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Simulations of pertussis epidemiology in the United States: effects of adult booster vaccinations

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Abstract

An expanded pertussis (whooping cough) vaccination program which includes adult boosters every 10 yr is studied using computer simulations of two models. These age-structured pertussis transmission models include waning of both infection-acquired and vaccine-induced immunity, and vaccination of children corresponding to the vaccination coverage since 1940. Adult vaccinations cause a larger boost in the immunity level in the second model than in the first model. In the simulations the addition of adult pertussis booster vaccinations every 10 yr is beneficial in reducing adult incidence, but causes only modest reductions in the incidence in infants and young children. These simulations suggest that a careful cost effectiveness analysis is needed before implementation of an adult pertussis vaccination program. © 1999 Published by Elsevier Science Inc. All rights reserved.

Keywords: Pertussis; Vaccination; Simulations; Models

1. Introduction

Pertussis gets its name from its infectious agent *Bordetella pertussis*, but it is also called whooping cough, because some infected people cough repeatedly and then make a whooping sound as they inhale [1]. Before pertussis vacci-

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nation began around 1940, the average age of a typical pertussis attack was about 5 yr and nearly all children in the United States had been infected by age 15 yr [2]. Childhood deaths from whooping cough were common in the pre-vaccine era [3]. In 1949 the DTP vaccine was formed by combining diphtheria and tetanus toxoids with killed whole-cell pertussis bacteria [1]. Although the vaccination program for pertussis in the United States has greatly reduced its morbidity and mortality since it started in the 1940s, pertussis has remained endemic. In contrast, diphtheria has almost disappeared in the United States [4].

Both infection-acquired and vaccine-induced immunity to pertussis wane with time [5–7]. Pertussis infections after vaccination or previous infection are often atypical and usually have different, milder symptoms than an initial infection in a fully-susceptible person, so that these atypical infections are often not recognized as pertussis [8,5]. Teenagers and adults seem to be a major reservoir for transmission of pertussis [9,3,10–14]. Because of vaccinations, fewer infants and young children now get pertussis, but for those who are infected, their parents are now more frequently reported as the source of infection [15–17,8].

New acellular pertussis vaccines (aP) consisting of pieces of the bacteria have recently been developed and tested. They cause fewer adverse reactions, but their vaccine efficacy may be lower than that of the killed pertussis bacteria vaccines [18–20]. The current recommended vaccination schedule in the United States has DTP or DTaP vaccinations at ages 2, 4, 6, and 15–18 months and at ages 4–6 yr [21]. Although the killed whole-cell pertussis vaccines were not recommended for adults, the new acellular pertussis vaccines are less reactogenic and can be used safely in adults [22]. Epidemiologists have suggested that acellular-vaccine booster doses be given to adolescents and adults [11,5,23,15,16,6,7,24,25]. It is hoped that reduction of the adult reservoir of pertussis infection would be great enough to significantly reduce the transmission to infants and undervaccinated children, who have high complication rates [26]. The new acellular pertussis vaccines would probably be combined with the tetanus-diphtheria (Td) booster, which is now recommended for adolescents and adults every 10 yr.

As a result of pertussis vaccination in the United States, the reported incidence of pertussis dropped by a factor of about 100 between the 1940s and the 1970s to a minimum of 1010 cases in 1976 [3,11]. Since 1976, reported pertussis incidence has continued to be cyclical with peaks every 3 or 4 yr, but there has been a generally increasing trend with 6586 cases reported in 1993, 4617 in 1994, 4315 in 1995, 7796 in 1996, and 5519 in 1997 [27,28,4]. Because pertussis has persisted and reported cases of pertussis have generally increased after 1976, a relevant question is whether this corresponds to an actual upward trend in pertussis incidence in the United States or to some other factor such as an increase in the fraction of pertussis cases being reported. Moreover, the future

effects of continuing the vaccination of children at the current level are of interest.

An epidemiologic–demographic model has been developed for pertussis transmission and vaccination in the United States [29]. This model consists of 12 classes for individuals who are in epidemiologic states corresponding to being susceptible, infectious, immune, or vaccinated. Parameter values in this model have been estimated from pertussis data. Computer simulations using this mathematical model have been shown to be generally consistent with various pertussis data since 1940 [29]. However, the pertussis incidence in these simulations decreases very slowly after 1976, in contrast to the slow upward trend since 1976 in reported pertussis cases. In these simulations there is an adult reservoir of infection before the vaccination program started in 1940 and this adult reservoir continues through 2040. Moreover, when the current vaccination program is continued, pertussis incidence in the simulations continues at about the current level, so no significant future changes are expected. The sensitivities of the results to the parameter values have been analyzed [29]. Previous modeling of pertussis in the United Kingdom is discussed in [29].

Since cases in the United States were first reported in 1922, the reported incidence of pertussis has been cyclical with a period of 3–4 yr. This cyclic phenomenon has been investigated using an epidemiologic-demographic pertussis model [30]. Because seasonal (i.e. 1 yr period) contact rates in models for measles led to subharmonic oscillations with a period of 2 yr, it was expected that a seasonal contact rate in the pertussis model would lead to similar multiyear oscillations, but this does not occur and the resulting oscillations in the computer simulations always have a period of 1 yr. However, 2% yearly stochasticity in the contact rate in the pertussis simulation model does lead to irregular oscillations with a period and a magnitude consistent with the reported pertussis data [30]. Thus a yearly random contact rate factor in the interval (0.98, 1.02) due to weather, imported cases, or other causes is a possible explanation for the observed cyclic pertussis incidence.

The new acellular pertussis vaccines have been suggested for adult booster vaccinations. Suppose that the acellular pertussis vaccine were combined with the tetanus-diphtheria (Td) boosters with an extra vaccine cost of about \$20, but no extra costs for vaccine administration, and that 1/10 of the approximately 230 million people in the United States over age 10 yr were given these Tdap vaccines each year. Then the annual cost to the United States people would be about $\$20 \times 23 \text{ million} = \460 million . Would the reduction in pertussis cases, disease-severity, and complications justify this annual expenditure? The answer requires estimates of the reductions in typical and atypical pertussis cases in all age groups and also estimates of the average costs per typical and atypical case in these age groups. The pertussis models and simulations here focus on estimating the reductions in cases when adult boosting is added to the current pertussis childhood vaccination program. No estimates of the average

costs of pertussis cases have been found, so that estimates of these quantities by health policy economists are needed in order to complete a cost-benefit analysis. These estimates could involve medical costs such as outpatient visits, emergency room visits, hospitalizations and deaths, and work-loss costs of the infectives or their parents.

Here computer simulations of two pertussis models are used to obtain estimates of the potential effects of the addition of adult pertussis booster vaccinations on pertussis incidence in adults and also in infants and young children, who have high rates of pertussis complications. The first model is the previously developed model [29] in which each pertussis booster moves the individual back up one vaccinated or removed class. Some epidemiologists believe that, for those who have had a sequence of at least four pertussis vaccinations or have had a previous pertussis infection, a pertussis booster would raise their immunity back up to the highest level. The second model incorporates this more optimistic view of the effectiveness of pertussis booster vaccinations.

