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# Mathematical modeling of delayed pertussis vaccination in infants

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ABSTRACT

Pertussis is an acute vaccine-preventable respiratory disease that remains a public health problem. In an attempt to improve the control of the disease, many countries have incorporated new boosters in their vaccination schedule. Since the incorporation of these boosters is relatively recent, there are not enough data about their impact to support and/or universalize their use. Alternative strategies such as the improvement in vaccine coverage and reduction in vaccination delays, in addition to the incorporation of boosters, could be implemented. Though these strategies are not new, they have not been adequately evaluated in order to be implemented and/or prioritized. To evaluate the potential impact of these alternative strategies on pertussis incidence, we developed a methodology that involves the use of data collected from vaccination centers and an age-structured deterministic mathematical model for pertussis transmission. The results obtained show that strategies that avoid delays in vaccination have a strong impact on incidence reduction in the most vulnerable population (infants less than 1y). In regions with high vaccination coverage (95%) the elimination of delays in the three primary doses decreases pertussis incidence in infants by approximately 20%. In regions where delays in the administration of vaccines are higher, the combined action to reduce delays and improve coverage leads to a significant improvement in disease control in infants. By repeating the calculations using different sets of parameters that describe different possible epidemiologic scenarios, we determined the robustness of our results.

All the results presented highlight the importance of having high vaccine coverage and shorter delays in vaccine administration in order to reduce the impact of the disease in infants.



## 1. Introduction

Pertussis is a highly contagious respiratory disease mainly caused by *Bordetella pertussis*. This disease, which causes uncontrollable violent coughing, most commonly affects infants and young children and can be fatal, especially in babies less than 1 year of age [1,2].

The best way to prevent pertussis is to get vaccinated. In fact, the introduction of massive pertussis vaccination in the fifties dramatically reduced the morbidity and mortality associated with the disease. However, in the last years the incidence rates of the disease have increased in many countries [3–6]. The World Health Organization estimates that about 16 million cases occur per year in the world with approximately 200,000 deaths [7]. Though most of these cases have been reported in countries with low vaccination coverage, pertussis outbreaks were also detected in countries with high vaccination coverage [3,4]. In the Americas, the number of cases varies between 1500 and 49,000 among countries, where Argentina, Brazil, Mexico, Chile, Colombia, Paraguay, Peru, and the United States have reported the highest number of cases [8–10]. In Argentina, the last outbreak occurred in 2011 when 76 deaths were reported mainly in children under 6 months [11]. In 2012, in the US 48,778 cases (the highest outbreak since 1955) including 20 pertussis-related deaths were reported. Incidence rates were very high in infants but also in the population of children (7–10 years) and adolescents (13–14 years) [12].

This epidemiological situation has forced health systems to revise their control actions to strengthen and/or implement short-term strategies to improve the situation, at least for the most vulnerable population represented by infants. Before the resurgence of the disease, recommended immunization schedules consisted of a primary series of 3 doses during the first year of life and a booster between 1 and 6 years of age, preferably during the second year of age. With the disease resurgence, more boosters

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were added following recommendations of international organizations [13–15]. In fact, the number of boosters increases year by year in many countries, probably as a consequence of failures in the used vaccines, in particular in acellular vaccines [16,17]. In this context, the evaluation of other alternative strategies, instead of the addition of the current acellular booster doses, is important for controlling the disease in the short term. In previous work, using an age-structured deterministic mathematical model for pertussis transmission designed by us, we estimated that improvements in the coverage of the first dose would lead to a larger reduction in the 0–1y disease incidence than that caused by the addition of an 11y booster [18]. The population dynamics of our model was described by transferring individuals among 9 epidemiological classes that differ in immune status and infectiousness. In the present work we evaluate the potential impact of shorter delays in the administration of the first three doses of pertussis vaccine on infants younger than 1y. With this aim, we developed a calculation method that involves the introduction of new epidemiological classes to keep track of the number of doses administered to the population in each epidemiological class. This method also allows us to accurately incorporate the vaccination coverage for each dose in the model.

The results obtained with our model and data gathered from vaccination centers in urban and suburban areas in an Argentine city show that a reduction in delayed vaccination would decrease the incidence of the disease in infants by at least 20%. The results from the model reveal that efforts to improve the administration of the first doses of the immunization schedule, either by enhancing coverage or strictly complying with the recommended scheduled age, would significantly decrease pertussis incidence in infants.

## 2. Materials and methods

### 2.1. Vaccination schedule and epidemiological data

In Argentina, the immunization schedule against pertussis includes three primary doses at 2, 4 and 6 months old, one booster dose at 18 months old, and another at 6 years (school entry) [19]. For all these doses, whole-cell pertussis vaccine is used (DTwP). According to the Ministry of Health, DTP3 coverage (DTP3-cov) for infants under 1y old was higher than 90%, but there are some regions with coverage below 80% [11]. Over the last few years, since the resurgence of pertussis, different protection strategies have been included in Argentina: immunization of adolescents, pregnant women and health workers with acellular vaccines.

The epidemiological data included in this work, consisting of 29,845 records of pertussis vaccination for children aged 0–12 months, are from La Plata (654,324 inhabitants), an Argentinian city located in Buenos Aires province. Specifically, we used retrospective data (January 2005–May 2012) on the distribution of applied DTP doses by age provided by the vaccination center of Elina de la Serna Hospital. At this center, which is one of the 10 vaccination centers located in the urban region of La Plata city, approximately 13% of La Plata population is vaccinated. Children whose age was undefined or unclear were excluded. Fig. 1A shows the number of vaccinated individuals per dose by age from January 2005 to May 2012.

In Fig. 1B we represent the same data as in Fig A, but as a fraction of vaccinated individuals at age $a_i$ with dose $d$ (hereafter referred to as $f_{di}$). These profiles were obtained by performing histograms with the data of Fig. 1A, where each histogram interval is taken as a month divided by four (a "week"), ages $a_i$ are assigned to the middle of the interval, and $f_{di}$ are normalized to one for each dose, $d$. The $f_{di}$ profiles and the vaccination coverages for each dose DTP-cov$d$ are the parameters that determine vaccine administration in our mathematical model.

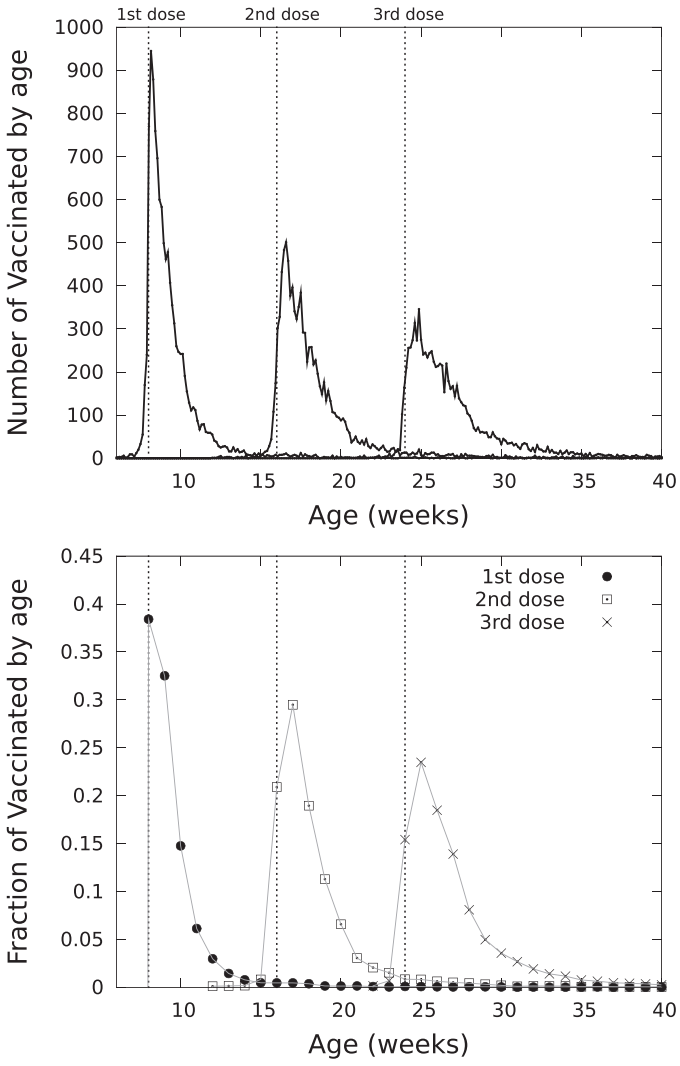


**Fig. 1.** (A) Number of vaccinated individuals per dose by age, between January 2005 and May 2012 (continuous lines). Data are from Elina de la Serna Hospital. (B) Fraction of vaccinated individuals with dose $d$, at age $a_i$ (in weeks), $f_{di}$ (gray lines are to guide the eye). Data are obtained from (A). In both figures dotted lines indicate the recommended age for primary doses of pertussis vaccination schedule in Argentina.

For comparison purposes, we also included epidemiological data from the periphery of La Plata city, where the population is younger than that from downtown, with 23% and 14% of inhabitants younger than 14 years old, respectively. There are 3.7 individuals per household on average, instead of the 2.7 individuals registered in the downtown area [20].

### 2.2. Mathematical model

The model used here to evaluate the effect of vaccination delays on pertussis transmission is based on a deterministic age-structured compartmental model developed previously by us [18]. The population dynamics of this model is described transferring individuals among 9 epidemiological classes at given rates as is shown in Fig. 2A. Each one of the 9 epidemiological classes is divided into age groups. To study the effect of delays in vaccination we have introduced modifications into the model that allow us to take into account the actual age at which the population receives the three primary doses of the pertussis vaccine, regardless of the age recommended by the national vaccination schedule.

On the other hand, the fact that vaccination does not have a 100% effectiveness is considered assuming that only a fraction of

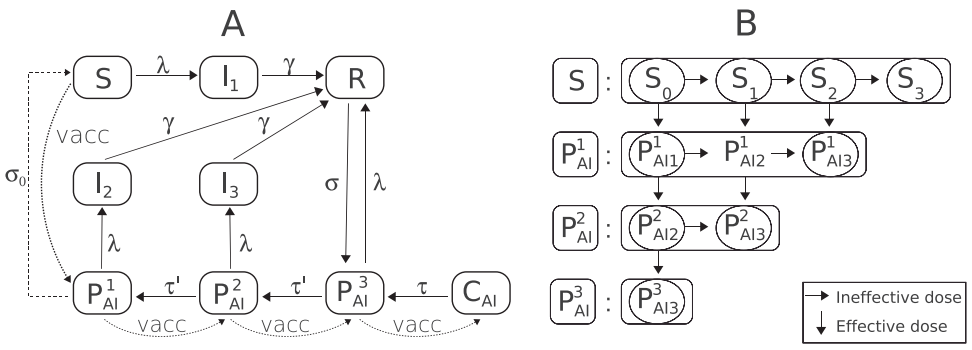


**Fig. 2.** (A) Schematic representation of the basic epidemiological model. Individuals are born in the susceptible class S and remain there unless they become infectious through contact with an infected individual and enter the full symptomatic infective class $I_1$, or they acquire the lowest level of immunity (via the application of the first effective vaccine dose) and enter $P^1_{AI}$ ($P_{AI}$: Partial Acquired Immunity). When receiving successive effective vaccination doses (dotted lines), individuals go through classes of increasing immunity and eventually reach the $C_{AI}$ (Complete Acquired Immunity) class. Individuals in classes $P^1_{AI}$ and $P^2_{AI}$ develop a less symptomatic illness when they get infectious, entering class $I_2$ (mild infection) or $I_3$ (weak infection), respectively. Infection fades at a rate $\gamma$ and individuals in classes $I_1$, $I_2$ or $I_3$ recover and enter R class. Waning immunity is considered by transferring population from classes R, $C_{AI}$ or $P_{AI}$ to classes of lower immunity at rates $\sigma$, $\tau$, $\tau'$, respectively. Each epidemiological class is divided into age groups. (B) Disaggregation of S and $P_{AI}$ classes by applied doses. The subindex indicates the number of applied doses. The superindex in $P_{AI}$ classes determines the immunity level of the class and corresponds to the number of effective doses. Arrows represent population transfers when an effective (vertical) or ineffective (horizontal) dose of vaccine is applied. This increase in the number of epidemiological classes holds for age groups from 0 to 1y. For people older than 1y, discrimination of the population by the number of applied doses is not necessary and 9 epidemiological classes as in (A) are considered.

