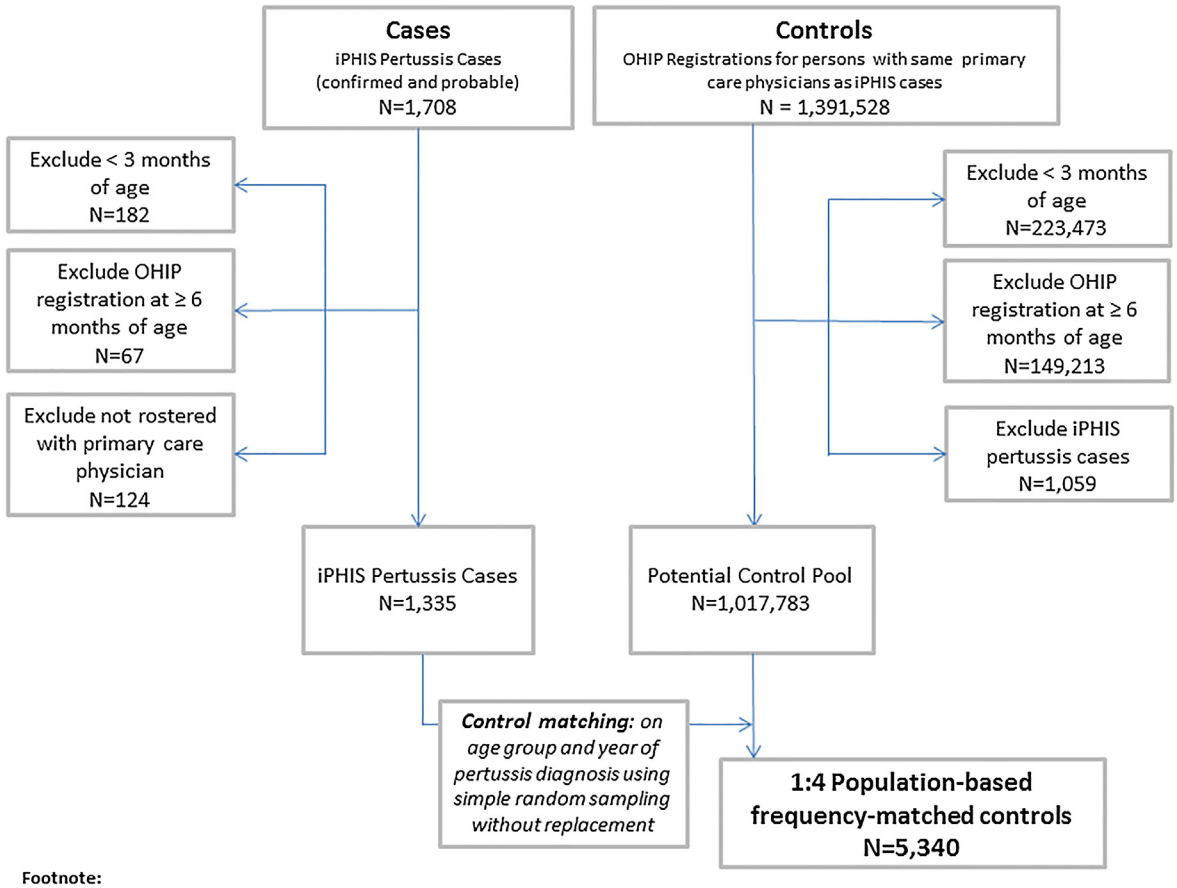

Fig. 1. Case and Control Selection, from Jan 1, 2009 to Mar 31, 2015 in persons born after Apr 1, 1992.

(incomplete primary, complete primary), or unvaccinated (Supplementary Table S2) from Ontario's immunization schedule which has not changed during the study period [16]. Specific vaccines in use during the study period were Sanofi Pasteur's Pediacel® in infants and Quadracel® for other doses, replaced by Adacel® in 2004. The number of age-appropriate doses is 1 dose at 3 months, 2 doses at 5 months, 3 doses at 7 months, 4 doses at 19 months, 5 doses at 7 years and 6 doses at 17 years. A priming series was defined as the first 3 doses of vaccine, regardless of age received. We analyzed VE by 2-year age groups and by time since last immunization in four categories: 15–364 days, 1–3 years, 4–7 years and ≥8 years. Doses given within 14 days of pertussis onset were excluded because this may be insufficient time to mount an immune response. We also calculated the proportion of the total study population that was a positive confirmed or probable iPHIS case for each year since last immunization.

