TITLE: Determining best strategies for maternally-targeted pertussis vaccination using an individual-based model

RUNNING HEAD: Modeling maternally-targeted pertussis vaccination

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ABBREVIATIONS: IQR, Interquartile Range; IRR, Incidence Rate Ratio; NIP, Australia’s National Immunisation Program;
ABSTRACT (200 words)
Rising pertussis incidence has prompted a number of countries to implement maternally-targeted vaccination to protect vulnerable infants, but questions remain about optimal design of such vaccination strategies. We simulated pertussis transmission within an individual based model parameterized to match Australian conditions, explicitly linking infants and their mothers to estimate the effectiveness of alternative maternally-targeted vaccination strategies (antenatal versus postnatal delivery) and the benefit of revaccination over multiple pregnancies. For firstborn infants aged less than two months, antenatal immunization reduced annual incidence by 60%, from 780 (interquartile range (IQR) 682–862) to 315 (IQR 260–370) per 100,000, while postnatal vaccination produced a minimal reduction, with incidence of 728 (IQR 628–789) per 100,000. Subsequent infants obtained limited protection from a single antenatal dose, but revaccinating during every pregnancy decreased incidence for these infants by 58%, from 1878 (IQR 1712–2076) to 791 (IQR 683–915) per 100,000. Subsequent infants also benefited from household-level herd immunity when antenatal vaccination for every pregnancy was combined with a toddler booster dose at 18 months, with incidence reduced to 626 (IQR 548–691) per 100,000. Our approach provides useful information to aid consideration of alternative maternally-targeted vaccination strategies and can inform development of outcome measures for program evaluation.

KEYWORDS: Computer Simulation; Disease Transmission, Infectious; Immunity, Maternally-Acquired; Pertussis Vaccine; Population Dynamics; Whooping Cough

MAIN TEXT: 3496 words
Control of pertussis remains problematic despite the implementation of high-coverage mass vaccination in many countries more than sixty years ago. Improved ability to identify mild cases has contributed to rising pertussis incidence from the 1990s in some populations (1). However, increased infant deaths in the United States and United Kingdom in recent epidemics provide evidence of genuine resurgence (2, 3). Maternally-targeted vaccination strategies, delivered either antenatally or postnatally (so-called ‘cocoon’ immunization), have been implemented in the United States (2), United Kingdom (3) and Australia (4) as emergency measures in an effort to regain control of pertussis. Questions remain about the sustainability and cost-effectiveness of household-targeted strategies in the long term, the relative benefits of antenatal vaccination versus cocooning, and the optimal application of maternal immunization approaches for protection over multiple pregnancies.

Households are an important identified source of infection for infants, but with no identified infector in around half of infant cases (5), how effective will strategies focused on reducing the risk of infection in the household be? Vaccinating mothers only in the post-partum period was found to provide a modest reduction in risk of pertussis transmission to the infant (6). When this cocoon strategy was extended to include vaccination of both parents, infant risk of pertussis was more than halved (4). Effectiveness of antenatal vaccination against laboratory confirmed pertussis in infants in the United Kingdom is much higher, at around 90%, reflecting the fact that this strategy also provides direct protection to the infant through placental transfer of maternal antibody during the third trimester (3, 7). While rapid waning of antibodies in the mother may limit the potential for transfers of sufficient levels of antibody for protection beyond a single pregnancy (8), the relative
benefits of repeated vaccination in subsequent pregnancies, and optimal vaccination interval have not yet been quantified.

We have simulated pertussis transmission and maternally-targeted vaccination strategies within an individual-based model framework that characterizes individuals by their sex, age and household. We compare infant infections in households in which the mother is immunized with those in which they are not to separately estimate the overall effectiveness of alternative antenatal and cocoon vaccination strategies at the household level, and their population impact on transmission. Our results inform optimal implementation approaches, and provide inputs necessary for cost-effectiveness analyses.

METHODS

Demographic model

We model a population using a stochastic individual-based model that tracks the occurrence of five life events: birth, death, couple formation and dissolution, and leaving home (9). The model is parameterized using available census and survey data to represent the age distribution, household composition and vital dynamics consistent with the Australian population across the 20th century (Web Appendix 1).

In traditional compartmental models, mixing relevant to infection transmission is configured using matrices that reflect the relative frequency of contact within and between age groups. An important limitation of these compartmental models is that they do not capture the greater intensity of contact that occurs within household settings and cannot explicitly link infants and their mothers. In contrast, household contact patterns arise endogenously in our demographic model as a result of the population structure and dynamics (10). Community
mixing patterns were derived using the mean daily number of contacts reported for the POLYMOD contact study conducted in Europe (11). Recent analyses of Australian mixing patterns support the use of POLYMOD data in our model, as qualitative trends such as intergenerational mixing and age assortativity are similar between the two settings, as are the average numbers of encounters per day (12). Further details on the demographic model are provided in Web Appendix 1, and contact parameterization in Web Appendix 2 and Web Table 1.

Epidemiologic model

**Population model of infection and immunity.** We apply a pertussis-specific transmission model to the population (Figure 1), similar to that used in previous work. In addition to their demographic characteristics, we also track the current state of infection or immunity of each individual.

Individuals who are naively susceptible to pertussis (Figure 1, Susceptible Naïve), having never been infected or vaccinated, become infected (Infectious Naïve) with a probability determined by their risks of household and community acquisition. These risks depend on an individual’s age-specific community mixing patterns, and the presence of infected individuals in their household and the wider community. Once recovered, individuals are fully protected against infection (Full Immunity).

Over time, an individual’s immunity wanes (Partial Immunity). Individuals who are exposed to infection at this stage have their immunity boosted at a rate equivalent to the force of infection, and regain full protection against infection (Full Immunity) without contributing to the force of infection. Individuals whose immunity wanes fully without being re-exposed
and boosted become susceptible once again (Susceptible Primed), with a reduced susceptibility to infection compared to their first infection. If reinfected (Infectious Primed) these individuals are also less infectious than those experiencing their first infection. As priming is assumed to permanently modify infection risk and characteristics (13), the model distinguishes between those naively susceptible, and those with immune systems primed by pertussis infection or vaccination.

The model includes parameters to quantify duration and degree of infectiousness, duration and degree of natural, vaccine and maternally acquired immunity, rates of community mixing between age groups and transmission coefficients for the household and community settings. Parameter values for each individual are selected from the distributions described in Table 1 and Web Table 2. The duration of infectiousness for cases in naïve and primed individuals has mean 3 weeks, consistent with published values (14). The contribution of infections in primed individuals to the force of infection is yet to be convincingly resolved for pertussis (1, 5); we assume infections arising in susceptible primed individuals are half as infectious as those in naïve individuals.