Because this paper builds on the model development, parameter estimation, and sensitivity analysis in the previous pertussis modeling paper [29], these aspects are treated briefly here. The first model is described in Section 2 and the second model is developed in Section 3. The results of computer simulations with the first and second models are given in Sections 4 and 5, respectively. The effects of the adult boosters in the pertussis simulations with the two models are compared and discussed in Section 6. In the simulations the effectiveness of a vaccination program is measured by the percentage decreases in typical (full-disease or highest-infectivity) pertussis cases (especially in young children whose complications rates are higher), and also by the percentage decreases in atypical (lower-disease or lower-infectivity) pertussis cases.

2. The first pertussis model

Because of the vaccination ages and the greater transmission in children, the 32 age groups chosen for the models are 0–1 months, 2–3 months, 4–5 months, 6–11 months, years 1, 2, 3, . . . , 18, 19, and the 5 or 10 yr intervals 20–24, 25–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89, and over 90. The demographic part of the models uses 1990 fertility and death rates in the United States for a theoretical population whose total size is constant and whose age distribution has reached a steady state age distribution. Newborns enter the 0–1 month age group. In each age group there is a daily death rate and a daily outflow corresponding to aging into the next age group [29].

In the first pertussis model [29], the population is divided into twelve distinct epidemiologic classes as shown in Fig. 1. When there is an adequate contact of a susceptible with an infective, transmission occurs and the susceptible becomes

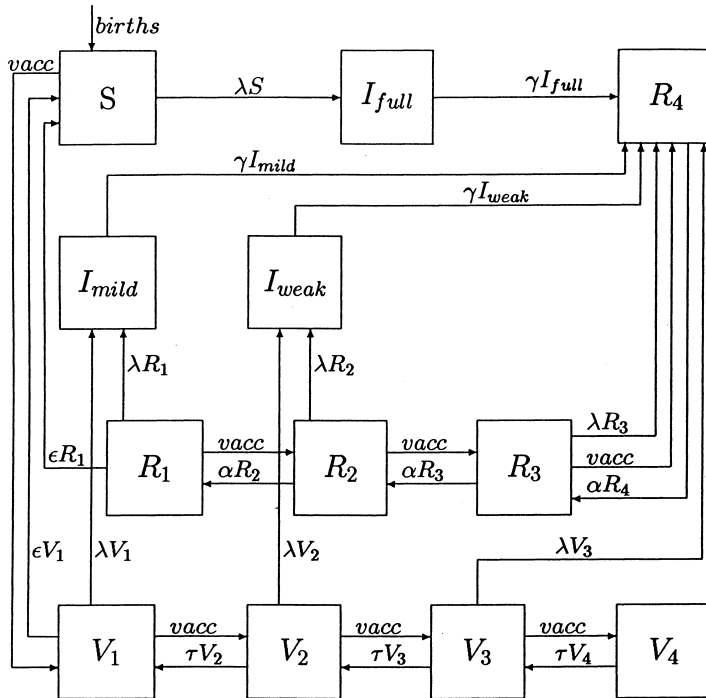


Fig. 1. Transfer diagram for the first pertussis model with vaccination.

infected. Infected individuals enter the class I_{full} of full-disease infectives at the rate λS , where S is the susceptible age distribution and the force of infection λ is the total infectivity-weighted contact rate with weak-, mild-, and full-disease infectives in all age groups. The latent period in which an individual is infected, but not yet infectious, is negligible, since it is only about one week for pertussis (Ref. [1]; Ref.[2] p. 340&341).

In the United States vaccinations with the DTP or the DTaP combination are recommended at the ages of 2, 4 and 6 months. Current vaccination recommendations also include a fourth primary vaccination of either DTP or DTaP vaccine at age 15 months and a booster dose of either DTP or DTaP vaccine before school entry at ages 4–6 [21]. Multiple doses are effective because each additional dose of pertussis vaccine seems to provide additional temporary protection against severe pertussis disease and multiple doses can provide temporary protection against pertussis infection.

The fraction of vaccinated susceptibles that has increased immunity and enters the first vaccinated class V_1 is called the vaccine efficacy (VE). When people in V_1 are given another dose, then the fraction VE of those vaccinated enter V_2 . Similarly, when people in the vaccinated classes V_2 and V_3 and in the

removed classes R_1 , R_2 , and R_3 are vaccinated, the fraction VE moves up to the class with the next higher immunity level as shown in Fig. 1. People in R_4 or V_4 who are vaccinated do not change classes. Vaccination at age two months is incorporated by moving, to the next higher removed or vaccination class, the appropriate fraction of those transferred due to aging between the 0–1 month and 2–3 month age groups. The transferred fraction is the product of the fraction vaccinated times the vaccine efficacy VE. The simulations of vaccinations at ages four months, six months, one yr and five yr, and of adult booster doses are analogous.

A pertussis infection provides immunity from infection for several years, but then an infection can occur and the severity of the disease depends on the time since the last infection or boosting exposure [23,6,7]. As shown in Fig. 1, this waning of infection-acquired immunity is modeled by moving recovered individuals through a sequence $R_4R_3R_2R_1$ of removed classes with decreasing immunity. As the vaccine-induced immunity wanes, people move down through the vaccinated classes $V_4V_3V_2V_1$ or the removed classes $R_4R_3R_2R_1$ and eventually return to the susceptible class S .

Individuals in classes R_4 or V_4 can not be infected due to their high immunity. People in R_3 have lower immunity, so if they have an adequate contact with an infective, they return to R_4 , because they either are boosted directly without becoming infectious or have an asymptomatic infection with negligible infectivity. People in V_3 who are exposed to an infective also move to R_4 . Upon adequate contact with an infective, a person in R_2 or V_2 enters the weak-disease infected class I_{weak} of people with low infectivity and then goes to R_4 after the infectious period. Those in R_1 or V_1 who are exposed enter the class I_{mild} of mild-disease infectious people with intermediate infectivity and then go to R_4 .

Although not all infectives entering one of the three infective classes have the same symptoms and infectivities, it is convenient to describe all of those in each class by their average disease severity and infectivity levels. Because many of the infectives in the full-disease class I_{full} have a full-disease, typical case of clinical pertussis with a paroxysmal cough for at least 21 days, their average infectivity is highest [6]. Most infectives in the mild-disease class I_{mild} have atypical pertussis and cough less, so their average infectivity is one-half of that of a full-disease infective. Most infectives in the weak-disease class I_{weak} cough even less and are less likely to infect a susceptible, so their average infectivity is only one-fourth of that of a full-disease infective. Note that it is implicitly assumed that individuals with more symptoms are more infectious; thus it would have been more direct to define the infectious classes in terms of their average relative infectivities as is done in the second pertussis model.

