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Evaluation of the effectiveness of maternal immunization against pertussis in Alberta using agent-based modeling: A Canadian immunization research network study

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ABSTRACT

Introduction: The re-emergence of pertussis has occurred in the past two decades in developed countries. The highest morbidity and mortality is seen among infants. Vaccination in pregnancy is recommended to reduce the pertussis burden in infants.
Methods: We developed and validated an agent-based model to characterize pertussis epidemiology in Alberta. We computed programmatic effectiveness of pertussis vaccination during pregnancy (PVE) in relation to maternal vaccine coverage and pertussis disease reporting thresholds. We estimated the population preventable fraction (PFP) of different levels of maternal vaccine coverage against counterfactual "no-vaccination" scenario. We modeled the effect of immunological blunting and measured protection through interruption of exposure pathways.
Results: PVE was inversely related to duration of passive immunity from maternal immunization across most simulations. In the scenario of 50% maternal vaccine coverage, PVE was 87% (95% quantiles 82–91%), with PFP of 44% (95% quantiles 41–45%). For monthly age intervals of 0–2, 2–4, 4–6 and 6–12, PVE ranged between 82 and 99%, and PFP ranged between 41 and 49%. At 75% maternal vaccine coverage, PVE and PFP were 90% (95% quantiles 86–92%) and 68% (95% quantiles 65–69%), respectively. At 50% maternal vaccine coverage and 10% blunting, PVE and PFP were 86% (95% quantiles 77–87%) and 43% (95% quantiles 39–44%), respectively, while at 50% blunting, the corresponding values of PVE and PFP were 76% (95% quantiles 70–81%) and 38% (95% quantiles 35–40%). PVE attributable to interruption of exposure pathways was 54–57%.
Conclusions: Our model predicts significant reduction in future pertussis cases in infants due to maternal vaccination, with immunological blunting slightly moderating its effectiveness. The model is most sensitive to maternal vaccination coverage. The interruption of exposure pathways plays a role in the reduction of pertussis burden in infants due to maternal immunization. The effect of maternal immunization on population other than infants remains to be elucidated.

Introduction

The past two decades has witnessed the re-emergence of pertussis as a public health concern in developed countries [1,2]. In Canada, the initial introduction of the whole-cell pertussis vaccination in the mid-20th century resulted in a decline in incidence that

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continued until the early 1990s [3]. Concerns with adverse events following immunization led to the development and introduction of acellular pertussis vaccines into the vaccination schedule in 1997/98. Since the 2010s, a noticeable increase in pertussis incidence has been observed, with some jurisdictions seeing outbreaks with the largest reported cases counts in decades [4]. Although the highest pertussis incidence is recorded in infants and in young adolescents, the greatest attributable morbidity and mortality from pertussis infection occur in infants under 12 months of age [5].

The cause of the recent increase in pertussis cases is not fully understood, but is thought to be the consequence of sub-optimal vaccine coverage in part resulting from vaccine hesitancy [6] combined with waning immunity from the acellular pertussis vaccine [7,8]. The switch to acellular vaccination in many jurisdictions has been suggested as an explanation for the recently observed increase in pertussis cases. Additionally, the *Bordetella pertussis* bacterium has undergone genetic mutations [9], while widespread improvements in case detection and molecular diagnosis may also account for increases in reported cases [10]. It is furthermore possible that the increase in pertussis cases corresponds to the end of what is referred to as the "honeymoon effect", a dynamic phenomenon following decades after the introduction of vaccination into a population [11,12]. Understanding and explaining recent epidemiological trends in pertussis is complicated by the lack of serological correlates of protection [13] and transmission from individuals with sub-clinical disease [14]. It is also possible that the degree of severity of clinical presentation of pertussis varies and that milder forms of pertussis may not be reported and included in public health surveillance data. It was estimated that just 37% of infected infants and 11% of individuals over 1 year of age are reported to public health [15]. Also, the methodology used to determine the degree of waning of immunity relies on estimating the risk of contracting pertussis in relation to the length of time which has elapsed from the last dose of pertussis vaccine [16]. This approach may not fully account for the possibility that the observed increased risk of pertussis derived from epidemiological studies may be due not only to immunological decay of protection but also due to increased opportunities for exposures leading to infections [17]. The elevation in risk of pertussis was estimated at 32% per successive year after receiving pertussis vaccine [18], but the immunological waning may be far lower [19]. Also, findings from immunogenicity studies may not always correspond to what is observed in epidemiological studies.