We assume recently exposed or vaccinated individuals have a short duration of full immunity (Full Immunity; sampled from an exponential distribution with mean 9 months) followed by a much longer duration of partial immunity (Partial Immunity)(15). We assume differences in the mean duration of partial immunity following exposure and vaccination of an order of magnitude (74 and 6 years, respectively), consistent with the findings of previous modelling studies (15, 16). No differentiation is made between pertussis vaccine formulations in the model – all recent evidence on maternal pertussis immunization relates
to the use of acellular pertussis vaccines (3, 7). Primed susceptibles are considered 0.6 times as likely to be infected as naïve susceptibles (15).

*Relationship between maternal and infant immunity.* Infants born to mothers who have full or partial immunity (Figure 1) acquire maternal protection. These infants are fully protected against infection until immunity is lost, when they become naïvely susceptible (Susceptible Naïve). All other infants are naïvely susceptible from birth.

Passive antibodies acquired by infants from their mothers wane rapidly, with time to depletion likely dependent on time elapsed since the mother’s last immunizing exposure (17). Given the uncertainty regarding duration of passive protection, we sample the duration of maternally-acquired immunity from a distribution with mean 12 weeks; values of 6 and 24 weeks are explored in a sensitivity analysis.

*Application of vaccination in the model.* Routine infant vaccination is applied in the model as a primary course at 2, 4 and 6 months followed by a variable number of booster doses, according to the historical and current Australian schedule and coverage (Web Figure 1). We assume that infants either receive all three primary doses, or none. Vaccine efficacy is modelled as ‘all-or-nothing’, with successfully vaccinated individuals obtaining full immunity (Full Immunity), and primary vaccine failures retaining their naïve susceptible state. Parameterization of dose response was based on published values (18) and is described in Web Appendix 2.

*Calibration.* In Australia, there are limited notification data available for model parameterization and calibration, with large gaps due to cessation of national surveillance from 1949 to 1979 (19). Even where data are available, there is limited comparability over
time due to changing ascertainment (20). We thus applied a qualitative approach to calibration similar to that we used for our previous pertussis modelling work, based on a similar epidemiological model (15).

For model calibration, we compared overall incidence patterns from both pre-vaccination and vaccination eras to known characteristics of pertussis and key features of observed Australian epidemiology, namely: (a) high levels of household transmission (80–100% of susceptible household members infected following introduction) (21) and community transmission (approximately 17 new secondary cases in a susceptible population) (22) (b) a pre-vaccine epidemic cycle length of between two and four years (19); (c) an increase in the proportion of infections occurring in primed individuals after the introduction of vaccination (15); and (d) an increase in the proportion of infections occurring in older age groups after the introduction of vaccination (20, 23, 24). The key objective of calibration was to ensure that the initial conditions of the model matched our understanding of the current state of immunity of the Australian population, guided by our previous pertussis modelling study and serological surveys (15), to aid prediction of likely vaccine impact. Incidence patterns for an exemplar realization of the model with the chosen transmission parameters (Web Figure 2) display a pre-vaccination epidemic cycle length of around three years; a more than ten-fold reduction in infections in naïve individuals occurring concurrently with an increase in infections in primed individuals; and an upward age shift in the incidence of infection, particularly capturing the rise to prominence of infections in adolescents through the 1990s. Further details of the calibration approach are provided in Web Appendix 2.

Simulation of alternative vaccination strategies
Four alternative vaccination strategies were simulated (100 simulation runs per scenario) to allow estimation of the likely impact of maternally-targeted approaches, commencing in model year 2010 and continuing for a period of 10 years:

1. Baseline national immunization program (NIP) schedule (2, 4, 6 months, 4 years, 15 years) at historical and current coverage levels (Web Figure 1);
2. Baseline NIP + cocoon vaccination (mother only, post-partum; first and every child, coverage 60%);
3. Baseline NIP + antenatal vaccination (first and every child, coverage 80%); and
4. Baseline NIP + antenatal vaccination (coverage 80%) + reintroduction of a toddler booster, delivered at 18 months of age (coverage 90%). The 18 month booster was absent from the Baseline NIP from 2004, but was reintroduced in 2016.

We measured incidence rate ratios (IRR) comparing infants in maternally-vaccinating households with infants in non-maternally-vaccinating households.

RESULTS

Role of households in transmission

According to the model, the proportion of neonates passively protected by maternal immunity would have declined rapidly following the introduction of vaccination in 1953 (Figure 2). This decline resulted from a reduction in pertussis circulation, reducing opportunities for boosting of adult immunity. In consequence, while most infants (around 90%) are likely to have been born with passive protection in the pre-vaccine era, it is possible that as few as 50% may benefit from passive protection today.
Concordant with observed epidemiology, the model suggested that households were the major source of infection for infants under one year old, with around 75% of infections acquired in the home (Web Appendix 3 and Web Figure 3). While the proportion of infant infections occurring in the household setting remained relatively stable over the 20th century, there was a marked shift in the age of the household member attributed as the source of infection (Figure 3). In the predominantly large households associated with the pre-vaccine era when disease prevalence was high, the source of infection was almost exclusively other children in the household, with only 12% of household infectors aged over 18 years. After the introduction of vaccination, disease prevalence decreased, and the source of infection was as likely to be a parent as a sibling, with 52% of household infectors aged over 18 years by the late 1990s. Declining fertility over the 20th century contributes to this shift: infants are born into households containing few, if any, siblings to pose risk of infection.

Vaccinating for first pregnancy only

We compared the effect, over a 10 year period, of four alternative vaccination strategies (baseline, cocoon, antenatal and antenatal plus 18 month) on infections of infants in their first year of life. We present results for infants less than 2 months of age (Figure 4), given that this group is the main focus of maternally-targeted vaccination, with results for infants less than 12 months of age reported in Web Figure 4 and discussed in Web Appendix 3. Results for firstborn (Figure 4A) and subsequent infants (Figure 4B) were compared, for a scenario where vaccination was administered only in relation to a woman’s first pregnancy occurring in the 10 year period. Figure 4 shows the age distribution of sources of household-
acquired infant infection, with the areas of each violin plot scaled proportionally to the incidence of infection in each scenario.

For firstborn children less than 2 months of age, the source of household-acquired infection was typically an adult family member. For these infants, the cocoon strategy produced little difference in annual incidence over the 10 year period, with median incidence 728 per 100,000 (interquartile range (IQR) 628–789) compared to 780 per 100,000 (IQR 682–862) under baseline conditions, reflecting ongoing risk to the infant of infection exposure in the community. Marked reductions in incidence were achieved when the mother was immunized antenatally, with median incidence reduced to 315 per 100,000 (IQR 260–370), improving further with the reintroduction of the 18-month dose (median incidence 264 per 100,000 (IQR 235–316)).

