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Pertussis booster vaccine for adolescents and young adults in São Paulo, Brazil

Avaliação de reforços vacinais contra a coqueluche para adolescentes e adultos na cidade de São Paulo

ABSTRACT

OBJECTIVE: To develop a model to assess different strategies of pertussis booster vaccination in the city of São Paulo.

METHODS: A dynamic stationary age-dependent compartmental model with waning immunity was developed. The "Who Acquires Infection from Whom" matrix was used to modeling age-dependent transmission rates. There were tested different strategies including vaccine boosters to the current vaccination schedule and three of them were reported: (i) 35% coverage at age 12, or (ii) 70% coverage at age 12, and (iii) 35% coverage at age 12 and 70% coverage at age 20 at the same time.

RESULTS: The strategy (i) achieved a 59% reduction of pertussis occurrence and a 53% reduction in infants while strategy (ii) produced 76% and 63% reduction and strategy (iii) 62% and 54%, respectively.

CONCLUSION: Pertussis booster vaccination at age 12 proved to be the best strategy among those tested in this study as it achieves the highest overall reduction and the greatest impact among infants who are more susceptible to pertussis complications.

DESCRIPTORS: Pertussis Vaccine, administration & dosage. Whooping Cough, prevention & control. Immunization Coverage. Mathematical Models.

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RESUMO

OBJETIVO: Desenvolver um modelo capaz de acessar resultados de diferentes possíveis estratégias de reforço vacinal contra a coqueluche, na cidade de São Paulo.

MÉTODOS: O modelo matemático dinâmico proposto é dependente da idade e considerou perda da imunidade vacinal com o avanço da idade. A matriz *"who acquire infection from whom"* foi utilizada para inserir as diferentes dinâmicas de contatos entre os grupos etários. Diferentes estratégias vacinais foram testadas, acrescentando reforços vacinais ao atual esquema utilizado, e três diferentes estratégias foram reportadas: (i) 35% ou (ii) 70% de cobertura vacinal na idade de 12 anos e (iii) coberturas vacinais de 35% aos 12 anos e 70% aos 20 anos ao mesmo tempo.

RESULTADOS: A estratégia (i) produziu redução de 59% nos casos de coqueluche e 53% de redução entre os menores de um ano; a estratégia (ii) alcançou redução de 76% nos casos e de 63% entre os menores de um ano; a estratégia (iii) reduziu em 62% o total de casos e 54% entre os menores de um ano.

DISCUSSÃO: Reforço vacinal contra a coqueluche aos 12 anos é a melhor estratégia dentre as testadas, pois gera maior redução de casos em todas as idades e alcança maior impacto entre os menores de um ano, os mais vulneráveis às complicações da coqueluche.

DESCRITORES: Vacina contra Coqueluche, administração & dosagem. Coqueluche, prevenção & controle. Cobertura Vacinal. Modelos Matemáticos.

INTRODUCTION

Whooping cough in infants can be clinically severe and progress to complications or sequelae including death. Immunization is complete after booster vaccination at the age of two and progressively wanes out by the age of six to 12. Pertussis reservoirs are infected people or asymptomatic carriers, either children or adults. Thus, disease may go undiagnosed. While whooping cough is often clinically exuberant in children, it can present as a chronic cough in adults.[24] Postels-Multani et al[19] reported 30.7% of undiagnosed pertussis infection in adults, of which 8% presented with typical whooping cough.

The Pan American Health Organization (PAHO) estimates that every year 20 to 40 millions people are affected globally.[18] Of these, 200 to 400 thousands die of pertussis, 90% in developing countries. These deaths are not evenly distributed by age and the great impact on infants has been long acknowledged. According Hill (1933),[13] "...improvement in the death-rates over the last seventy years, though very considerable at all ages under five, was least in infancy and most at ages over two years". Pertussis is primarily controlled through vaccination. Mass immunization began in the 1950s when the diphtheria-tetanus-pertussis (DTP) vaccine was implemented in different countries leading to a reduction greater than 90% in disease incidence and mortality.[24] A regular pertussis vaccination program was introduced in Brazil in the 1970s. The vaccine schedule consists of three doses for infants and boosters at 15 to 18 months and five to six years of age. There has been reported coverage greater than 90% for infants and booster vaccine coverage estimated at 82% and 89% for 15-18 month-olds and 5-6 year-olds, respectively, in the last decades in Brazil.[a]

Although effective for disease prevention, pertussis vaccination does not prevent bacteria circulation even when coverage is high.[24] In the last ten to 20 years, despite adequate vaccination coverage, many countries reported disease outbreaks with increasing incidence among adolescents and adults,[11,17,24] which in turn increases the risk of infection in infants.[11,23,24]