2.4. Statistical analysis

We used multivariable logistic regression to estimate crude and adjusted odds ratios (OR). VE was calculated using the formula (1-OR) × 100. To measure waning immunity, we estimated VE by both age group and time since last immunization. Estimates of VE for children who were up-to-date for immunization were obtained for the four time periods of: under 1 year (15–364 d), 1–3 years, 4–7 years and greater than 8 years since last immunization. In the multivariable analysis, we adjusted for sex (male or female), neighbourhood income quintile (lowest (1) to highest (5)), rurality (rural versus urban), healthcare use (≥2 emergency department visits, ≥1 hospital admissions or ≥8 physician visits in the past year) and having one or more complex chronic conditions [17]. In a sensitivity analysis we excluded the year 2012, during which a localized outbreak had occurred, since outbreaks can affect estimates of VE. We also applied a quantitative exposure misclassification sensitivity analysis to adjust for potential non-differential misclassification in determining immunization status [18].

The impact of the 1997 introduction of the acellular vaccine was compared with older whole cell vaccine by estimating the odds of pertussis with the main exposure separated into acellular priming versus whole cell priming versus a combination of both. This analysis was limited to those who had received ≥5 doses of vaccine and were ≥10 years of age.

3. Results

3.1. Study population

We included 1335 cases and 5340 controls (Fig. 1). 141 (11%) cases in iPHIS could not be linked. A total of 805 physicians were associated with the cases, and the patients of these physicians were used as the sampling frame for the controls. The total number

of vaccine doses for all included cases and controls from April 1, 1992 to March 31, 2015 was 33,716 using immunization billing codes (Supplementary Table S1). The majority, 96%, of immunization codes were G538 (“immunization with visit”) or G359 (“immunization only”). 903 subjects (cases and controls) were unvaccinated. Cases and controls were comparable for key demographic characteristics apart from cases being less likely to be vaccinated ($p < 0.001$), less likely to be from rural areas ($p < 0.001$) and having fewer emergency department visits in the previous year ($p < 0.001$) (Table 1).

3.2. VE and waning immunity

VE was sustained between 92.0% (95%CI: 87.6–94.8%) in 2–3 year olds and 90.3% (95%CI: 80.2–95.2%) in 8–9 year olds, but then fell to a low of 48.6% (95%CI: 1.5–73.2%) in children 12–13 years of age (Fig. 2). VE following the teenage booster given at 14–16 years in Ontario reached 76.3% (95%CI: 52.1–88.3%) in 14–16 year olds and 77.7% (95%CI: −31.2 to 96.2%) in 16–22 year olds. VE changed non-linearly between the booster at 4 years of age and 14 years of age (Fig. 2). In children with up-to-date immunization status, adjusted VE was higher, starting at 87.0% (95%CI: 83.5–89.8%) in the first year following immunization and falling progressively each year to 73.8% (95%CI: 62.8–81.5%) by 8 years or more since last immunization (Table 2). We stratified the up-to-date children by age group and time since last immunization and found in adjusted results that VE was highest for the age group 4–14 years, peaking at 92.8% (95%CI: 86.4–96.1%) in the period up to one year following the pre-school booster (Table 3). In the 14–22-year old age group, the point estimate for VE in the year following immunization was 92.5% (95%CI: 74.1–97.8%). VE subsequently waned to a nadir of 66.5% (95%CI: 35.3–82.7%) by 8 or more years after the last vaccine dose (Table 3).