the individuals that received one dose of vaccine is transferred to an epidemiological class with a higher level of immunity. The rest of the individuals that after receiving the extra dose did not modify their immunological status are transferred to a new class that comprises a population of individuals with the same status of immunity but with an additional dose. In the previous model [18], when the dose was not effective, the individual remained in the original epidemiological class and no records of the number of doses administered were kept. Here this discrimination of transfer to another epidemiological class is necessary since the second dose is only given to individuals who have already received the first one (and the same for the third dose with respect to the second). The new compartments added to the model to account for this effect are shown in Fig. 2B. When an effective dose $d$ is given at age $a_i$, a fraction $p_{di}$*VE (of those moved due to aging) is transferred to an increased immunity class (indicated with vertical arrows in the figure). If the dose $d$ is ineffective, a fraction $p_{di}$*(1-VE) is transferred to a class with the same level of immunity and one more dose given (horizontal arrow), while a fraction 1-$p_{di}$ does not receive the dose and remains in the same class. Here, VE is the vaccine efficacy, $p_{di}$ is the fraction of the aged $a_i$ population with $d$-1 doses that receives dose $d$ at age $a_i$, and is obtained from the fraction of vaccinated individuals by age $f_{di}$, and the corresponding vaccination coverage, DTP$d$-cov (computed as the fraction of infants vaccinated before 1y old). The set of ages $a_i$ is taken weekly from 2m to 1y (we assume each month has 4 weeks, a detailed explanation of the implementation of the vaccination procedure in the model is presented in the Supplementary Material). The dynamics of the model is described by a set of coupled nonlinear differential equations that are solved numerically to obtain the stationary state of the system. The incidences of the disease are then computed through expressions

$$\mathrm{Inc}_{1i} = \lambda_i(S_i + S_{1i} + S_{2i} + S_{3i}), \quad \mathrm{Inc}_{2i} = \lambda_i(P^1_{AI1^i} + P^1_{AI2^i} + P^1_{AI3^i})$$

where $\mathrm{Inc}_{1i}$ and $\mathrm{Inc}_{2i}$ are the incidences of fully and mild symptomatic pertussis cases, respectively for age group $i$. $\mathrm{Inc}_{1i}$ is computed as the product of the force of infection $\lambda_i$ and the total population of susceptible individuals in the corresponding age group, which is composed of unvaccinated individuals ($S_i$) and vaccinated individuals with 1, 2 or 3 doses of vaccine that have been ineffective for them ($S_{1i}$, $S_{2i}$, $S_{3i}$, respectively). $\mathrm{Inc}_{2i}$ is computed in the same way, but the population considered is in the first acquired immunity class as they have received 1 effective dose of vaccine.

## 3. Results

For all calculations presented here, we considered the parameters corresponding to a previously defined CP1A-MDI scenario (see Ref. [18], where contact parameters obtained from forces of infection in the pre-vaccine era and intermediate values reported for the duration of pertussis immunity are considered). In the Supplementary Material, the complete set of parameters used in this work is presented, and the results obtained for other scenarios are discussed.

### 3.1. Assessment of the effect of delayed vaccination for different coverages

The aim of this work is to assess the impact on the pertussis incidence in infants due to the reduction in the delays in DTP vaccination. With this purpose, we compared the incidences predicted by the model when the vaccination is delayed and when the recommended vaccination schedule is adhered to without any delay. To compute the 0–1y incidences in the case of delayed vaccination in our model, we included the weekly vaccination profile shown in Fig. 1B, and considered two possible values for DTP3-cov: 95% and 80%. To reach these coverages, we assume that DTP1-cov > DTP2-cov > DTP3-cov. We arbitrarily consider two sets: DTP1-cov = 99%, DTP2-cov = 97% DTP3-cov = 95%, and DTP1-cov = 90%, DTP2-cov = 85%, DTP3-cov = 80%. As there are other possible combinations of coverages to reach the same DTP3-cov, we repeated the calculations for the case that all individuals that receive DTP1 also receive the following doses (DTP1-cov = DTP2-cov = DTP3-cov, see Supplementary Material).

Fig. 3 shows the incidences in the 0–1y group considering a delay in vaccination and the ideal situation without delay.

As expected, when DTP3-cov = 95% and without delay, the predicted incidences are the lowest. When the delay is considered, both $\mathrm{Inc}_1$ and $\mathrm{Inc}_2$ increase. A similar trend is observed when DTP3-cov = 80%.

It should be noted that although no delayed vaccination is an unreal situation, the strategy of evolving from a stage DTP3-cov = 80% with delay to a stage DTP3-cov = 95% without delay results in an incidence ($\mathrm{Inc}_1 + \mathrm{Inc}_2$) reduction of 39% with respect to the initial situation.

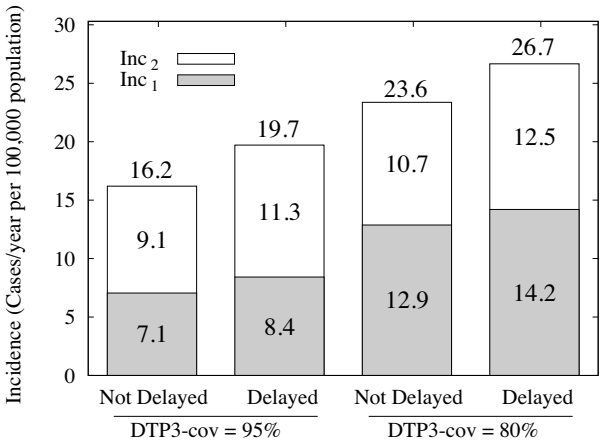


**Fig. 3.** Effect of the delay on incidences $Inc_1$ and $Inc_2$ for DTP3-cov 95% and 80%. The numbers inside the bars indicate the $Inc_1$ and $Inc_2$ values, and the numbers above correspond to $Inc_1 + Inc_2$. The label "Delayed" corresponds to the profile of Fig. 1(B), while the label "not delayed" corresponds to the case where all individuals receive the first, second and third vaccination doses at 2m, 4m and 6m, respectively.

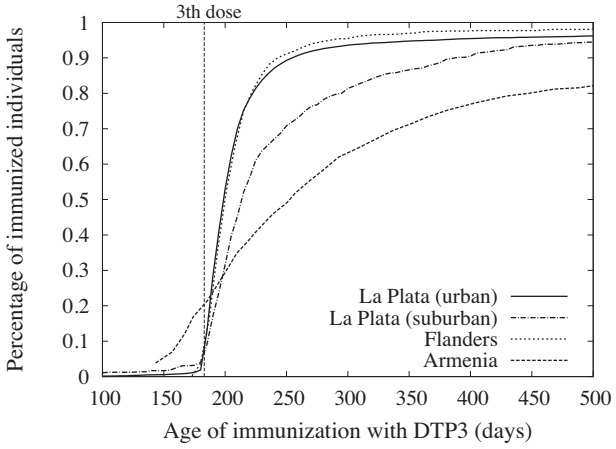


**Fig. 4.** Age-specific coverage for DTP3 in La Plata, Argentina (urban and suburban areas). Data from Flanders (Belgium) [21] and Armenia [22] are shown for comparative purposes. The vertical line indicates the age of immunization recommended by the Argentinean and Armenian National Vaccination Schedules. The curve for Belgium was shifted 2 months to superimpose on the recommended age of vaccination in the other countries. La Plata urban data were obtained from Fig. 1(A), assuming DTP3-cov = 95%. For the suburban curve we included 1764 records of DTP vaccinations in infants between 0 and 12 months old obtained from Public Health Centers on the outskirts of La Plata (December 2012 and March 2013), assuming DTP3-cov = 87%.

### 3.2. Assessment of some strategies for delay reduction

In this section we evaluate different strategies to diminish the delays detected in the urban region (Fig. 1B, case I). For these calculations we considered DTP3-cov = 95%, as was reported for different urban areas of our country by Gentile et al. [23].

We first assessed the effect of completely avoiding the delay in the first dose (case II). The calculation shows that $Inc_1 + Inc_2$ remains as in case I (19.7 cases/year/100,000 inhabitants). However, reducing $Inc_1$ (7.4 in case II instead of 8.4 in case I) at the expense of $Inc_2$ (12.3 in case II vs. 11.3 in case I) decreases the number of severe pertussis cases.

We also assessed the effect of avoiding the cumulative delays in DTP2 and DTP3 (case III). Here DTP1 is administered with delay, but with strict compliance with the recommended interval (2 months) between the following doses. As a result, $Inc_1 + Inc_2$ decreases by 13.9% with respect to case I, while a minor change for $Inc_1$ results (3.3%).

In case IV, DTP1 dose is administered as in case I, but the following doses are given without any delay, at the minimum interval between consecutive doses recommended by WHO. In this situation, as expected, the predicted $Inc_1 + Inc_2$ is slightly lower than that for case III (16.7 in case IV vs. 17.0 in case III) but higher than that for case V (16.7 in case IV vs. 16.2 in case V).

Case V corresponds to no delayed vaccination, in which $Inc_1$ and $Inc_2$ decrease with respect to case I by 16.3% and 19%, respectively. This improvement is even higher (49.6% for $Inc_1$ and 19% for $Inc_2$) if only the 2–12m group, which is the one susceptible to be directly affected by vaccination, is considered (Table 1).

### 3.3. Assessment of the effect of changing the vaccination profile of a suburban area to that of an urban area

In the suburban area of La Plata we detected a different vaccination profile with greater delays. The detail of the data is included in the supplementary material (Fig. S4). In Fig. 4 we show the age-specific coverage of DTP3 for the urban and suburban areas of La Plata and also include the ones for Flanders (Belgium) [21] and Armenia [22] to show that the delays detected in other regions are similar to those found in La Plata, or they could be even greater.