The possible causes of this reemergence are: progressive loss of immunity as vaccinated children grow older; improved medical diagnosis; reduction of vaccination effect; potential genetic changes in *Bordetella pertussis*, improved epidemiological surveillance, and availability of more accurate diagnostic tests.[4] In fact, recent studies

[a] Shimizu SMM, Espindola LCF. Adolescent hepatites B vaccine coverage at São Paulo City:2001 to 2005 [essay]. São Paulo: Faculdade de Saúde Pública da Universidade de São Paulo; 2006.

on genetic changes conducted in Japan, Canada, US and several European countries have suggested that though these changes are detected they cannot explain the increase in whooping cough rates.[4,10,11]

The annual incidence rate of whooping cough in Brazil was 30 x 10^{-5} in 1980. Since the introduction of regular children vaccination, this rate steeply declined to 1 x 10^{-5} and less than 2,000 cases are reported each year since 1996.[b] In the state of São Paulo, southeastern Brazil, the annual incidence rate by age from 2000 to 2007 showed that infants are the most affected.[c] The incidence rate in 2002 was 7.43 x 10^{-5} and an increasing number of cases are reported every year, reaching 16.6 x 10^{-5} in 2005 when an outbreak was detected. Children aged one to four years are the second most affected group with rates ranging from 0.2 to 0.3 x 10^{-5} in recent years. The rates in other age groups mainly reported in 2001, 2005 and 2007 were not as high. This is in agreement with a known cyclic behavior of pertussis disease which could produce peaks every three to four years even when there is high vaccine coverage.[7]

Current surveillance data in Brazil do not show a significant rise in pertussis incidence rates. However, these data are not reliable since several clinical forms of pertussis are not easily diagnosed, and because pertussis incidence is passively reported in Brazil. Luz et al[17] modeling of pertussis epidemic in Rio de Janeiro, southeastern Brazil, showed a 31% increase in pertussis cases by the year 2020 assuming that the current pertussis vaccination schedule in Brazil remains unchanged.

This study aimed to develop a model to assess different strategies of pertussis booster vaccination.

METHODS

A model was proposed and constructed based on the classical susceptible-infected-removed (SIR) disease model.[1] This is a dynamic stationary age-dependent compartmental model with waning immunity after disease or vaccine designed to assess whooping cough dynamics across age groups in different scenarios of pertussis booster vaccination at ages 12 and 20 in the city of São Paulo. Disease behavior was assumed steady over time, i.e., frequency distribution of subsets within compartments do not change over time. The model (Figure 1), described by a system of differential equations, was designed with five compartments, each one with subsets of the age groups studied. The assumption of steady epidemiological profile was not preposterous since a narrow time period was considered and a few decades would be required to assess changes over time.

The following differential equations describe the dynamics suggested in Figure 1:

$$(1)\frac{dSp}{da} = -\lambda(a) * Sp - pv1(a) * Sp - \mu(a) * Sp$$

$$(2)\frac{dI}{da} = \lambda(a) * Sp + \lambda(a) * Ss - \gamma(a) * I - \mu(a) * I - \mu d(a) * I$$

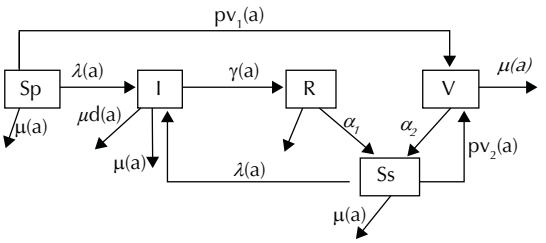
$$(3)\frac{dR}{da} = \gamma(a) * I - \alpha 1 * R - \mu(a) * R$$

$$(4)\frac{dV}{da} = pv1(a) * Sp + pv2(a) * Ss - \alpha 2 * V - \mu(a) * V$$

$$(5)\frac{dSs}{da} = -\lambda(a) * Ss + \alpha 1 * R + \alpha 2 * V - pv2(a) * Ss - \mu(a) * Ss$$

where $(6)\lambda(a) = \lambda_i = \sum_j \beta_{ij} * I_j$ was the transmission rate (λ_i) for a given age group a = *i* from all *j* age groups according to *j*'s contact rate (β_{ij}) and *j*'s infected compartment (*I*). Seven different values (a = 1, 2, …7) of age groups were used according to the categories as defined in the Brazilian health database (DATASUS) (<1 year; 1 to 4; 5 to 9; 10 to 14; 15 to 19; 20 to 39; 40 or more). This is a realistic approach that can provide information where age is a discrete variable, though higher accuracy was sought through calculation of monthly rates.