The mathematical model corresponding to the transfer diagram in Fig. 1 consists of 384 nonlinear differential equations giving the rate of daily transfers among the 12 epidemiologic classes and the 32 age groups. The computer simulations are the numerical solutions of these differential equations with

vaccinations of specific age groups. Before vaccination begins in the year 1940, it is assumed that the steady state epidemiologic age distribution has been reached and is being maintained. When the vaccination starts, the epidemiologic distribution shifts away from the no-vaccination steady state epidemiologic distribution. More details about the epidemiologic model are given in the related paper [29].

2.1. *Estimates of the epidemiological parameters*

The average infectious period for pertussis is about 21 days (Ref. [1]; Ref. [2] p. 340&341), so that the rate constant γ is $1/21$. The transfer rate constant $\alpha = 1/(5 \times 365)$ corresponds to a 5 yr average waiting period in classes R_4 , R_3 , and R_2 . There is rapid decay out of the classes V_4 , V_3 and V_2 with a mean period of 2 yr, so that $\tau = 1/(2 \times 365)$. Because full disease during a pertussis infection in previously-infected or previously-vaccinated people is uncommon, the rate constant ϵ for the transfer from classes R_1 or V_1 is chosen so that movement back to the susceptible class S is very slow. With the value $\epsilon = 0.01/365$, only 10%, 18% and 26% have been transferred back to the susceptible class S within 10, 20 and 30 yr, respectively. These values are shown to be consistent [29] with recent pertussis studies [6,7,5,16,24,25].

Although it has not been done in the United States, the forces of infection as a function of age for pertussis have been estimated in England and Wales in 1956 (before vaccination started there) from reported incidence data (Ref. [31], p. 164). Based on these values, the forces of infection have been chosen for 13 aggregated age intervals. People of different ages have different daily encounters in families, schools, workplaces, public places, etc. In the contact matrix, the number of adequate contacts between the susceptibles in one age group and the infectives in another age group is assumed to be proportional to the mixing activity levels and sizes of the two groups. This proportionate mixing contact matrix can be found from the forces of infection and the numbers of infectives. For the pertussis forces of infection, the activity level is highest for the 5–9 yr old children [29].

The vaccine efficacy VE of 0.9 in moving vaccinated people up to the next higher removed or vaccination class has been shown to be consistent with pertussis data [29]. Estimates of the percentages of children vaccinated for pertussis have not been found for the early years of the vaccine, but low level pertussis vaccination seems to have started around 1940. The whole-cell pertussis vaccine was officially licensed in 1948 and the DTP combination was licensed in 1949 [32]. In the model the vaccination rates for the first three doses increase linearly from zero in 1940 to the values 0.8, 0.78, and 0.76 in 1950. Then they increase linearly up to the values 0.96, 0.94, and 0.92 in 1995 and are constant after 1995. For the fourth dose the vaccination rate at age 1 yr increases linearly from zero in 1940 to 0.7 in 1960; then it increases linearly up to

0.86 in 1995 and is constant after 1995. For the booster dose at age 5 yr, the vaccination rate increases linearly from zero in 1940 to 0.6 in 1970; then it increases up to 0.8 in 1995 and is constant after 1995. These values have been shown to be roughly consistent with the data in immunization surveys. More details about parameter estimation are given in the related paper [29].

3. The second pertussis model

It is immunologically plausible that, for people who have had a series of at least four pertussis vaccinations or have had a previous pertussis infection, a pertussis booster vaccination would raise their pertussis immunity back up to the highest level. The second pertussis model uses the same demographic basis and general notation as the first model, but it adopts the concept above for pertussis boosters. As shown in Fig. 2, it has sixteen epidemiological classes with four infectious classes, four removed classes, and seven vaccination classes. The waning of immunity is modeled by the movement down through the removed and vaccinated classes over time. The four infectious classes are defined by the average level of infectivity rather than the average disease symptom statuses that were used in the first model. The four average levels of infectivity are: highest for the susceptibles who become infected, high infectivity for those infected from the removed and vaccinated classes with lowest immunity, medium infectivity for those in the second-level immunity removed and vaccinated classes, and low infectivity for those in the third-level immunity removed and vaccinated classes. The relative infectivity for these four classes is 1, 0.75, 0.5, and 0.25, respectively. The new vaccinated classes W_1 , W_2 , and W_3 correspond to those who have had at least 4 pertussis vaccinations, but now have lower immunity due to waning. The major difference from the first pertussis model is that when people in the removed classes R_1 , R_2 , and R_3 are vaccinated, the fraction VE moves up to R_4 , the highest immunity removed class. Similarly, when people in the vaccinated classes W_1 , W_2 , and W_3 are vaccinated, the fraction VE moves up to the W_4 , the highest-immunity vaccinated class. Another difference from the first model is that people never return to the fully susceptible class S due to the loss of all immunity.

As in the first model, the 1990 fertility and death rates are used to obtain a constant population size and a steady state age distribution. The epidemiological parameters estimated for the first model are also used for the second model. Thus the rate constant γ is $1/21$, and the transfer rate constant $\alpha = 1/(5 * 365)$ corresponds to a 5 yr average waiting period in classes R_4 , R_3 , and R_2 . There is rapid decay out of the vaccinated classes V_4 , V_3 , V_2 , W_3 , and W_2 with a mean period of 2 yr, so that $\tau = 1/(2 * 365)$. Here the proportionate mixing contact matrix is also found from the forces of infection and the numbers of infectives. Vaccinations are incorporated into the second model just as in the

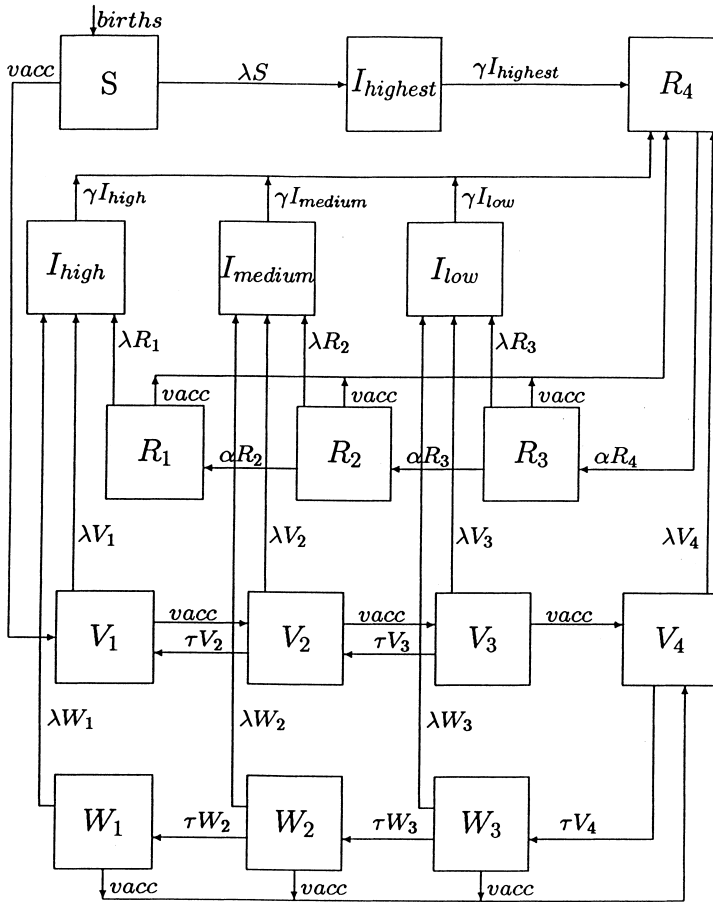


Fig. 2. Transfer diagram for the second pertussis model with vaccination.

first model. The vaccine efficacy VE of 0.9 and the same pattern of vaccination coverage are also used in the computer simulations for the second model. The computer simulations corresponding to the transfer diagram in Fig. 2 are the numerical solutions, with vaccinations of specific age groups starting in 1940, of the 512 differential equations, which give the rate of daily transfers among the 16 epidemiologic classes and the 32 age groups.

