*Epidemiol. Infect.* (2006), **134**, 850–862. © 2005 Cambridge University Press
doi:10.1017/S095026880500539X Printed in the United Kingdom

# A modelling analysis of pertussis transmission and vaccination in Rio de Janeiro, Brazil

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(*Accepted 17 August 2005, first published online 29 November 2005*)

## SUMMARY

Pertussis is an infectious respiratory disease for which mass vaccination is an effective preventive strategy. In many developed countries, where high vaccination coverage has been maintained for approximately 50 years, re-emergence of the disease has been observed in all age groups. In the municipality of Rio de Janeiro (RJ), where vaccination started in the 1980s, surveillance data show no sign of disease re-emergence. We developed a mathematical model that incorporates the major demographic aspects of a large urban centre in a developing nation, in addition to the most important epidemiological aspects of disease transmission. Parameter values were estimated based on RJ demographic and vaccine coverage data. Overall, all vaccination strategies determined a major decrease (over 95% decrease when compared to the pre-vaccine era) in the incidence of primary infections (occurring in individuals who have never been immunized through infection or vaccine). On the other hand, the strategies (*a*) three doses at age 2–11 months, (*b*) three doses plus booster at age 12–23 months, (*c*) three doses plus booster at age 4–5 years, and (*d*) three doses plus both boosters, differently affected the incidence of secondary infections (occurring in previously infected/vaccinated individuals). Given that the immunity against pertussis wanes with time and that the infectious agent has not been eliminated from the population, it is expected that pertussis will continue to be a problem in RJ. Actually, since immunity acquired from vaccine wanes faster than disease-acquired immunity and the possibility of natural boosters has decreased with mass vaccination, an increase in the incidence of secondary infections among older age groups is expected (and predicted by the model). Possible explanations as to why this dynamics is not captured by the RJ surveillance system are discussed. A poorly effective surveillance system and a lack of awareness regarding loss of immunity and the possibility of pertussis infection in older age groups are among them. Finally, we bring attention to the need of (i) field studies for the measurement of pertussis incidence in adolescents and adults; (ii) better understanding of the transmission dynamics currently occurring in RJ, and (iii) re-evaluation of vaccination strategies with the possible introduction of acellular vaccines for the vaccination of older individuals.

## OVERVIEW OF PERTUSSIS DYNAMICS

Pertussis is an infectious disease, producing respiratory symptoms, especially coughs. The most common aetiological agent is the bacteria *Bordetella pertussis* [1]. Worldwide, approximately 50 million cases and 300 000 deaths occur each year [2]. A severe primary infection can be prevented through the proper

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immunization of an individual. The whole-cell vaccine usually given in association with diphtheria and tetanus vaccine (DPT vaccine), is used in Brazil, where the schedule consists of five doses: three doses before the age of 1 year and two boosters at 15–18 months and 4–5 years. A few acellular vaccines (DaPT) are also available which can be administered to children older than 6 years. DaPT vaccine is currently used in many developed countries.

Vaccination of children is an effective preventive strategy against severe cases of pertussis. However, despite high vaccination coverage for more than 50 years, pertussis is now classified as a re-emerging disease in many developed countries [3]. Loss of naturally or artificially acquired immunity stands out as an obvious reason for re-emergence [4–6]. Mass vaccination determines a decrease in transmission of the bacteria, preventing the occurrence of natural boosters and consequently, making adolescents and adults more susceptible than in the pre-vaccine era. Vaccinated individuals, as time passes, become susceptible to the disease and, given that the parasite is still circulating, may acquire the disease once again. Some authors suggest that the reason for the observed re-emergence is an increased awareness of waning immunity by health professionals which allows for disease diagnosis [5, 6].

However, the transmission dynamics observed in Canada and Australia suggest a different reason; namely a cohort effect [7]. In these countries, the increase in incidence is more profound in specific age groups, and the higher incidence accompanies the cohort with time. Although the dynamics are very similar in the two countries, the reasons are somewhat different: a vaccine batch with low efficacy used in Canada, and an absence of a booster dose in Australia. On the other hand, in The Netherlands, field studies suggest the evolution of the bacteria as the cause for pertussis re-emergence. Mass vaccination for more than 50 years determined a genetic modification of the parasite, now less affected by the immunity produced following vaccination [8]. The development of new diagnostic methods that are more sensitive and specific is also suggested as a reasonable explanation for the re-emergence of pertussis [9].

In Brazil, mass vaccination with DPT whole-cell vaccine began during the 1970s, and by 1980s an increasing proportion of children aged $<1$ year were being vaccinated. At approximately the same time, the national surveillance system was implemented

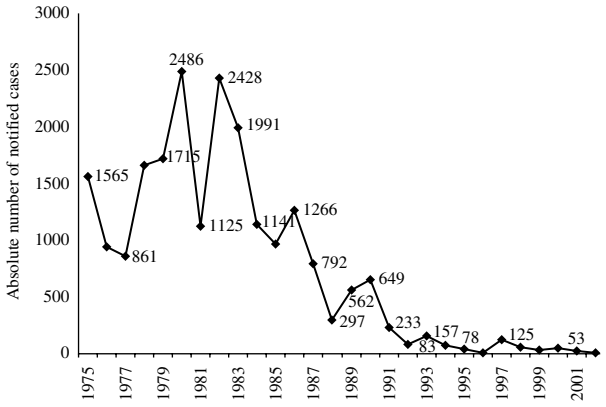


**Fig. 1.** Absolute number of reported pertussis cases in the municipality of Rio de Janeiro from 1975 to 2002. (Source: Secretaria Municipal de Saúde do Rio de Janeiro, 2003 [10].)

with mandatory notification of pertussis cases. Since then, the reported time series for pertussis indicates a decrease in incidence with the introduction of vaccination, and an increase in vaccination coverage. Here, we concentrate in the municipality of Rio de Janeiro (RJ) which presents the same dynamics [10]. The absolute number of reported cases is decreasing (see Fig. 1) and the vaccine coverage is increasing. However, it is possible that the surveillance system may not be capturing the whole picture due to underreporting problems. Pertussis suffers from underreporting in many countries since (i) there exists no universal case definition, (ii) laboratory procedures for bacterial identification are not very sensitive or specific, and (iii) pertussis clinical symptoms resemble other upper-respiratory diseases [11]. In addition, only a fraction of health professionals are believed to be aware of loss of immunity of pertussis. This means that a significant fraction of Brazilian health professionals, when in the presence of an adolescent or adult with a cough, generally do not include pertussis in the differential diagnostic disease spectrum.

