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A nested case-control study measuring pertussis vaccine effectiveness and duration of protection in Manitoba, Canada, 1992–2015: A Canadian Immunization Research Network Study

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ABSTRACT

Background: Pertussis persists in Manitoba despite the universal availability of pertussis vaccines. Recent cases have included previously vaccinated individuals, raising concerns about declining vaccine effectiveness (VE). We measured pertussis VE and duration of protection using Manitoba's provincial immunization and communicable disease registries.

Methods: Using a nested case-control design, individuals with laboratory-confirmed pertussis in Manitoba diagnosed between April 1, 1992, and March 31, 2015, were matched to up to five population-based controls on age, gender, geography, and case physician or number of physician visits. Conditional logistic regression was used to estimate VE against pertussis for both the whole-cell (wP) and acellular (aP) pertussis vaccines. Duration of protection was assessed using time since last dose.

Results: Data on 534 eligible cases and 2614 controls were available for analysis. The adjusted VE estimate for aP-containing vaccines was 85% (95%CI: 74–91%); VE was 89% (66–96%) one to three years after the last vaccination. The adjusted VE of wP-containing vaccines was –15% (–91–31%) during a large outbreak in 1994 and 1995 compared to 35% (–26–66%) during non-outbreak years.

Conclusions: Our estimates suggest that the aP vaccine was effective in preventing pertussis since its introduction in Manitoba. VE was lower during a large outbreak, highlighting the importance of separately analyzing outbreak periods when estimating pertussis VE over time.

1. Introduction

Pertussis (whooping cough) is a highly contagious respiratory disease that remains one of the most common vaccine-preventable diseases reported in Canada [1]. Whole-cell pertussis vaccination was first introduced in Canada in 1943 and the annual incidence dropped from 160 cases per 100,000 people in the pre-vaccine era to less than 20 cases per 100,000 people by the 1980s [2]. This pattern changed, however, in the 1990s, with a rise in incidence largely attributed to the low efficacy of the whole-cell vaccine in use in Canada during that time [3]. Due to concerns about the safety and low efficacy of the whole-cell pertussis vaccine, Canada switched to a combination vaccine that included an acellular pertussis component in 1997, which led to a long period of good pertussis control. Then, in 2012, incidence of the disease increased in several parts of Canada [2].

Abbreviations: aP, acellular pertussis; CDS, communicable disease surveillance; DTaP, diphtheria tetanus acellular pertussis; DPIN, Drug Program Information Network; HAD, Hospital Abstracts Database; ICD, International Classification of Diseases; MH, Manitoba Health; MHR, Manitoba Health Registry; MIMS, Manitoba Immunization Monitoring System; MSD, Medical Services Database; OR, odds ratio; PHIN, Personal Health Identification Number; Tdap, tetanus diphtheria acellular pertussis; VE, vaccine effectiveness; wP, whole-cell pertussis.

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Manitoba, a Canadian province with a population of almost 1.3 million, had a large pertussis outbreak in the mid-1990s, which was followed by an extended period of low pertussis activity [2]. Disease incidence rose from 1.2 cases per 100,000 people in 2008 to 9.4 cases per 100,000 people in 2012 [5]. Pertussis incidence increased elsewhere around the same time and patients were older and more likely to be fully-vaccinated against pertussis compared to earlier outbreaks [6–8], raising concerns that the immunity conferred by the acellular pertussis (aP) vaccine may wane over time [8–11].

To better understand the limitations of current and past pertussis vaccine programs, we measured the vaccine effectiveness (VE) and duration of protection of both the wP and aP vaccines in Manitoba. We estimated wP VE separately for cases diagnosed during the large disease outbreak of 1994/1995 to assess for effect modification by this outbreak.

2. Methods

We conducted a population-based nested case-control study linking the Manitoba Immunization Monitoring System (MIMS) with public health surveillance, hospital, physician, and prescription claims databases housed at the Manitoba Centre for Health Policy [12–14]. Manitoba Health (MH) is a government agency that provides universal publicly funded health care to the province's residents; insured services include hospital, physician, and preventive services such as vaccinations. The electronic databases used to record provided services are linkable using a unique lifetime personal health identification number (PHIN). We deterministically linked (using the PHIN) six MH administrative and public health databases to establish the study cohort, identify individuals diagnosed with pertussis, and match population-based controls. This study was approved by the University of Manitoba Research Ethics Board and by MH's Health Information Privacy Committee.