A number of strategies have been proposed to improve pertussis control. While development of new highly immunogenic and efficacious pertussis vaccines is desirable, broadening of vaccination strategies – including immunization of pregnant women and neonates as well as improving on-time adherence to vaccination schedules and human challenge studies to examine pertussis infection and vaccination – were recommended by international expert groups [20]. Pragmatically, strategies with vaccines currently available to public health programs are likely to play an important role in the short- and medium-term while developing new vaccines offers the best long-term strategy. As the main goal of most immunization programs is to protect vulnerable infants who are too young to be vaccinated, immunization of pregnant women in the third trimester of each pregnancy has been recommended in several developed countries, including the USA, UK and Canada. In Alberta, pertussis immunization of pregnant women was initiated in 2019 [21]. Other strategies proposed to control pertussis in infants include "cocooning", whereby family members of newborn infants are immunized soon after birth, and immunizing infants shortly after birth (neonatal immunization). Cocooning secures benefit through interruption of pertussis transmission from the closest caregivers, while neonatal immunization would provide direct protection between birth and 2 months of age, when the first dose of pertussis vaccine is administered to an infant [22,23]. By contrast, maternal immunization provides protection through transplacental transfer of antibodies (passive immunity) in addition to reducing the probability of infant exposure to pertussis through the mother, who benefits from recent vaccination. The increase in the concentration of pertussis antibodies in the infant's serum after maternal immunization in the third trimester of pregnancy was demonstrated in immunogenicity studies, but was short-lived [24]. Additional concerns were raised about the possibility of passive immunity interfering with active immune response in an infant, an effect which is described as blunting [25]. On the other hand, epidemiological studies demonstrate reductions in incidence of pertussis among infants whose mothers received a pertussis vaccine during pregnancy [26].

The objective of this study was to develop an agent-based model of pertussis transmission and to evaluate the effect of immunization during pregnancy on pertussis control in Alberta, Canada. Our aim was to replicate transmission dynamics in Alberta and to estimate programmatic vaccine effectiveness and the population preventable fraction with varying maternal vaccine coverage. We further investigated uncertainties in clinical reporting of pertussis, estimated the effects of blunting over time on incidence of pertussis in infants and children as well as differentiated the effects of protection through passive transfer of maternal antibodies from the cocooning effect.

Methods

We developed an agent-based model to depict pertussis epidemiology in Alberta in order to measure the effect of pertussis vaccination during pregnancy on the burden of disease in infants. The model included explicit dynamic depictions of population demography, social mixing, infection and immunology, vaccine scheduling and varied adherence. The model was programmed with general components, and its input variables and components were selected based on data obtained for Alberta. For variables which could not be fixed as input based on available data, we conducted parameter optimization and validation to match model dynamics to those observed in Alberta. More detailed descriptions of model structure and components, as well as variable definitions, are provided in the supplementary material (denoted ESM). This study was approved by the University of Alberta Research Ethics Board (REB, Pro00075391).

Model structure

Population

Individual agents in the model were designated a location on a spatial plane either at birth or at the start of a simulation. Individuals were grouped into households such that the numbers of parents and children, as well as all individuals' ages, were selected according to distributions reported in Alberta's 2016 census [27]. Fertility rates used within the model were based on both the age and number of previous children of individual females, which were computed from vital statistics data [28]. As the individuals aged, they were subject to routine vaccination depending on their household's attitude toward vaccines, entered nearby schools based on their age, and were placed into new households upon reaching adulthood. Schools each had a capacity and offered a number of the K–12 grades, and were initialized in simulations by sampling from real school information obtained through the Alberta Department of Education [29].

Contact and transmission

Beginning at birth, individuals made social contact with other individuals in the geographic area around them, with members of their household, and later their school classmates. We defined 'contact' such that if an infected individual makes contact with a susceptible individual, transmission of infection may occur. Following are the three types of contact that can lead to infection (see §4.1 for more information):

1. ***Background Contact:*** All individuals within a fixed model distance of one another (d_b) have a probability of making contact, which is adjusted for age [30].
2. ***School Contact:*** Children assigned to the same school can make contact with one another during school hours, with most contacts occurring among children of the same age-group, while allowing some dissortative contacts among children of different grades.
3. ***Household Contact:*** All individuals in the same household make contact with one another at a fixed rate while they are at home. Mothers have an increased rate of contact with their infants (c_{hm}) [31].

In addition, we introduced a small number of additional exposures into the population at random based on a fixed hazard rate, defined as ***exogenous infection*** (λ_{e}). This mechanism represents the contribution to the force of infection by individuals from elsewhere.