Subsequent children had more than twice the infection risk of firstborn children (for example, baseline incidence for subsequent children less than 2 months of age was 1878 per 100,000 (IQR 1712–2076)), due to the fact that their older siblings provided an additional source of household infection exposure. Minimal benefit was conferred on subsequent children by the cocoon strategy administered in relation to a previous pregnancy (median incidence 1620 per 100,000 (IQR 1510–1755)). By comparison, the antenatal strategy reduced median incidence to 1099 per 100,000 (IQR 984–1272) and the antenatal plus 18-month strategy substantially reduced the number of infant infections caused by both siblings and parents (median incidence 885 per 100,000 (IQR 753–1002)). By enhancing vaccine protection for both parents and siblings, the antenatal plus 18-month strategy was more effective in limiting household infection introduction, amplifying herd protection of the infant within the household (Web Figure 4).
Comparison of maternal vaccination delivery options

When given only once, antenatal vaccination was clearly more effective at reducing incidence of infection among infants than cocoon vaccination (Figure 4). To establish the potential benefits of multiple antenatal vaccinations, we further compared the effectiveness of vaccinating the mother during every pregnancy, versus the first pregnancy only. Finally, we compared the additional benefit obtained from reintroduction of the 18-month booster dose. We calculated the pertussis infection IRRs for each simulation run independently, comparing infants born to mothers who received antenatal vaccination to infants born to mothers who did not. We report the distribution of values obtained in the 100 simulation runs for each scenario.

Vaccinating in every pregnancy reduced the risk of pertussis infection among subsequent children less than 2 months of age (median IRR 0.23 (IQR 0.17–0.33)) (Figure 5B) visibly more than vaccinating during the first pregnancy only (median IRR 0.62 (IQR 0.49–0.83)) (Figure 5A). The addition of an 18 month dose did not substantially reduce these IRRs, as the benefit of this approach was to reduce the overall level of infection, affecting infants in both maternally-vaccinating and non-maternally-vaccinating households. In Web Figure 5, we extend these results to include the addition of an 18 month dose when vaccination is provided for the first pregnancy only, and in Web Figure 6, we extend cocoon vaccination to both parents.

In Web Appendix 4 we present the results of a sensitivity analysis on three key parameters that define the dynamics of pertussis immunity: time to mount an immune response (Web
Figure 7); duration of infant passive protection (Web Figure 8) and duration of adult protection following vaccination (Web Figure 9).

DISCUSSION

Our individual based model of pertussis transmission shows that maternal vaccination reduces infection incidence in young infants and delivers a clear benefit to households in which mothers are immunized compared with those not so immunized. We found that by providing passive direct protection to infants over a short period, antenatal vaccination is more effective at reducing incidence than postnatal ‘cocoon’ approaches. As maternal immunity is anticipated to wane substantially in the interval between deliveries, revaccination is required for optimal protection in subsequent pregnancies. The contribution of pre-school aged siblings to household transmission can be greatly reduced through the inclusion of a toddler booster on the vaccination schedule, further enhancing household-level herd protection.

Ours is the first pertussis modeling study of which we are aware to consider the implementation of maternally-targeted immunization approaches within a structured population model. Advantages of this approach include the ability to infer benefits at the level of the family unit, making model outputs readily comparable with estimates of protection obtained from case-control or cohort studies. By explicitly configuring mother-infant pairs within a household context, we are able to assess vaccine protection in the setting in which the force of infection (given introduction) is anticipated to be greatest. These targeted outcomes of immunization can reliably be observed within the household as a unit of observation, regardless of the population prevalence of infection, or level of vaccine coverage achieved. The additional flexibility to follow subsequent pregnancies
allows exploration of the requirement for reimmunization within a maternal vaccination program, and the contribution of siblings to infection risk.

Previous age-structured population dynamic models that have considered the impact of targeted (cocoon) and general adult immunization strategies on infant disease have drawn disparate conclusions (25, 26). While Van Rie and colleagues found that strategies including cocoon vaccination reduced infant disease more than general adolescent and adult immunization did, results were sensitive to the proportion of infants assumed to be infected through household exposure (25). In contrast, Coudeville and colleagues’ adaptation of the Van Rie model found a more favorable result for routine adult vaccination than cocooning (26). A major difference between the models was the contribution of household members to pertussis transmission, wherein the values used by Coudeville were around half that of Van Rie. Although our findings reveal the majority of infant infections occur in the home, closer to the values used by Van Rie (25), our more modest estimate of cocoon effectiveness is on account of the incorporation of a delay in achieving a protective cocoon following postnatal vaccination and the contribution of siblings, fathers and community contacts to infection.

We have calibrated parameters conferring vaccine protection against effectiveness estimates from available case-control and observational studies (3, 4, 6-8, 27), while recognizing the challenges associated with case ascertainment and confirmation of ‘control’ status in real-world settings. The relative contribution of family members to infant infection risk appears to decline during years of high epidemic activity (28). This observation may contribute to marked variations in observed effectiveness of cocooning between studies, despite the demonstrated importance of mothers to infant infection risk within the
In addition, emerging data from the United States caution against systematic sources of bias in estimates of the effectiveness of maternal immunization arising from very low levels of vaccine uptake in women of lower socio-economic status (30), whose infants may also be at greater risk of pertussis infection (31).

The certainty of several key assumptions in our model, as for all other models of pertussis, is necessarily constrained by an absence of robust evidence. Without a definitive correlate of vaccine protection (32) it is difficult to confidently infer a reduction in disease risk on the basis of observed immunogenicity, necessitating our reliance on clinical endpoint studies (3, 4, 6-8, 27). Given the recency of implementation of antenatal vaccine approaches, there is a relative paucity of data informing estimates of persistence of protection in the newborn, and persistence of antibody in the mother over various intervals between gestations (8). Studies of avidity of passively transferred antibody suggest that the timing of maternal immunization during the third trimester may be associated with differences in achievable protection (33). Moreover, maternal immunization in late pregnancy or the perinatal period additionally stimulates production of pertussis-specific secretory immunoglobulin A (34), which may be associated with enhanced protection among breast-fed (34) infants, compared with those receiving formula. As the clinical implications of these latter observations are not known, we do not consider subtle differences in protection that may arise from such mechanisms.

Early studies have demonstrated blunting of vaccine responses in infants of mothers immunized during pregnancy following the primary infant vaccine series, resolving following a booster in the second year of life (35, 36). Given the uncertain clinical implications of this finding, we have not considered any adverse outcomes of vaccination in pregnancy on
protection following completion of the primary infant course in the present model. However, should emerging evidence indicate that any reduction in vaccine protection is observed among such infants, our model can be updated to consider the implications of this finding, for both firstborn and subsequent children.

The model presented provides a structured framework within which to consider emerging evidence on targeted maternal pertussis immunization, through logical synthesis of available evidence. Our approach is sufficiently flexible to be updated with emerging evidence, further improving the robustness of model predictions, and will be adapted to consider maternal immunization approaches for alternative antigens, including influenza and emerging viral vaccines. Our approach provides useful information to aid consideration of alternative maternally-targeted vaccination strategies, including provision of inputs for cost-effectiveness models. Moreover, by defining expectations of such programs, it can be used to guide development of outcome measures for program evaluation.