In this paper we work with the hypothesis that RJ surveillance data are not a realistic representation of pertussis dynamics at this location. We developed an age-structured mathematical model to theoretically reconstitute the past and present dynamics of pertussis in RJ and suggest some scenarios for the future. Moreover, we analysed the vaccine strategies regarding booster doses that could be adopted. Our model has two components: one captures the demographic dynamics of RJ population, while the other

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captures the dynamics of the disease within age groups. In the next sections, we present the model, the results, and discuss the public health consequences of our findings.

## PERTUSSIS MODEL

The mathematical model developed aimed at simulating pertussis dynamics in an age-structured population. It is subdivided into two sub-models, one capturing the demographic and the other the epidemiological dynamics. Our model structure draws from previously published models which allows for adequate comparison of results [12–15]. The demographic sub-model simulates the dynamics of the RJ population from 1970 (~10 years before systematic vaccination of children) to 2020. During this period, a major demographic change has occurred, as the average life expectancy has greatly increased. The demographic pyramid has changed dramatically from 1970 to 2000, approaching the shape of a population pyramid of developed countries. We selected 12 age groups according to their epidemiological relevance: 0–1, 2–11, 12–23 months, 2–3, 4–5, 6–9, 10–14, 15–19, 20–29, 30–39, 40–49 years and ⩾50 (maximum age 79 years). Only individuals within the range of 15–49 years are considered fertile.

Parameter estimates for the demographic model were drawn from RJ's demographic databases available via the Internet [16]. Since estimates of mortality and fertility rates for all study years are not available, we decided to use 2000 as the reference, for which all data needed were available (deaths, newborns and number of males and females per age group). Mortality and fertility rates were calculated by age group. The simulated demographic dynamics is deterministic and fits reasonably well to the observed data (data not shown).

The epidemiological sub-model is divided into nine epidemiological stages, as shown in Figure 2, where arrows indicate the flow between compartments. The dynamics are as follows: individuals are born susceptible ($S$), and throughout their lives they are at risk of acquiring a primary infection ($I_p$). The infection determines a period of bacteria transmission to other individuals, the transmission period. After recovery, individuals move through progressive immunological stages, from $R_3$, full immunity, to $R_2$, intermediate immunity, to $R_1$, minimum immunity (at rate $\alpha$ per stage). Individuals in the $R_1$ stage are at risk of acquiring a secondary infection, $I_s$. This

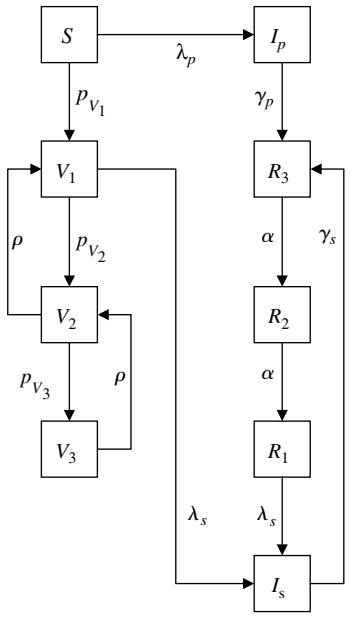


**Fig. 2.** Schematic representation of the epidemiological sub-model. $S$, susceptible; $I_p$, primary infection; $R_3$, high immunity from infection; $R_2$, intermediate immunity from infection; $R_1$, low immunity from infection; $I_s$, secondary infection; $V_1$, received first dose of DTP vaccine; $V_2$, received second dose of DPT vaccine; $V_3$, received third dose of DPT vaccine. (See Table 1 for the definitions of the transition rates between compartments.)

infection is milder than the primary infection, although still infectious to other individuals.

At a specific moment in the simulation (year 1980), vaccination begins to be implemented. From this moment on, a fraction $p_{V_1}$ of the individuals who are at least 2 months old receive their first dose of DPT vaccine (and move to compartment $V_1$). A fraction $p_{V_2}$ of those who received the first dose receive the second ($V_2$), and a fraction $p_{V_3}$ of those in the $V_2$ compartment evolve to compartment $V_3$. These vaccine doses determine an immune status that protects against infection. However, this immunity also wanes with time: individuals progress backwards from $V_3$ to $V_2$ to $V_1$ at a rate $\rho$ per stage. Vaccine-acquired immunity wanes faster than the disease-induced immunity ($\rho > \alpha$). Individuals in compartment $V_1$ have a low immunity status and are at risk of a secondary infection ($I_s$). For the baseline simulation we incorporated three doses of DPT vaccine given to the 2–11 months age group. The simulation of booster doses was incorporated into the model by removing individuals from stages $V_2$ and $V_1$ and placing them in $V_3$, and by removing individuals from stages $R_2$ and $R_1$ and placing them in $R_3$. This transition has been assumed by other authors and