When social contact takes place between a discordant pair, the probability of transmission depends on the intensity of infection of the infected individual ($\gamma(t)$), and the degree of immunity of the susceptible individual (p). Following transmission, an individual's level of infectiousness remains at $\gamma(t) = \gamma_{\max}$ for a specified period, until the individual recovers and $\gamma(t) = 0$. The level of infection determines the probability of transmission to a susceptible individual, and therefore transmissibility depends on the exact time of contact. All individuals in the model were attributed a degree of immunity on a continuous scale. We implemented a threshold in the degree of immunity (α_{i}), above which an individual cannot become infected. Below this threshold, an individual can become infected upon exposure, and with a maximum level of infection $\gamma_{\max} = 1 - p$ at the time of infection. The degree of immunity of an individual is a combination of naturally acquired immunity (from a previous infection, p_{an}), vaccine-derived immunity (p_{av}), and passive immunity (p_{p}) transferred from the mother during pregnancy (for an infant). Specifics of transmission mechanisms can be found in the supplementary material (§2.2).

The process of reporting instances of pertussis infection as cases is subject to under-reporting, which has been previously studied and shown to vary with age [15]. We implemented under-reporting such that only infections reaching a sufficient intensity ($\alpha_{\mathrm{i}} > \alpha_{\mathrm{r}}$) are reported, and we referred to this as the reporting threshold. Reflecting differences in pertussis detection among age-groups, we implemented different reporting thresholds for infants (age 0–1), children (1–17), and adults (18+).

Vaccination attitudes and coverage

We modeled vaccine coverage as a simulation output, rather than as a parameterized input [32]. This was incorporated into the model by assigning an attitude toward vaccination to each individual (v_{att}) which governs their (or their family's) probability of compliance with the vaccination schedule. Initial attitudes were selected randomly, with geographic clustering throughout the population, and all members of a household sharing the same attitude. Parameters governing the random assignment of attitudes toward vaccination were calibrated such that the coverage for all doses matched closely to that of Alberta, for same ages of observation (age 2 for doses 1–4, age 6 for dose 5, and age 14 for dose 6, see §2.1.2 and Fig. 1).

Immunity and maternal immunization

The degree of immunity of an individual depends on their history, with natural infections and vaccination doses increasing immunity, and all forms of immunity waning over time at rates depending on the source of immunity. Contracting infection confers the maximum degree of immunity ($p_{\mathrm{an}} = 1$) and wanes most slowly. In the model, infants received their childhood vaccinations according to Alberta's schedule [21]. Based on aforementioned attitudes toward vaccination, we determined whether individuals depart from the recommended schedule, adhere to it, or return to it and catch up on missed doses. The probability of maternal immunization described later in the main experiment (§2.3) is determined independently of the attitude mechanism that governs childhood immunization. Each dose increases the active immunity of the individual by 0.25, such that three successful doses preclude infection immediately following the third dose, and four doses achieve the maximum degree of immunity prior to waning. The probability of primary vaccine failure was fixed to be 15% following three doses [33,34]. Vaccine-derived immunity wanes at a rate of 2% per year ($\omega_{\mathrm{a}} = 0.02$/year was drawn from de Celles et al. [19], and the ratio $\omega_{\mathrm{a}}/\omega_{\mathrm{n}}$ from Wendelboe et al. [35]). Based on these assumptions, the duration of immunity from natural disease also approximates what was reported by Wearing and Rohani [36]. We also computed the risk-ratio of contracting pertussis per year after dose 5, which we use as a validation metric. If a mother receives a booster dose during her third trimester, her active immunity is transferred to her newborn infant as passive immunity (p_{p}). As translation of the rate of waning of this passive immunity (ω_m) into clinical cases is uncertain, we investigated and reported findings for various rates (see §3). We also investigated the theoretical special case where no passive immunity is conferred to the infant despite the mother receiving a prenatal booster dose, thereby measuring the degree to which the infant is protected solely due to the restriction of a pathway of transmission through the mother (*i.e.,* cocooning, see §3 and §4).

Calibration and Validation

To quantify model-data agreement, we identified dynamic phenomena observed in incidence data and compared them with model realizations. We selected four summary statistics for which we compared model output to twenty years of Alberta data [37,38]. We adjusted a number of key model parameters in order to obtain simulations that, on average, closely matched the behaviour of Alberta data. These were the relative magnitudes of contact in households, schools, and the background, along with the exogenous infection rate (see §2.1.2). Below we described the statistical features used in the calibration process:

1. The mean annual incidence observed across all age-groups and years.
2. The cumulative density of yearly incidence totals, with ten 10% quantiles, measuring how the total number of cases in single years are distributed.
3. The auto-correlation of yearly incidence, where each number represents the degree of correlation with a given number of lag years.
4. The mean annual incidence observed for each of childhood age-groups 0–1, 1–4, 4–10, and 10–17 years of age.