4. Simulations with the first pertussis model

A computer simulation of the first pertussis transmission and vaccination model with the estimated parameter values has been used to approximate the

spread of pertussis from 1940 to 2040 using the estimated vaccination coverage up to 1995 and then continuing to vaccinate at these 1995 vaccination levels for children. The simulation has also been done with the addition in the year 2000 of booster vaccinations for adults and 10 yr old children with 100% vaccination coverage of the age groups at ages 10, 20, 30,..., 90 yr. Hereafter this is called complete adult boosting. The results of the pertussis vaccination simulations are presented in Figs. 3–6. In all figures the solid lines correspond to vaccinations limited to children and the dashed lines correspond to the addition of complete adult boosting starting in the year 2000.

Fig. 3 summarizes the simulation results by showing the incidences in the susceptible, removed and vaccinated classes. In 1940 the full-disease incidence in the susceptible class is about 1.1 times the annual birth rate and the mild- and weak-disease incidence is about 2.6 times the annual birth rate, so that in the prevaccine era some people got more than one full-disease infection and people had an average of 2.6 atypical cases of pertussis during their lifetime. During the period 1940–1995 when vaccination coverage increases, the full-

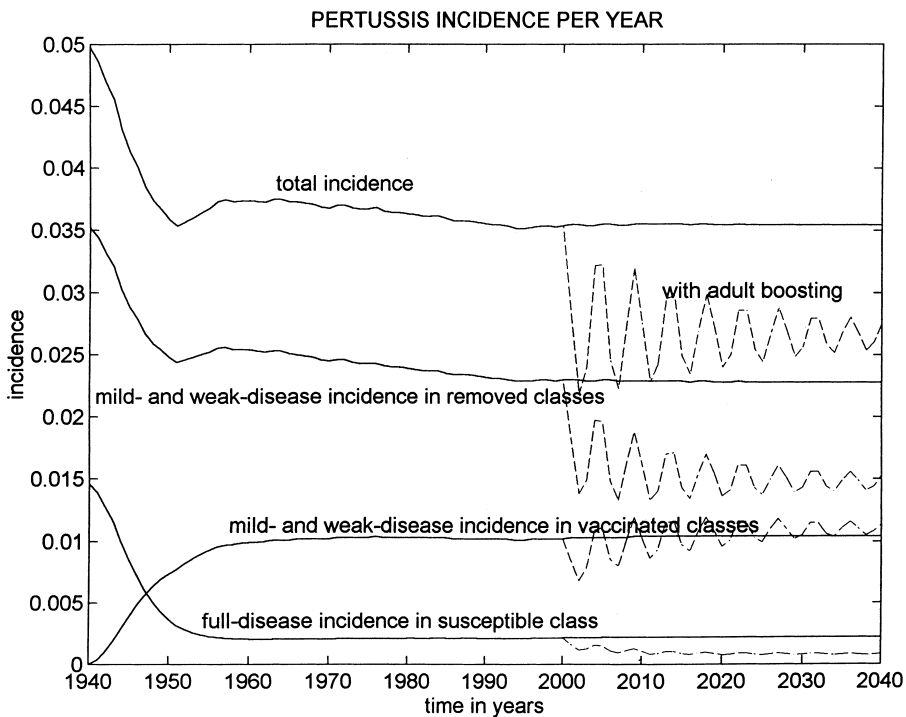


Fig. 3. Pertussis incidences per year using the first simulation model with the baseline parameter set (solid lines) and with the addition of complete adult boosting (dashed lines). All figures give incidences as a fraction of the total population.

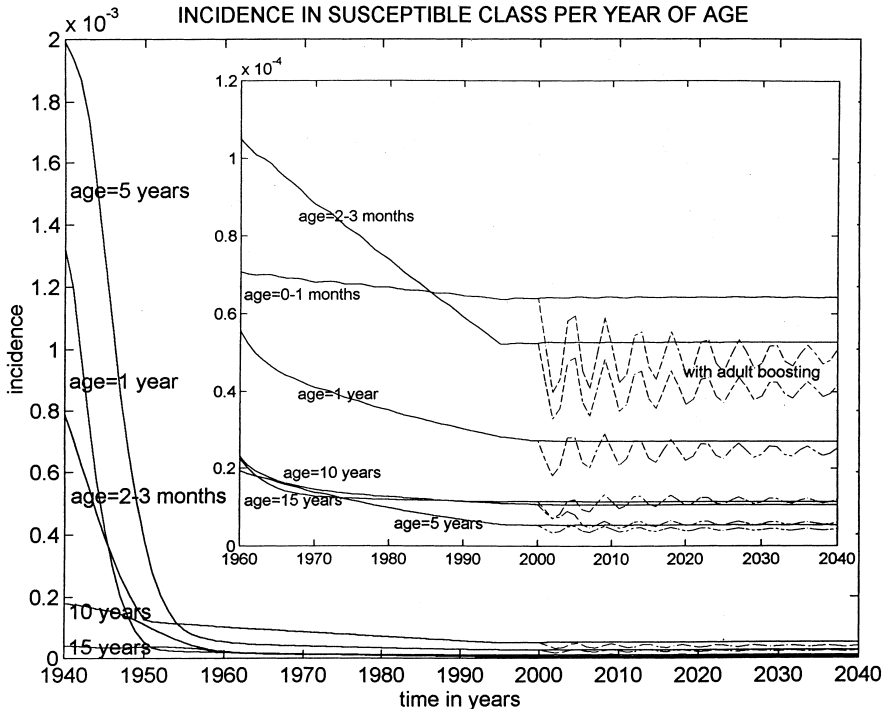


Fig. 4. Full-disease pertussis incidence in younger age groups for various years using the first simulation model.

disease incidence in the susceptible class, the mild- and weak-disease incidence in the removed classes, and the total incidence generally decrease. As people move into the vaccinated classes, the mild- and weak-disease incidence in the vaccinated classes increases. The largest changes in incidences occur between 1940 and 1960 as the vaccination coverage increases rapidly. In 1995 there are about 0.16 typical, full-disease cases and about 2.5 atypical, lower-disease cases per person during their lifetime.