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Table 1. *Parameter values for the epidemiological sub-model [the range of plausible values assigned to each parameter is given in the form of a probability distribution where U(min, max) stands for the Uniform Probability Distribution with minimum and maximum values]*

| Parameter | Definition | Fixed value | Plausible range | Reference |
|---|---|---|---|---|
| $\sigma$ | Susceptibility of $S(\sigma_p)$, $R_1$ and $V_1(\sigma_s)$ | $\sigma_p = 1$<br>$\sigma_s = 0{\cdot}7$ | $\sigma_p$: $U(0{\cdot}8, 1{\cdot}0)$<br>$\sigma_s$: $U(0{\cdot}6, 0{\cdot}8)$ | [12] |
| $\eta$ | Infectiousness of $I_p$ and $I_s$ | $\eta_p = 1$<br>$\eta_s = 0{\cdot}5$ | $\eta_p$: $U(0{\cdot}7, 1{\cdot}0)$<br>$\eta_s$: $U(0{\cdot}4, 0{\cdot}7)$ | [12, 17, 18] |
| $\tau$ | Proportion of vaccine coverage | $\tau_{V_1} = 0{\cdot}40$–$0{\cdot}90$<br>$\tau_{V_2} = 0{\cdot}35$–$0{\cdot}85$<br>$\tau_{V_3} = 0{\cdot}30$–$0{\cdot}80$ | – | [10]* |
| $\varepsilon$ | Vaccine efficacy | $\varepsilon = 0{\cdot}70$ | $U(0{\cdot}5, 0{\cdot}9)$ | [19, 20] |
| $\gamma$ | Rate of recovery from the infectious period | $\gamma_p = 0{\cdot}333$<br>$\gamma_s = 0{\cdot}666$ | $\gamma_p$:$U(0{\cdot}25, 0{\cdot}5)$<br>$\gamma_s$:$U(0{\cdot}33, 1{\cdot}0)$ | [12, 17] |
| $\alpha$ | Rate of loss of infection-acquired immunity | $\alpha = 0{\cdot}0019$ | $U(0{\cdot}0016, 0{\cdot}0024)$ | [6, 12] |
| $\rho$ | Rate of loss of vaccine-acquired immunity | $\rho = 0{\cdot}0032$ | $U(0{\cdot}0024, 0{\cdot}0038)$ | [6, 12] |

* Vaccination starts in 1980 with a bi-annual increase of 10%.

seems reasonable since booster doses are given to children >1 year old, when the immune system is more mature [15].

The transition rates between the epidemiological stages shown in Figure 2 are described in Table 1. Model details are given in the Appendix. Given the importance of the social network in determining the transmission of pertussis to young infants, we decided to model the force of infection, $\lambda_k$ ($k = p, s$) as depending on five other parameters:

(1) the number of contacts ($n_i$) made by individuals in age group $i$;
(2) the proportion of contacts ($C_{ij}$) made by age group $i$ with each age group $j$;
(3) the proportion of infected individuals ($P_{I_{p,i}}$ and $P_{I_{s,i}}$) in each age group;
(4) the relative infectivity ($\eta$) of individuals in compartments $I_p$ and $I_s$;
(5) the relative susceptibility ($\sigma$) of individuals in compartments $S$, $R_1$, $V_1$.

Vaccination was simulated as a function of: (i) vaccine coverage ($\tau$, which varies with time and dose) and (ii) vaccine efficacy ($\varepsilon$). The model was first simulated without vaccination until an equilibrium was reached, corresponding to the pre-vaccine era. The steady state reached was used as the initial condition for further simulations. Further, we introduced three doses of DPT vaccine at age 2–11 months, and finally, the booster dose was introduced first at age 12–23 months, then at 4–5 years and last for both age groups (the fixed values assigned to each parameter are presented in Table 1). For the uncertainty and sensitivity analysis, we used three procedures described in Saltelli et al. [21]. For these, it was necessary to establish a range of plausible values for each parameter which are presented in Table 1 in the form of a probability distribution, where $U$ (min, max) stands for the Uniform probability distribution with minimum and maximum values. MATLAB 6.5 software (version 6.5, release 13, The Math Works, Inc.) was used for the simulation of the model, and SIMLAB 2.2 software for the uncertainty and sensitivity analysis [22].

## RESULTS

Using the fixed value for each parameter, as presented in Table 1, a simulation of the pre-vaccine era was performed. Table 2 shows the estimated annual incidence for year 2020 of primary and secondary infections by age group if vaccination had never been implemented. The results are consistent with the pre-vaccine era, when the majority of infections occurred in children <6 years of age (see Table 2). We also observed that even in the pre-vaccine era, the occurrence of secondary infections is predicted by the model, with the highest incidence occurring in the 20–29 years age group: 5058 new secondary infections per 100 000 individuals.

### Three doses of DPT vaccine

Further, we simulated the model incorporating three doses of DPT vaccine given to infants aged 2–11 months. The proportion of vaccine coverage assumed

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Table 2. *Estimated annual incidence for year 2020 of pertussis* (*per 100 000*) *as predicted by the simulation of the mathematical model*

| Age groups | 0–1 mo. | 2–11 mos. | 12–23 mos. | 2–3 yr | 4–5 yr | 6–9 yr |
|---|---|---|---|---|---|---|
| Pre-vaccine | | | | | | |
| Primary incidence | 24 515 | 20 230 | 16 132 | 29 156 | 2510 | 113 |
| Secondary incidence | 0 | 16 | 72 | 1536 | 2366 | 3458 |
| Three doses | | | | | | |
| Primary incidence | 15 876 | 570 | 180 | 329 | 135 | 35 |
| Secondary incidence | 0 | 409 | 617 | 3509 | 4380 | 5210 |
| Booster at 12–23 mos. | | | | | | |
| Primary incidence | 15 337 | 551 | 175 | 317 | 138 | 38 |
| Secondary incidence | 0 | 395 | 18 | 1489 | 3023 | 4667 |
| Booster at 4–5 yr | | | | | | |
| Primary incidence | 13 511 | 486 | 157 | 330 | 140 | 38 |
| Secondary incidence | 0 | 348 | 534 | 3435 | 81 | 2614 |
| Both boosters | | | | | | |
| Primary incidence | 13 484 | 485 | 157 | 317 | 142 | 41 |
| Secondary incidence | 0 | 348 | 16 | 1453 | 36 | 2569 |