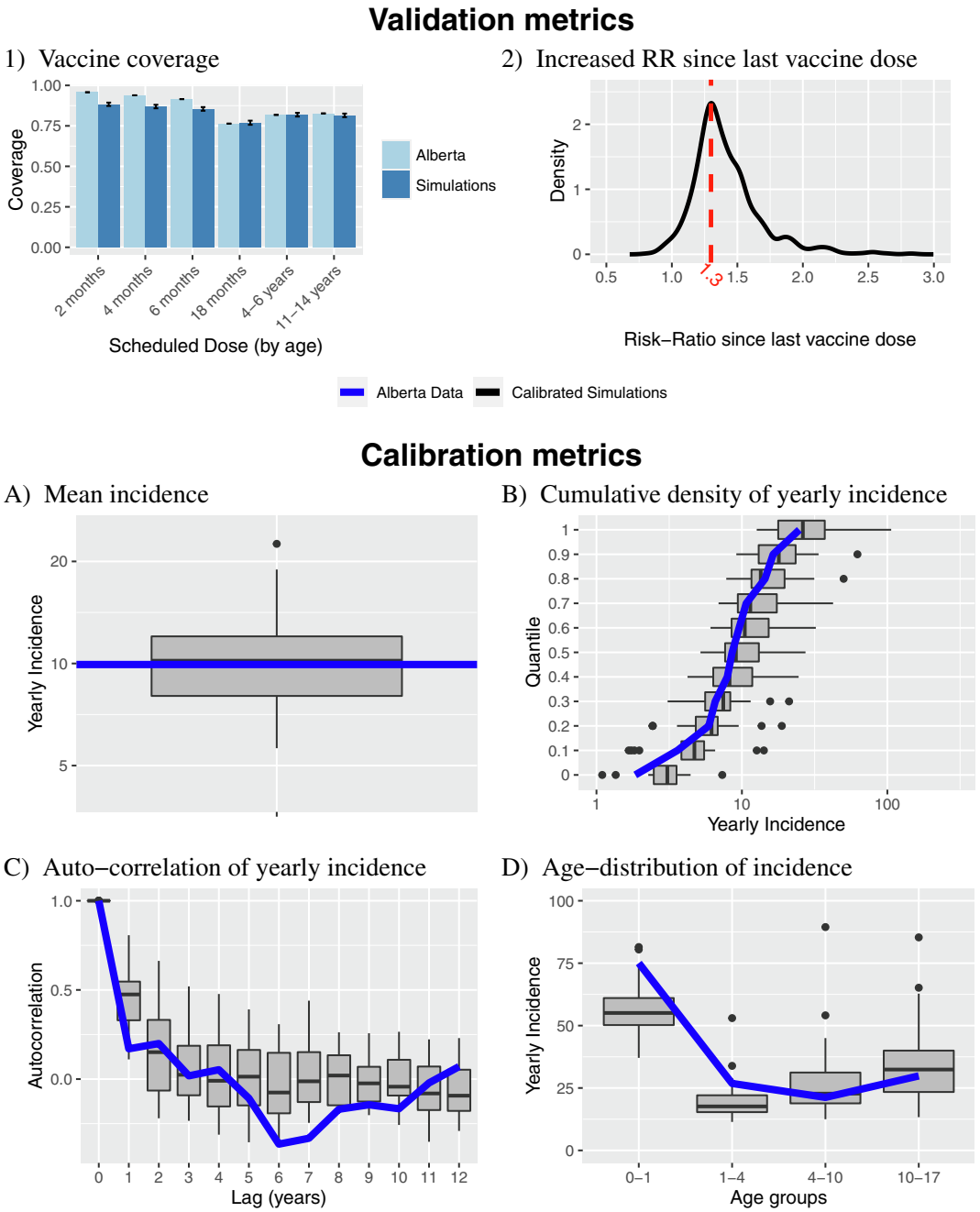

Fig. 1. Validation and Calibration metrics for final parameterization of the agent-based pertussis model. (1) Vaccine coverage for four infant (DTaP) and two booster (Tdap) doses as scheduled and measured in Alberta. (2) Density function of the risk-ratio (RR) of contracting pertussis per year after dose 5. (A) Mean incidence of all pertussis cases. (B) Cumulative density distribution computed for yearly incidence levels. (C) Auto-correlation of yearly incidence time-series. (D) Mean incidence computed within age groups 0–1, 1–4, 4–10, and 10–17.

We calibrated model parameters using the OptQuest Engine, which is used by AnyLogic and employs Tabu Search optimization methodology [39]. Comparisons between final parameterization of the model and Alberta data is shown in Fig. 1.

We further used vaccine coverage and increased risk-ratio since last dose as validation metrics, as described above.