Even though the total incidence decreases only 29% its components do change. In 1940, 31% are typical, full-disease cases and 69% are atypical cases in the removed classes. In 1995 only 6% are full-disease cases, 65% are atypical cases in the removed classes and 29% are atypical cases in the vaccinated classes. Between 1940 and 1995 the full-disease cases in the susceptible class decrease by 85% overall, by 6% in those at least 10 yr old, and by 99% for those under age 10 yr. In 1940 most children had a full-disease case, but by 1995 many children are vaccinated and then have a lower-disease case. The net result of this shifting from full-disease to lower disease cases and a slightly smaller reservoir of infection is that the total mild- and weak-disease cases in the re-

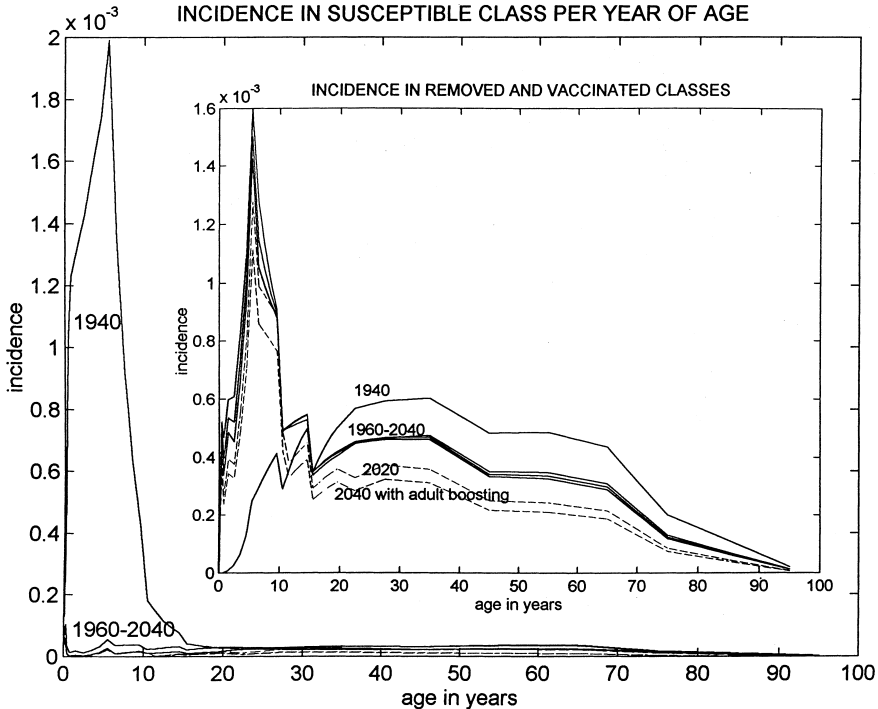


Fig. 5. Pertussis incidence in the susceptible, removed and vaccinated classes for various years using the first simulation model.

moved and vaccinated classes decrease by only 6% between 1940 and 1995. After 1995 the vaccination coverage is constant and the resulting pertussis incidence remains nearly constant, since it is almost at an epidemiologic equilibrium.

Results of the simulation with the addition of complete adult boosting in the year 2000 are shown by the dashed lines in Fig. 3. When 100% adult boosting every 10 yr is suddenly added in 2000, the incidences quickly move down from the 1999 incidences and have a damped oscillatory behavior with a period of about 4 yr as they approach a new equilibrium. Between the years 2000 and 2040, complete adult boosting causes the full-disease cases in the susceptible class to decrease by 62% overall, by 66% in those at least age 10 yr, and by 3% in those less than 10 yr old. These decreases are consistent with the direct protection of adults by vaccination. Between 2000 and 2040 the mild- and weak-disease cases drop by 20% overall in the removed and vaccinated classes, and by 33% in the removed classes, but there is no change in the vaccinated classes. With complete adult boosting only about 6% of the population in 2040 ever gets full-disease pertussis, which is lower than the value of 17% when only

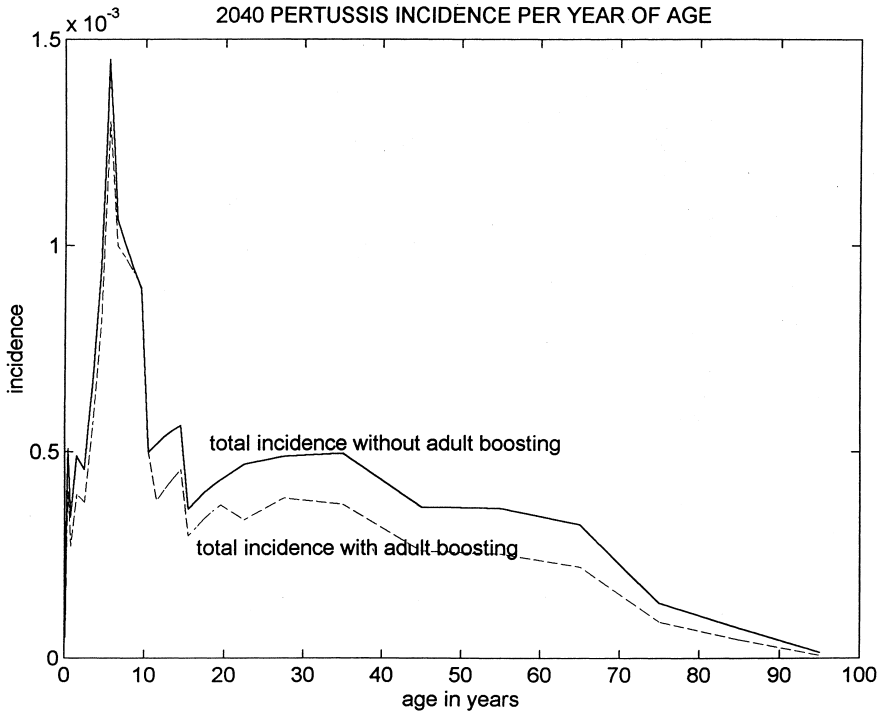


Fig. 6. Total pertussis incidence per year of age for various years using the first simulation model.

children are vaccinated. In this case people in 2040 have a lifetime average of 2 atypical pertussis infections, which is lower than the 2.5 atypical cases when only children are vaccinated.

The full-disease pertussis incidences in the susceptible class between 1940 and 2040 for various age groups are shown in Fig. 4. When only children are vaccinated, the full-disease incidences decrease in the 0–15 yr old age groups. The largest decreases in the full-disease incidences occur in the 1–5 yr age groups, because these groups are given direct temporary protection by vaccination. Because there is no direct vaccination in the 0–1 month age group, the decrease in full-disease pertussis is smaller in this group. The delay due to temporary vaccine-induced immunity leads to more susceptibles in the older age groups and hence to more full-disease pertussis infections, so that the incidences in the age groups over 30 yr eventually increase (see Fig. 9 in [29]). When the 1995 pertussis vaccination levels in children are continued, there are no major changes in incidences after 1995. This suggests that the incidence is near a vaccination-induced equilibrium.