| Age groups | 10–14 yr | 15–19 yr | 20–29 yr | 30–39 yr | 40–49 yr | ⩾50 yr |
|---|---|---|---|---|---|---|
| Pre-vaccine | | | | | | |
| Primary incidence | 3 | 0 | 0 | 0 | 0 | 0 |
| Secondary incidence | 3598 | 4196 | 5085 | 4824 | 4708 | 4635 |
| Three doses | | | | | | |
| Primary incidence | 7 | 1 | 0 | 0 | 0 | 0 |
| Secondary incidence | 5542 | 5248 | 5389 | 4848 | 4190 | 3909 |
| Booster at 12–23 mos. | | | | | | |
| Primary incidence | 9 | 2 | 0 | 0 | 0 | 0 |
| Secondary incidence | 5492 | 5338 | 5440 | 4858 | 4133 | 3847 |
| Booster at 4–5 yr | | | | | | |
| Primary incidence | 8 | 2 | 0 | 0 | 0 | 0 |
| Secondary incidence | 4316 | 5123 | 5552 | 4893 | 4115 | 3808 |
| Both boosters | | | | | | |
| Primary incidence | 1 | 2 | 0 | 0 | 0 | 0 |
| Secondary incidence | 4412 | 5193 | 5568 | 4897 | 4073 | 3766 |

in the model increases during the 1980s. We started by assuming 40% of vaccine coverage for the years 1981–1982 and increased this value by 10% every 2 years until 90% coverage is achieved in the 1990s (the same process is assumed for the subsequent doses). This pattern is consistent with RJ's reported vaccine coverage for DPT vaccine [10].

Figure 3 compares the absolute number of primary and secondary infections in the presence or absence of vaccination. We can see that vaccination clearly decreases the number of primary infections, which are the most symptomatic. For secondary infections, on the other hand, we initially observed a decrease but, by the end of the 1980s, an increase in the number of secondary infections is predicted. This is coherent since immunity acquired through infection lasts longer than immunity acquired through vaccination, i.e. with the introduction of vaccination, individuals, on average, lose their immunity faster than in the pre-vaccine era and, therefore, with time, more individuals will become susceptible to a secondary infection. The increase in the number of secondary infections can also be understood as the vaccination increasing the average age of infection, which is consistent with the results of other studies [14]. In addition, the introduction of mass vaccination decreases the chance of natural boosters making individuals even more susceptible than in the pre-vaccine era. Two other interesting observations can be made from Figure 3. First, that the major modifications in disease

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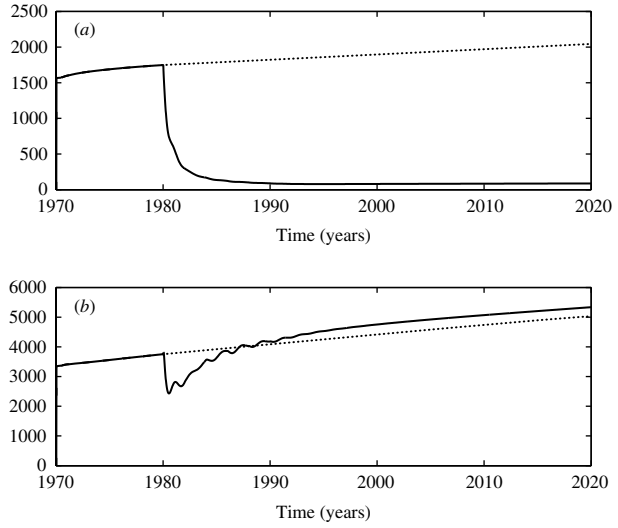


**Fig. 3.** Comparison of the absolute number of (*a*) primary and (*b*) secondary infections in the presence (—) or absence (·····) of vaccination (three doses of DPT vaccine at age 2–11 months).

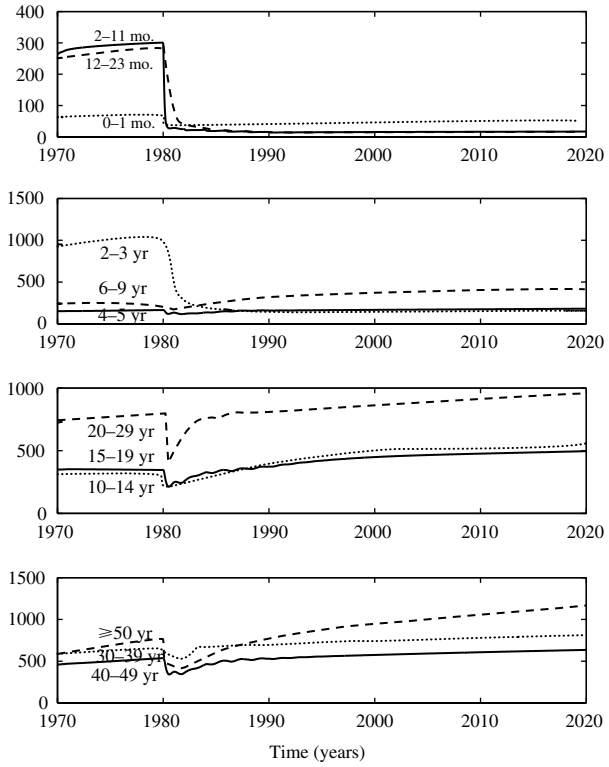


**Fig. 4.** Total number of new infections (primary and secondary) per week per age group when incorporating three doses of DPT vaccine at age 2–11 months.

incidence determined by vaccination occur within 10 years of vaccine implementation, and second, that vaccination determines a period of disease oscillations that extends until approximately 2000, when a new equilibrium is reached, a pattern also observed by other authors [12].

Figure 4 shows the absolute number of infections (primary plus secondary) per age group. We can see from Figure 4 that children <4 years old are the ones that benefit most from vaccination. We observed a remarkable decrease in the number of infections occurring in the age group being vaccinated (2–11 months) and in the two age groups that follow it (12–23 months and 2–3 years). In addition, we also noticed a significant decrease in the number of infections occurring in the 0–1 month age group, an indirect effect of the vaccine since this age group is not being vaccinated. Figure 4 also shows the disturbance caused by the introduction of vaccination. As noticed previously (Fig. 3), with the introduction of vaccination, the number of secondary infections increases. We can see from Figure 4 that this increase is almost restricted to four age groups: older children/adolescents (10–14 and 15–19 years age groups), young adults (20–29 years age group) and old adults (>50 years age group). In adults older than 30 years, vaccination determines a period of disease turbulence (occurring from 1980 until 1995, approximately), after which the same pre-vaccine equilibrium is reached.