Main experiment and analysis

We ran simulations with the final model baseline parameterization, with 50% of mothers receiving the pertussis vaccine in the third trimester of pregnancy. Each experiment consisted of 30 simulations run for 50 years, where maternal immunization began after year 20. Since we did not have an *a priori* estimate of the duration of passive protection for infants, we evaluated scenarios positing passive protection durations of 1.5, 3, 6, 9, 12, and 18 months. We additionally ran experiments in which 75% of mothers were immunized during pregnancy. We ran further alternative experiments in which the presence of passive immunity in infants reduced the effect of primary series vaccinations, also known as blunting, in which the increase in protection from primary infant vaccinations was reduced by 10% and 50% for 1 year in the presence of passive immunity from maternal immunization [40].

We measured the effectiveness of maternal immunization by calculating the programmatic vaccine effectiveness (PVE). The total number of cases in infants of mothers who were immunized during pregnancy is denoted by c_v, and the total number of cases in infants without intervention is denoted by c_u. We computed PVE as described by Farrington [41]:

$$\begin{aligned}\mathrm{PVE} &= 1 - \left[\frac{\mathrm{PCV}}{1-\mathrm{PCV}}\frac{1-\mathrm{PPV}}{\mathrm{PPV}}\right] \\ &= 1 - \left(\frac{c_v}{c_u+c_v} \div \frac{c_u}{c_u+c_v}\right)\left(\frac{1-v}{v}\right) = 1 - \frac{c_v}{c_u}\left(\frac{1-v}{v}\right) \end{aligned} \quad (1)$$

where v is the vaccine coverage parameter inputted into the model. We additionally calculated the population preventable fraction (PFP) by modified Miettinen formula [42] as follows:

$$\mathrm{PFP} = \frac{\mathrm{PCV}\times\mathrm{PVE}}{1-\mathrm{PVE}(1-\mathrm{PCV})} \quad (2)$$

This proportion estimates the reduction in the burden of pertussis in infants that has occurred due to modeled maternal immunization levels, compared to the scenario where mothers did not receive vaccination during pregnancy. We also calculated 95% quantiles for PVE and PFP of individual simulations for each experiment. This PVE measures the reduced probability of infection due to a combination of cocooning and passive immunity, but is not confounded by childhood vaccinations, since our methodology selects mothers for maternal immunization indepenently of any other mechanism.

Results

A summary of validation and calibration metrics are shown in Fig. 1. The overall model-generated vaccine coverage for all doses was within 7.4% of the vaccine coverage observed/estimated in Alberta, with the closest match for doses 4–6. Simulations produced a risk ratio of contracting pertussis per year after dose 5 of 1.3, in line with that reported in literature [18]. The median annual all-ages pertussis incidence in the model was 10.4 per 100,000 population (25–75% IQR 8.45 to 14.3 per 100,000) with the actual mean annual incidence rate reported in Alberta being 9.92 per 100,000 [37]. The mean age-specific annual pertussis incidence rates for infants under 1, children 1–4, 4–10 and 10–17 years old were 55.7 (IQR 49.5–63.0), 17.7 (IQR 15.5–21.5), 23.5 (IQR 18.2–29.4) and 32.4 (IQR 23.4–44.8) per 100,000 population, comparable to those reported in Liu et al. [38]. There was a minimal autocorrelation of the yearly incidence time series in the model. Cumulative density of yearly incidence in Alberta fall within the 25%–75% IQR of simulations for all but the lowest 10% quantile.

Programmatic vaccine effectiveness of maternal immunization during pregnancy at different ages in infants, in relation to the varying duration of passive immunity and different reporting thresholds, is shown in Fig. 2. PVE was inversely related to duration of passive immunity from maternal immunization across most simulations in our model. For a mean duration of passive immunity of 12 and 18 months, PVE remained above 80% at all age points and for all reporting thresholds and above 90% at 2 and 4 months of age. There was a step-wise reduction in PVE at 0.65–0.7 reporting thresholds at 2 and 4 months of age for the 9–18 months' mean duration of passive immunity. The shortest $1/\omega_m$ of 1.5 and 3 months at 6 and 12 months were associated with the lowest PVE and were least dependent on the reporting threshold. We found a reporting threshold of 0.75, and a mean passive immunity duration of $1/\omega_m = 12$ months to be most plausible.