To estimate the effect of the suburban-area delays on 0–1y pertussis incidence, we consider that the coverage for DTP3 is 87% instead of the 95% that we took for the urban area. We assume DTP3-cov = 87% since from the information recorded in several vaccination centers of the suburban region, we found that 13% of the children who had completed their DTP3 vaccination dose received the third dose between 1 year and 3 years of age. Then, assuming that at the age of three 100% of the children received the DTP3 dose, at 1 year of age only 87% of the children have received the three recommended pertussis vaccine doses. If we assume that the proportions in such records are preserved in the whole suburban population, DTP3-cov should be at most 87%. The results of our calculations are shown in Fig. 5. When the delays in vaccination were reduced from those in the suburban profile (DTP3-cov = 87%) to the ones in the urban profile (DTP3-cov = 95%) of La Plata, a 27% decrease in $Inc_1 + Inc_2$, 35.1% in $Inc_1$, and 19.5% in $Inc_2$ was observed. In the figure we also included the results obtained for two other coverages for the suburban area: 80%, because this value can

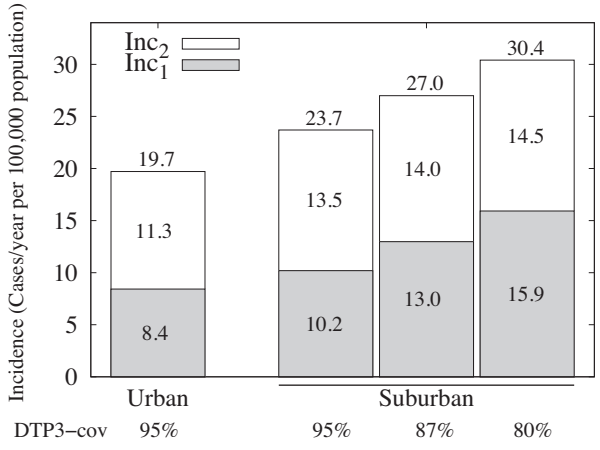


**Fig. 5.** Comparison of incidences $Inc_1$ and $Inc_2$ for the 0–1y age group for urban and suburban vaccination profiles of La Plata. DTP3-cov = 95% was used for the urban profile, while for the suburban profile three different DTP3-cov values were considered: DTP3-cov = 95% (higher than expected from the data), DTP3-cov = 87% (upper limit supported by current data) and the more realistic DTP3-cov = 80%. When DTP3-cov = 87% we take DTP1-cov = 94.5% and DTP2-cov = 91%. For the other cases, we take the same coverages as in Section 3.1 for the first 2 doses.

**Table 1**
Effect of the delay in the incidence by age for infants with less than 1y. Comparison of $Inc_1$ and $Inc_2$ values between delayed (Case I, Fig. 1(B)) and not delayed (Case V, Section 3.2) vaccination using DTP3-cov = 95%.

| DTP3-cov 95% | $Inc_1$ Cases/year per 100,000 population | | $Inc_2$ Cases/year per 100,000 population | |
|---|---|---|---|---|
| Age (m) | Delayed Case I | Not delayed Case V | Delayed Case I | Not delayed Case V |
| 0–2 | 5.7 | 5.7 | 0.0 | 0.0 |
| 2–4 | 1.4 | 0.6 | 4.2 | 5.0 |
| 4–6 | 0.7 | 0.3 | 4.5 | 2.4 |
| 6–12 | 0.6 | 0.5 | 2.6 | 1.7 |
| 0–12 | 8.4 | 7.1 | 11.3 | 9.1 |

be detected in this region, as was reported by Gentile et al. [23], and 95%, which although not being realistic, from an academic point of view, it is interesting to separately observe the effects of coverage and delays when comparing them with those of the urban profile. The decrease in incidence predicted by the model in changing from a suburban to an urban profile was more pronounced than that resulting from the reduction in the urban profile up to fully compliance with the immunization schedule. In the Supplementary Material we discuss the robustness of our results considering different scenarios including the duration of immunity, the contact matrix, and vaccine effectiveness.

## 4. Discussion

For pertussis and other vaccine-preventable diseases, the delay in the acquisition of immunity through late immunization could negatively impact on the disease transmission [24–27]. In fact, it is generally accepted that immunization at the earliest appropriate age is an important public health goal. Several countries such as US, Sweden and Australia have reported age properly immunized around 48–75% [28]. In Argentina, delay in vaccination was also detected in different populations [29–31]. The impact of delayed vaccination on the incidence of pertussis has been scarcely studied, and the effect of reducing it is even less known [24,32].

In this work, we assessed the impact on the incidence in the most vulnerable group due to the reduction in the delays of the primary doses of pertussis vaccine. With this aim, we used an age-structured deterministic mathematical model for pertussis transmission and data collected from an urban vaccination center in Argentina.

With our model, we evaluated the impact of completely avoiding the delays in each one of the three recommended primary doses for pertussis control. The results show that incidence reduction is important for both analyzed coverage: 95% (adequate) and 80% (suboptimal), being more noticeable in the first coverage scenario. Avoiding delays in the administration of primary doses would have a different impact on the 0–2m group than on the 2–12m group. As expected, in the 0–2m group the impact of reducing the delays is hardly noticeable (only reduction due to herd immunity, which in this case is low) since this age group is not given any vaccine according to immunization schedules like that of Argentina. For the 2–4m group no delays decrease the number of severe cases ($Inc_1$ decreases by 56.4% for 95% coverage) and for the 4–6m and the 6–12m groups with 95% coverage, $Inc_1 + Inc_2$ decreases up to 48.5% and 31.1%, respectively. Although this reduction in delayed vaccination up to full compliance with the immunization schedule seems highly unlikely due to the numerous uncontrollable reasons that may cause it [29,31], our results point out the magnitude of the improvement that could be achieved by implementing such health-care actions. Our method also allowed us to analyze other strategies that could be more easily implemented by the health system. Thus, we observed that when there are no delays in DTP1 administration, although the total incidence cannot be decreased, the total number of severe cases is lower (lower $Inc_1$ at the expense of $Inc_2$). This strategy should be recommended by pediatricians to newborns' parents.

Moreover, when delays are not cumulative (i.e., when after the first dose the 2 month interval is strictly preserved) $Inc_1 + Inc_2$ decreases by 13.8%. Comparatively, the elimination of the vaccination delays in both the second and third doses causes a smaller effect on incidence reduction, mainly affecting the $Inc_2$ value. This strategy should be mainly recommended by vaccinators.

We could also observe that when the delay in suburban areas could be reduced to those in the urban area, a reduction of 27% in $Inc_1 + Inc_2$ could be detected. Although the delays and profiles we worked with are from Argentina, they are comparable to those in other countries, as shown in Fig. 4.

The robustness of our results was tested by repeating the calculations using different sets of parameters allowing us to extend our conclusions to other possible epidemiological scenarios (Supplementary material).

All these results undoubtedly show that the reduction in the delays has a positive impact on incidence reduction, mainly in the severe cases in the 0–1y group. This could be helpful to support the implementation of this kind of strategy.

Moreover, our work also highlights the importance of mathematical modeling of infectious diseases as a powerful tool to evaluate control strategies [18,33,34]. In particular, here we present a new methodology, applied to a deterministic, compartmental, and age-structured model, to assess the effect of delays in the primary pertussis vaccination schedule. However, this methodology (see details in Supplementary Material) could also be easily adapted to assess the impact of vaccination delays in other models that describe pertussis transmission or other infectious vaccine-preventable diseases.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2015.07.005

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# Supplementary Material for:

# "Mathematical modeling of delayed pertussis vaccination in infants"

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# 1 Description of the Model

Here we present here the complete description of the model used in this work to perform the calculations. In our compartmental model the population is divided into epidemiological classes X, each of one is subdivided into age groups defined by a set of ages $a_i$, $i$=0,... $n_A$. The variables of the model are the fractions of the population in class X and age group $i$: $X_i$, where the age group $i$ contains people whose age is in the interval: $(a_i, a_{i+1})$.

The transfer of population among classes was briefly described in Fig.2 in the main text (reproduced here as Fig.S1). The transfer of population because of aging (in the absence of vaccination) is taken into account extracting a fraction of population from class X (age group $i$) at a rate $X_i/(a_{i+1} - a_i)$ and adding it to class X (age group $i + 1$) at the same rate.

In Section 1.1 we describe the methodology that we developed to account for delayed vaccination and the modifications we had to introduce to our previous model. In Section 1.2 we give the system of equations that describe the dynamic evolution of the model and in Section 1.3, all the parameters required to reproduce the calculations presented in the present paper. Section 1.1 was written for explanatory purposes and may be avoided if a direct description of the model (given in Sections 1.2 and 1.3) is preferred.

It has to be mentioned that even when the procedure presented in Section 1.1 is discussed in connection to a previous model [1], the general ideas may be easily adapted to other epidemiological models that describe pertussis or other infectious diseases controlled by vaccination.

## 1.1 Vaccination

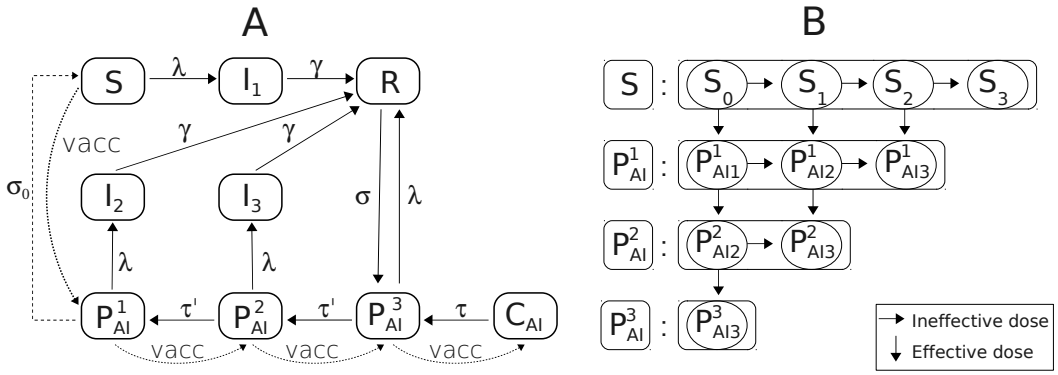
### Previous model

In our previous model [1] (following Hethcote [2]):

- vaccination was considered at an age $a_i$ if (and only if) $a_i$ matches the age at which any dose indicated in the vaccination schedule is given.
- The administration of a vaccine dose was considered for the population in $S$ or $P_{AI}$ classes.
- When a vaccine dose was given (for example) at age $a_i$, a fraction $vacc_i$ of those transferred because of aging was placed in an increased immunity epidemiological class, while a fraction $1 - vacc_i$ remained in the same epidemiological class. The fraction $vacc_i$ that was successfully immunized at age $a_i$ was computed as the product of the fraction that was vaccinated at age $a_i$ and the vaccine efficacy, VE.

Following this procedure, the second dose indicated in the vaccination schedule is not necessarily the second dose received by part of the population in some epidemiological classes. For example, suppose the vaccination schedule indicates the 1st dose at age 2m and the 2nd dose at age 4m. Then, vaccination at 4m was considered in the model transferring, a fraction $vacc_{4m}$ of those transferred

Figure S1: (the same as Figure 2 in the main text) A - Schematic representation of the basic epidemiological model. Individuals are born in the susceptible class S and remain there unless they become infectious through contact with an infected individual and enter the full symptomatic infective class $I_1$, or they acquire the lowest level of immunity (via the application of the first effective vaccine dose) and enter $P^1_{AI}$ ($P_{AI}$: Partial Acquired Immunity). When receiving successive effective vaccination doses (dotted lines), individuals go through classes of increasing immunity and eventually reach the $C_{AI}$ (Complete Acquired Immunity) class. Individuals in classes $P^1_{AI}$ and $P^2_{AI}$ develop a less symptomatic illness when they get infectious, entering class $I_2$ (mild infection) or $I_3$ (weak infection), respectively. Infection fades at a rate $\gamma$ and individuals in classes $I_1$, $I_2$ or $I_3$ recover and enter R class. Waning immunity is considered by transferring population from classes R, $C_{AI}$ or $P_{AI}$ to classes of lower immunity at rates $\sigma$, $\tau$, $\tau'$, respectively. At a very slow rate $\sigma_0$ individuals in $P^1_{AI}$ class may eventually enter S class. Each epidemiological class is divided into age groups. B - Disaggregation of S and $P_{AI}$ classes by applied doses. The subindex indicates the number of applied doses. The superindex in $P_{AI}$ classes determines the immunity level of the class and corresponds to the number of effective doses. Arrows represent population transfers when an effective (vertical) or ineffective (horizontal) dose of vaccine is applied. This increase in the number of epidemiological classes holds for age groups from 0 to 1y. For people older than 1y, discrimination of the population by the number of applied doses is not necessary and 9 epidemiological classes as in Fig.A are considered.




because of aging from $S$(2-4m age group) to $P^1_{AI}$(4-6m) and from $P^1_{AI}$(2-4m) to $P^2_{AI}$(4-6m), while a fraction $1 - vacc_{4m}$ is transferred from $S$(2-4m) to $S$(4-6m) and from $P^1_{AI}$(2-4m) to $P^1_{AI}$(4-6m). But the population in class $S$(2-4m) includes infants that have received an ineffective dose at 2m and also infants that have not been vaccinated, so the model does not distinguish whether the dose applied at 4m is in fact the first or the second one for people in S class and in the 2-4m age group.