Excluding the outbreak year of 2012 led to a slightly higher estimate of adjusted VE at 76.7% (95%CI: 65.7–84.2%) by 8 years or more after last immunization (Fig. 3). Cases were not more likely to have been primed with acellular vaccine than whole cell vaccine (aOR = 0.98, 95%CI 0.74–1.3) or to have received at least one dose of whole cell vaccine (aOR = 1.04, 95%CI 0.80–1.3). Only 208/1335 (16%) cases were classified as probable, and removing these in a sensitivity analysis did not significantly alter the results (data not shown).

4. Discussion

We found that pertussis VE is high during the first few years, starting at close to 90%, but wanes with time since last immunization in the period leading up to the teenage booster given at 14–16 years of age. Although VE was generally higher and waned more slowly than we found previously by using the test-negative method of control selection [3], overall patterns of waning were similar. The findings of this study are consistent with the localized outbreaks that have occurred in recent years in high school-aged children [19]. In the period of this study, Ontario did not experience widespread outbreaks or any deaths of infants, which seems to support substantial and sustained VE, but the epidemiology

Table 1
Characteristics of pertussis cases and controls.

Characteristic		Cases N = 1335 n (%)	Controls N = 5340 n (%)	p-value*
Age	Mean years (min, max)	7.11 (0, 22)	7.13 (0, 21)	1.00
	Median (lower and upper quartile)	7.00 (2, 12)	7.00 (2, 12)	
	3 months to <2 years	276 (21)	1104 (21)	
	2 and 3 years	198 (15)	792 (15)	
	4 and 5 years	132 (10)	528 (10)	
	6 and 7 years	111 (8)	444 (8)	
	8 and 9 years	119 (9)	476 (9)	
	10 and 11 years	129 (10)	516 (10)	
	12 and 13 years	162 (12)	648 (12)	
	14 and 15 years	133 (10)	532 (10)	
	16 and 17 years	51 (4)	204 (4)	
	18–22 years	24 (2)	96 (2)	
Sex	Female	694 (52)	2628 (49)	0.07
	Male	641 (48)	2712 (51)	
Neighbourhood Income quintile	1 (lowest)	237 (18)	925 (17)	0.51
	2	251 (19)	992 (19)	
	3	278 (21)	1106 (21)	
	4	265 (20)	1187 (22)	
	5 (highest)	295 (22)	1094 (20)	
	Missing**	9 (1)	36 (1)	
Rurality	Rural	348 (26)	619 (12)	<0.001
	Missing**	≤5 (0)	23 (0)	
Any complex chronic medical condition [15]		31 (2)	124 (2)	1.0
Healthcare utilization	≥2 emergency department visits	202 (15)	588 (11)	<0.001
	≥1 hospital admissions	182 (14)	688 (13)	0.47
	≥8 physician office visits	207 (16)	894 (17)	0.28
Birth Year	1992–1996	126 (9)	540 (10)	0.45
	1997–2000	285 (21)	1097 (21)	
	2001–2004	258 (19)	1110 (21)	
	2005–2008	326 (24)	1205 (23)	
	2009–2014	340 (25)	1388 (26)	
Vaccine Status	Unvaccinated	466 (35)	437 (8)	<0.001
	Incomplete Primary	145 (11)	595 (11)	
	Complete Primary	182 (14)	754 (14)	
	Up-to-Date	542 (41)	3554 (67)	

* From Chi-square test.
** Missing values were excluded from the models.