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REFERENCES

### Table 1: Parameter Distributions for the Epidemiologic Model

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FIGURE LEGEND

**FIGURE 1.** Pertussis transmission model. Infants born to immune mothers (Full Immunity or Partial Immunity) start their lives with maternal protection and are fully protected against infection, before waning into the naïve susceptible state. Naïve individuals are infected at a rate $\lambda(t)$, and are fully protected on recovery (Full Immunity), before waning into a partially immune state from which their immunity can be boosted (Partial Immunity). If not re-exposed, individuals wane to a primed susceptible state (Susceptible Primed) in which their rate of infection, $\sigma\lambda(t)$, is reduced compared to naïve susceptibles ($\sigma = 0.6$). If infected from this primed state, individuals are less infectious than those experiencing their first infection (Infectious Primed). Successfully vaccinated individuals acquire full immunity (Full Immunity) and thereafter follow the same state transitions as those with immunity acquired following exposure, although with a reduced mean duration of protection. Mean duration in the partial immune state is 74 years following infection and 6 years following vaccination. Other durations in the infectious and immune states are shown, with details provided in Table 1.

**FIGURE 2.** Neonatal passive protection emergent from the model. The proportion of infants born each year with maternal protection against infection declined rapidly following the introduction of vaccination in the 1950s. This decline resulted from a reduction in pertussis circulation, leading to fewer opportunities for boosting of adult immunity (and thus, fewer mothers with immunity).

**FIGURE 3.** Emergent age distribution of sources of household-acquired infant infections from 1910 to 2009. In the pre-vaccine era, when the median age of infection was around four years of age, infants were predominantly infected by their older siblings. Since the introduction of vaccination, fewer infant infections have been caused by siblings, with an
increasing role for parents as infectors. Distributions are scaled to have equal area to more clearly demonstrate the age shift over a period characterised by a substantial decrease in incidence.

**FIGURE 4.** Age distribution of sources of household-acquired infant (< 2mths) infections, when maternal vaccination is delivered for the first birth only. Top row, part A: firstborn children; Bottom row, part B: subsequent children. Areas are scaled proportionally to the incidence of infection in each scenario (across 100 simulation runs). The source of household-acquired infection for firstborn infants was typically an adult, with the exception of a small number of blended households containing older children. The antenatal strategies (with or without the 18-month booster) substantially reduced infections, while the cocoon strategy did not provide a discernible reduction. For subsequent children, who were infected by both parents and siblings, maternal vaccination delivered only for the first pregnancy provided only a minimal incidence reduction. Assumed maternal vaccination coverage was 60% for the cocoon strategy and 80% for the antenatal strategies.

**FIGURE 5.** Incidence Rate Ratios (IRR) comparing infants born to mothers who received antenatal vaccination to infants born to mothers who did not, under three different antenatal strategies: first birth, every birth, every birth plus reintroduction of an 18-month booster. Results are shown for firstborn children (first column, parts A, C, and E) and for subsequent children (second column, parts B, D, and F), with rows representing 0–2 month (parts A and B), 2–6 month (parts C and D) and 6–12 month (parts E and F) age groups. Boxplots display the median IRR and interquartile ranges over 100 simulation runs for each scenario. Vaccinating for every pregnancy was clearly more effective than for the first pregnancy only, especially for the most vulnerable 0–2 month age group. The addition of an
18-month dose did not substantially reduce these IRRs, as the benefit of this approach was to reduce the overall level of infection, affecting infants in both maternally-vaccinating and non-maternally-vaccinating households. Assumed maternal vaccination coverage for the antenatal strategies was 80%.
Web Material

Determining best strategies for maternally-targeted pertussis vaccination using an individual-based model

Patricia Therese Campbell, Jodie McVernon, Nicholas Geard

Web Appendix 1
Outline of the demographic model
We use an individual based model, in which each individual is characterised by age, sex, household of residence, and family ties. Over time, individuals are born, age, form and dissolve couples and household units, and die, with probabilities determined by their sex, current age and life stage. The population demography is updated at each time step of the simulation (in the simulations reported here, at weekly intervals) according to the following procedure:

1. The age of each individual is incremented by the appropriate number of days.

2. For each individual \( i \), one of the following may occur:

   (a) **Death**: with a probability based on \( i \)'s age and sex, \( i \) dies and is removed from the population. An individual \( j \) is chosen to be the mother of a replacement individual as follows:
      
      i. The target age of the mother is determined on the basis of age-specific fertility rates.
      
      ii. A set of candidate mothers is determined on the basis of age, eligibility to give birth (i.e., not having given birth in the previous 9 month period) and household status (for simplicity, individuals are not eligible to give birth while living with their own parents).
      
      iii. \( j \) is selected at random from the pool of candidate mothers.

   If the death of \( i \) results in a household containing only children, these individuals are reallocated as follows:
      
      i. Any children aged 18 or older form new single-person households.
      
      ii. Any children aged less than 18 are randomly allocated (fostered) to other households containing at least one child.

   (b) **Couple formation**: if \( i \) is currently single, with a probability based on \( i \)'s age, \( i \) forms a couple with an individual \( j \), chosen as follows:
i. The target age of the partner $j$ is determined on the basis of $i$’s age.

ii. A set of candidate partners is determined on the basis of age, sex, and not currently being a member of a couple.

iii. $j$ is selected at random from the pool of candidate partners.

The households of $i$ and $j$ are merged (along with any children currently residing with them) or, if both previously lived with their parents, a new household of size two is created.

(c) **Leaving home**: if $i$ is currently living with their parents, with a probability based on $i$’s age, $i$ leaves their parents’ household and forms a new household of size one.

(d) **Couple separation**: if $i$ is currently in a couple, with a probability based on $i$’s age, $i$ separates from that couple and forms a new household; for simplicity, we assume that any children residing with the couple when they separate join the mother’s household.

3. To simulate a growing (or shrinking) population, the number of additional births (or deaths) required to occur in the current time step to match the target growth rate is calculated and additional birth (or death) events are triggered.

**Population model parameters and data sources**

**Mortality**: Age-specific mortality rates for Australia during the 20th century were sourced from the Australian Bureau of Statistics [3, 5]. For convenience, we assume that no individual survives beyond 100 years, and the probability of death at 100 years was fixed at 1.0.

**Fertility**: Age-specific fertility rates for Australia during the 20th century were sourced from the Australian Bureau of Statistics [3, 4]. These rates were not used directly to generate births in our model, but rather used to estimate relative probabilities of births being attributable to mothers of a particular age. When a birth event was triggered (e.g., by a death, in a scenario with replacement fertility), these relative probabilities were then used to ascertain the age of the mother, and hence the subset of the female population eligible to be randomly chosen as the mother.