2.1. Data sources

The Manitoba Health Insurance Registry (MHR) tracks addresses and dates of birth, insurance coverage, and death for all insured persons in the province. Postal codes are updated semi-annually, making it possible to track residents' locations over time. MIMS is the population-based province-wide registry that contains records of all childhood vaccinations administered in Manitoba since 1988 and all adult vaccinations since 2000. Information, including vaccine type and administration date, is captured either through direct data entry (for vaccines administered by public health staff) or through physician billing claims. Estimates of the completeness and accuracy of vaccination information are high, with 2% or fewer immunizations coded incorrectly [15]. Vaccine coverage in our study was consistent with estimates from both Manitoba Health and the National Childhood Immunization Survey [16,17].

The Communicable Disease Surveillance Database (CDS) records all cases of notifiable diseases reported by clinicians and laboratories to MH since 1992. Under *The Manitoba Public Health Act*, clinicians must report all cases and deaths due to pertussis and laboratories must report any positive pertussis tests. The CDS database stores information on laboratory specimen type, collection date, and test results. The Hospital Abstracts Database (HAD) records virtually all services provided since 1971 by hospitals in the province (including admissions and day surgeries) using the International Classification of Diseases, Tenth Revision, Canadian Edition (ICD-10-CA) since 2004 and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) prior to that. The Medical Services Database (MSD), also in operation since 1971, collects similar information on services provided by physicians and other clinicians in offices, hospitals and outpatient departments across the province. The Drug Program Information Network (DPIN) captures data from pharmacy claims since 1995 for formulary drugs dispensed to all Manitobans including those without prescription drug insurance.

2.2. Study cohort

We defined an eligible participant as any individual who was born after 1988 and was continuously registered in the MHR within two months of birth at any time between April 1, 1992, and March 31, 2015 (the study period). Participants entered the study cohort at the start of the study period (if born between 1988 and March 31, 1992) or at birth (if born after April 1, 1992) and exited the study cohort on earliest of the date they lost MH coverage for any reason, the end of the study period, or the date of pertussis diagnosis (see below).

2.3. Definition of cases and controls

We defined a pertussis case as any member of the study cohort who tested positive for pertussis by any microbial testing method, as recorded in the CDS database, during the study period. Using risk-set (incidence density) sampling, we matched each case to up to 5 members of the study cohort who (1) had not been diagnosed with pertussis by the case's date of diagnosis (the index date) and (2) who had the same age (±365 days), gender, and place of residence as the case (Supplementary Table 1). To account for possible bias due to systematic between-physician differences in testing and vaccine administration practices, we also matched on the principal physician (most frequently visited physician in the year prior to index date). We filled incomplete sets (*i.e.,* sets where cases had no principal physician or had less than five physician-matched controls) by matching on the number of physician visits to any physician in the year prior to index date. Cohort members diagnosed with non-laboratory confirmed pertussis ("clinical case") in the CDS database, or a healthcare encounter coded as ICD-9 code = 033* or ICD-10 code = A37* in the MSD or HAD exited the cohort at the date of diagnosis.

2.4. Vaccination history and covariates

We obtained pertussis vaccination histories for both cases and controls using pertussis-specific tariff codes in MIMS (Supplementary Table 2) [18,19]. Manitoba used adsorbed wP vaccine from the early 1980s until the province moved to the aP vaccine in 1997 [20,21].

Pertussis vaccine schedules change over time. We used the vaccine schedules in place between an individual's birth and index dates to determine the recommended number of pertussis vaccine doses they should have received by their index date (Supplementary Table 3). An *up-to-date* person had received the recommended number of pertussis vaccine doses, a *partially vaccinated* person had received at least one pertussis vaccine dose but had not received the recommended number of doses, an *unvaccinated* person had not received any pertussis vaccine doses. The product used (wP only, aP only, mixed/both wP and aP) was based on all vaccines received between birth and the index date. Cases and controls with pertussis vaccine received $\leq$14 days before their index date were excluded.

We obtained household income level from the 2006 Canadian census using neighbourhood-level income quintiles. Information on health services utilization and comorbidities prior to the index date was obtained from the HAD, MSD, and DPIN using previously validated algorithms. A complete list of study variables

and definitions is available in the supplementary material (Supplementary Table 1).