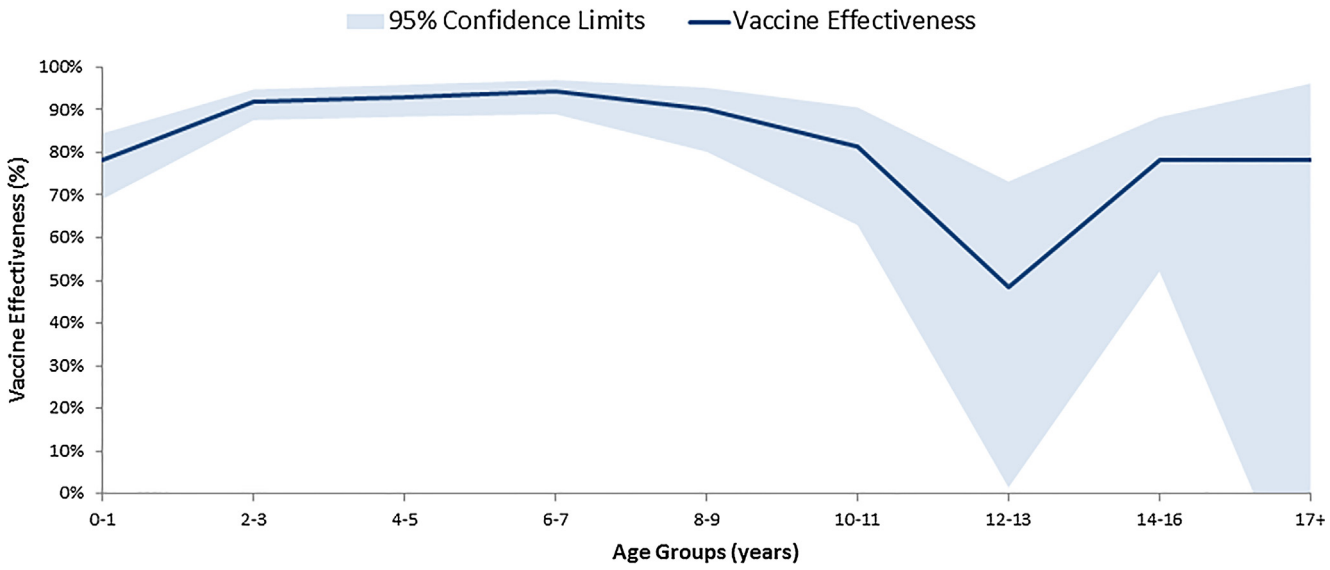

Fig. 2. Adjusted Pertussis Vaccine Effectiveness and 95% confidence intervals in Ontario by frequency-matched case-control design, 2009–2015, by age group, up-to-date compared to unvaccinated as the reference standard.

Table 2
Crude and adjusted[†] estimates of pertussis vaccine effectiveness (VE) by time period since last vaccination and vaccination status.[*]

Vaccination status	Time period since last vaccination	Crude VE % (95%CI)	Adjusted[†] VE % (95%CI)
Up-to-date vaccination	15–364 days	88.4 (85.6–90.6)	87.0 (83.5–89.8)
	1–3 years	88.8 (86.1–91.1)	87.9 (84.6–90.5)
	4–7 years	81.3 (76.6–85)	76.6 (69.0–82.3)
	≥8 years	78.0 (72–82.7)	73.8 (62.8–81.5)
Partially vaccinated (incomplete primary doses and completed primary doses)			
Incomplete primary doses[**]	15–364 days	83.4 (74.2–89.3)	82.6 (72.3–89)
	1–3 years	77.6 (66.9–84.9)	76.7 (64.9–84.6)
	4–7 years	73.6 (56.2–84)	71.1 (50.9–83)
	≥ 8 years	68.8 (52.2–79.6)	67.6 (46.9–80.2)
Completed primary doses[***]	15–364 days	84.1 (−33.1 to 98.1)	83.8 (−86.9 to 97.5)
	1–3 years	88.0 (69.3–95.3)	86.6 (64.6–94.9)
	4–7 years	81.4 (72.2–87.6)	79.5 (72–85)
	≥8 years	75.3 (67.8–81)	72.0 (59.4–80.7)
Excluding 2012 outbreak cases	15–364 days	87.0 (83.7–89.7)	86.3 (82.1–89.5)
	1–3 years	87.7 (84.3–90.3)	87.2 (83.3–90.2)
	4–7 years	81.5 (76.1–85.7)	80.5 (69.9–87.4)
	≥8 years	78.2 (71.4–83.4)	76.7 (65.7–84.2)

[*] Reference group is unvaccinated population.
[**] Excludes children with fewer than 3 doses in the first year of life.
[***] Excludes all children less than 7 months old.
[†] Adjusted for sex, socioeconomic status, rurality, healthcare utilization and comorbidity.