The compartments were: primary susceptible (Sp) (individuals with no previous exposure to either pertussis bacteria or vaccine, given the mean live birth rate in the city of São Paulo in the last five years); infected (I) (individuals infected with *Bordetella pertussis* who became ill and infective; the estimated whooping cough incidence rates, adjusted to ages groups, in the city of São Paulo); vaccinated (V) (vaccinated individuals



Sp: primary susceptible; Ss: secondary susceptible; I: infected; R: recovered from disease and immune; V: immune after vaccine; λ(a): age-dependent transmission rate; γ(a): age-dependent recovery rate; α_1 and α_2: rates of waning immunity; pv_1(a) and pv_2(a): age-dependent immunization rates; μ(a): age-dependent mortality rate; μd(a): age-dependent pertussis mortality rate.

Figure 1. Whooping cough age-dependent compartmental model.

[b] Ministério da Saúde. DATASUS. Série histórica de casos de óbitos de doenças de notificação compulsória – Brasil. 1980 a 2005 [cited 2007 Jan 2]. Available from: http://portal.saude.gov.br/portal/arquivos/pdf/planilhas_dnc_casos_e_obitos_todas_2006.pdf

[c] Secretaria de Estado da Saúde de São Paulo, Centro de Vigilância Epidemiológica "Prof. Alexandre Vranjac". Coqueluche: distribuição de casos confirmados, óbitos, coeficiente de incidência e letalidade, segundo ano de início de sintomas e faixa etária, Estado de São Paulo, 2000 a 2011 [cited 2008 Apr 20]. Available from: http://www.cve.saude.sp.gov.br/htm/resp/coque_tab.htm

within an estimated eight-year window of protection); recovered (R) (individuals who recovered from disease within an estimated 12–year window of protection); secondary susceptible (Ss) (individuals who became susceptible after being immune by either disease or vaccine).

Transmission rate or force of infection, **(**λ (a)) defined for each age group, ascertained the speed at which cases of disease were brought into this group from all age groups included in the susceptible compartments (Sp & Ss) according to effective contact rates (β_{ij}) and number of infected people (I_j).

(λ (a)): <1 year = 33.5 x 10^{-5}; one to four years = 0.94 x 10^{-5}; five to nine years = 2.43 x 10^{-5}; ten to 14 years = 2.62 x 10^{-5}; 15 to 19 years = 3.77 x 10^{-5}; 20 to 39 years = 0.59 x 10^{-5}; and >40 years = 0.32 x 10^{-5}.

It was thus designed to take into consideration differences by age but not the nature of susceptibility (primary or secondary). One could wonder whether incidence rates in primary susceptible could be greater than in secondary susceptible individuals. Nevertheless, given the high coverage of DTP vaccine in children in São Paulo, primary susceptible individuals were mainly restricted to infants who have not achieved proper age for vaccination, and secondary susceptible ones were older individuals with incidence rate differences adjusted for age.

As there was no appropriate data on incidence rate available in São Paulo, the estimates for the infected compartment according to age group **(**I_j) was based on data from the city of Ribeirão Preto, southeastern Brazil. Ribeirão Preto is a large city in the state of São Paulo with similar patterns of social exposures, and had an active epidemiological surveillance system for whooping cough. Cases were those with clinically suspected pertussis, confirmed through oropharyngeal swab culture or by evidence of exposure to previously confirmed case.

Crude incidence rates were calculated at a monthly basis and standardized by the reference age group of less than one year in 2005. Data for the last available six years were processed and mean ages were estimated as the initial transmission rate, or force of infection (λ (a)) using Berkeley Madonna® software. A numerical solution taking into account the age groups of São Paulo population ascertained the number of infected individuals by age group **(**I_j) .

The contact rate (β_{ij}) estimated the probability that an individual gets infected through this exposure. Anderson & May[2] Who Acquires Infection from Whom (WAIFW) matrix was used to assess the impact of exposure on each age group (Figure 2**)**. Suggestions for effective exposure rates (β_{ij}) were taken from a study conducted by Baptista et al.[3] This study assessed vaccine efficacy and sources of infection in infants providing patterns of exposure across age groups.

Determinant calculus was used to estimate contact rate β_{ij} by means of equation 6. Both vectors (λ)and I_j had seven components related to seven age groups. I_j was calculated by the equation 2 using the force of infection $\lambda_i = (\lambda\,(a))$ and assuming no new vaccine introduction.