2.5. Statistical analysis

We used conditional logistic regression to estimate odds ratios (OR) and 95% confidence intervals (95%CI) of the association between overall and type-specific vaccination and pertussis while adjusting for number of physician visits and hospitalizations in the previous year (as a proxy for healthcare-seeking behaviour), and having a pre-existing chronic or immunocompromising condition. VE was calculated as (1-OR) × 100. We also estimated duration of VE using time since last dose as the exposure variable in conditional logistic regression models; up-to-date vaccine status was determined *a priori* as the exposure variable for estimates of VE duration. Estimates of pertussis VE tend to be lower in epidemic periods and Manitoba experienced a large outbreak in 1994 and 1995 [2,22,23]. To assess for effect modification by this outbreak, we estimated VE separately for cases diagnosed during the outbreak years [24]. To assess the robustness of matching (principal physician vs. number of physician visits), we repeated the analysis after restricting to controls selected by each method.

3. Results

We identified 604 pertussis cases diagnosed among the study population during the study period. We excluded 40 (7%) cases with non-continuous MH coverage, 25 (4%) cases with a pertussis vaccine 14 days before the index date, and 5 (1%) cases without a suitable match (Supplementary Table 4). The final study population included 534 cases (of which 232 [43%] were diagnosed during the 1994–95 outbreak) and 2614 matched controls (Table 1).

Over the study period, most laboratory-confirmed pertussis cases in Manitoba were younger than 14 years old (Table 1). Chronic disease and immunocompromising conditions were more common in cases than controls, but only during the non-outbreak years. Of the 302 cases diagnosed in non-outbreak years, 52% were up-to-date on their pertussis vaccination compared to 62% of controls. During outbreak years, there were no significant differences in vaccination status between cases and controls, but there were more partially vaccinated persons compared to non-outbreak years (30% vs 25%). Only 10% of cases diagnosed during outbreak years were never vaccinated compared to about 25% of cases in non-outbreak years (Table 1). Cases in the acellular vaccine cohort were more likely to have up-to-date or partial vaccine status compared to cases in the whole-cell vaccine cohort (Supplementary Table 5).

During non-outbreak years, the adjusted VE estimates of any pertussis vaccine against laboratory-confirmed pertussis were 73% (95%CI 61–82%) for up-to-date vaccination and 70% (54–81%) for partial vaccination (Table 2). The corresponding estimates for those who only received a wP vaccine, 35% (–26–66%) and 11% (–82–57%), were both lower and less precise than those for persons who received the aP vaccine only: 85% (74–91%) and 85% (70–92%) respectively. During the outbreak years, only the wP vaccine was used in Manitoba and the VE estimates during that period were imprecise, but consistent with lower effectiveness (Table 3).

During non-outbreak years (Table 2), the overall adjusted VE against laboratory-confirmed pertussis for individuals with up-to-date vaccine status was 76% (57–87%) in the 1–3 years following vaccination and 22% (–305–85%) more than eight years post-vaccination. For the wP vaccine, the adjusted VE was 48% (–23–78%) in the 1–3 years following vaccination and 13% (–672–90%) more than 8 years post-vaccination. For the aP vaccine, VE was 89% (66–96%) at 1–3 years post-vaccination and 41% (–926–97%) more than 8 years post-vaccination (Table 2). Adjusted VE estimates for individuals partially vaccinated with aP vaccine were 92% (67–98%) at 1–3 years post vaccination and, although imprecise, were consistent with declining effectiveness by eight years post-vaccination (Supplementary Table 6). Considering all vaccinated persons together did not change our interpretation of the results.

A total of 170 (28%) and 9 (1.5%) cases were excluded due to the inability to identify a suitable match when restricting analysis to physician seen most frequently or to number of physician visits in the year prior to index date respectively (Supplementary Table 4). In a sensitivity analysis, VE estimates were similar in both control groups (Supplementary Table 7).

4. Discussion

We estimated that the overall VE was higher for the aP vaccine at 85% (74–91%) compared to 35% (−26–66%) for the wP vaccine during non-outbreak years. The data were also consistent with declining VE over time.