## Present model

### Administration of the first three doses

In the model used in this work we assume that not all the infants receive the first 3 vaccine doses at the ages recommended in the vaccination schedule. In order to consider that vaccines may be given at other ages we take a weekly discretization of ages, $a_i$, from 2 months to 1 year and assume that individuals may be vaccinated at any of these ages. We consider that:

(i) a fraction $\text{cov}_d$ of the total population receives dose $d$ before 1y old,

(ii) a fraction $f_{di}$ of those that are vaccinated with dose $d$ before 1y old receives the dose at age $a_i$,

(iii) $\text{cov}_d$ and $f_{di}$ do not vary with time, and

(iv) the number of people of all ages is the same until they die (type I mortality [3]).

With these assumptions/definitions: $\sum_i f_{di} = 1$, $\text{cov}_d$ is the vaccination coverage of dose $d$ (*) and $f_{di}.\text{cov}_d$ is the vaccination coverage of dose $d$ per week.

In order to consider (ii) in the model, we have to take into account that dose $d+1$ should only be given to people that have already received dose $d$. Therefore, epidemiological classes that distinguish populations with different numbers of applied doses in addition to the level of immunity of the population were considered. This is addressed including additional classes in the model that account for the number of applied doses for each susceptible or partial immunity class, as is shown in Fig.S1(B).

Now, due to vaccination at age $a_i$, a given fraction $Q_{di}$ of those transferred due to aging is moved from class $X$ (age group $i-1$) to class $Y$ (age group $i$), where:

- population in class Y has one more dose and one more level of immunity than the population in class X if an effective dose has been given,
- population in class Y has one more dose but the same level of immunity than the population in class X if an ineffective dose has been given,
- and Y=X if no dose has been given.

(*) In the main text we used the notation DTP$d$-cov to mention the percentage coverage of dose $d$: DTP$d$-cov=100 $\text{cov}_d$.

Table S1: Population transfers due to vaccination at age $a_i$ when $a_i \leq 1$ year. The factor $Q_{di}$ is the fraction of those moved due to aging that is transferred from class $X$ (age group $i-1$) to class $Y$ (age group $i$) when dose $d$ is given. VE is the vaccine efficacy and $p_{di}$ is the fraction of the population of age $a_i$ having $d$-1 doses that receives dose $d$.

| d | X | Y | $Q_{di}$ | d | X | Y | $Q_{di}$ |
|---|---|---|---|---|---|---|---|
| 1 | $S_0$ | $P^1_{AI1}$ | $p_{1i}VE$ | 3 | $S_2$ | $P^1_{AI3}$ | $p_{3i}VE$ |
| 1 | $S_0$ | $S_1$ | $p_{1i}(1-VE)$ | 3 | $S_2$ | $S_3$ | $p_{3i}(1-VE)$ |
| 1 | $S_0$ | $S_0$ | $1-p_{1i}$ | 3 | $S_2$ | $S_2$ | $1-p_{3i}$ |
| 2 | $S_1$ | $P^1_{AI2}$ | $p_{2i}VE$ | 3 | $P^1_{AI2}$ | $P^2_{AI3}$ | $p_{3i}VE$ |
| 2 | $S_1$ | $S_2$ | $p_{2i}(1-VE)$ | 3 | $P^1_{AI2}$ | $P^1_{AI3}$ | $p_{3i}(1-VE)$ |
| 2 | $S_1$ | $S_1$ | $1-p_{2i}$ | 3 | $P^1_{AI2}$ | $P^1_{AI2}$ | $1-p_{3i}$ |
| 2 | $P^1_{AI1}$ | $P^2_{AI2}$ | $p_{2i}VE$ | 3 | $P^2_{AI2}$ | $P^3_{AI3}$ | $p_{3i}VE$ |
| 2 | $P^1_{AI1}$ | $P^1_{AI2}$ | $p_{2i}(1-VE)$ | 3 | $P^2_{AI2}$ | $P^2_{AI3}$ | $p_{3i}(1-VE)$ |
| 2 | $P^1_{AI1}$ | $P^1_{AI1}$ | $1-p_{2i}$ | 3 | $P^2_{AI2}$ | $P^2_{AI2}$ | $1-p_{3i}$ |

The fractions $Q_{di}$ are $p_{di}$.VE, $p_{di}$.(1-VE), and (1-$p_{di}$) respectively for the three cases mentioned above. VE is the vaccine efficacy and $p_{di}$ is the fraction of the population of age $a_i$ having $d$-1 doses that at age $a_i$ receives dose $d$, and is obtained from the fraction of vaccinated individuals by age, $f_{di}$, and the corresponding vaccination coverage, $\text{cov}_d$.

In Table S1 we explicitly show the transfers between different epidemiological classes due to vaccination at age $a_i$.

### Computation of $p_{di}$ from $f_{di}$ and $\text{cov}_d$

$f_{di}$ and $\text{cov}_d$ can be obtained from epidemiological data and $p_{di}$ are the parameters that control the transfers of population among classes due to vaccination in the model. Here we establish the relationship among these epidemiological and model parameters.

We introduce the following notation for the coverage per week of dose $d$: $\tilde{f}_{di} = f_{di}.\text{cov}_d$,which is the fraction of 1y old infants that has received dose $d$ at age $a_i$. Note that, because of assumption (iv), it is also the fraction of infants of age $a_i$ that receives dose $d$ at this age. On the other hand, $p_{di}$ is the fraction of infants of age $a_i$ having $d-1$ doses that receives dose $d$ at this age. As dose $d$ is only given to those that have $d-1$ doses, it is straightforward to see that:

$$p_{di} = \frac{\tilde{f}_{di}}{\text{fraction of infants of age } a_i \text{ that has } d-1 \text{ doses}}$$

The set of ages $a_i$ up to 1y are taken: 0, 2m, 2m+1week, 2m+2weeks, ... continuing weekly up to 1y, and index $i$: 0, 1, 2,..., so $\tilde{f}_{di}$ and $p_{di}$ are defined for $i \geq 1$.

**First dose ($d$=1)**

As the first dose is administered since age $a_1$=2m, all the population that arrives at this age has no vaccine dose applied and $p_{11} = \tilde{f}_{11}$.

At age $a_2$=2m+1week, the fraction $\tilde{f}_{12}$ of infants of age $a_2$ that are vaccinated represent a greater fraction $p_{12}$ of the infants in conditions of receiving the dose at this age, since a fraction $\tilde{f}_{11}$ of them has already received the first dose at age $a_1$=2m. So,

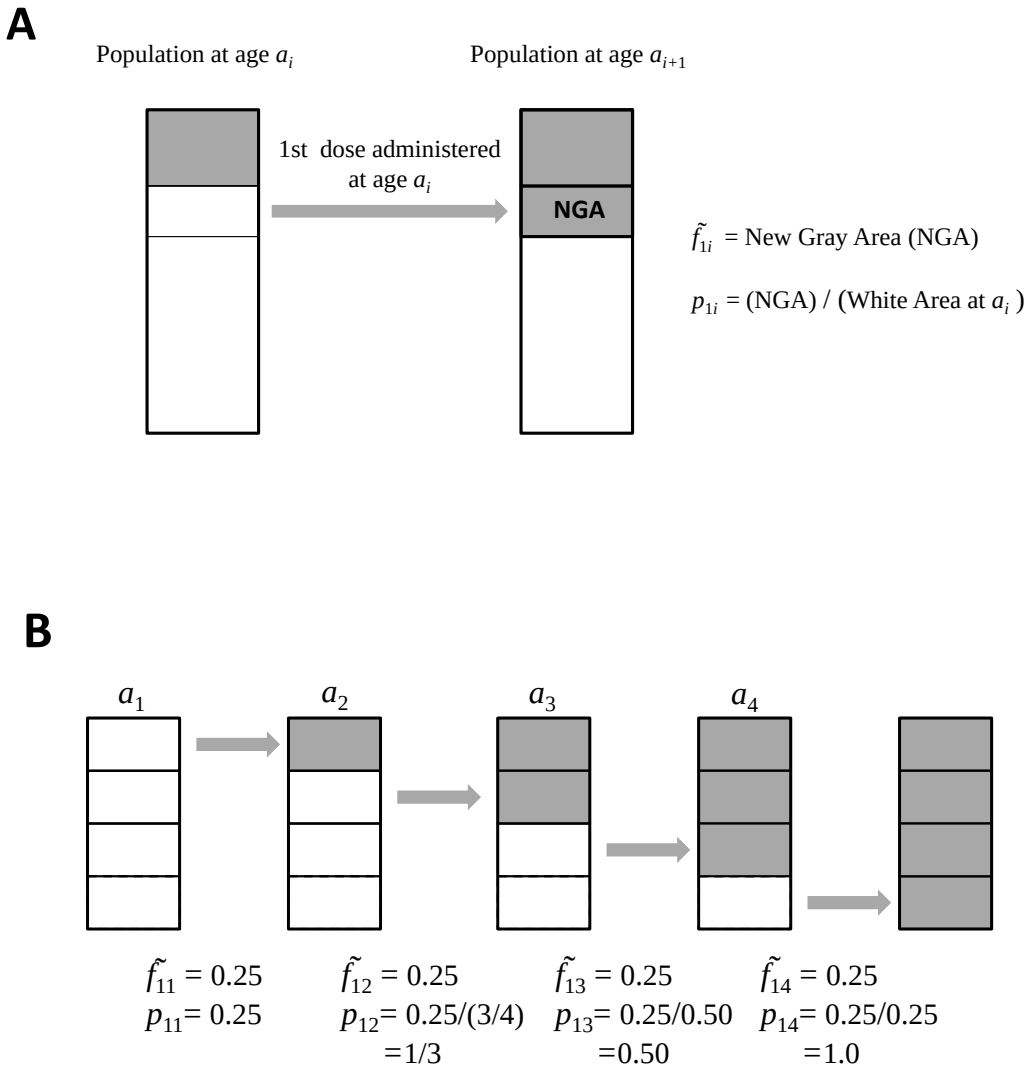
$$p_{12} = \frac{\tilde{f}_{12}}{1 - \tilde{f}_{11}}$$

Following this reasoning for the application of the first dose at age $a_i$, we obtain:

$$p_{1i} = \frac{\tilde{f}_{1i}}{1 - \sum_{j=1}^{i-1} \tilde{f}_{1j}}, \ i = 1, ...n \ \ (a_n = 1y) \tag{1}$$

In Fig.S2 we present a more intuitive, graphical representation of $\tilde{f}_{1i}$ and $p_{1i}$. In particular, in Fig.S2b, an example is given where the coverage of the first dose is 100%, the percentage of vaccinated individuals each time a dose is administered being 25%.

Figure S2: Schematic representation of the first dose administration. A - Representation of an administration of the first dose at age $a_i$. The whole boxes have unit area and represent the total population at a given age. The white area represents the fraction of unvaccinated people at a given age and gray area the fraction of people that has received one vaccine dose. In this representation $\tilde{f}_{1i}$ is the area that becomes gray when administering the dose at age $a_i$, and $p_{1i}$ is the fraction of the white area in the left box that becomes gray when administering the dose. B - Graphical computation of the parameters $\tilde{f}_{1i}$ and $p_{1i}$ for a particular example where 100% of the population receives the first dose in four administrations, 25% of individuals being vaccinated each time.