**Couple formation and separation, leaving home**: Probabilities were estimated on the basis of data on the Australian population reported by the Australian Institute of Family studies [9] and the Household Income and Labour Dynamics Survey [30]. This estimation combined data reported both on rates of marriage and divorce with data on rates of de-facto relationships, as the primary focus of our model was the dynamics of household units, rather than the status of relationships. We assume that individuals become eligible to leave their parents’ household, either independently or as a member of a couple, at 18 years. As a consequence, individuals also become eligible to separate from a couple at 18 years. We assume that individuals cease being eligible to
form or separate from couples at 60 years. The annual probability of a single individual entering a couple is 0.075. The annual probability of a couple separating is 0.01, increasing linearly to 0.1 for 80 years, and then to 0.2 over the following 20 years. The annual probability of a single individual leaving home and forming a one person household is 0.01, increasing to 0.1 over the 100 year period.

**Population growth:** Population growth rates for Australia during the 20th century were sourced from the Australian Bureau of Statistics [6].

**Comparison to Australian population:** During the simulated time period corresponding to the century from 1910–2010, the median age of the model population increases from 23 to 40 years, while mean household size decreases from 4.5 to 2.6 people. Over a similar time period, the median age of the Australian population increased from 22 to 37 years, while the mean household size decreased from 4.5 to 2.6 [15].

It should be noted that the primary aims of the demographic model were to capture a reasonable approximation of the size and composition of households in the Australian population over the last century and to execute in a computationally efficient fashion. It is not feasible that the model accurately capture all the demographic complexity of a real population and, as described above, several simplifying assumptions have been made in the name of model parsimony. For example, our model currently simulates dynamics of households containing one or two adults/parents (of opposite sex) and zero or more children (as defined by their familial relationship to the parents in the household; they may themselves be adults who are yet to leave home). Clearly, this does not exhaust the potential range of household types observed in real populations. Furthermore, our model currently incorporates population growth attributable to fertility, but not that resulting from immigration, which may introduce individuals of a range of ages.

Demographic rates were assumed to remain stable over the 10 year period covered by the scenarios compared in the paper, on the basis that fertility rates — a key demographic driver of epidemiological dynamics — have remained relatively stable (at just under 2 births per woman) over recent decades in Australia.

**Web Appendix 2**

**Outline of the epidemiologic model**

The epidemiological model extends the demographic model described in Web Appendix 1, tracking the current disease state of each individual according to the state transition model (Figure 1 in the main body of the paper). The disease state of the population is updated at each time step of the simulation (in the simulations reported here, at weekly intervals) according to the following procedure:

1. Population demography is updated, as described in Web Appendix 1.
2. Periodically (at 5 year intervals in the simulations reported here), the community contact matrix (see below for detail) is updated to account for the changing age structure of the population.

3. Individuals born in the current time step are assigned the maternal protection state if their mother is currently in the full immunity or partial immunity state, otherwise they are assigned the susceptible naïve disease state.

4. Individuals eligible for vaccination on the basis of their age and previous vaccine status are vaccinated with time- and scenario-dependent probabilities as described below. Vaccinated individuals are assigned the full immunity state.

5. For each individual who is currently susceptible to infection (naïve), the force of infection acting on that individual is calculated according to Web Equation 2, and used to specify the probability of that individual becoming infected in the current time step.

6. For each individual who is currently susceptible to infection (primed), the force of infection acting on that individual is calculated according to Web Equation 2, reduced by a factor $\sigma$, and used to specify the probability of that individual becoming infected in the current time step.

7. The set of individuals who are exposed to infection is determined stochastically; this includes both susceptible individuals who will become infected, and full immunity or partial immunity individuals who will have their protection boosted.

8. The disease states of all individuals are updated simultaneously; that is, the state of the population at time $t + 1$ is determined by the state of the population at time $t$. Newly infected individuals are assigned a counter corresponding to their infectious duration as described below.

9. Individuals in the states maternal protection, infected, full immunity or partial immunity have their relevant counter decremented. Individuals whose counter reaches zero will attain the full immunity state if they were previously infected, partial immunity if they were previously in the full immunity state or susceptible (primed) if they were previously in the partial immunity state.

The length of time that an individual remains in the maternal protection or infected states is drawn at random from a Gamma distribution with shape parameter $k = 3$ and mean parameter $\mu$ specified in Table 1 in the main paper. The length of time that an individual remains in the full immunity or partial immunity states is drawn at random from an exponential distribution with mean specified in Table 1 in the main paper.

Note that a single set of full immunity and partial immunity states is used to capture protection arising from both first and subsequent infections, and from primary course and booster vaccinations. However, the time duration that an individual remains in that state will vary depending on the source of that protection. When a currently protected individual has their immunity boosted
(as a result of vaccination or exposure), we enforce a rule that they can never have their duration of protection reduced. For example, an individual who has 35 years of protection as a result of natural infection will not have their duration of protection reduced if they are subsequently vaccinated.

**Contact model and parameterisation**

The probability of a susceptible individual becoming infected, or of a protected individual having their immunity boosted was determined by the presence of infection in their household, and their age-specific patterns of contact in the community.

**Household contacts:** Household structure and contact patterns arise endogenously in the demographic model as a result of the population structure and dynamics [11]. We assume here that mixing and transmission within households are independent of age. While real populations do exhibit age- and sex-dependent transmission characteristics — such as increased levels of transmission between mothers and young children [18, 23] — the effect of these is likely to be diminished at the high levels of household transmission considered in this study. For less transmissible pathogens, such as influenza, age- and sex-dependent patterns of within-household mixing are likely to play a more significant role.

**Community contacts:** We use community contact to encompass all contact occurring outside of the household; e.g., in schools, workplaces and the general community. In contrast to the household co-location matrix, the community mixing matrix ($\eta_{ij}$ values) is an input parameter of the model. The approach taken here, following Hethcote [13], is to base mixing matrices on age-specific activity levels, using a combination of proportionate and age-assortative mixing, such that the per-capita rate of contact between individuals of ages $i$ and $j$,

$$c_{ij} = \epsilon \frac{a_i a_j}{D} + (1 - \epsilon) \frac{a_i}{N_j} \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left(\frac{(j-i)^2}{2\sigma^2}\right)$$

where $\epsilon$ in the interval $[0, 1]$ is a convex combination parameter governing the strength of preferential (within age-group) mixing, $a_i$ is the mean daily number of community contacts made by a person of age $i$, $D = \sum_{k=1}^{n} a_k N_k$ is the total number of contacts made by all people in the population, and $\sigma^2$ is the variance in the Gaussian kernel used to smooth out mixing among nearby ages. As the Gaussian kernel are truncated for some ages, contact rates for each age are normalised such that densities sum to one.

Web Equation 1 provides per-capita rates of contact. The mean number of contacts between a person of age $i$ and people of age $j$ is given by $\eta_{ij} = c_{ij} N_j$. While the age of each individual was updated at each time step, contact rates were computed for each year of age from 0 to 100 years.
Web Table 1: Mean daily number of community contacts, adapted from Mossong et al. [21] as described in text.