Table 2 shows the impact of vaccination on the annual incidence for year 2020 by type of infection and age group. We noticed that, overall, vaccination decreases the incidence of primary infections, especially in the age group receiving vaccination and the age groups that immediately follow it. The decrease in incidence of primary infections is clearly evident for children <10 years old. When considering all age groups together, the three doses of DPT vaccine determine a 95·7% decrease in the total number of primary infections in year 2020. On the other hand, vaccination increases the incidence of secondary infections. Almost all age groups, including the age group receiving vaccination, experience an increase in the incidence of secondary infections. The total number of secondary infections (regardless of the age group) increases by 7·4% by 2020, when the three doses are introduced. However, although the incidence of secondary infections increases, we interpret the disturbance caused by vaccination as being extremely beneficial since secondary infections are usually only mildly symptomatic. Again, we understood this new pattern as vaccination increasing the average age of infection, determining the occurrence

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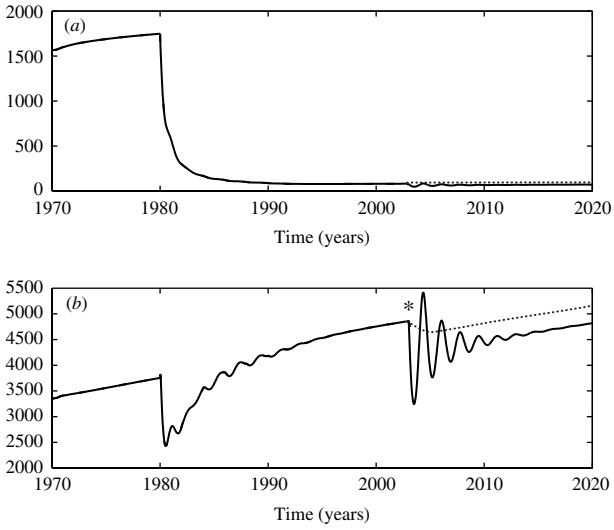


**Fig. 5.** Comparison of the absolute number of (*a*) primary and (*b*) secondary infections per week when incorporating a booster dose at 12–23 months (·····) or 4–5 years (—). Boosting starts in 2002 (indicated by an '*'), we assume 60 % vaccination coverage for the booster dose.

of infections in older individuals whose immune system is more mature and has already been challenged with a less virulent pathogen (the vaccine) with the consequence of a mild disease.

### Introducing booster doses

In the year 2002, we simulated the introduction of the booster dose. Figure 5 shows the impact of the introduction of a booster dose at age 12–23 months or 4–5 years on the total number of primary and secondary infections. The impact of either strategy on the number of primary infections is the same as the one achieved with the three doses at age 2–11 months. The per cent decrease in the number of primary infections in 2020 in comparison to the pre-vaccine era is 95·8 % for the booster at 12–23 months and 96·2 % for the booster at 4–5 years. For secondary infections, the booster at 12–23 months disturbs the dynamics and with time an increase of 3·3 % in the number of secondary infections is predicted when compared to the pre-vaccine era. The booster dose administered at 4–5 years determines a period of significant oscillations and a slight decrease in the number of infections (3·0 % decrease when compared to the pre-vaccine era). These dynamics can also be observed in Table 2 by age group. The immediate impact of the booster dose on the age group to which the vaccine is being applied is obvious: when the booster dose is given to children aged 12–23 months, this exact age group is the one with greatest decrease in incidence (see Table 2). Finally, the simulation incorporating both boosters determined an even greater decrease in the number of secondary infections (4·9 % when compared to the pre-vaccine era). The per cent decrease in the number of primary infections in relation to the pre-vaccine was the same as the one achieved with either booster (96·2 %).

### Uncertainty and sensitivity analysis

For this work, we understood uncertainty and sensitivity analysis as the study of how the uncertainty in the model input parameters affects the uncertainty in the output of the model. For that, we used the approaches proposed by Saltelli et al. [21] and SIMLAB 2.2 software [22]. More specifically, we chose methods with two important properties: (i) multidimensional averaging, that is, a global sensitivity method that is capable of evaluating the effect of a factor while all others are also varying, (ii) model independence, that is, a method that works regardless of the linear or additive properties of a model [21]. In performing an uncertainty/sensitivity analysis, it is important to specify what our goal is. Accordingly, in this study, we aimed at analysing which of the input factors (among the many existing in the model) are really important in determining the number of primary and secondary infections, and at estimating an interval of variation for these output variables. The question of which input factors are most influential is relevant since it might guide us to a simpler version of the model. In addition, it may guide empirical studies as to which are the most interesting parameters to be estimated in field studies, that may further guide the modelling practices [21].

Screening designs are very interesting in determining what subset of input factors are responsible for the majority of the variability in the output, and which input factors could be fixed at any given value over their range without significantly reducing the output variance [21]. The screening design used in this study is the method proposed by Morris [23] and described in detail in Saltelli et al. [21] because it requires a small number of model evaluations. However, a drawback of the method is that is provides a qualitative sensitive analysis, in that, it ranks the input factors in order of importance but does not quantify how much one factor is more important than another. With the results obtained with the

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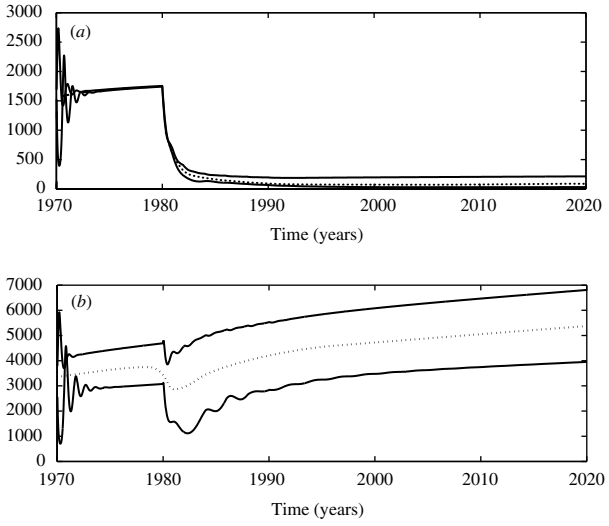