We further computed the values of PVE and PFP from the parameterized model as described above, which are shown in Table 1. In each experiment, we conducted 30 realizations (each simulating 50 years) resulting in observations of approximately 22.5 million modeled infant-years (varying due to the dynamic births process) to evaluate the benefits of immunization for infants of mothers who underwent maternal immunization. Where 50% of all mothers received pertussis vaccination during pregnancy, and for all infants under 12 months of age, there were 8404 pertussis cases recorded over all model simulations' periods among infants whose mothers did not receive pertussis vaccine during pregnancy *versus* 1123 cases among infants whose mothers did received pertussis vaccine during pregnancy. In this scenario of 50% maternal vaccine coverage and reporting threshold $\alpha_r = 0.75$, the PVE was 87% (95% quantiles 82–91%), with a PFP of 44% (95% quantiles 41–45%). The PVE and PFP ranged between 82 and 99% and between 41 and 49% at 0–2, 2–4, 4–6 and 6–12 months age intervals, respectively. At 75% maternal vaccine coverage, the PVE and PFP were higher at 90% (95% quantiles 86–92%) and 68% (95% quantiles 65–69%), respectively, with a similar gradient across 0–2, 2–4, 4–6 and 6–12 months age groups. In a sensitivity analysis examining the potential effect of blunting, 10% and 50% immunological blunting had minimal to moderate impact on overall protection afforded by maternal vaccination. At 10% blunting persisting for 1 year, the PVE and PFP were 86% (95% quantiles 77%–87%) and 43% (95% quantiles 39%–44%), respectively, while at 50% blunting, the corresponding values of PVE and PFP were 76% (95% quantiles 70–81%) and 38% (95% quantiles 35–40%). In a separate experiment to measure the model-predicted reduction in cases due to the mother's boosted immunity alone, we assumed that maternal immunization offers no passive protection to infants, and calculated the PVE induced by this cocooning effect to be 54–57%.

Discussion

In this study we used a mathematical model to simulate pertussis epidemiology in Alberta, using it to assess the reduction of pertussis cases in infants due to maternal immunization over a range of rates of waning passive immunity, reporting thresholds and to examine the effect of immunological blunting on this reduction. Key advantages of mathematical modeling lie in its predictive and explanatory power. To this end, any model must simplify the real world system being studied sufficiently to be intelligible, but not to such a degree that key dynamics are absent from the model. For this reason, we employed agent-based modeling in our study, an approach recommended for its ready incorporation of per-individual heterogeneity, context, history and continuous dynamics. Specifically, we represented each individual separately in order to capture age, spatial and vaccine-history heterogeneity, immunological dynamics and within–household dynamics, in particular the fact that the interactions between infants, their mothers, and their immediate household contacts is a dynamic that cannot be simply captured by means of more aggregate models. Our modeling approach allowed us to link and examine findings from immunogenicity and epidemiological studies in the same simulations.

Our study demonstrated robust protection for infants whose mothers received pertussis immunization during pregnancy up to the age of 12 months, ranging from 82% and 99%. Protection was predictably dependent on the vaccine coverage achieved, with higher vaccine coverage leading to a higher population preventable fraction due to maternal vaccination. Our findings are consistent with other epidemiological studies which examined the same topic. Using a screening method [26], the study by Amirthalingam et al. estimated the vaccine effectiveness among infants in the UK whose mother received pertussis vaccine during pregnancy as being 91% at 3 months of age. Similar observations were made in cohort and case-control studies in California, Brazil, Argentina