<table>
<thead>
<tr>
<th>age class</th>
<th>community contacts</th>
<th>age class</th>
<th>community contacts</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4</td>
<td>7.34</td>
<td>40–44</td>
<td>11.47</td>
</tr>
<tr>
<td>5–9</td>
<td>11.74</td>
<td>45–49</td>
<td>11.83</td>
</tr>
<tr>
<td>10–14</td>
<td>15.07</td>
<td>50–54</td>
<td>10.41</td>
</tr>
<tr>
<td>15–19</td>
<td>14.89</td>
<td>55–59</td>
<td>11.02</td>
</tr>
<tr>
<td>20–24</td>
<td>11.66</td>
<td>60–64</td>
<td>8.09</td>
</tr>
<tr>
<td>25–29</td>
<td>11.71</td>
<td>65–69</td>
<td>8.21</td>
</tr>
<tr>
<td>30–34</td>
<td>12.03</td>
<td>70–74</td>
<td>6.08</td>
</tr>
<tr>
<td>35–39</td>
<td>11.69</td>
<td>75–79</td>
<td>6.32</td>
</tr>
</tbody>
</table>

Values for the mean daily number of community contacts for each age group $a_i$ were derived from Mossong et al. [21] as follows. Mossong et al. [21] report contact data collected in eight European countries. Participants completed a contact diary over the course of a single day, recording the number of different individuals contacted. These data were reported broken down by age of participants and location of contact. Mossong et al. [21] observe that approximately 23% of contacts occur in the home, although this is not further broken down by age. We assume that our model population experiences the same mean daily number of contacts as reported in Mossong et al. [21], and that contacts occurring within the home are exclusively with other household members, as determined from the demographic model described above. Therefore our age-specific mean daily number of community contacts is equal to the age-specific mean daily number of total contacts reported in Mossong et al. [21] reduced by the age-specific mean number of housemates in our modelled population (Web Table 1). Here, we assume that an individual encounters all of their housemates each day, hence this number of people can be deducted from the total number of contacts to give the number of different people contacted outside of the household setting. This results in 16.2% of contacts occurring in the home. However, if we consider the possibility that contacts occurring in the home could include contacts with people who are not members of that household (i.e., visitors), and assume that each person has, on average, contact with one additional person in the home, then home contacts account for 24.1% of contacts, comparable with the level reported in [21]. Activity levels were smoothed across ages by fitting a polynomial of degree 9 to the available data points.

Estimating the degree to which community mixing is age-assortative or proportionate (i.e., in the absence of household mixing) is challenging, as POLYMOD and similar studies tend not to differentiate between contacts on the basis of context. After initial exploration of parameter space, we chose values of $\epsilon = 0.8 \sigma = 10.0$, corresponding to the plausible situation where approximately 36% of an individual’s contacts are within three years of their age and 65% are within eight years of their age. Realistically, this value is likely to vary with age and may differ considerably between, for example, school-age students and retirees [20]. A more detailed model could explicitly incorporate multiple mixing locations, such as schools and workplaces; however, this
**Web Table 2: Parameter distributions for the epidemiologic model.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Distribution type</th>
<th>Mean/Fixed value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of infectiousness (naïve and primed)</td>
<td>Gamma</td>
<td>3 weeks</td>
</tr>
<tr>
<td>Infectiousness in primed individuals relative to naïve</td>
<td>Fixed value</td>
<td>0.5</td>
</tr>
<tr>
<td>Duration in Full immunity state</td>
<td>Exponential</td>
<td>9 months</td>
</tr>
<tr>
<td>Duration in Partial immunity state – following infection</td>
<td>Exponential</td>
<td>74 years</td>
</tr>
<tr>
<td>Duration of in Partial immunity state – following vaccination</td>
<td>Exponential</td>
<td>6 years</td>
</tr>
<tr>
<td>Susceptibility in primed individuals relative to naïve</td>
<td>Fixed value</td>
<td>0.6</td>
</tr>
<tr>
<td>Duration of maternally acquired immunity</td>
<td>Gamma</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Household transmission coefficient, ( q_h )</td>
<td>Fixed value</td>
<td>0.8</td>
</tr>
<tr>
<td>Community transmission coefficient, ( q_c )</td>
<td>Fixed value</td>
<td>0.01</td>
</tr>
</tbody>
</table>

...would come at the cost of additional model and parameter complexity.

**Household and community transmission parameters:** The probability of a susceptible person, \( p_i \) in age class \( i \) becoming infected in a given time period is a combination of the prevalence of infection in their household, and in the broader community, weighted by the contact matrix described above. This per time step probability of infection of person \( p = 1 - e^{-\lambda_p(t)\Delta t} \), where

\[
\lambda_p(t) = \sum_{k \in H} \zeta \frac{q_h I_k(t)}{N_H(t)} + \sum_j \eta_{ij} \frac{q_c I_j(t)}{N_j(t)},
\]

where \( H \) is \( p \)'s household, \( N_H(t) \) is the number of people in \( H \), \( k \) is a housemate of \( p \), \( \zeta \) is the number of effective contacts per day between \( p \) and their housemates (here, \( \zeta = 1 \)), \( I_k(t) = 1 \) if \( k \) is infectious and 0 otherwise, \( q_h \) is the per contact household transmission coefficient, \( i \) is the age of \( p \), \( \eta_{ij} \) is the mean number of contacts in the community per day between people of age \( i \) and people of age \( j \), \( q_c \) is the per contact community transmission coefficient, \( I_j(t) \) is the number of infectious people of age \( j \) and \( N_j(t) \) is the total number of people of age \( j \).

Within the community, we make the standard assumption for large populations that transmission is frequency dependent. The degree to which transmission within the household is frequency or density dependent is not well-established, but for a highly transmissible pathogen such as pertussis, the resulting dynamics are relatively invariant [11], and the results reported here use frequency dependent household transmission.

Parameter distributions for the epidemiologic model are provided in Web Table 2.
Vaccination dose response and coverage

The probabilities for success at each primary course dose were calculated to achieve effective protection after 1, 2 and 3 doses of 53%, 81% and 85% of vaccine recipients respectively, based on published Australian vaccine effectiveness values in the acellular era [28]. We apply a moderate probability of 0.13 for booster failure against infection, consistent with booster responses at different ages [7], and make the simplifying assumption booster response is independent of primary course response. As a general principle, individuals cannot have their duration of immunity reduced as a result of successive exposures or vaccination. Mothers receiving antenatal or postnatal vaccination are treated in the same manner as children receiving boosters.