**Fig. 6.** Two time series (with highest and lowest value at equilibrium) estimated for the absolute number of (*a*) primary and (*b*) secondary infections per week obtained when varying the input parameters within the ranges shown in Table 1 (solid line). Dotted line indicates time series already shown above when the three doses are incorporated and the parameters assume their fixed value.

method of Morris, we were able to rank input factors according to their overall influence on the output. For the number of primary infections in the equilibrium (year 2020), the three most important factors in decreasing order were (i) duration of the infectious period of secondary infections, (ii) number of contacts made by the 0–1 month age group and (iii) infectiousness of secondary infections. These factors were shown to be associated with the number of primary infections in a nonlinear manner. The efficacy of the vaccine is also an important factor in determining the number of primary infections, although in a more linear manner (overall effect). For the number of secondary infections in the equilibrium (year 2020), four factors were identified as most affecting the output. The duration of infection-acquired immunity and the duration of vaccine-acquired immunity had high overall effect. The duration of the infectious period of secondary infections and the infectiousness of secondary infections are related to the output in a nonlinear manner.

Subsequently, we performed a Latin Hypercube Sampling, which is a sampling procedure that achieves better coverage of the sample space of the input factors. Using this procedure, we sampled 500 values for each parameter from the plausible range assigned to each input parameter (as presented in Table 1). The values were mixed at random to produce 500 sets of input values which were used to feed the simulations. The aim at this point was to generate 500 time series for the number of primary and secondary infections (per week) so that we could have an idea of how these time series vary as a function of the varying input parameters. Figure 6 shows three time series for the number of primary and secondary infections: the solid lines are two time series as estimated by the procedure described here (time series with highest and smallest values for the equilibrium). The dotted line is the time series (already shown above), with the three doses incorporated and the input parameters assumed at their fixed values.

Table 3. *Summary descriptive statistics as estimated by the FAST method for the distributions of number of primary and secondary infections in 2020*

| | Primary infections | Secondary infections |
|---|---|---|
| Mean | 4880·87 | 283 409·16 |
| Standard deviation | 1831·97 | 31 032·59 |
| Minimum | 1582·35 | 198 003·51 |
| Median | 4618·82 | 282 962·46 |
| Maximum | 14 044·76 | 365 611·38 |

Finally, a last sensitivity analysis (Fourier amplitude sensitivity test; FAST) was performed that allows the estimation of some descriptive statistics shown in Table 3 [21]. These results are similar to the ones estimated by the model when using the fixed values shown in Table 1: 4529·03 primary infections and 278 138·06 secondary infections in 2020. In addition, this method provides us with an estimate of 'first-order effects', which are good model-free sensitivity measures that give the expected reduction in the variance of the output that would be obtained if one could fix an input factor. For primary infections, the input factors: (*a*) duration of the infectious period of secondary infections, (*b*) number of contacts made by the 0–1 month age group and (*c*) infectiousness of secondary infections are the ones that, if fixed, would determine the greatest reduction in the output variance (54·0, 28·2 and 19·7% reduction in the variance if fixed, respectively). The results achieved are in accordance with the results for other sensitivity measures (as shown in previous sections). For secondary infections, the results achieved for the 'first-order effects' indicated the input factors: (*a*) duration of infection-acquired immunity, (*b*) duration of the infectious period of secondary infections and

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(*c*) duration of vaccine-acquired immunity would determine a reduction of 41·7, 11·9 and 9·9% in the variance of the output, if fixed to a value.

### Analysing the impact of the vaccination coverage and contact matrix assumed

Although we do not have reliable information regarding vaccination coverage in RJ, we believe that, currently, it oscillates around 80% for the three doses of the DPT vaccine. In the simulations, we assumed that vaccination coverage increased slowly in the 1980s, reaching ~85% in the 1990s. To analyse the impact of this assumption, we simulated the model assuming much lower vaccination coverage. By decreasing the proportion being vaccinated by 25% of its value, the highest proportion of vaccination coverage achieved for three doses of DPT vaccine is ~63%. The impact of this assumption is an increase of 31·3% in the number of primary infections for the year 2020, and a 0·8% increase in the number of secondary infections for the year 2020.

Another strong assumption we made concerns to the social structuring of the population. In this model, we stratified the rate of interaction between individuals as a function of their age (see Appendix for details). To analyse the impact of this assumption we assumed homogeneous mixing and simulated the model. The results indicate an important impact of this assumption on the number of primary infections: an increase of 129·8% for the year 2020 is estimated. On the other hand, the number of secondary infections only increases by 7·9%, meaning that this assumption has a much greater impact on the social structuring/network of the young children who present primary infections.

In summary, these results indicate that the most important input factors to be estimated in field studies to reduce uncertainty of the estimation of the number of primary/secondary infections would be the duration of the infection/vaccine-acquired immunities and the duration of the infectious period. In addition, although not assumed in the model, it would be even more interesting to be able to estimate these input factors as well as their correlated structure. By that we mean that, for example, it sounds coherent that the duration of the immunity will be correlated with, upon infection, the duration of the infectious period which, in turn, will be correlated with the infectiousness of the individual. Therefore, the estimation of these factors in field studies should be done in an integrated manner. With regards to the social contacts, the precision of the social networks of infants would yield greater impact to the understanding of disease dynamics, especially of the primary infections which are usually more symptomatic.

## DISCUSSION

The aim of this study was to create a mathematical model for the analysis of pertussis dynamics in a large urban centre such as RJ. The model developed was capable of incorporating the demographic structure of RJ, as well as sufficient information regarding pertussis epidemiology. The fixed values used for model parameterization are consistent with other published studies of pertussis dynamics in developed countries [12–15]. As with any mathematical model of disease dynamics, there exist limitations [24]. First, models are a simple representation of the real dynamics and, therefore, suffer from the assumptions made by their developers [24]. Although many other aspects could be important to disease dynamics, such as individual natural resistance to disease, more complicated social network or spatial patterns, we believe enough information was incorporated for the simulation of the time series of the disease in our community.