**Second dose ($d$=2)**

A fraction $\mathrm{cov}_2$ of infants of age 1y has been vaccinated with the second dose. Suppose the first application of the second dose is at age $a_k$. Then, a fraction $\tilde{f}_{2k}$ is vaccinated at age $a_k$, a fraction $\tilde{f}_{2(k+1)}$ is vaccinated at age $a_{k+1}$, and so on, such that $\sum_{j=k}^{n} \tilde{f}_{2j} = \mathrm{cov}_2$.

The fraction $\tilde{f}_{2k}$ of infants of age $a_k$ that receives the first administration of the second dose is related to $p_{2k}$ by:

$$p_{2k} = \frac{\tilde{f}_{2k}}{\sum_{j=1}^{k-1} \tilde{f}_{1j}}$$

If at age $a_k$ all the infants have already received the first dose, $p_{2k}$ would be simply $\tilde{f}_{2k}/\mathrm{cov}_1$, but in general it is not the case and when some infants are given the second dose, there still remains population with the first dose to be administered.

At age $a_{k+1}$, a fraction $\tilde{f}_{2(k+1)}$ has to be vaccinated. In this case:

$$p_{2(k+1)} = \frac{\tilde{f}_{2(k+1)}}{\sum_{j=1}^{k} \tilde{f}_{1j} - \tilde{f}_{2k}}$$

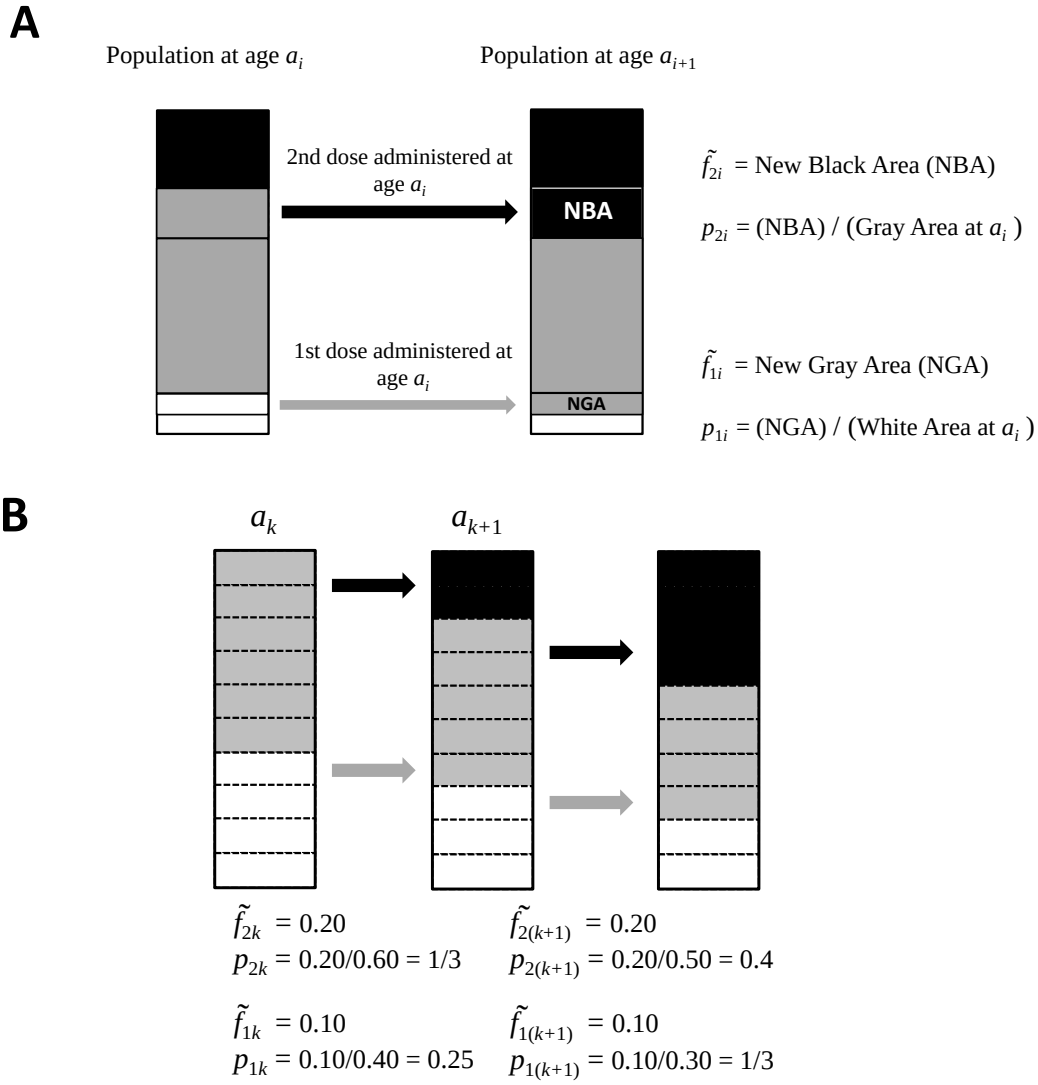
In general, at age $a_i$, a fraction $\tilde{f}_{2i}$ is vaccinated with the second dose and

$$p_{2i} = \frac{\tilde{f}_{2i}}{\sum_{j=1}^{i-1} \tilde{f}_{1j} - \sum_{j=1}^{i-1} \tilde{f}_{2j}} \tag{2}$$

where in the denominator we add the fraction of infants that has previously received the first dose and subtract the fraction of those that has already received the second one. Note that the sum including $\tilde{f}_{2j}$ terms begins in fact with $j = k$, but for simplicity we take $j = 1$ as $\tilde{f}_{2j}$=0 for $j < k$.

In Fig.S3 we attempt to clarify this process with a graphical representation of $\tilde{f}_{2i}$ and $p_{2i}$.

Figure S3: Schematic representation of the second dose administration. A - Representation of an administration of the second dose at age $a_i$, when the first dose is still being administered. The whole boxes have unit area and represent the total population at a given age. The white area represents the fraction of unvaccinated people at a given age, the gray area the fraction of people that have received one vaccine dose, and the black area the fraction of people that have received two vaccine doses. B- Numerical example showing the computation of the factors $\tilde{f}_{di}$ and $p_{di}$ for the first two administrations of the second dose. Note that when the second dose is being administered, there are people still receiving the first one. The dashed lines divide the box into equal parts of size 0.1. If no more doses were administered in this example, it would result in $\text{cov}_1$=0.80 and $\text{cov}_2$=0.40.



**Third dose ($d$=3)**

For the administration of the third dose the expressions for $p_{3i}$ are identical to those for $p_{2i}$ by changing $\tilde{f}_{1j}$ by $\tilde{f}_{2j}$ and $\tilde{f}_{2j}$ by $\tilde{f}_{3j}$:

$$p_{3i} = \frac{\tilde{f}_{3i}}{\sum_{j=1}^{i-1} \tilde{f}_{2j} - \sum_{j=1}^{i-1} \tilde{f}_{3j}} \tag{3}$$

**Administration of doses at 18 months, 6 and 11 years**

The administration of these boosters is modeled as in the previous model. Dose at 6y, for example, is not "the fifth dose", it is a dose given to children that are 6 years old regardless of the number of doses they have previously received.

## 1.2 Equations that describe the disease transmission dynamics

Because of the extra classes included for infants in 0-1y age groups in order to account for delays in vaccination, we have two systems of equations, one for age groups included in the 0-1y interval, and the other for age groups included in 1-75y. Both systems of equations are coupled through the forces of infection $\lambda_i$ and through transfers of population at age 1y.

### Interval 0-1y

$$\frac{dS_{0i}}{dt} = -\lambda_i S_{0i} - \mu_i S_{0i} + c_{i-1}(1-p_{1i})S_{0i-1} - c_i S_{0i} + \delta_{i,0} B$$

$$\frac{dS_{1i}}{dt} = -\lambda_i S_{1i} + \sigma_0 P^1_{AI1i} - \mu_i S_{1i} + c_{i-1}\, p_{1i}(1-VE)S_{0i-1} + c_{i-1}(1-p_{2i})S_{1i-1} - c_i S_{1i}$$

$$\frac{dS_{2i}}{dt} = -\lambda_i S_{2i} + \sigma_0 P^1_{AI2i} - \mu_i S_{2i} + c_{i-1}\, p_{2i}(1-VE)S_{1i-1} + c_{i-1}(1-p_{3i})S_{2i-1} - c_i S_{2i}$$

$$\frac{dS_{3i}}{dt} = -\lambda_i S_{3i} + \sigma_0 P^1_{AI3i} - \mu_i S_{3i} + c_{i-1}\, p_{3i}(1-VE)S_{2i-1} + c_{i-1} S_{3i-1} - c_i S_{3i}$$

$$\frac{dP^1_{AI1i}}{dt} = -\lambda_i P^1_{AI1i} - \sigma_0 P^1_{AI1i} - \mu_i P^1_{AI1i} + c_{i-1}\, (1-p_{2i})P^1_{AI1i-1} - c_i P^1_{AI1i} + c_{i-1} p_{1i} VE\; S_{0i-1}$$

$$\begin{aligned}\frac{dP^1_{AI2i}}{dt} =& -\lambda_i P^1_{AI2i} - \sigma_0 P^1_{AI2i} + \tau' P^2_{AI2i} - \mu_i P^1_{AI2i} + c_{i-1}\ (1-p_{3i}) P^1_{AI2i-1} - c_i P^1_{AI2i} \\ &+ c_{i-1} p_{2i} VE\ S_{1i-1} + c_{i-1} p_{2i}(1-VE)\ P^1_{AI1i-1}\end{aligned}$$

$$\begin{aligned}\frac{dP^1_{AI3i}}{dt} =& -\lambda_i P^1_{AI3i} - \sigma_0 P^1_{AI3i} + \tau' P^2_{AI3i} - \mu_i P^1_{AI3i} + c_{i-1} P^1_{AI3i-1} - c_i P^1_{AI3i} \\ &+ c_{i-1} p_{3i} VE\ S_{2i-1} + c_{i-1} p_{3i}(1-VE)\ P^1_{AI2i-1}\end{aligned}$$

$$\frac{dP^2_{AI2i}}{dt} = -\lambda_i P^2_{AI2i} - \tau' P^2_{AI2i} - \mu_i P^2_{AI2i} + c_{i-1}\ (1-p_{3i}) P^2_{AI2i-1} - c_i P^2_{AI2i} + c_{i-1} p_{2i} VE\ P^1_{AI1i-1}$$

$$\begin{aligned}\frac{dP^2_{AI3i}}{dt} =& -\lambda_i P^2_{AI3i} - \tau' P^2_{AI3i} + \tau' P^3_{AIi} - \mu_i P^2_{AI3i} + c_{i-1} P^2_{AI3i-1} - c_i P^2_{AI3i} \\ &+ c_{i-1} p_{3i} VE\ P^1_{AI2i-1} + c_{i-1} p_{3i}(1-VE)\ P^2_{AI2i-1}\end{aligned}$$

$$\frac{dP^3_{AIi}}{dt} = -\lambda_i P^3_{AIi} - \tau' P^3_{AIi} - \mu_i P^3_{AIi} + \sigma R_i + c_{i-1} P^3_{AIi-1} - c_i P^3_{AIi} + c_{i-1} p_{3i} VE\ P^2_{AI2i-1}$$

$$\frac{dI_{1i}}{dt} = \quad \lambda_i S_i - \gamma I_{1i} - \mu_i I_{1i} + c_{i-1} I_{1i-1} - c_i I_{1i}$$

$$\frac{dI_{2i}}{dt} = \quad \lambda_i P^1_{AIi} - \gamma I_{2i} - \mu_i I_{2i} + c_{i-1} I_{2i-1} - c_i I_{2i}$$

$$\frac{dI_{3i}}{dt} = \quad \lambda_i P^2_{AIi} - \gamma I_{3i} - \mu_i I_{3i} + c_{i-1} I_{3i-1} - c_i I_{3i}$$

$$\frac{dR_i}{dt} = \quad \lambda_i P^3_{AIi} + \gamma(I_{1i} + I_{2i} + I_{3i}) - \sigma R_i - \mu_i R_i + c_{i-1} R_{i-1} - c_i R_i$$