Routine infant vaccination is applied in the model as a primary course at 2, 4 and 6 months followed by a variable number of booster doses, according to the historical and current Australian schedule and coverage (Web Figure 1). Prior to the implementation of the Australian Childhood Immunisation Register (ACIR) in 1996, vaccination coverage across Australia was collected on an irregular basis using population surveys conducted by the ABS and state and local governments [19]. Methodologies for estimating coverage differ over time, making it difficult to compare values. The sources used to estimate vaccination coverage included the previously published pertussis model for Australia [14]; ABS population survey [2]; ACIR coverage estimates published in Communicable Diseases Intelligence [8, 16, 19, 24]; and published adolescent coverage data [28].
Model calibration:

Household and community transmission coefficients ($q_h$ and $q_c$) were selected to match target levels of household and population transmission. We conducted a two-dimensional parameter sweep over $q_h$ and $q_c$, seeding a completely susceptible population with a random infectious individual, updating the disease state of the population using a time step equivalent to the generation time of the disease, and recording the proportion of susceptible individuals infected in the seed’s household and the total number of individuals infected in the population. This process was repeated 5,000 times for each parameter combination, and the mean number of individuals infected in the household and total population were computed.

For the simulations reported here, values of $q_h$ and $q_c$ were selected such that around 80-100% of the seed’s household were infected, and around 17 individuals in total across the population were infected. Differences in the order of magnitude of $q_h$ and $q_c$ reflect the greater opportunities for prolonged and close contact within the household, consistent with observed household transmission studies such as Jardine et al [17]. We also compared model-generated incidence patterns for both the pre-vaccination and vaccination era to key features of observed pertussis epidemiology in Australia, ensuring that selected values of $q_h$ and $q_c$ were able to reproduce the following features:

- a pre-vaccination inter-epidemic period of between two and four years [12];
- an increase in the proportion of infections occurring in primed individuals after the introduction of vaccination; and
- an upward age shift in the incidence of infection as vaccination coverage increased and a pre-school booster was added to the schedule [1, 25, 29].

Incidence patterns in naïve and primed individuals for an exemplar stochastic realization of the model (Web Figure 2) demonstrate that the chosen values of $q_h$ and $q_c$ were able to capture these robust characteristics of Australia’s pertussis experience.

Generating the starting population

In the absence of historical data on household composition, the starting population for our comparison (approximately 200,000 individuals with demographic characteristics corresponding to an Australian population circa 2010) was obtained by simulating a population over a period of 100 years, with life event probabilities derived from historical data (i.e., commencing with an initial population corresponding to an Australian population circa 1910). We generate this starting population as follows:

1. An initial ‘bootstrap’ population is created by randomly generating individuals with ages drawn from the target age age distribution.
Web Figure 2: Model generated incidence of infection in naïve and primed children (0–<10yrs), adolescents (10–<20yrs) and adults (20+yrs). The pre-vaccination epidemic cycle length was around 3 yrs, persisting in the vaccine era. Following the introduction of vaccination, there was a large reduction in naïve incidence and an increasing proportion of infections occurring in primed adolescents and adults.

2. These individuals are assigned to households at random according to the target household size distribution. Households of size one or two are assigned one or two adults respectively, while households of size three or greater are assigned two adults and one or more children. This initial population structure will diverge in several ways from a real population; for example, constraints on birth interval and inter-generational age difference will not be respected.

3. 0–100 years: The model is then run for 100 years, by which time all of these bootstrap individuals and households will have been replaced. At this stage, internal model constraints on population structure such as birth interval and inter-generation age differences will be respected. During this period, we assume that age-specific mortality rates and relative fertility by age are constant over time, and that that the population grows at a specified rate. During this period, the disease process is not simulated (i.e., the population is susceptible and there is no importation of infection).

4. 100–200 years: The model is then run for a further 100 years, with disease, to establish a population at (approximately) an endemic disease equilibrium with plausible age-specific patterns of infection and immunity. During this period, age-specific mortality rates and relative fertility by age remain constant over time, and the population size continues to increase; population size is increasing.

5. 200–300 years: The model is then run for a further 100 years, corresponding to the historical time period 1910–2010. During this period, age-specific mortality rates and relative fertility by age are updated based on available historical rates, and the population size continues to increase. Vaccination is introduced in the year corresponding to 1953.
Model implementation

The model is implemented in Python 2.7 and makes use of the external libraries NumPy (http://www.numpy.org/), PyTables (http://www.pytables.org/), matplotlib (http://matplotlib.org/) and MPI for Python (http://mpi4py.scipy.org/). Source code for the model is available from (http://bitbucket.org/ngeard/pertussis-maternal-pub). Simulations were run on x86 HPC clusters provided by the Victorian Life Sciences Computation Initiative (VLSCI, http://www.vlsci.org.au) and the National eResearch Collaboration Tools and Resources (Nectar) Project (http://www.nectar.org.au/).

Web Appendix 3
Additional results

Fraction of household-acquired infant infections: Concordant with observed epidemiology [10, 17], we found that in our model households were the major source of infection for infants under one year old. Around 75% of infant infections were acquired in the home (Web Figure 3), with this proportion remaining relatively stable over the 20th century.

Impact of maternally-targeted vaccination strategies: We compared the effect, over a 10 year period, of four alternative vaccination strategies (baseline, cocoon (postnatal), antenatal and antenatal plus 18 month) on infections of infants in their first year of life. In the first column of Web Figure 4, we replicate the results presented in Figure 4 of the main paper for infants less than 2 months of age. For first-born children, the cocoon strategy was not effective at reducing
incidence in infants less than 2 months of age, possibly due to the delayed immune response in mothers following vaccination at the time of birth. In first-born infants aged 2–6 months and 6–12 months, antenatal and cocoon strategies provided similar incidence reductions, likely explained by the equivalence of these strategies once infant passive protection has waned. For subsequent children, vaccination provided only for the first pregnancy produced limited incidence reduction in 2–12 month old infants.

As anticipated, for first-born infants, antenatal vaccination for every birth produced no discernible difference in incidence rate ratios (IRR) compared to vaccination for first birth only (Web Figure 5), across the first 18 months of life. In Web Figure 5, we extend the results presented in Figure 5 of the main paper, with the addition of a ‘First+18-month’ strategy, in which vaccination is provided for the first pregnancy only and an 18-month dose is reintroduced. The addition of an 18-month dose did not substantially reduce these IRRs, as the benefit of this approach was to reduce the overall level of infection, affecting infants in both maternally-vaccinating and non-maternally-vaccinating households.