The pertussis incidences as a function of age for various years are shown in Fig. 5. The outer graph shows that the full-disease incidence in the susceptible

class is large in those less than 10 yr of age in 1940, but by 1960 it is low in all age groups. The inner graph shows that the mild- and weak-disease incidence in the removed and vaccinated classes occurs in older age groups in 1940, but by 1960, it is higher in the age groups under 10 yr and decreased somewhat in those over age 20 yr. The addition of complete adult boosting in 2000 further decreases the incidences in the susceptible, removed and vaccinated classes for the age groups over age 10 yr. Most of this decrease is due to a decrease in the mild-disease incidence, because people often get boosted before they get back to the R_1 and V_1 classes where they would get mild-disease cases.

The effects of adult boosting are seen clearly in Fig. 6, which gives total incidences in 2040. Note that complete adult boosting decreases the combined typical and atypical incidence in those at least age 10 yr by 26%, and it causes decreases of 9% in this combined incidence of those under age 10 yr. However, these declines are not uniform in the typical and atypical cases. Complete adult boosting causes the typical, full-disease cases in the susceptible class to decrease by 66% in those at least age 10 yr and by only 3% in those under 10 yr.

4.1. Computer simulations with different parameters

The sensitivity of the baseline simulation results above using the best parameter estimates has been evaluated by comparing with simulations using different parameter values [29]. Increasing or decreasing all of the forces of infection does not have much effect on the simulation results, but halving the forces of infection for those over age 15 causes large decreases in the incidences in adults. In general, changes in most epidemiologic parameter values lead to some quantitative changes in the incidences, but the qualitative patterns are similar. The simulation results are most sensitive to changes in the duration of infection-acquired and vaccination-induced immunity.

Doubling the waiting times in the removed classes from 5 to 10 yr prolongs the protection given by infection, so that in the prevaccine era the average person has about 1.3 (instead of 2.6) atypical pertussis infections as an adult. Between 1940 and 1995 the full-disease cases in the susceptible class decrease by 91% overall, by 8% in those at least age 10 yr and by 99% for those under age 10 yr [29]. With complete adult boosting between the years 2000 and 2040, the full-disease cases in the susceptible class decrease by 64% overall, by 71% in those at least age 10 yr old, and by 3% in those less than 10 yr old. With complete adult boosting only about 4% of the population in 2040 ever gets full-disease pertussis, which is lower than the value of 10% when only children are vaccinated. In this case people in 2040 have a lifetime average of 1.4 atypical pertussis infections, which is lower than the 1.7 atypical cases when only children are vaccinated. Thus prolonging the protection given by infection causes some larger percentage decreases, but the overall pattern is unchanged and the effects of adult boosting are quite similar.

If the mean waiting times in the last three vaccinated classes are changed from 2 to 4 yr, then vaccination provides longer protection. In the simulations between 1940 and 1995, the full-disease cases in the susceptible class decrease by 86% overall, by 9% in those at least age 10 yr and by 99% for those under age 10 yr [29]. With complete adult boosting between 2000 and 2040, the full-disease cases in the susceptible class decrease by 75% overall, by 77% in those at least age 10 yr, and by 30% in those less than 10 yr old. With complete adult boosting only about 4% of the population in 2040 ever gets full-disease pertussis; this is lower than the value of 16% when only children are vaccinated. People in 2040 have a lifetime average of 1.1 atypical pertussis infections, which is lower than the 1.9 atypical cases when only children are vaccinated. With longer vaccination protection using $1/\alpha = 4$ yr (respectively, baseline using $1/\alpha = 2$ yr), adult boosting causes decreases in total pertussis cases of 34% (9%) in those under age 10 yr and 47% (26%) in those at least age 10 yr. Thus boosting has a larger impact when the vaccination protection lasts longer.

Because the fraction successfully immunized is the product of the vaccine efficacy and the vaccination coverage, changes in the vaccine efficacy have the same effects as the corresponding changes in the vaccination coverage. If the vaccine efficacy or the vaccination coverages for each of the five doses were decreased by 10% (the vaccine efficacy would go from 0.9 down to 0.81), then in the simulations there are more full-disease cases in children and increases of about 5% in the full-, mild- and weak-disease incidences in 1995. But the percentage decreases in incidences due to the childhood vaccination program and the adult booster program are similar to those for the baseline simulations. An increase of 3% in the vaccination coverages at each of the five ages leads to slightly fewer full-disease cases in children, but has very little effect on the total incidences and the percentage changes. One might expect that changes in the vaccine efficacy or vaccination coverage would have a larger impact on the incidences. However, the redundancy of vaccinating at five ages makes the fraction immunized successfully at each age less important. Moreover, the lower-disease cases in adults serve as a reservoir of infection that guarantees the persistence of pertussis. More details are given in [29].

5. Simulations with the second pertussis model

The computer simulations with the second model use the same epidemiological and demographic parameter values, forces of infection, vaccination coverages of children, and complete adult boosting as in the first model. These simulation results are shown in Figs. 7–10. In 1940 the highest-infectivity, typical incidence in the susceptible class is 0.99 times the annual birth rate, so that almost every child has a serious pertussis infection. Moreover, the lower-infectivity (high, medium and low) cases are 5.1 times the annual birth rate, so

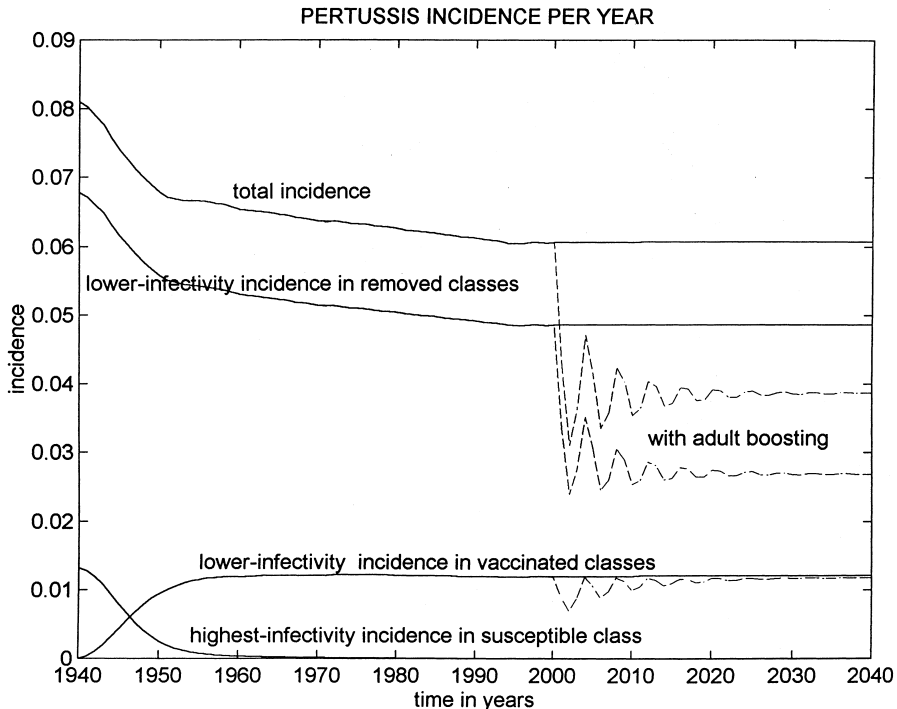


Fig. 7. Pertussis incidences per year of age using the second simulation model with the baseline parameter set (solid lines) and with the addition of complete adult boosting (dashed lines).

that in the prevaccine era people have an average of 5.1 atypical cases of pertussis during their lifetime. Fig. 7 shows that, as in the first model, the largest changes in incidences occur between 1940 and 1960 as the vaccination coverage increases rapidly. In 1995 there are about 0.003 typical, highest-infectivity cases and about 4.5 atypical, lower-infectivity cases per person during their lifetime.