Where $\quad S_i = S_{0i} + S_{1i} + S_{2i} + S_{3i}, \quad P^1_{AIi} = P^1_{AI1i} + P^1_{AI2i} + P^1_{AI3i},$

$$P^2_{AIi} = P^2_{AI2i} + P^2_{AI3i}, \qquad P^3_{AIi} \equiv P^3_{AI3i}$$

## Interval 1-75y

$$\frac{dS_i}{dt} = -\lambda_i S_i + \sigma_0 P^1_{AIi} - \mu_i S_i + c_{i-1}(1-vacc_i)S_{i-1} - c_i S_i$$

$$\frac{dP^1_{AIi}}{dt} = -\lambda_i P^1_{AIi} - \sigma_0 P^1_{AIi} + \tau' P^2_{AIi} - \mu_i P^1_{AIi} + c_{i-1}\ (1-vacc_i)P^1_{AIi-1} - c_i P^1_{AIi} + c_{i-1}vacc_i\ S_{i-1}$$

$$\frac{dP^2_{AIi}}{dt} = -\lambda_i P^2_{AIi} - \tau' P^2_{AIi} + \tau' P^3_{AIi} - \mu_i P^2_{AIi} + c_{i-1}\ (1-vacc_i)P^2_{AIi-1} - c_i P^2_{AIi} + c_{i-1}vacc_i\ P^1_{AIi-1}$$

$$\frac{dP^3_{AIi}}{dt} = -\lambda_i P^3_{AIi} - \tau' P^3_{AIi} + \tau C_{AIi} - \mu_i P^3_{AIi} + \sigma R_i + c_{i-1}(1-vacc_i)P^3_{AIi-1} - c_i P^3_{AIi} + c_{i-1}vacc_i\ P^2_{AIi-1}$$

$$\frac{dC_{AIi}}{dt} = -\tau C_{AIi} - \mu_i C_{AIi} + c_{i-1}C_{AIi-1} - c_i C_{AIi} + c_{i-1}vacc_i\ P^3_{AIi-1}$$

$$\frac{dI_{1i}}{dt} = \lambda_i Si - \gamma I_{1i} - \mu_i I_{1i} + c_{i-1}I_{1i-1} - c_i I_{1i}$$

$$\frac{dI_{2i}}{dt} = \lambda_i P^1_{AIi} - \gamma I_{2i} - \mu_i I_{2i} + c_{i-1}I_{2i-1} - c_i I_{2i}$$

$$\frac{dI_{3i}}{dt} = \lambda_i P^2_{AIi} - \gamma I_{3i} - \mu_i I_{3i} + c_{i-1}I_{3i-1} - c_i I_{3i}$$

$$\frac{dR_i}{dt} = \lambda_i P^3_{AIi} + \gamma(I_{1i} + I_{2i} + I_{3i}) - \sigma R_i - \mu_i R_i + c_{i-1}R_{i-1} - c_i R_i$$

Where $X_i$ is the fraction of the total population that is in class X and age group $i$. Epidemiological classes are defined in the caption of Fig.S1. For equations in the 0-1y interval we omitted class $C_{AI}$ as it is always "empty" (at least 4 vaccine doses are necessary in order to reach class $C_{AI}$, while in the 0-1y range at most 3 doses are given).

The rates that control the transfers of population among classes are constant (also defined in Fig.S1) except for the force of infection $\lambda_i$ that depends on dynamical variables of the model by expression

$$\lambda_i = \sum_j N_C(i,j)(I_j^*/N_j) = \sum_j \beta_{ij} I_j^* \quad ; \quad I_j^* = I_{1j} + \rho_1 I_{2j} + \rho_2 I_{3j} \tag{4}$$

Where $N_C(i,j)$ is the number of infective contacts per unit of time between an individual of age group $i$ with individuals of age group $j$, and $I_j^*/Nj$ represents the effective probability that an individual in age group $j$ is infective. For "infective contact" we mean a contact such that if an individual in group $j$ is fully infected ($I_1$) and an individual in group $i$ is partially or completely susceptible, then an individual in group $i$ will acquire infection. The contact parameter matrix, $\beta_{ij} = N_C(i,j)/N_j$, gives a measure of the contact rate between individuals of different age groups that is independent of age group sizes. Factors $\rho_1$ and $\rho_2$ are taken smaller than 1 to consider that individual in classes $I_2$ and $I_3$ are less infective. As we assume type I mortality (everybody dies exactly at an age equal to the life expectancy: L [3]), all the mortality rates $\mu_i$ are 0 with exception of the one corresponding to the oldest group, $i = n_A - 1$, which takes the value: $1/(a_{nA} - a_{nA-1})$. As the total population is constant, all the $N_i$ are also constant in time: $N_i = (a_{i+1} - a_i)/L$, $L = a_{nA}$ (the highest age considered)=75y in this work. Parameter $c_i$ is the rate at which individuals are transferred from an age group to the next because of aging. We take $c_i = 1/(a_{i+1} - a_i)$ for $i = 0, ...n_A - 2$, in that way, for $I_1$ class for example, in an interval $\Delta t$ a fraction $\Delta t/(a_i - a_{i-1})$ of individuals in age group $i-1$ are transferred to group $i$ because of aging, while a fraction $\Delta t/(a_{i+1} - a_i)$ of individuals in age group $i$ leaves group $i$ to enter $i+1$. Note that there is no younger group than $i = 0$ or older than $n_A - 1$, so we take $c_{-1} = c_{nA-1} = 0$ in order to cancel the corresponding terms in the set of differential equations. The last term in the first equation of the system for 0-1y represents the birth rate. The symbol $\delta$ is the Kroenecker delta, so, $\delta_{i0}$ indicates that the term is present only for $i = 0$. We assume that every individual is born susceptible, so $B$ is the per capita birth rate and is included in equation for $S_{00}$. In order to keep the total population constant, $B$ should equal the per capita mortality rate:

$$B = \sum_{i=1}^{n_A - 1} \mu_i N_i = 1/L \tag{5}$$

Vaccination (explained in detail in Section 1.1) is introduced to the model in a different way for the first 3 doses and for the subsequent boosters. For the first three doses (infants younger than 1y) vaccination is taken into account transferring people between classes with a different number of applied doses, and is controlled by the vaccine efficacy, VE, and parameters $p_{di}$. These parameters can be computed through equations (1)-(3) and the knowledge of $\tilde{f}_{di} = f_{di}.\text{cov}_d$, where parameters $f_{di}$ are the fraction of those individuals that were vaccinated with dose $d$ before 1y old that receives the dose at age $a_i$, and $\text{cov}_d$ is the vaccination coverage of dose $d$. Both parameters $f_{di}$ and $\text{cov}_d$ can be taken from epidemiological data.

For the subsequent boosters at 18m, 6y and 11y, vaccination is taken into account by transferring individuals from the $S$ or $P_{AI}$ classes to the following increased-immunity class when an effective

vaccine dose is given. This is introduced to the model through function $vacc_i$ , the fraction of individuals at age $a_i$ that is successfully immunized:

$$vacc_i = \sum_{j=1}^{n_d} p_j \text{VE } \delta_{i,j} \ , \quad \delta_{i,j} = \begin{cases} 1 & \text{if } a_i = d_j \\ 0 & \text{if not} \end{cases} \tag{6}$$

$vacc_i$ is different from 0 only when $a_i$ coincides with the age of one of the boosters, $d_j$ (18m, 6y or 11y), $p_j$.VE is the fraction of people at age $d_j$ successfully immunized, $p_j$ is the coverage of dose $j$, and $n_d$ the number of boosters ($n_d = 3$ in our case). In order that this scheme works, the ages $a_i$ have to be chosen in such a way that each $d_k$ coincides with some $a_i$.

Once the parameters are assigned, the system is solved using Euler algorithm taking a small enough time interval, $\Delta t$, until the stationary state is reached.

# 2 Model Parameters

To assign the parameter values to the model, different epidemiological scenarios that include different contact patterns among individuals and different durations of natural or vaccine-induced immunity were considered. This methodology was developed and described in detail in ref. [1]. In Section 2.1 we give the values of the parameters considered for each epidemiological scenario. In Section 2.2 we describe the parameters considered in the present work to account for vaccination that also involve different possible scenarios. For the recovery rate, we take $\gamma = 1/21$ days independently of the degree of infection as in previous work [1, 4].

## 2.1 Duration of immunity and contact rate parameters

Although it is well known that pertussis vaccination or infection does not provide lifelong immunity, the precise duration of protection is not known [2,5,6]. Therefore, three immunity parameterizations were considered: SDI, MDI and LDI for Short, Medium or Long Duration of Immunity, based on data from reference [5]. It is assumed that the duration of natural immunity ($t_N$) is the time elapsed since an individual has recovered from infection (entering class $R$) until reaching class $P^1_{AI}$ where they may acquire a mild infection. The duration of immunity acquired through vaccination ($t_V$) is the time elapsed since an individual has been completely immunized (entering class $C_{AI}$) until reaching class $P^1_{AI}$. Table S2 lists the values used for these parameters in the three immunity conditions considered.

Table S2: Parameter values for the different pertussis immunity durations considered in this study. The parameters $\sigma, \tau$ and $\tau'$ are the rates at which population is transferred from R, $C_{AI}$ and $P^3_{AI}$ or $P^2_{AI}$ to the lower immunity class, respectively. The rate at which immunized individuals become completely susceptible is controlled by the slow rate, $\sigma_0$. All the values in the table are in years.

| Duration of pertussis immunity | $1/\sigma$ | $1/\tau$ | $1/\tau'$ | $1/\sigma_0$ |
|---|---|---|---|---|
| Short duration immunity (SDI) | 5 | 1 | 1.5 | 100 |
| Medium duration immunity (MDI) | 11 | 2 | 2 | 100 |
| Long duration immunity (LDI) | 14 | 4 | 3 | 100 |

The transmission of infection takes place through contact between infected and susceptible (or partially immunized) individuals. Quantitatively, this process is controlled by the expression given above for the force of infection $\lambda_i$. For $\rho_1$ and $\rho_2$ we take 0.5 and 0.25 as in ref. [2]. For the contact transmission rate parameters $\beta_{ij}$ we considered values obtained from three different methods in order to check that our results do not depend on the way parametrization is performed.