Although imprecise, our estimate of wP VE during non-outbreak years (35%; −26–66%) is consistent with the range of estimates (20–60%) reported in Canada for wP vaccine used between 1984 and 1998 [3]. Due to this low VE and concerns around its safety, the wP vaccine was replaced by aP vaccines throughout Canada by 1998 [25]. Estimates for the whole-cell products currently in use in other countries are higher at 94% (88–97%) [26]. Similarly, our aP VE estimates against laboratory-confirmed pertussis (85%; 74–91%) are consistent with those seen in a recent test-negative case-control study carried out in the Canadian province of Ontario, which demonstrated VE for the acellular vaccine of 84% (77–89%) for up-to-date vaccination in the first three years following vaccination [9]. Our estimates are also comparable to VE estimates from the 2016 systematic review and meta-analysis done by Fulton et al., which showed a pooled short-term protective effect of 84% (81–87%) for the aP vaccine [26].

The Ontario study further suggested that the protective effect of the aP vaccine declines over time and observed that the odds of pertussis increased by 27% per year since last vaccination [9]. A systematic review and meta-analysis that pooled 11 long-term studies from multiple countries had similar results, with the odds of pertussis increasing by 33% per year since last vaccination [27]. The meta-analysis and Ontario study both concluded that protection against pertussis would not be expected to extend longer than 7–8.5 years for most individuals after the last acellular pertussis dose. Although imprecise, our estimates are consistent with those reported in these other studies.

We saw lower wP VE during a large outbreak in 1994 and 1995, consistent with a contemporaneous outbreak of pertussis in the Canadian province of Nova Scotia that reported wP VE estimates against laboratory-confirmed pertussis for up-to-date vaccination among children of 14% (–158–71%) [20]. Previous pertussis VE studies have also demonstrated lower estimates of effectiveness in outbreak periods as compared to non-outbreak periods [22,23]. The differences in VE estimates may be attributed to testing bias; since VE estimates are higher for typical/severe cases, heightened physician awareness and enhanced testing and reporting of cases with atypical/milder disease during outbreaks could result in lower VE estimates [22]. It is also possible that the pertussis vaccine offers less protection during periods of intense exposure which may contribute to the lower VE seen in outbreak periods [22,23].

4.1. Strengths and limitations

A major strength of our study was the population-based design; the availability of accurate, high-quality health administrative

Table 1
Socioeconomic and clinical characteristics of pertussis cases and population-based controls by outbreak status.

	Non-outbreak years		Outbreak years*	
	Case (N = 302)	Control (N = 1531)	Case (N = 232)	Control (N = 1083)
Male	157 (52.0%)	806 (52.6%)	113 (48.7%)	516 (47.6%)
Age group (years)				
<1	59 (19.5%)	301 (19.7%)	24 (10.3%)	80 (7.4%)
1–2	43 (14.2%)	227 (14.8%)	48 (20.7%)	228 (21.1%)
3–5	66 (21.9%)	340 (22.2%)	119 (51.3%)	607 (56.0%)
6–8	63 (20.9%)	316 (20.6%)	41 (17.7%)	168 (15.5%)
9–13	59 (19.5%)	270 (17.6%)	0 (0.0%)	0 (0.0%)
≥14	12 (4.0%)	77 (5.0%)	0 (0.0%)	0 (0.0%)
Rural residence	151 (50.0%)	777 (50.8%)	62 (26.7%)	290 (26.8%)
Income in lower 40%	134 (44.4%)	720 (47.0%)	80 (34.5%)	390 (36.0%)
Has chronic condition	44 (14.6%)	166 (10.8%)	14 (6.0%)	66 (6.1%)
Immunocompromised	34 (11.3%)	120 (7.8%)	< 6 (<2.6%)	9 (0.8%)
Four or more physician visits†	151 (50.0%)	734 (47.9%)	116 (50.0%)	476 (44.0%)
One or more hospitalizations†	62 (20.5%)	309 (20.2%)	< 6 (<2.6%)	< 6 (<0.6%)
Two or more prescriptions†	95 (31.5%)	495 (32.3%)	19 (8.2%)	69 (6.4%)
Year of index date				
1992–1996	40 (13.2%)	223 (14.6%)	232 (100.0%)	1,083 (100.0%)
1997–2001	119 (39.4%)	611 (39.9%)	N/A	N/A
2002–2006	45 (14.9%)	214 (14.0%)	N/A	N/A
2007–2011	51 (16.9%)	250 (16.3%)	N/A	N/A
2012–2015	47 (15.6%)	233 (15.2%)	N/A	N/A
Vaccine status‡				
Unvaccinated	76 (25.2%)	182 (11.9%)	24 (10.3%)	131 (12.1%)
Partial	70 (23.2%)	408 (26.6%)	71 (30.6%)	315 (29.1%)
Up-to-date	156 (51.7%)	941 (61.5%)	137 (59.1%)	637 (58.8%)
Product used in vaccination series				
Unvaccinated	76 (25.2%)	182 (11.9%)	24 (10.3%)	131 (12.1%)
Acellular	60 (19.9%)	467 (30.5%)	N/A	N/A
Mixed	21 (7.0%)	162 (10.6%)	N/A	N/A
Whole-cell	145 (48.0%)	720 (47.0%)	208 (89.7%)	952 (87.9%)
Time since most recent vaccination				
Unvaccinated	76 (25.2%)	182 (11.9%)	24 (10.3%)	131 (12.1%)
15–364 days	56 (18.5%)	450 (29.4%)	69 (29.7%)	337 (31.1%)
1–3 years	92 (30.5%)	572 (37.4%)	125 (53.9%)	579 (53.5%)
4–7 years	58 (19.2%)	248 (16.2%)	14 (6.0%)	36 (3.3%)
≥ 8 years	20 (6.6%)	79 (5.2%)	0 (0.0%)	0 (0.0%)