The total incidence shown in Fig. 7 decreases only 25% between 1940 and 1995, but its components change radically. In 1940, 16% are typical, full-disease, highest-infectivity cases in the susceptible class, but in 1995 less than 1% are of this type. Between 1940 and 1995 the highest-infectivity cases in the susceptible class decrease by 99% overall and also decrease by 99% for those under age 10 yr. Most of the children with typical cases in 1940 are replaced in 1995 by vaccinated children who have atypical cases, so that the total high-, medium- and low-infectivity, atypical cases in the removed and vaccinated classes decrease by only 11% between 1940 and 1995. The incidences remain almost constant after 1995, when the vaccination coverage does not change.

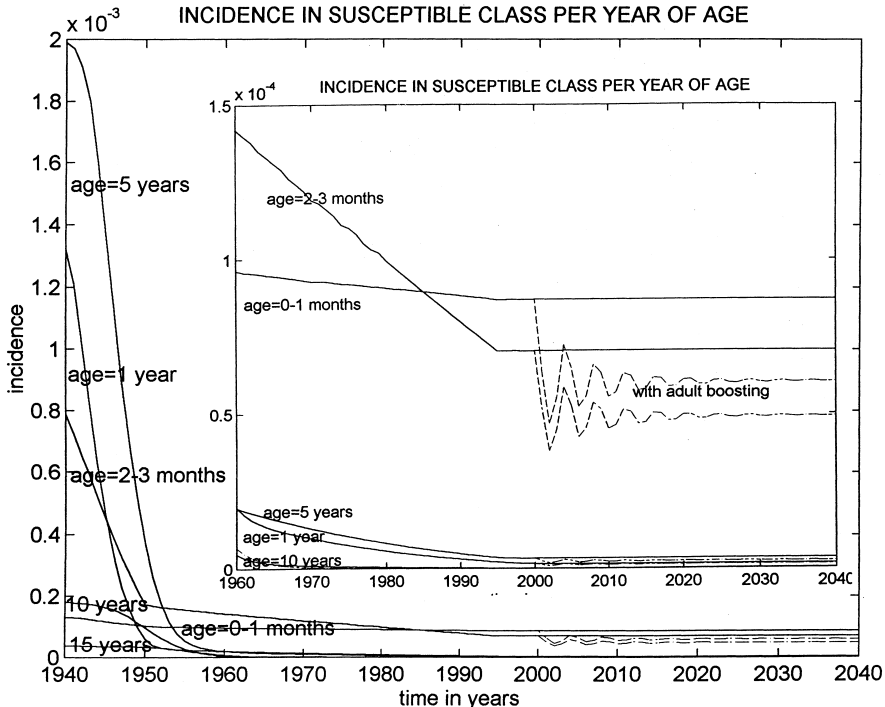


Fig. 8. Full-disease pertussis incidence in younger age groups for various years using the second simulation model.

Between the years 2000 and 2040, complete adult boosting causes the full-disease cases in the susceptible class to decrease by 29% overall, and by 28% in those less than 10 yr. These decreases are due to the direct protection of adults by vaccination and the decreased transmission of infection from adults to children. Between 2000 and 2040 the lower-infectivity (high-, medium- and low-infectivity), atypical cases drop by 36% overall in the removed and vaccinated classes, by 45% in the removed classes, and by 2% in the vaccinated classes. With complete adult boosting only about 0.2% of the population in 2040 ever gets full-disease pertussis, which is lower than the value of 0.3% when only children are vaccinated. With adult boosting the average person in 2040 has a lifetime average of 2.9 atypical pertussis infections, which is lower than the 4.5 atypical cases when only children are vaccinated.

In the simulations of the second pertussis model, cases in the younger age groups are shown in Fig. 8. Note that the highest-infectivity, typical cases in the susceptible class drop rapidly in the groups under 5 yr of age that are directly protected by vaccination and then drop later in the 1960s in the older age groups, when the susceptibles are disappearing due to increases in the

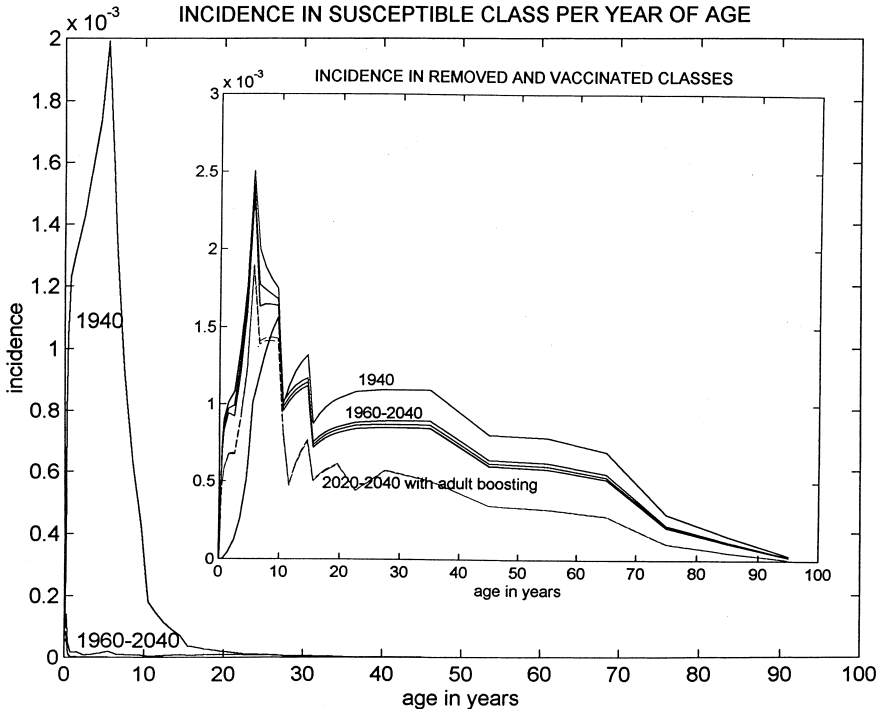


Fig. 9. Pertussis incidence in the susceptible, removed and vaccinated classes for various years using the second simulation model.

vaccination coverage. In contrast to the first model, this second model does not have any removed or vaccinated people returning to the susceptible class, so that there are no older susceptibles who could get a highest-infectivity, typical case. As in the first model, when the 1995 vaccination levels in children are continued, there are no major changes in the age group incidences after 1995. The addition of complete adult boosting in 2000 provides direct temporary protection of adults, which causes decreases in incidences in both child and adult age groups. Note that adult boosting has a larger impact in this second model, because the second model uses a more optimistic mechanism for boosting.