Table 3
Vaccine effectiveness (VE) and time period since last vaccination stratified by age for children and adolescents who are up-to-date for immunizations.

Age	Time period since last vaccination	Crude VE % (95%CI)	Adjusted[†] VE % (95%CI)
6–18 months	15–364 days	84.9 (77.4–89.9)	85.7 (76.3–91.3)
18 months to 4 years	15–364 days	93.2 (89.4–95.7)	91.7 (86.4–94.9)
	1–3 years	90.0 (85.1–93.3)	89.0 (82.9–92.9)
4–14 years	15–364 days	94.3 (89.6–96.9)	92.8 (86.4–96.1)
	1–3 years	91.8 (88.8–94.1)	90.4 (86.5–93.1)
	4–7 years	86.0 (81.4–89.4)	84.0 (78.4–88.2)
	≥8 years	85.3 (79.1–89.7)	80.4 (71.3–86.6)
14–22 years	15–364 days	87.9 (67.1–95.5)	92.5 (74.1–97.8)
	1–3 years	76.8 (48.9–89.4)	82.8 (57.3–93.1)
	4–7 years	63.3 (38.9–83.8)	78.3 (40.8–87.1)
	≥8 years	59.3 (23.7–78.3)	66.5 (35.3–82.7)

[†] Adjusted for sex, socioeconomic status, rurality, healthcare utilization and comorbidity.

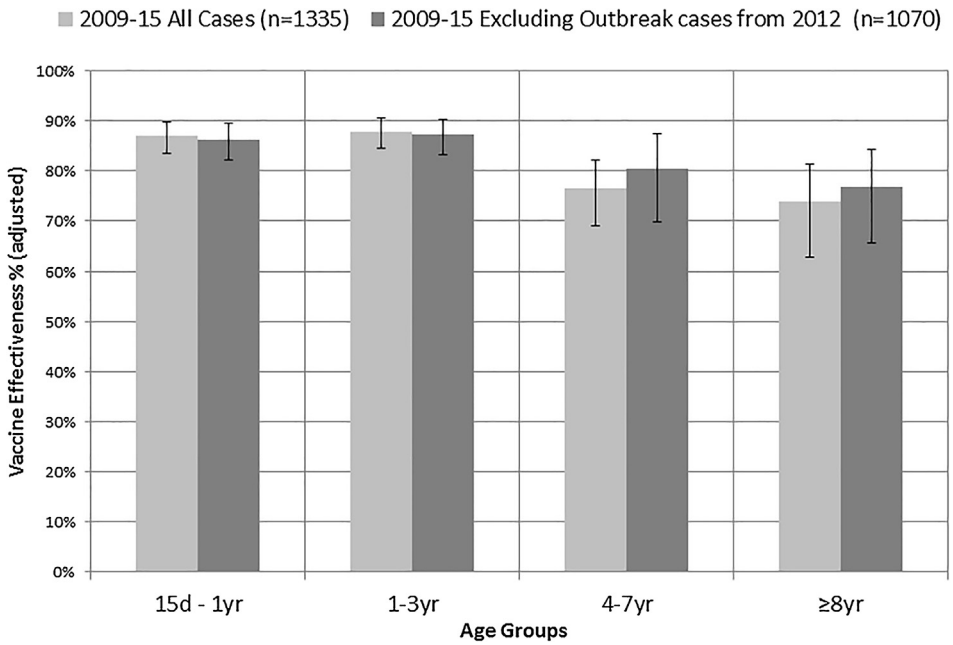

Fig. 3. Adjusted Vaccine Effectiveness in 2009–15, all cases and controls, and excluding 265 cases linked to an outbreak in 2012.

may be influenced by immunity from past infection of the older age groups. Widespread outbreaks of pertussis in the 1990s may have left its imprint in herd immunity due to past infection in women currently of childbearing age, and this may be protecting infants, since the duration of immunity after infection may be quite prolonged [20]. If so, this protection can be anticipated to disappear as the more recent birth cohorts reach childbearing age. In the coming years, Canadian-born mothers will be less likely to have been infected as children because they grew up during low incidence of pertussis, and would have received only acellular pertussis vaccines. The risk to infants born in Ontario may therefore be about to increase, reinforcing the need for more action to protect infants including immunization in pregnancy, which is recommended in Canada by the National Advisory Committee on Immunization, but not fully implemented across the country [21].