The recovery rate $\left(\gamma(a): \dfrac{1}{\text{mean infective lasting time}}\right)$ assessed the rate of moving from the Infected (I) to the Immune compartment after disease (R) regardless of clinical status (active and inactive disease). It was calculated as the inverse of the mean time an individual is supposedly infective after being infected. The reference values were taken from Edwards & Decker.[7] Simulations showed that few children reached the age of 10 without being exposed to either vaccine or disease, and that few cases of disease among these came from the secondary susceptible compartment. The recovery rate was assessed on a monthly basis (<10 years = 1.71 and ≥10 years = 3.53).

The rate at which immunity wanes $\left(\alpha_1 \,\&\, \alpha_2 : \dfrac{1}{\text{mean immunity lasting time}}\right)$ ascertained speed of migration from the compartments of immune individuals (R and V) to that of secondary susceptible (Ss) on a monthly basis [after disease (α_1) = 1/144 months (12 years) = 0.0069 and after vaccine (α_2) = 1/96 months (8 years) = 0.0104]. The assumption of the ages eight and 12 was based on a recent literature

$$\begin{pmatrix} \beta1 & \beta2 & \beta2 & \beta2 & \beta5 & \beta6 & \beta7 \\ \beta2 & \beta2 & \beta2 & \beta2 & \beta2 & \beta6 & \beta7 \\ \beta2 & \beta2 & \beta3 & \beta3 & \beta5 & \beta6 & \beta7 \\ \beta2 & \beta2 & \beta3 & \beta4 & \beta5 & \beta6 & \beta7 \\ \beta5 & \beta2 & \beta5 & \beta5 & \beta5 & \beta6 & \beta7 \\ \beta6 & \beta2 & \beta6 & \beta6 & \beta6 & \beta6 & \beta7 \\ \beta7 & \beta2 & \beta7 & \beta7 & \beta7 & \beta7 & \beta7 \end{pmatrix} = \begin{pmatrix} 8.15*10^{-7} & 1.1*10^{-8} & 1.1*10^{-8} & 1.1*10^{-8} & 4.93*10^{-8} & 6.25*10^{-9} & 2.9*10^{-9} \\ 1.1*10^{-8} & 1.1*10^{-8} & 1.1*10^{-8} & 1.1*10^{-8} & 1.1*10^{-8} & 6.25*10^{-9} & 2.9*10^{-9} \\ 1.1*10^{-8} & 1.1*10^{-8} & 5.73*10^{-8} & 5.73*10^{-8} & 4.93*10^{-8} & 6.25*10^{-9} & 2.9*10^{-9} \\ 1.1*10^{-8} & 1.1*10^{-8} & 5.73*10^{-8} & 8.17*10^{-8} & 4.93*10^{-8} & 6.25*10^{-9} & 2.9*10^{-9} \\ 4.93*10^{-8} & 1.1*10^{-8} & 4.93*10^{-8} & 4.93*10^{-8} & 4.93*10^{-8} & 6.25*10^{-9} & 2.9*10^{-9} \\ 6.25*10^{-9} & 1.1*10^{-8} & 6.25*10^{-9} & 6.25*10^{-9} & 6.25*10^{-9} & 6.25*10^{-9} & 2.9*10^{-9} \\ 2.9*10^{-9} & 1.1*10^{-8} & 2.9*10^{-9} & 2.9*10^{-9} & 2.9*10^{-9} & 2.9*10^{-9} & 2.9*10^{-9} \end{pmatrix}$$

Figure 2. The Who Acquires Infection From Whom (WAIFW) matrix showing the estimated effective contact rates (β_{ij}) across age groups. City of São Paulo, southeastern Brazil.

review study by De Carvalho & Pereira.[4]

The age-dependent mortality rate (μ(a)) assessed the rate at which individuals exited the system due to death regardless of its causes. It was estimated as mean monthly mortality rate in the age groups in São Paulo from 2000 to 2004 (<1 year = 13.3 x 10^{-4}; one to four years = 0.5 x 10^{-4}; five to 14 years = 0.2 x 10^{-4}; 15 to 39 years = 1.7 x 10^{-4}; 40 to 49 years = 3.8 x 10^{-4}; 50 to 59 = 7.9 x 10^{-4}; and >60 years = 26 x 10^{-4}).

The age-dependent pertussis mortality rate (μd(a)) determined disease fatality on a monthly basis. São Paulo health authorities reported[a] a yearly fatality rate of 17.5 × 10^{-3} among infants and no deaths in any other age group. Thus, monthly age-dependent pertussis mortality rate was applied only to infants as μd(infants) = 0.15× 10^{-3}.