Table S3: Structure of Who Acquires Infection From Whom (WAIFW) matrix. $\beta_{ij}$ parameters are determined by assigning the corresponding $b_k$ value. Note that $\beta_{ij}$ is the same for any age group $i(j)$ contained in the corresponding wider age group of the row (column) matrix. The missing elements of the matrix are omitted for simplicity as the matrix is symmetric. (Previously published in ref. [1] as Table S1)

| Age | 0-4m | 4m-1y | 1-3y | 3-5y | 5-10y | 10-15y | 15-35y | 35-55y | 55-75y |
|---|---|---|---|---|---|---|---|---|---|
| 0-4m | $b_1$ | $b_1$ | $b_1$ | $b_1$ | $b_1$ | $b_1$ | $b_2$ | $b_2$ | $b_2$ |
| 4m-1y | | $b_2$ | $b_2$ | $b_2$ | $b_2$ | $b_2$ | $b_3$ | $b_3$ | $b_3$ |
| 1-3y | | | $b_3$ | $b_3$ | $b_3$ | $b_3$ | $b_3$ | $b_3$ | $b_3$ |
| 3-5y | | | | $b_4$ | $b_4$ | $b_3$ | $b_3$ | $b_3$ | $b_3$ |
| 5-10y | | | | | $b_5$ | $b_6$ | $b_3$ | $b_3$ | $b_3$ |
| 10-15y | | | | | | $b_6$ | $b_7$ | $b_8$ | $b_9$ |
| 15-35y | | | | | | | $b_7$ | $b_8$ | $b_9$ |
| 35-55y | | | | | | | | $b_8$ | $b_9$ |
| 55-75y | | | | | | | | | $b_9$ |

Procedure 1: In this procedure epidemiological data are used to determine forces of infection and a given structure for $\beta_{ij}$ matrix is assumed (see table S3).

We consider two sources of epidemiological data:

Procedure 1A: Forces of infection are obtained from epidemiological data corresponding to England and Wales in the pre-vaccine era.

Procedure 1B: Forces of infection are obtained from epidemiological data corresponding to several European countries in the vaccine era.

Procedure 2: In this procedure direct measures of social contact patterns ($c_{ij}$), performed by Mossong *et al.* [7] for eight European countries, are used. We take $\beta_{ij}$=K*$c_{ij}$ and determine K so that the model reproduces the mean age of first infection known for pertussis in pre-vaccine era (4.5y).

As in both procedures the model has to be used to determine the $\beta_{ij}$ values that reproduce specific epidemiological features, the results depend on other parameters of the model, in particular on those that account for duration of immunity. So, we obtain three sets (SDI, MDI, LDI) of parameters for each of the three methods outlined above. The values of $\beta_{ij}$ obtained following procedures 1A, 1B and 2 are listed in Tables S4 and S5. For more details see ref. [1].

Table S4: Values of $b_k$ (in 1/day) obtained by Procedure 1. The $b_k$-values define $\beta_{ij}$ with the WAIFW matrix of Table S3. $CP_{1A}$ and $CP_{1B}$ denote that the contact parameters are obtained by Procedure 1 (case A) or Procedure 1 (case B), respectively. (Previously published in ref. [1] as Table S2)

| | $b_1$ | $b_2$ | $b_3$ | $b_4$ | $b_5$ | $b_6$ | $b_7$ | $b_8$ | $b_9$ |
|---|---|---|---|---|---|---|---|---|---|
| $CP_{1A}$-SDI | 0.04 | 0.06 | 0.18 | 0.61 | 2.12 | 0.77 | 0.35 | 0.12 | 0.00 |
| $CP_{1A}$-MDI | 0.02 | 0.12 | 0.23 | 0.73 | 2.47 | 0.95 | 0.54 | 0.16 | 0.00 |
| $CP_{1A}$-LDI | 0.02 | 0.16 | 0.26 | 0.80 | 2.64 | 1.04 | 0.70 | 0.17 | 0.00 |
| $CP_{1B}$-SDI | 0.06 | 0.03 | 0.16 | 0.94 | 1.07 | 0.76 | 0.24 | 0.36 | 0.14 |
| $CP_{1B}$-MDI | 0.04 | 0.09 | 0.23 | 1.09 | 1.29 | 0.99 | 0.38 | 0.59 | 0.19 |
| $CP_{1B}$-LDI | 0.04 | 0.13 | 0.28 | 1.16 | 1.40 | 1.12 | 0.49 | 0.78 | 0.23 |

Table S5: Values of $\beta_{ij}$ (in 1/day) obtained for $CP_2$-MDI scenario. For $CP_2$-SDI and $CP_2$-LDI scenarios, $\beta_{ij}$-values are obtained by multiplying those in the table by the factors: 0.025/0.029 and 0.030/0.029, respectively (see Procedure 2 for details) (Previously published in ref. [1] as Table S3)

| Age (years) | 0-1 | 1-5 | 5-10 | 10-15 | 15-20 | 20-25 | 25-30 | 30-35 | 35-40 | 40-45 | 45-50 | 50-55 | 55-60 | 60-65 | 65-75 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 - 1 | 0.36 | 0.36 | 0.18 | 0.07 | 0.04 | 0.07 | 0.13 | 0.19 | 0.17 | 0.10 | 0.06 | 0.07 | 0.06 | 0.06 | 0.04 |
| 1 - 5 | 0.36 | 0.72 | 0.37 | 0.15 | 0.09 | 0.14 | 0.27 | 0.37 | 0.33 | 0.19 | 0.13 | 0.14 | 0.13 | 0.12 | 0.08 |
| 5 - 10 | 0.13 | 0.26 | 1.68 | 0.34 | 0.10 | 0.08 | 0.17 | 0.28 | 0.34 | 0.29 | 0.14 | 0.10 | 0.10 | 0.09 | 0.06 |
| 10 - 15 | 0.04 | 0.09 | 0.28 | 2.15 | 0.41 | 0.09 | 0.07 | 0.13 | 0.24 | 0.33 | 0.20 | 0.09 | 0.05 | 0.05 | 0.05 |
| 15 - 20 | 0.03 | 0.06 | 0.11 | 0.31 | 2.10 | 0.36 | 0.12 | 0.07 | 0.14 | 0.21 | 0.23 | 0.12 | 0.07 | 0.03 | 0.03 |
| 20 - 25 | 0.04 | 0.08 | 0.06 | 0.07 | 0.39 | 0.94 | 0.41 | 0.19 | 0.12 | 0.13 | 0.22 | 0.18 | 0.09 | 0.04 | 0.03 |
| 25 - 30 | 0.09 | 0.18 | 0.14 | 0.04 | 0.12 | 0.43 | 0.61 | 0.36 | 0.19 | 0.16 | 0.15 | 0.17 | 0.12 | 0.08 | 0.04 |
| 30 - 35 | 0.14 | 0.28 | 0.25 | 0.13 | 0.07 | 0.15 | 0.27 | 0.44 | 0.37 | 0.22 | 0.15 | 0.14 | 0.11 | 0.09 | 0.06 |
| 35 - 40 | 0.10 | 0.20 | 0.29 | 0.21 | 0.10 | 0.11 | 0.19 | 0.29 | 0.49 | 0.31 | 0.16 | 0.13 | 0.10 | 0.10 | 0.09 |
| 40 - 45 | 0.08 | 0.16 | 0.19 | 0.27 | 0.27 | 0.16 | 0.14 | 0.19 | 0.27 | 0.43 | 0.28 | 0.17 | 0.08 | 0.08 | 0.06 |
| 45 - 50 | 0.07 | 0.13 | 0.10 | 0.15 | 0.27 | 0.17 | 0.16 | 0.19 | 0.18 | 0.26 | 0.37 | 0.24 | 0.13 | 0.06 | 0.05 |
| 50 - 55 | 0.05 | 0.09 | 0.13 | 0.11 | 0.12 | 0.14 | 0.21 | 0.16 | 0.16 | 0.20 | 0.24 | 0.34 | 0.21 | 0.10 | 0.05 |
| 55 - 60 | 0.05 | 0.09 | 0.10 | 0.06 | 0.08 | 0.12 | 0.18 | 0.18 | 0.14 | 0.15 | 0.17 | 0.25 | 0.34 | 0.15 | 0.08 |
| 60 - 65 | 0.06 | 0.12 | 0.09 | 0.06 | 0.05 | 0.07 | 0.13 | 0.18 | 0.17 | 0.17 | 0.13 | 0.15 | 0.22 | 0.29 | 0.17 |
| 65 - 75 | 0.04 | 0.07 | 0.09 | 0.06 | 0.05 | 0.06 | 0.07 | 0.11 | 0.11 | 0.15 | 0.10 | 0.12 | 0.14 | 0.20 | 0.23 |

Table S6: Different coverages considered for the 3 primary doses

| DTP3-cov | Case | DTP1-cov | DTP2-cov | DTP3-cov |
|---|---|---|---|---|
| 95% | A | 99% | 97% | 95% |
| | B | 95% | 95% | 95% |
| 80% | A | 90% | 85% | 80% |
| | B | 80% | 80% | 80% |

## 2.2 Vaccination parameters

### 2.2.1 Vaccination coverages

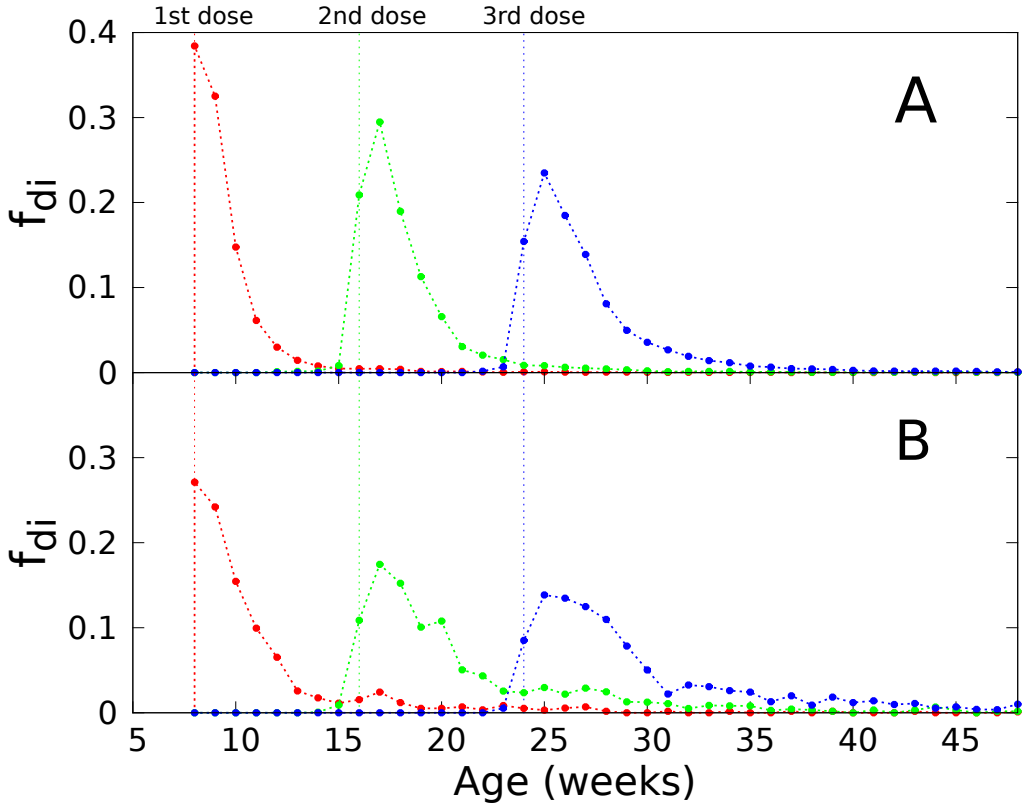
We considered two values for the vaccination coverage of the third dose: 95% (adequate) and 80%(suboptimal). We also considered two alternatives to reach the proposed coverage for the third dose. One of them verifies $cov_1 > cov_2 > cov_3$ (case A), assuming that the failure in schedule compliance is progressive. In the other we assume that all the people that receive the first dose also receive the following doses: $cov_1 = cov_2 = cov_3$ (case B). The values of the coverages considered are shown in Table S6. In the main text we consider coverages corresponding to case A as they show better agreement with most epidemiological data. But in Section 3.2 results for case B are also discussed.

For the coverages of the boosters at 18m, 6y and 11y we take 85%, 95% and 85%, respectively when DTP3-cov=95%, and 70%, 80% and 70% when DTP3-cov=80%. We are assuming the empirical fact that coverage for the 18m booster is always lower than DTP3 coverage, and that at school entry it grows again. For the 11y coverage we assume it is the same as for the 18m booster, but it is probably lower and highly dependent on the geographical region, in particular in Argentina where it has recently been included in the vaccination schedule.