A protective effect of whole cell vaccine priming has been found in a few other studies [22,23]. It is unclear why we did not find this effect in this study, particularly when it was evident when using the test-negative design in the same setting [3]. The frequency-matched controls in older age groups in our study may have been too similar to cases in some way, leading to VE of whole cell vaccine being underestimated. Alternatively, selection bias in test-negative studies may be a factor, if this leads to a greater proportion of controls being unvaccinated than found in the general population. These methodological differences in studying pertussis VE warrant further study.

Limitations of the frequency-matched case-control design include the risk that VE may have been over-estimated for a number of reasons. Given the strict case definition in Ontario, the cases we used in this analysis identified through statutory pertussis surveillance may be biased towards more severe disease. The case definition for a confirmed case is highly specific, requiring a confirmed case to have laboratory confirmation or an epidemiological link to a laboratory-confirmed case and at least one typical symptom. A probable case is required to have at least 2 weeks of cough associated with paroxysms, whoop, vomiting or gagging, or apnea. VE estimates are higher when using stricter case definitions, including more stringent laboratory diagnostic methods [24,25]. Changes occurred to the surveillance system during the study period that increased specificity of the case definition and of laboratory diagnosis. In 2012, Public Health Ontario stopped reporting indeterminate polymerase chain reaction (PCR) results (defined as threshold cycle values of 36–40), and reinforced the message to public health units to stop testing asymptomatic contacts [26]. Also in 2012, primers targeting a 50 bp segment of the recA gene were included to distinguish *Bordetella pertussis* from *Bordetella holmesii* [3]. Such changes would have increased specificity of diagnosis and reporting during the time period, also leading towards a small bias in favour of over-estimating VE, due to the relative rarity of *Bordetella holmesii* in Ontario [27]. Furthermore, we have found strong evidence for under-ascertainment of pertussis in Ontario that may be particularly pronounced in milder cases [28]. Such under-ascertainment, or low sensitivity of surveillance, has been shown to be less important than specificity of the case definition for measuring influenza VE [29]. However, this finding has not been validated for pertussis.

Strengths of our study include the large sample size and the rigorous approach to control selection aimed to minimize bias and confounding, including non-differential misclassification bias of immunization status. This approach also aimed to ensure that controls had comparable opportunity to be detected as cases and be better matched for aspects such as healthcare-seeking behaviour than is sometimes found in non-matched administrative controls.

A study conducted in California using both test-negative and population controls during a large outbreak found that pertussis VE fell extremely rapidly after the fifth dose [12]. In the population-controlled analysis, the authors found that protection fell by 50% per year. The equivalent fall in our study would be from 92.5% to 46.3% in one year, but we observed a much slower decline to 82.8% (95%CI: 57.3–93.1%) over 1–3 years. Our estimates would do not fall as low as the California study would suggest even at 8 or more years following vaccination; at that point we estimate VE at 66.5% (95%CI: 35.3–82.7%). However, although confidence intervals were narrow in earlier years, by 8 or more years they became quite wide, indicating that we should be cautious in drawing conclusions.

5. Conclusions

The epidemiology of pertussis during the period of this study supports our findings that, while VE in Ontario may be higher than

previously reported, protection wanes over time. Our findings are policy-relevant and indicate that the current schedule seems to be working quite well, while reinforcing the need for additional measures to protect infants including immunization during pregnancy. Although the relative merits of the test-negative and frequency-matched population methods of control selection remain unclear, the consistent findings to emphasize for policy-makers are that immunity wanes regardless of study design. Further research should evaluate different methods of pertussis VE evaluation in order to optimize methods. This will ensure generation of robust evidence on how to improve protection of infants from this devastating disease.

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Conflicts of interest

There were no conflicts of interest of any of the authors.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.02.047.

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