The age-dependent immunization rates (pv_1 (a) & pv_2 (a)) assessed the effect of vaccination according to age, vaccine coverage, and efficacy. They reflected how fast individuals from primary susceptible and secondary susceptible compartments moved to the vaccinated compartment. It was assumed an 80% vaccine efficacy.[7,22] The rate pv_1(a) described the transition from compartment Sp (primary susceptible) to V (vaccinated) in the ages two to six months. The rate pv_2(a) described the transition from compartment Ss (secondary susceptible) to V (vaccinated) in the ages 15 to 18 months (first booster) and four to six years (second booster) in the current vaccination schedule. When new booster vaccinations were introduced for adolescents, pv_2(a) described these transitions at these ages.

The pv_1 and pv_2 values were drawn from the numeric calculus obtained from each iteration step during integration of differential equations. It provided the right number of individuals moving from the susceptible to the vaccinated compartment based on vaccine efficacy and coverage for each age group vaccinated. Coverage rates were conservatively set at 35% based on data from the current hepatitis B vaccine coverage in adolescents in the city of São Paulo, and a more vigorous scenario was considered by doubling this figure (70%).

Basic reproduction ratio by age group ($R_{0,i}$) was assessed using the equation provided by Anderson & May.[2] This calculus showed which age group was responsible for disease dissemination.

$R_{0,i} = \frac{1}{\gamma(i)} \int N(i)\beta(i,a)da$, where

$\gamma(i)$ = recovery rate in the ith age group;

$N(i)$ = = population in the ith age group;

$\beta(i,a)$ = is the matrix β_{ij} referred above.

Data was retrieved from public databases (DATASUS, Ministry of Health) and databases at the state level (Epidemiological Surveillance System, São Paulo State Health Department). General data on disease behavior including infection and immunity duration were obtained from the literature.

Different intervention strategies were tested with the use of the Berkeley Madonna® (integration of differential equations) and Microsoft Excel® (impact of new dose vaccine on all age groups) in successive iterations (Appendix 1 and Appendix 2). The scenarios tested were based on the current vaccination schedule in Brazil (National Immunization Program): DTP at two, four, and six months; DTP booster at 15 to 18 months; DTP booster at four to six years of age. Boosters at 12 and/or 20 years were examined according to different coverage rates.

Effective vaccination by age group (vaccine coverage plus vaccine efficacy) was applied to susceptible (Sp, Ss) individuals to provide the number of immunized (V) using the Madonna function "squarepulse," an adapted Dirac delta function. The effects on the age groups were assessed in Excel using the WAIFW matrix (Appendix 1). This second step corrected Madonna output that does not evaluate the effect on age groups younger than those at which booster vaccination is introduced.

A second Appendix was added to describe step 5 in the Appendix 1 concerning adjustment of the infected compartment. It describes the procedures for correcting the number of infected individuals which could be overlooked otherwise. We were not able to estimate the baseline number of infected (expected number in a non-vaccinated population) because the population was being actively vaccinated. The initial β_{ij} matrix was tainted by existing immunization and, correction was needed to avoid overestimating the effect of vaccine introduction (repeat vaccination).

The model was validated by correctly simulating the average of the last six years pertussis incidence rate by age group Ribeirão Preto before running the model with São Paulo data.

Changes in parameters were tested (sensitivity analysis):

Crude incidence rate: tested against the standardized $\lambda(a)$ as previously described;

Recovery rate without controlling for age: calculated as a single $\gamma = 1,71$ tested against stratified recovery rate as previously described;

Age-dependent pertussis mortality rate reduced to μd = 0.10 × 10^{-3} tested against the original μd = 0.15 × 10^{-3}.

The WAIFW matrix was not included in the sensitivity analysis for lack of a valid alternative. The WAIFW matrix used was designed based on assumptions from the literature and a Brazilian study,[3] as formerly

described. If any alternative were to be tested, it should have a more solid ground that the one considered and, thus, rather than taken for sensitivity analysis should replace the initial choice at once.

RESULTS

After testing of different scenarios of vaccine coverage and ages for booster vaccination, the results converged to three solutions summarized trends. Table 1 shows the basic reproduction ratio (R_0) and expected whooping cough reduction by age group.

Young adult vaccine booster did not seem to add a significant impact to adolescent booster even with a high coverage at this age. A single adolescent booster may provide substantial reduction of overall pertussis occurrence and can particularly contribute with disease reduction among infants. The basic reproduction ratio (R_0) suggests that for a non-immunized population individuals aged less than one year and five to nine years would likely spread the disease. Since they are already targeted in the current vaccination schedule, it would be reasonable to consider that disease spread could move forward to the next age group. This is consistent with the finding that booster vaccination at the age of 12 provides the best results.