* 1994 and 1995.
† In the 365 days prior to index date.
‡ According to the recommended number of pertussis vaccine doses for their age and birth cohort.

Table 2
Pertussis vaccine effectiveness (%) during non-outbreak years in Manitoba by vaccine type and certain vaccination characteristics.

	Whole-cell vaccine		Acellular vaccine		Any vaccine	
	Model A* (95% CI)	Model B† (95% CI)	Model A* (95% CI)	Model B† (95% CI)	Model A† (95% CI)	Model B† (95% CI)
Vaccine status§						
Unvaccinated	ref	ref	ref	ref	ref	ref
Partial	14 (−76–58)	11 (−82–57)	84 (69–92)	85 (70–92)	69 (53–80)	70 (54–81)
Up-to-date	32 (−30–65)	35 (−26–66)	85 (73–91)	85 (74–91)	72 (60–81)	73 (61–82)
Elapsed time since most recent vaccination‡						
Unvaccinated	ref	ref	ref	ref	ref	ref
15–364 days	36 (−68–75)	42 (−56–78)	83 (68–91)	83 (67–91)	74 (57–84)	75 (59–85)
1–3 years	43 (−33–76)	48 (−23–78)	87 (62–96)	89 (66–96)	75 (54–86)	76 (57–87)
4–7 years	0 (−248–71)	15 (−211–77)	83 (−108–99)	83 (−114–99)	45 (−53–80)	51 (−37–82)
≥8 years	−46 (−1041–81)	13 (−672–90)	47 (−825–97)	41 (−926–97)	−3 (−420–79)	22 (−305–85)

* Model A is adjusted for the matching variables (age, gender, residence, physician or number of physician visits).
† Model B is adjusted for the matching variables, ≤ 4 physician visits (median for study cohort), hospitalized in previous year, chronic disease and immunocompromised status; ref = reference group.
‡ Elapsed time estimates use up-to-date vaccine status.
§ According to the recommended number of pertussis vaccine doses for their age and birth cohort.

databases in Manitoba makes our VE estimates less susceptible to misclassification of vaccine status and to the selection and recall biases that often affect observational studies.

Pertussis remains a relatively uncommon occurrence in Manitoba and a limitation of our study was the low number of pertussis cases available for analysis. The need to present separate analyses

Table 3
Whole-cell pertussis vaccine effectiveness (%) during outbreak years 1994 and 1995 in Manitoba by certain vaccination characteristics.