### Comparing the results with notification data

The results achieved by simulating the model without vaccination are coherent with the pre-vaccine era, when the vast majority of infections occurred in children <6 years old [25]. The introduction of vaccination determined a major decrease in the number of primary infections in children. In addition, it determined a decrease in the circulation of the disease since age groups not vaccinated, such as infants <2 months old, also experienced a decrease in incidence. However, given that the immunity against pertussis wanes with time and that the infectious agent has not been eliminated from the population, it is expected that pertussis will continue to be a problem. Actually, since immunity acquired from vaccine wanes faster than disease-acquired immunity [6], an increase in incidence among older age groups is expected (and predicted by the model).

The comparison of the number of cases reported in RJ and the number of infections expected as estimated by the model is a difficult task. If we take

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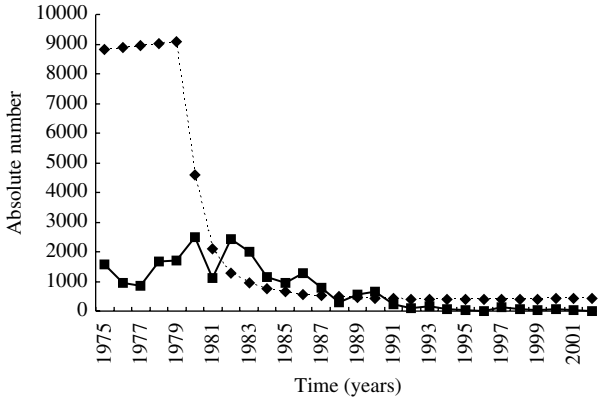


**Fig. 7.** –■–, Reported cases in RJ from 1975 to 2002 [10]. ···◆···, 10% of the primary infections estimated by the model per year from 1975 to 2002 when incorporating three doses of the vaccine at age 2–11 months.

the crude model estimates and compare them to surveillance data, we might conclude that either the model greatly exaggerates the number of infections or that surveillance system is very poorly effective. The latter is partially true since it is estimated that only 1–2% of the actual infections are reported [11]. Many reasons contribute to the underreporting of pertussis, such as: (i) absence of a universally accepted case definition, (ii) laboratory procedures for bacteria identification are not very sensitive or specific, and (iii) clinical symptoms resemble other respiratory diseases. Therefore, in order to compare the model results to surveillance system data, some authors have made three assumptions regarding the reported cases, these are: (*a*) reported cases correspond to primary infections only; (*b*) approximately 10% of the infections are actually reported; and (*c*) only infections occurring in children aged <10 years are reported [12]. Hethcote argues that these assumptions are reasonable and coherent with seroepidemiological studies [12]. If we make the same assumptions, the results predicted by the model are not so different from the surveillance system data.

Figure 7 shows both the number of reported cases in RJ from 1975 to 2002 and 10% of the primary infections occurring in children aged <10 years estimated annually by the model. Mandatory notification of pertussis cases was initiated in the 1980s which explains the discrepancy observed for the years before 1980. The beginning of the 1980s is marked by a major decrease in the number of reported cases. For the 1990s, we see that the time series are similar (see Fig. 7), although the number of reported cases is always smaller than the 10% estimate for primary infections. From this data, we conclude that the surveillance system does capture a fraction of pertussis dynamics in our community: a percentage of the symptomatic infections in children <10 years of age. However, as previously mentioned, there might exist other dynamics that are not being captured by the surveillance system; these are the mildly or asymptomatic infections occurring in all age groups. The need to be aware of these other dynamics is urgent. The reason is that given the 'immobility' of infants <6 months old, who have not been properly immunized, these asymptomatic individuals are responsible for the spread of the disease to this otherwise unreachable population, in whom the disease is a great burden.

### Comparing the different vaccination strategies

As our baseline vaccination scenario, we simulated the model incorporating three doses of DPT vaccine at age 2–11 months, assuming reasonably high vaccination coverage. Although two additional booster doses are available for children in RJ, we either found no reliable data for the vaccine coverage of booster doses or the data found indicated a very low coverage (<30%, data not shown). As a result, we opted for the simulation of these booster doses assuming reasonable 60% coverage in order to estimate the relative efficacy of these strategies. Overall, all strategies determine a major decrease in the number of primary infections (over 95% decrease when compared to the pre-vaccine era). This result is consistent with published studies for developed countries [6, 9, 26]. For secondary infections, however, the three-dose strategy determines an increase of 7·4% in the number of infections. The booster dose at age 1 year also determines a slight increase in the number of secondary infections when compared to the pre-vaccine era (3·3%). The number of secondary infections only decreases if the booster dose is given at age 4–5 years, when the decrease is of 3·0%. Finally, both boosters cause an even greater impact, a decrease of 4·9% in the number of secondary infections. However, we assumed in the model a proportion of vaccine coverage for booster dose currently not achieved. Therefore, we believe that, if the elimination of one booster dose could guarantee an increase in coverage, then the one-booster strategy would be more effective, in which case, we would suggest the maintenance of the booster dose at 4–5 years of age.

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## Final remarks

In conclusion, it is biologically plausible that pertussis might be re-emerging given (i) mass vaccination of children and (ii) wane of immunity. Mass vaccination of children, which has been practised for ~30 years in RJ, decreases the circulation of the bacteria and, therefore, reduces the occurrence of natural boosters. Thus, as individuals age, they become even more susceptible than in the pre-vaccine era. In addition, it is believed that immunity conferred by vaccination lasts less than infection-acquired immunity again determining a faster loss of immunity when compared to the pre-vaccine era. In this work, we have also shown that it is mathematically plausible that the incidence of pertussis might be higher than the reported incidence.

Why, therefore, are there no reported cases of pertussis among older children, adolescents and adults in RJ? We believe the reasons are two-fold. First, a significant fraction of health professionals lack knowledge of the waning immunity of pertussis (be it vaccine or infection induced), and, therefore, when in the presence of a mildly symptomatic patient, pertussis is rarely a disease that is considered in the differential diagnosis disease spectrum. Second, childhood mass vaccination began ~25 years ago. In the model, the introduction of vaccination determines a period of disturbance, when the number of cases oscillates and slowly increases to a new equilibrium in older age groups (children aged >6 years). Therefore, we might still be experiencing the transition period, after which the incidence will further increase and become evident to health professionals. Most of the developed countries that experience the re-emergence of the disease only became aware of its occurrence 30–40 years after the introduction of vaccination, i.e. in the 1990s.