Based on the previously defined conditions for sensitivity analysis, if crude incidence rates were used, booster vaccination of 12-year-olds would require 90% coverage to achieve a reduction that would mostly be seen among adolescents. Among infants, it would have an impact lower than 10%. A 95% of coverage would be required for a booster vaccination of 12-years-old to achieve a 20% reduction among infants. If a booster vaccination of 20–years-old were added, the impact among infants would be no more than 27% reduction (Table). This suggests that the model was sensitive to changes in incidence rate estimates. The standardization of raw data was an important adjustment procedure that is required when dealing with incomplete or scarce raw data. The model was not sensitive to changes in recovery rate and fatality rate.

DISCUSSION

The proposed model is an efficient tool for evaluating the introduction of booster vaccination when there is little information available. Resorting to the available data and current knowledge, and using procedures of standardization and stratification some nontrivial conclusions were achieved. The intuitive idea that adult vaccination should improve disease control was found to be of little importance while booster vaccination of adolescents can provide important results when there is good coverage. Forsyth[9] pointed out that though high coverage of adult vaccination can reduce adult cases high compliance with this initiative is not expected since public awareness about the disease is low. Apart from its feasibility, adult vaccination is expensive and may not be cost-effective as suggested by Lee et al.[16] They tested different strategies assessing cost per case prevented and cost per quality-adjusted life years saved by means of a Markov model and concluded that adolescent vaccination seemed preferable.

Van Rie & Hethcote[21] and Coudeville et al[5] studies on adolescent booster vaccination suggested that a reduction would be expected in those younger than 20 and those older than 40 but at the expense of an increase among individuals aged 20 to 40, which would recommend a young adult booster vaccination. This contrasts with our results but these authors used much lower infant transmission rates than those studied here. In addition, the age groups were different: transmission rates in those one to 18 were twice as high as that in those less than one year, making it a *tabula rasa* of immunity waning over one to 18 years of age. Van

Table. The basic reproduction ratio (R_0) by age group and expected whooping cough reduction (%) by age group, and standardized or crude incidences rates in the city of São Paulo after the introduction of booster vaccination at given ages and coverage. São Paulo, Southeastern Brazil, 2007.

Age group (years)	R_0	Vaccine coverage	Standardized incidence rate			Crude incidence rate		
			35% in 12–year-olds (%)	70% in 12-year-olds (%)	35% in 12-year-olds 70% in 20-year-olds (%)	90% in 12-year-olds (%)	95% in 12–year-olds (%)	95% in 12-year-olds 90% in 20–year-olds (%)
<1	1.75		53	66	54	9	20	27
1 to 4	0.50		56	78	67	29	29	43
5 to 9	1.31		67	78	63	31	46	46
10 to 14	0.71		68	82	71	62	69	69
15 to 19	0.61		66	80	66	48	57	61
20 to 39	0.20		61	75	69	28	39	57
>40	0.13		56	76	64	17	25	42
		Total	59	73	62	21	32	40

Boven et al[20] emphasized the importance of taking into consideration waning immunity when investigating the causes of the 1996–1997 pertussis epidemics in the Netherlands. They constructed a time-and age-dependent dynamic model and found that an increased rate of waning immunity was a major factor associated with the outbreak probably due to some pathogen change. The same emphasis on waning immunity and pathogen changes was recently given in a study of pertussis epidemiological profile in Poland and Argentina.[12,14]

Van Rie & Hethcote[21] study showed that concomitant adolescent and young adult booster vaccination seem to significantly reduce pertussis rates in all age groups including infants. Nevertheless, similar to Coudeville et al[5] results, no evidence of any important contribution of an added young adult vaccination was shown over single vaccination of adolescents. This is relevant in the case of São Paulo, not only from a cost perspective but also concerning compliance since the current adult diphtheria and tetanus (dT) vaccine booster coverage is lower than 10%.[d] Assuring adequate immunization coverage of adults would be a even greater challenge than that of adolescents. Both these studies considered alternative schedules as "cocoon strategy" or regular boosters at fixed times which were not examined in the current study.

Edwards & Halasa[8] acknowledged the increase in pertussis incidence and suggested that each country should have a tailored monitoring system and develop the most effective strategy based on their own data. Although mathematical modeling is a well-established epidemiological tool since Kermack & McKendrick[15] seminal paper in 1927, there are few pertussis modeling experiences in the literature, they are all limited because a unclear association of many factors in pertussis epidemiology, and they are all hardly comparable, as recently pointed out by Crowcroft & Pebody.[6] Tackling pertussis demands local efforts for understanding disease behavior. The Global Pertussis Initiative[10] emphasizes that research and discussion should focus on "preventing infant morbidity and mortality from pertussis and tailoring strategies to fit the needs of each country".