### 2.2.2 Fraction of vaccinated individuals by age ($f_{di}$)

The data provided by vaccination centers were: the date of administration of a given dose and the date of birth of the vaccinated individual. With this information, the number of vaccinated individuals by age was computed with an age precision of a day. The $f_{di}$ parameters were determined for doses $d$=1, 2 and 3, and for age groups $i$ that were chosen weekly from 2m to 1y. We take a week as a quarter of a month, and a month as a twelfth of an year, so the "week" used in our calculations has 7.6 days. We compute the fractions of individuals vaccinated at age $a_i$, $f_{di}$, from the number of vaccinated individuals by age (provided in days) in the interval ($a_i$-0.5w, $a_i$+0.5w) and normalizing $f_{di}$ to one for each dose $d$. The number of vaccinated individuals at the points: $a_i$-0.5w and $a_i$+0.5w (non-integer in days) were obtained by linear interpolation. In Fig.S4 we show the profiles obtained from data taken from urban and suburban vaccination centers from La Plata city. From this information we built other profiles to compute the effect of specific strategies to reduce the delay in vaccination that were discussed in section 3.2 of the main text.

Figure S4: Fraction of vaccinated individuals with dose $d$ at age $a_i$ ($f_{di}$). A - Urban profile (data are from Elina de la Serna Hospital). B - Suburban profile (data are from Public Health Centers on the outskirts of La Plata). Vertical lines indicate the recommended age for primary doses of pertussis vaccination schedule in Argentina.




### 2.2.3 Vaccine efficacy (VE)

For the vaccine efficacy of each DTwP vaccine dose we take the value 0.9 as in ref. [2]. By taking this value and a medium duration of immunity (MDI) our model reproduces the fact obtained by Hethcote that in the period 1-2y after receiving the third-dose, from 62% to 81% of vaccinated infants would be protected from severe or mild pertussis disease (being in $P^1_{AI}$, $P^2_{AI}$ or $P^3_{AI}$ classes). This is consistent with reported data about vaccine efficacy of both DTwP and DTaP formulations [2,8–11]. More recent studies indicate that the range of variation of immunity conferred by DTwP vaccine could be even larger [12]. So, in the results presented in the main text we took VE=0.9 for the first 3 doses, and in Section 3.3 we checked the sensitivity of our results to this parameter taking the values VE=0.85 and VE=0.95. Taking VE=0.95 corresponds to protection from 68% to 86% in the 1-2y interval after administration of the third dose, as discussed above, while VE=0.85 corresponds to protection from 57% to 75%. For boosters at 18m and 6y we considered VE=0.9 since in Argentine

vaccination schedule DTwP formulation is used. For Tdap-11y booster we considered a lower efficacy, VE=0.5. May be that VE is higher for 11y booster, but it is also probable that we are overestimating the booster coverage, as mentioned in Section 2.2.1. Since the parameter that enters the model is the product of both factors, we think the value taken is good enough.

# 3 Robustness of the results presented in the present work

In this section we check the robustness of the main conclusions of our work against variations in the parameters of the model. These variations may arise because of uncertainties in the determination of some of them and also because some parameters may change from place to place because of different epidemiological conditions.

## 3.1 Different epidemiological scenarios

In Table S7 we show the effect of reduction in vaccination delays for the scenarios that include different durations of immunity and different contact rate parameters. Independently of the scenario considered, the percentage of incidence reduction is around 20% when going from the Urban to the Not Delayed profile and a bit more when going from the Suburban to the Urban profile. The only exception is the $CP_2$ scenario, where the reduction is around 11% when going from the Urban to the Not Delayed profile. This difference may be explained because in the $CP_2$ scenario the relation Inc(0-2m)/Inc(2-12m) is larger than for $CP_{1A}$ and $CP_{1B}$ scenarios. Since population in the 0-2m age group is not directly affected by vaccination, the effect of delays is relatively lower for $CP_2$ scenario. The larger value of the incidence in the 0-2m age group may be caused by an overestimation of the contact rates for younger infants in $CP_2$ scenario. As in ref. [7] contacts are obtained by averaging within 5y age groups; we assumed uniform contact rates within 0-1y age group and estimated them as half the values provided for 0-5y age group [1]. The need of empirical contact data for infants has recently been mentioned as a key point for pertussis [13].

## 3.2 Effect of changing vaccination coverage of the different doses on 0-1y incidences.

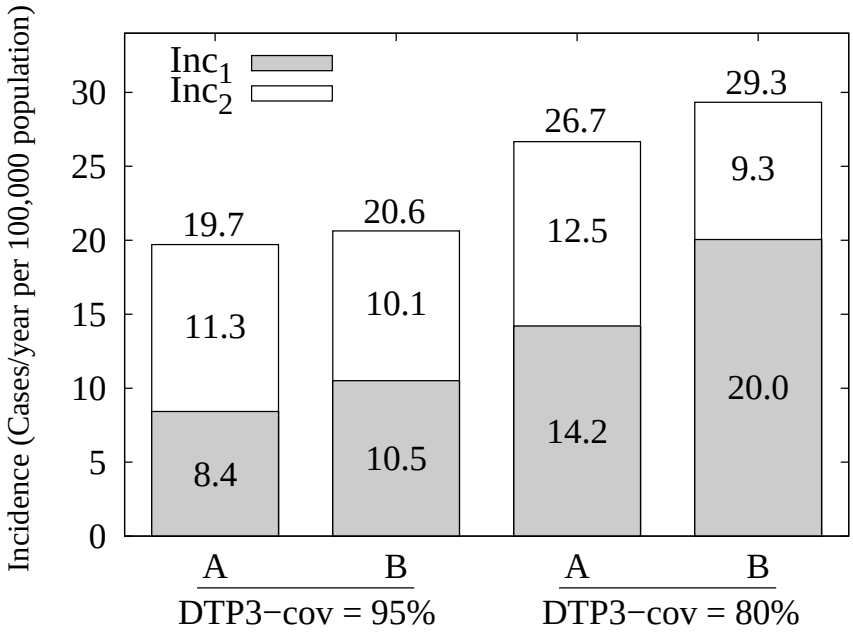
Here we present results for the urban profile when the coverage of the third dose is reached in two different ways, as was described in Section 2.2.1 (Table S6). Even when case A is the more likely situation, here we explored the effect of having $cov_1$=$cov_2$=$cov_3$(case B). This may be the case for populations where the accessibility to vaccination centers is uneven. So, people who can have access to vaccination centers get every dose, while people who can not get none. In Fig.3.2. we show the results for parameters corresponding to $CP_{1A}$-MDI scenario. For DTP3-cov=80% there is an 9.1% increase in 0-1y incidence ($Inc_1$ +$Inc_2$) for case B with respect to case A. The increase is much higher for $Inc_1$ (41%), which is reasonable since DTP1-cov is 10% greater in case A than in case B and this change impacts directly on $Inc_1$. The results are qualitatively similar for DTP3-cov=95% but quantitatively less significant since the difference between case A and case B coverages is much lower for DTP3-cov=95%. These results show again the importance of having a high coverage of the first dose to reduce severe pertussis cases.

Table S7: Incidences in the 0-1y age group ($Inc_1$+$Inc_2$) for delayed and not-delayed vaccination profiles for different epidemiological scenarios. For the Not Delayed case (ND) the profile corresponds to vaccination at ages indicated in the vaccination schedule (2m, 4m, 6m) and DTP3-cov=95%. The delayed profiles: Urban (U) and Suburban (S) are the ones shown in Fig.S4. For the Urban and Suburban cases a DTP3 coverage of 95% and 87%, respectively, was taken. Parameters for different epidemiological scenarios are given in Section 2.1

.

| Scenario | Not Delayed | Delayed | | Percentage improvement | |
|---|---|---|---|---|---|
| | (ND) | Urban (U) | Suburban (S) | 100*(U-ND)/U | 100*(S-U)/S |
| CP1A-SDI | 15.1 | 18.9 | 26.5 | 19.9 | 28.7 |
| CP1A-MDI | 16.2 | 19.7 | 27.0 | 17.8 | 27.0 |
| CP1A-LDI | 15.5 | 18.5 | 25.2 | 16.4 | 26.5 |
| CP1B-SDI | 18.8 | 24.2 | 34.2 | 22.3 | 29.3 |
| CP1B-MDI | 21.0 | 26.0 | 35.2 | 19.2 | 26.2 |
| CP1B-LDI | 21.5 | 26.2 | 34.0 | 17.9 | 23.0 |
| CP2-SDI | 25.1 | 28.2 | 35.0 | 10.9 | 19.5 |
| CP2-MDI | 18.6 | 20.8 | 26.3 | 11.0 | 20.9 |
| CP2-LDI | 14.1 | 15.8 | 20.3 | 11.0 | 22.1 |

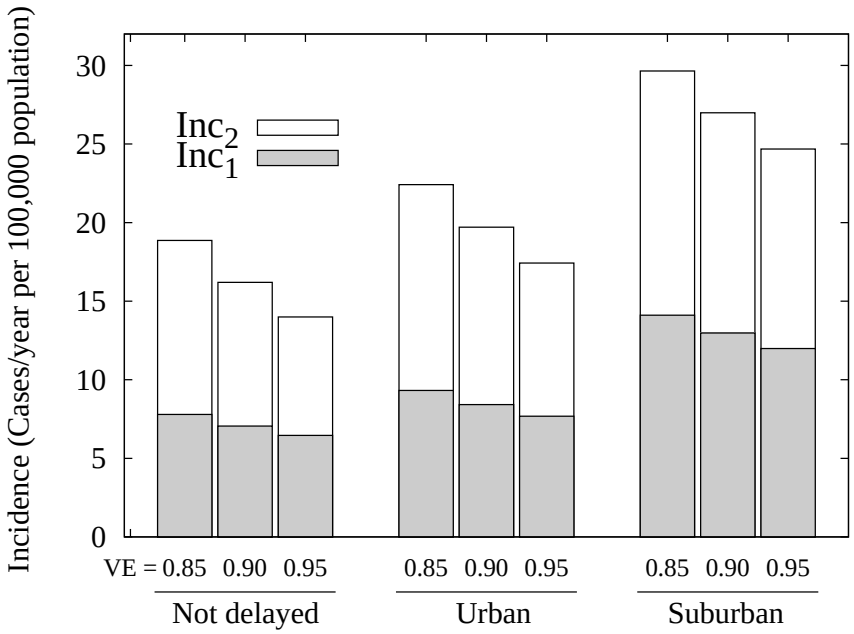
Figure S5: Incidences in the 0-1y age group for the Urban profile and different coverages. Cases A and B correspond to coverages given in Table S6.



## 3.3 Effect of changing the vaccine efficacy (VE)

As was discussed in Section 2.2.3, there is some uncertainty in the efficacy of each vaccination dose. We repeated the calculations for the $CP_{1A}$-MDI scenario and profiles corresponding to delayed and not delayed vaccination for different values of the vaccine efficacy (VE) of DTwP. The results are shown in Fig.S6. As expected, in all the cases the incidence is higher when VE is lower for a given vaccination profile. The qualitative impact of delay in vaccination is the same for the three values of VE considered. However, for higher values of VE, the percentage improvement obtained by reducing delays is higher. This is also reasonable: the more effective a dose is, the more is lost by not giving it on time.

Figure S6: Incidences in the 0-1y age group for different values of vaccine efficacy (VE). Three different vaccination profiles were considered: not delayed (with DTP3-cov=95%), urban (with DTP3-cov=95%) and suburban (with DTP3-cov=87%).



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