The public health implications of the results for our community are many. Since it is plausible that pertussis is already re-emerging in RJ, the information regarding the possible occurrence of pertussis in older children, adolescents and adults that have or have not been vaccinated has to be promptly disseminated among health professionals. In addition, we suggest conducting field studies for the active diagnosis of pertussis in adolescents and adults. Such studies have been done in developed countries, which have determined the identification of pertussis infection in these age groups. It is not only for older age groups that a more active surveillance system is presently needed to allow a more accurate understanding of the current pertussis situation in all age groups (i.e. better diagnostic methods and notification). We have also become aware with this study that there are some factors which greatly determine the number of infections occurring in the population. We suggest that field studies are conducted to estimate the duration of the infection/vaccine-acquired immunity and the duration of the infectious period of differently symptomatic infections. A better knowledge of these factors would allow for a more precise estimation of disease dynamics.

Regarding the social contact of the population, we also suggest a better understanding of this variable by estimating this factor in field studies. The need to understand the social structure of the very young is urgent if the prevention of pertussis infection in this age group is to be achieved. Finally, regarding the vaccination schedule, we also need to better understand the vaccine coverage in RJ. The data we found indicated very low vaccine coverage for booster doses. Moreover, since studies have shown that progressive child immunization is not random, i.e. children that have been properly vaccinated are probably the ones receiving the booster doses, which means that we are capturing the same child in the first and second booster while many are left out. Since the gains achieved with two boosters are only slightly better than that achieved with one booster, we suggest concentrating efforts to achieve high coverage with one booster dose (in which case we advocate the 4–5 years booster). We bring attention to the acellular vaccines also, soon enough the need to consider new vaccination schedules will arise. In summary, as noted by van Rie & Hethcote there is no best strategy since the relative effectiveness of each depends upon the local epidemiological dynamics of pertussis, the reachable vaccine coverage, the costs of pertussis cases and hospitalizations (i.e. if preventing few cases in the very young is more cost-effective than preventing a large number of mild cases in adolescents/adults), on current local vaccination schedules and on costs of mass vaccination [14]. We urge a better understanding of pertussis in third-world settings (and of all factors that affect its dynamics), since local actions need to be thought out specifically for the local community.

## APPENDIX

We modelled the force of infection, $\lambda_{k,i}$ ($k=p$, $s$ and $i=1, \ldots, 12$), as a function of five parameters: (1) the

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number of contacts ($n_i$) made by individuals in age group $i$; (2) the proportion of contacts ($C_{ij}$) made by age group $i$ with each age group $j$; (3) the proportion of infected individuals ($P_{I_p}$ and $P_{I_s}$) in each age group; (4) the relative infectivity ($\eta$) of individuals in compartments $I_p$ and $I_s$; (5) the relative susceptibility ($\sigma$) of individuals in compartments $S$, $R_1$, $V_1$. Given a contact between a susceptible individual of age group $i$ and an infectious individual, we assumed that the risk of transmission is constant in each contact for that age group ($p_i$, $i=1, \ldots, 12$), and that it occurs independently for each of the $n_i$ contacts of that age group $i$ (the structure assumed for the force of infection is a generalized form of the Reed–Frost model [27]. Parameterization of the chances of contact between age groups was done based on two field studies [28, 29]. The time step of the model is 1 week. Mathematically, we have:

$$\lambda_{k,i} = \sigma_k [1-(1-p_i)^{n_i}], \tag{1}$$

where

$$p_i = \sum_{j=1}^{12} C_{ij} (P_{I_p j}\eta_p + P_{I_s j}\eta_s) \tag{2}$$

and $k=p, s$.

As for the chance of receiving subsequent vaccine doses, we modelled $p_l$ ($l=V_1, V_2, V_3$) as:

$$p_l = \tau_l \cdot \varepsilon, \tag{3}$$

where $l=V_1, V_2, V_3$; $\tau$ is the proportion of vaccine coverage achieved and $\varepsilon$ is the vaccine efficacy.

The system of difference equations that translates the dynamics presented in Figure 2, for each age group, is given below:

$$\left.\begin{aligned}
S(t+1) &= S(t) - \lambda_p \cdot S(t) - p_{v1} \cdot S(t) \\
I_p(t+1) &= I_p(t) + \lambda_p \cdot S(t) - \gamma_p \cdot I_p(t) \\
R_3(t+1) &= R_3(t) + \gamma_p \cdot I_p(t) + \gamma_s \cdot I_s(t) - \alpha \cdot R_3(t) \\
R_2(t+1) &= R_2(t) + \alpha \cdot R_3(t) - \alpha \cdot R_2(t) \\
R_1(t+1) &= R_1(t) + \alpha \cdot R_2(t) - \lambda_s \cdot R_1(t) \\
I_s(t+1) &= I_s(t) + \lambda_s \cdot R_1(t) + \lambda_s \cdot V_1(t) - \gamma_s \cdot I_s(t) \\
V_1(t+1) &= V_1(t) + p_{v1} \cdot S(t) + \rho \cdot V_2(t) \\
&\quad - \lambda_s \cdot V_1(t) - p_{v2} \cdot V_1(t) \\
V_2(t+1) &= V_2(t) + p_{v2} \cdot V_1(t) + \rho \cdot V_3(t) \\
&\quad - p_{v3} \cdot V_2(t) - \rho \cdot V_2(t) \\
V_3(t+1) &= V_3(t) + p_{v3} \cdot V_2(t) - \rho \cdot V_3(t).
\end{aligned}\right\} \tag{4}$$

## ACKNOWLEDGEMENTS

The authors are very grateful to Professors Eduardo Massad, Jose Ueleres Braga and Herbert Hethcote for their thoughtful insights on the modelling process. Also, thanks are due to Dr Paulo Feijo and Dr José Cerbino for their important help regarding pertussis incidence/burden in Brazil. This work was funded by the Brazilian Research Council (479566/2003-8) and the Rio de Janeiro Research Funding Agency (FAPERJ).

## DECLARATION OF INTEREST

None.

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