As in any study based on the axiomatic method, inference is limited by the model's premises. An adolescent booster vaccination should be considered under the light of each and every item of methodological definition discussed in the methods. They were built upon the best available information, but were any of them (e.g., stationary model, borrowed transmission rates, or else) to be disputed and different conclusions could be achieved.

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[d] Secretaria de Estado da Saúde de São Paulo, Centro de Vigilância Epidemiológica "Prof. Alexandre Vranjac". Programa Estadual de Imunizações. Tabulação de doses aplicadas e cobertura [cited 2007 Jan 2]. Available from: http://www.cve.saude.sp.gov.br/tabpni.htm

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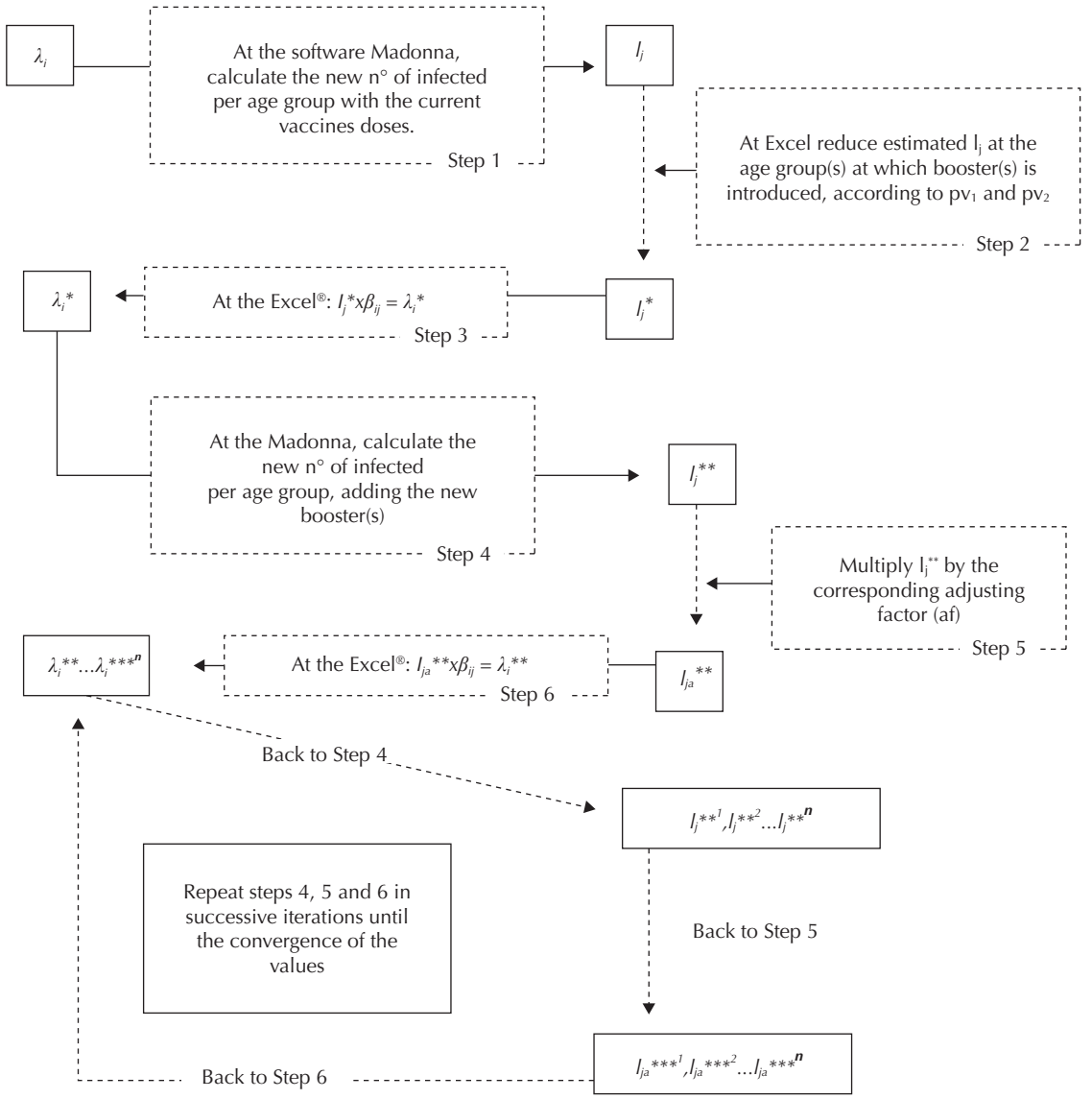