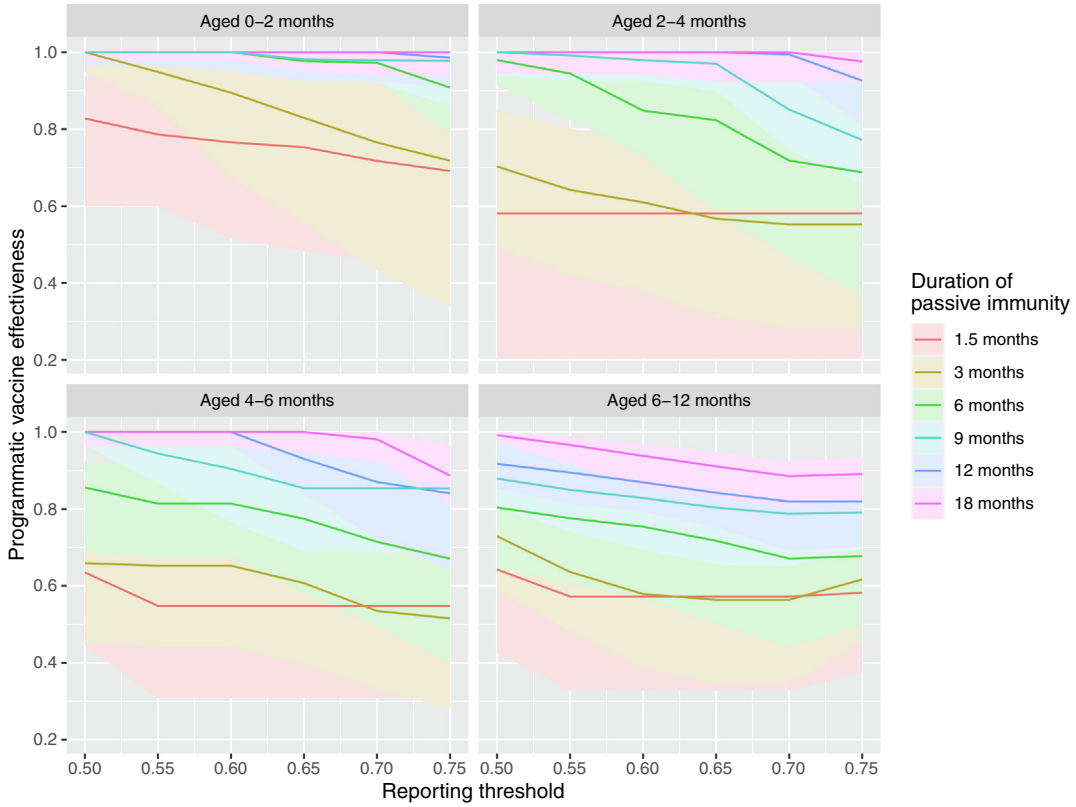

Fig. 2. Programmatic vaccine effectiveness of maternal immunization (PVE) *versus* reporting threshold for infant infections. Maternal immunization coverage was 50% for all simulations. Separate lines and 95% quantiles are shown for six values of the rate of waning of passive immunity, ω_m, where the mean duration of passive immunity is defined as $1/\omega_m$.

Table 1
PVE and PFP for maternal prenatal immunization with pertussis vaccine, by infants' age and maternal vaccine coverage. Quantiles show range of variation among 30 year full-population simulations.

Simulated effects of maternal immunization on pertussis in infants	**50% coverage**			
	Number of cases		**PVE** (95% quantiles)	**PFP** (95% quantiles)
	Unvaccinated	Vaccinated		
0–2 months of age	1471	27	98.6% (90.9%,100%)	48.7% (45.5%,49.3%)
2–4 "	1385	114	92.6% (81.2%,100%)	46.2% (40.6%,48.8%)
4–6 "	1436	237	84% (64.1%,95.7%)	42% (32.1%,47.8%)
6–12 "	4112	745	82% (70.2%,88.2%)	41% (35.1%,44.1%)
0–12 months	8404	1123	87.1% (82.1%,90.5%)	43.6% (41%,45.2%)
			75% coverage	
0–2 "	1033	43	98.8% (95.2%,100%)	74% (71.4%,74.5%)
2–4 "	878	194	92.3% (83.1%,97.7%)	69.2% (62.3%,73.3%)
4–6 "	910	336	87.5% (81.1%,93.8%)	65.6% (60.8%,70.3%)
6–12 "	2723	1056	87.2% (81.2%,90%)	65.4% (60.9%,67.5%)
0–12 months	5544	1629	90.1% (86.2%,92%)	67.6% (64.7%,69%)

and Spain, with reported VE ranging from 80.7% to 90.9% [43–46]. By contrast, a study in Australia found a lower VE at 69% at 3 months of age and non-significant protection at 39% at <6 months of age [47]. Another study from the UK examined longer term protection to infants afforded by a maternal immunization program, finding that VE against laboratory-confirmed pertussis has been sustained at greater than 90% in the 3 years following introduction of maternal immunization [48].

One of the important and often debated considerations with respect to modeling of pertussis epidemiology is the waning of immunity after acellular vaccines. There is considerable evidence pointing out that protection after acellular vaccines decreases over time [49,50,8], however quantitative estimation of immunological decline in protection is not straightforward. Numerous epidemiological studies have measured the increased risk of contracting pertussis following vaccination in order to estimate this rate of waning immunity, and the systematic review by McGirr et al. showed that the pooled relative risk for each successive year after the last dose of pertussis vaccine was 1.32 [18]. The study by de Celles et al., however, found that the increase in risk of contracting pertussis after vaccination can be explained with a much slower waning rate as long as changes in the age-specific contact rates are taken into account [19]. The approach we took in our model is to replicate the increased risk ratio (RR) of contracting pertussis in each year following the fifth dose in our parameterized simulations. We obtained the RR of 30%, which is comparable to results

obtained from the aforementioned epidemiological studies. We achieved this with the immunological/intrinsic decay of protection (ω_a) at 2% per year for vaccine-derived immunity and at 1% per year for natural disease immunity; the latter value is based on the study by Wendelboe suggesting that immunity from natural disease lasts twice as long as that from vaccination [35].