	Model A* (95% CI)	Model B† (95% CI)
Vaccine status§		
Unvaccinated	ref	ref
Partial	−37 (−140–22)	−37 (−139–22)
Up-to-date	−15 (−92–31)	−15 (−91–31)
Elapsed time since most recent vaccination‡		
Unvaccinated	ref	ref
15–364 days	−2 (−88–44)	−0 (−84–45)
1–3 years	−8 (−100–42)	−6 (−98–43)
4–7 years	N/A	N/A
≥8 years	N/A	N/A

* Model A is adjusted for the matching variables (age, gender, residence, physician or number of physician visits).
† Model B is adjusted for the matching variables, ≤ 4 physician visits (median for study cohort), hospitalized in previous year, chronic disease and immunocompromised status; ref = reference group.
‡ Elapsed time estimates use up-to-date vaccine status.
§ According to the recommended number of pertussis vaccine doses for their age and birth cohort.
N/A = not applicable.

for the outbreak and non-outbreak periods due to effect modification further limited the precision of our estimates. Although our point estimates suggested declining protection over time, the confidence intervals were wide and often overlapped. Our point estimates were consistent with previous studies; they could, however, also be interpreted as showing no VE, especially for the whole-cell pertussis vaccine. We did not exclude off-schedule doses or doses administered too close together (which may result in a suboptimal immune response). Each time period since the most recent vaccination included different mixes of ages and number of doses; due to the low number of cases, we were unable to stratify by both elapsed time and age together. We also lacked the power to analyze the VE of Tdap separately, because our study consisted mostly of children younger than the recommended Tdap booster age (97% of our population). There is emerging evidence that individuals primed with acellular pertussis vaccine have increased odds of disease compared to individuals primed with whole-cell vaccine [9]. We were unable to assess the role of the priming dose as only 21 of our cases received both vaccines.

Since cases were restricted to individuals with diagnosed pertussis-related episodes, our estimates reflect VE against medically attended pertussis and are not necessarily generalizable to all cases of pertussis infection. Although classic whooping cough illness is described by paroxysmal cough, post-tussive vomiting, and inspiratory whoop lasting over a prolonged period of time, evidence has shown that previously vaccinated individuals may still be infected, but experience reduced disease severity and duration [28]. Individuals with mild disease of a shorter duration may be less inclined to seek medical attention and thus would not be included in these analyses.

A national survey in the US exploring physician practices for managing pertussis in adolescents suggested that a substantial number of primary care physicians may not be able to recognize the clinical symptoms of pertussis in adolescents and that nearly one out of six physicians do not test adolescents for pertussis as part of their clinical practice [29]. This could confound VE estimation if these physicians are also less (or more) likely to administer pertussis vaccines. To minimize confounding, we matched cases and controls on physician seen most frequently in the year prior to the index date. However, not all cases had documented physician visits in the year before the index date, and for these cases we instead matched on frequency of physician visits before the index date. In sensitivity analyses, estimates from the physician-matched controls were similar to the visit frequency-matched controls, suggesting that either approach is a reasonable choice, especially given that our results were similar to those obtained from test-negative study designs where all participants were tested for pertussis [30,31].

In conclusion, our estimates suggest that the aP vaccine was effective in preventing pertussis since its introduction in Manitoba, albeit with a possible decline in effectiveness by eight years post-vaccination. VE was lower during a large outbreak, highlighting the importance of separately analyzing outbreak periods when estimating pertussis VE over time.

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6. Data sharing

Data used in this article was derived from administrative health and social data as a secondary use. The data was provided under specific data sharing agreements only for approved use at MCHP. The original source data is not owned by the researchers or Manitoba Centre for Health Policy (MCHP) and as such cannot be provided to a public repository. The original data source and approval for use has been noted in the acknowledgments of the article. Where necessary, source data specific to this article or project may be reviewed at MCHP with the consent of the original data providers, along with the required privacy and ethical review bodies.

7. Authors' contribution

SMM designed the study and supervised the analysis. KW and CHR analyzed the data. KW, CHR, and SMM interpreted the data. KW, CHR, and SMM drafted the manuscript. JCK, KLS, MLR, and NSC assisted with study design and interpretation of the results. All authors critically revised the manuscript for intellectual content and approved the final draft for submission.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [SMM has received unrestricted research grants from Merck, GlaxoSmithKline, Sanofi Pasteur, Pfizer and Roche-Assurex for unrelated studies. SMM has received fees as an advisory board member for Sanofi Pasteur. KW, CHR, JCK, KLS, MLR, NSC have no conflicts of interest to report.].

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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.2019.09.064.

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Further reading

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