The impact of cocoon vaccination for both parents, compared with vaccinating mothers only:

In the main body of our paper, we considered only scenarios in which mothers were vaccinated to protect their infants. In practice, cocoon strategies have generally been applied to a wider circle of infant contacts, including for example, fathers and grandparents [27]. To ascertain any advantages to be gained by vaccinating fathers in addition to mothers, we simulated two implementation scenarios for cocoon vaccination, in which vaccination was provided for the first pregnancy only: vaccinating mothers only, and vaccinating both mothers and fathers. We found that vaccinating fathers provided no additional benefit for infants (Web Figure 6). Our results show there is an upper bound for the impact achievable with cocoon vaccination strategies, as these strategies cannot reduce infant infections acquired from the community.
Web Figure 4: Age of household source of infection for infants across the first year of life. Four vaccination strategies are shown, with antenatal and cocoon vaccination delivered for first pregnancy only (where applicable): baseline (current schedule), cocoon vaccination (mother only), antenatal vaccination, and antenatal vaccination plus reintroduction of 18mth dose. Results are shown for first-born children (top row) and subsequent children (bottom row). Areas are scaled by incidence.
Web Figure 5: Incidence Rate Ratios comparing infants born to mothers who received antenatal vaccination to infants born to mothers who did not. Four different antenatal strategies are shown: first birth, first birth plus reintroduction of 18mth dose, every birth, and every birth plus reintroduction of 18mth dose, across the first 18 months of life. Results are shown for first born children (top row) and subsequent children (bottom row).
Web Figure 6: Incidence Rate Ratios (IRR) comparing infants born into cocoon-vaccinated and non cocoon-vaccinated households for two implementation strategies: mother vaccinated first pregnancy only (blue) vs both parents vaccinated first pregnancy only (red). Cocoon vaccination has the greatest impact for infants less than 2 months and, for first born children, incidence remains lower than for infants in non cocoon-vaccinated households throughout the first year of life. Cocoon vaccination for the first pregnancy only has a limited effect for subsequent children, especially once delivery of the primary course has commenced. Vaccinating fathers provided no additional benefit.
Web Appendix 4

Sensitivity analysis

There is considerable uncertainty surrounding many of the biological and immunological processes influencing pertussis transmission. In particular, the dynamics of pertussis immunity are not well understood due to the lack of an agreed serologic correlate of protection. We performed a sensitivity analysis to assess how much the estimated effectiveness of maternally-targeted approaches to immunization depends upon our assumptions about unknown durations of immunity. In the scenarios detailed hereunder, we report univariate sensitivity analyses for three key parameters that define the dynamics of pertussis immunity, with all other scenario parameters used at the values in the main paper (Web Table 2). We ran 100 simulations per scenario-parameter value combination, with maternal immunization provided for the first pregnancy only.

Cocoon vaccination – impact of the time to mount an immune response: We expect that there will be some variation in the time it takes for mothers to be effectively vaccinated, as this delay depends on both behavioral (getting vaccinated) and biological (mounting an immune response) aspects, which are likely to be considerably heterogeneous. In the main body of our paper, we assumed that mothers are effectively vaccinated three weeks after the birth of their baby. To ascertain how the effectiveness of cocoon vaccination depends on this assumed delay, we simulated cocoon vaccination using four different delays: 0, 3, 6, and 12 weeks. For both first-born and subsequent children, and across the entire first year of life, we found that the length of the delay did not affect the IRRs achieved by cocoon vaccination (Web Figure 7). This result was anticipated for subsequent children (for whom the delay does not exist, since vaccination was provided for the first pregnancy only), and the lack of sensitivity for infants aged less than 2 months may reflect the risk of infection from other sources, such as fathers and the community. Even if postnatal vaccination is substantially delayed, it can still reduce the incidence of infection for infants under 1 year of age.

Antenatal vaccination – impact of the duration of infant passive protection: Although transplacental transfer of pertussis antibody from mothers to infants is generally effective, these antibodies have a relatively short half-life ranging from 6 weeks to 5 months or longer in different settings [22]. In the main body of our paper, we sampled the duration of passive protection from a Gamma distribution with mean 12 weeks. To determine how the effectiveness of antenatal vaccination depends on the duration of passive protection, we simulated antenatal vaccination using three different durations: 6, 12 and 24 weeks. We found that the duration of passive protection did not affect the IRRs for infants less than 12 months of age (Web Figure 8). It is worth noting that for first-born infants less than 2 months of age, the IRRs were based on very small numbers of infections due to the overall success of the antenatal vaccination strategy. For infants aged 2–12 months, the lack of influence of the duration of passive protection reflects the predominance of the infant primary course for protection once commenced. As direct vaccination is applied to
infants born to both immunized and non-immunized mothers, any previous differential benefit wears off very quickly.

**Antenatal vaccination – impact of the duration of adult protection following vaccination:** With no serologic correlate of protection for pertussis, the duration of adult protection against infection following vaccination is uncertain and difficult to measure. In addition, pertussis vaccines suitable for adults (Tdap) have been available only since the early 2000s [26], limiting the evidence available to assess persistence. In the main body of our paper, we sampled the duration of adult protection following vaccination from an exponential distribution with mean 6 years. In order to understand how the effectiveness of antenatal vaccination strategies is influenced by the assumed duration of adult protection, we simulated antenatal vaccination using three different durations: 3, 6 and 12 years. For first-born infants, results were similar for all durations of protection, across the first year of life (Web Figure 9). As anticipated, increasing the duration of protection that the mother obtains from antenatal vaccination results in greater protection for subsequent children (even if mother is only vaccinated before birth of first child).
Web Figure 7: Incidence Rate Ratios (IRR) comparing infants born into cocoon-vaccinated and non cocoon-vaccinated households, assessing the impact of the time it takes for mothers to mount an immune response following vaccination. The implementation strategy shown is vaccination of the mother only, for first pregnancy only. Results presented in the main paper (delay = 3 weeks) are robust to the assumed delay to protection, with minimal difference in IRRs across the delays simulated.
Web Figure 8: Incidence Rate Ratios (IRR) comparing infants born to mothers who received antenatal vaccination to infants born to mothers who did not, for three different durations of infant passive immunity. Results presented in the main paper sampled the duration of passive immunity from a Gamma distribution with mean 12 weeks (here shown in blue), with the values of 6 weeks (red) and 24 weeks (green) explored in our sensitivity analysis. IRRs were reasonably robust to the duration of passive immunity for infants less than 2 months old, with results more variable over the rest of the first year of life, once direct vaccination had commenced.
Web Figure 9: Incidence Rate Ratios (IRR) comparing infants born to mothers who received antenatal vaccination to infants born to mothers who did not, for three different durations of protection in the mother following vaccination. Results presented in the main paper sampled the duration of protection following booster vaccination from a Gamma distribution with mean 6 years (here shown in blue), with the values of 3 years (red) and 12 years (green) explored in our sensitivity analysis, with antenatal vaccination delivered for the first pregnancy only. IRRs for first born children were reasonably robust to the duration of protection following booster vaccination. As anticipated, a longer duration of protection increased the effectiveness for subsequent children of a single antenatal booster, as many more mothers would have remained protected over multiple pregnancies.
References


Maternal Protection

Susceptible Naïve

Infectious Naïve

Full Immunity

Partial Immunity

Births

12 Weeks

\( \lambda(t) \)

9 Mths

Susceptible Primed

Infectious Primed

\( \sigma\lambda(t) \)

3 Weeks

3 Weeks

Vaccination

\( \lambda(t) \)