In relation to maternal immunization, the phenomenon of waning of immunity also applies to immunity passively transferred from the mother to infant. An immunogenicity study by Halperin et al. [24] found that the presence of pertussis toxoid in infants whose mothers were immunized with Tdap diminished from its initial value at birth by 26% at 2 months, after which the infant begins his/her primary vaccination. Assuming that this rate of decay represents an exponential rate of decay of passive protection against pertussis, then the mean duration of passive protection is approximately 1.5 months. However, it is unlikely that the reduction in antibodies from maternal immunization is linearly related to the loss of epidemiological protection, as a higher level of protection against the disease was observed in epidemiological studies [26]. We found that a duration of passive immunity of 12 months was most consistent with VE observations from epidemiological studies, suggesting that protection may last longer than the rate of decay of maternal antibodies in infants would suggest. Furthermore this protection is likely to be explained by a combination of residual passive immunity, active immunity from infant's immunization and the change in the exposure from the immunization of the mother. Maternal and infant immunization are implemented independently in our model, but contribute to the overall level of protection at a given age. As VE observed by epidemiological studies cannot separate the effect of maternal antibodies offering passive protection to the infant and the reduced chance of the mother infecting the infant due to her boosted immunity, we estimated these contributions quantitatively in our modeling study. In this respect, our results in Fig. 2 suggest that even for a rapid waning of passive waning $1/\omega_m = 1.5$ months, PVE in our model remains greater than 50% for the first year of life, and in the absence of simulated passive protection, PVE was nonetheless 54–57% as a consequence of the mother's boosted immunity restricting the primary pathway of transmission to the infant. This is an important contribution to our understanding of protection by maternal immunization, as previous research results on the cocooning effect have been mixed, with Rosenblum et al. [23] finding cocooning could be successful, but Healy et al. [51] showed that cocooning did not reduce pertussis illness in infants under 6 months of age. This value is likely to be sensitive to the augmented contact rate between infants and mothers implemented in our model. We would also argue that the cocooning effect may be less pronounced in larger households.

As there are many cases of pertussis which may present with non-typical clinical picture — particularly in older children and adults — cases reported through surveillance systems are known to underestimate the count of cases. Previously, reporting efficiency was found to be 37% for infants and 11% for other age-groups [15]. Our study linked reporting efficiency to intensity of infection by means of the reporting threshold (all cases above a given intensity are reported as cases), implemented reporting thresholds by age (0–1, 1–17 and 18+), and examined the relationship between different reporting thresholds and programmatic vaccine effectiveness. While low reporting efficiency allowed our model to reproduce realistic case numbers in non-infants, we found that we were only able to simulate incidence in infants comparable to Alberta by allowing most cases in infants to be reported ($\alpha_r = 0.75$).

One of the concerns often raised with respect to maternal pertussis immunization is the effect of the immunological "blunting" on protection afforded by maternal immunization, whereby antibodies transferred passively from mother to infant may interfere with active immune response to primary series of vaccination given to an infant. The study by Zimmermann et. al. showed that antibodies levels among children whose mothers received pertussis immunization during pregnancy was approximately 50% lower in comparison to infants whose mothers did not receive such vaccination [52]. We therefore performed sensitivity analysis where we examined both a 50% blunting effect as well as a less pronounced 10% blunting while assuming blunting was persistent for 1 year, but found only moderate resulting reduction in programmatic vaccine effectiveness and population preventable fraction.

Our study has advantages and limitations. Primary advantages of our study are that we examine effects of discretized phenomena in the population: households, schools, communities clustered by attitude, individual mother–child pairs with unique immunological histories, characterization of dynamics of infectiveness and strength of immunity. Capturing these dynamics was essential to our investigation, and accounts for our choice of this modeling strategy. We were able to achieve systematic similarity with real-world data reflecting mean annual incidence, age-specific incidence rates, auto-correlation and cumulative density functions. We were also able to replicate findings from epidemiological studies. The availability of high quality surveillance data of sufficient granularity enabled us to conduct this study. This study can be used by policy makers to estimate the benefits at the population level of implementing or continuing pertussis immunization in pregnancy based on projected vaccine coverage. The model also contributed to the understanding of interplay between passive immunity protection and cocooning effects and the possible effect of immunological blunting. Study limitations include the need to impose assumptions absent empirical data to represent high levels of details in the model and reliance on calibration to estimate some parameters. The influence of whether mothers received whole-cell *versus* acellular vaccine or had history of pertussis in the past [53] can be examined in the future iterations of the model. An additional limitation shared by most models is that similar data and calibration is required for the study of other jurisdictions. In our study, we do not model changing vaccine attitudes over time. These attitudes may change either continuously or incrementally in both directions (become more positive or more negative) and may be age-dependent [54,55]. The effect of maternal immunization on population other than infants remains to be elucidated. Future research could examine the effect of interventions with a more detailed household contact profile along with considering the different outcomes in single vs two-parent households. Future studies should also examine cost-effectiveness of maternal pertussis immunization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2022.12.071.

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