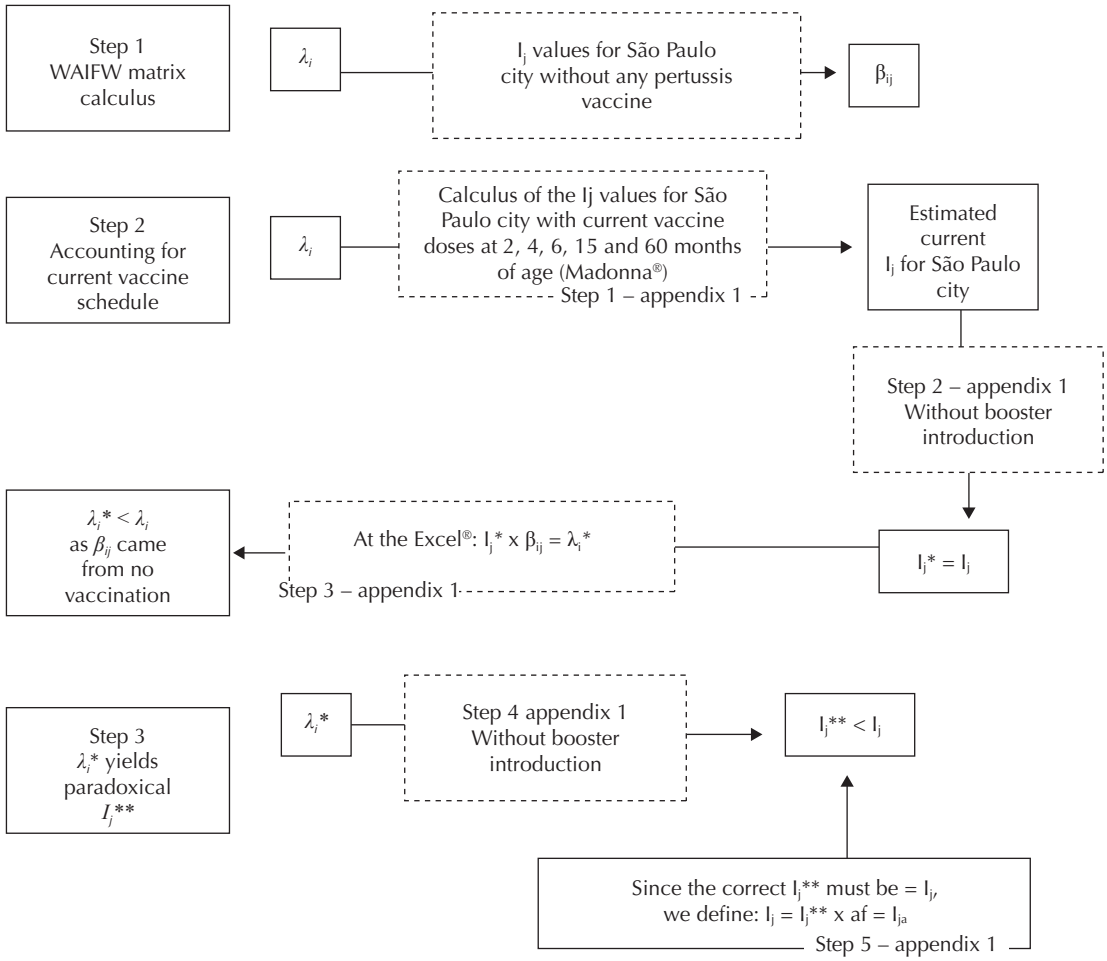


λ_i: age-dependent transmission rate, I_j: number of infected by age group, I_{ja}: adjusted number of infected by age group, β_{ij}: WAIFW matrix, af: adjusting factor (see Appendix 2), * (uppercase asterisk) means updated parameter.

Appendix 1. Steps for the estimation of force of infection (λ_i)and number of infected people (I_j) after the introduction of booster vaccination in adolescents and young adults.



λ_i: age-dependent transmission rate, I_j: number of infected by age group, $I_{ja:}$ adjusted number of infected by age group, β_{ij}: WAIFW matrix, af: adjusting factor, * (uppercase asterisk) means updated parameter.

Appendix 2. Adjusting factor (af): adjustment of compartment I to provide adequate λ_i. This shows why step 5 is required in the procedures described in Appendix 1.