Fig. 9 shows the pertussis incidences as a function of age for various yr. The outer graph shows that the highest-infectivity, typical incidence in the susceptible class is large in those less than 10 yr of age in 1940, but by 1960 it is low in all age groups. The inner graph shows that the lower (high-, medium- and low-) infectivity, atypical incidence in the removed and vaccinated classes occurs mostly in groups over age 10 yr in 1940, but by 1960, it is higher in the age groups under 10 yr and decreased somewhat in those over age 10 yr. The

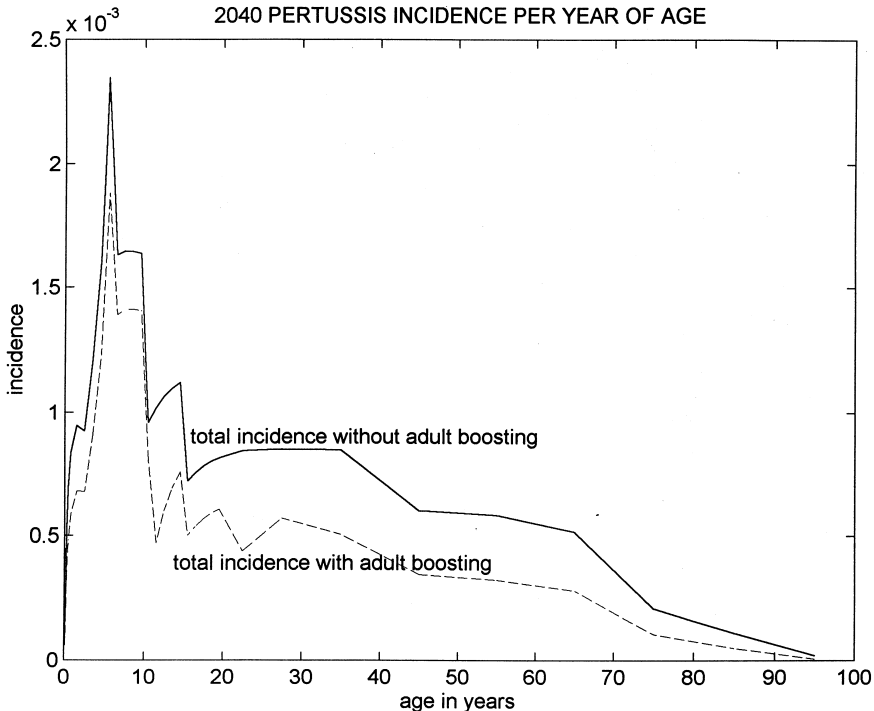


Fig. 10. Total pertussis incidence per year of age for various years using the second simulation model.

addition of complete adult boosting in 2000 further decreases the incidence in the removed and vaccinated classes for the age groups over age 10 yr.

Fig. 10 showing the total incidences in 2040 demonstrates the effects of adult boosting. As in the first model, complete adult boosting decreases the total pertussis incidence in all age groups. The total typical and atypical cases decrease by 42% for those over age 10 yr who receive directly temporary protection from the booster vaccinations, and they decrease by 20% in those under age 10 yr. As in the first model, these declines are not uniform in the typical and atypical cases. Complete adult boosting causes the typical, highest-infectivity cases in the susceptible class to almost disappear in those at least age 10 yr and to decrease by 28% in those under 10 yr of age.

5.1. Computer simulations with different parameters

The sensitivity to parameter value changes has also been evaluated for the second pertussis model. If the waiting times in the removed classes are changed from 5 to 10 yr, then the protection given by an infection lasts longer. In this

case the average person in 1940 has about 3.5 (instead of 5.1) atypical pertussis infections as an adult. Between 1940 and 1995 the full-disease cases in the susceptible class almost disappear in all age groups. With complete adult boosting only about 0.2% of the population in 2040 ever gets full-disease pertussis, which is less than the value of 0.3% without adult boosting. In this case people in 2040 have a lifetime average of 2.3 atypical pertussis infections, which is lower than the 3.5 atypical cases when only children are vaccinated. With complete adult boosting, the total typical and atypical cases are lower in 2040 by 41% for those over age 10 yr and by 13% in those under age 10 yr. Thus prolonging the protection given by infection causes changes in the percentages, but the overall pattern is unchanged and the effects of adult boosting are quite similar.

If the mean waiting times in the last three vaccinated classes are changed from 2 to 4 yr, then vaccination provides longer protection. In the simulations between 1940 and 1995, the highest-infectivity, typical cases in the susceptible class disappear in all classes. With complete adult boosting only about 0.14% of the population in 2040 ever gets highest-infectivity, typical pertussis; this is lower than the value of 0.25% when only children are vaccinated. With complete adult boosting, people in 2040 have a lifetime average of 2.0 atypical pertussis infections, which is lower than the 3.9 atypical cases when only children are vaccinated. With longer vaccination protection using $1/\alpha = 4$ yr (respectively, baseline using $1/\alpha = 2$ yr), adult boosting causes case decreases of 33% (20%) in those under age 10 yr and 52% (42%) in those at least age 10 yr. Thus adult boosting has a much larger impact on cases in children when the vaccination protection lasts longer.

As in the first model, changes in the vaccine efficacy have the same effects as the corresponding changes in the vaccination coverage. If the vaccine efficacy or the vaccination coverages for each of the five doses were decreased by 10% from the estimated levels, then in the simulations there are more highest-infectivity, typical cases in children and increases of about 4% in the total incidences in 1995. Most of the percentage decreases with the childhood vaccination program and the adult booster program are similar to those for the baseline simulations, but the total typical and atypical cases with adult boosting decrease by 16% for those less than age 10 yr and by 37% in those at least age 10 yr. As in the first model, the redundancy of the multiple vaccinations means that the fractions immunized successfully at each age are less important.

6. Discussion

The simulations here with two pertussis models attempt to describe pertussis transmission and vaccination in the United States. The first pertussis model as shown in Fig. 1 makes the modest assumption that a booster vaccination of a

person raises the immunity slightly, so that the person moves up to the compartment with the next higher immunity level. The second pertussis model as shown in Fig. 2 makes the more optimistic assumption that, for a person with a previous pertussis infection or a previous sequence of at least four pertussis vaccinations, a booster vaccination moves the person up to the compartment with the highest level of immunity. In this sense the two models represent pessimistic and optimistic extremes.

The parameters used in the baseline simulations are those that are most consistent with the available data on pertussis forces of infection, the average infectious period, waning of infection-acquired and vaccination-induced pertussis immunity, and vaccine efficacy [29]. Changes in the parameter values used in the simulations do not lead to major changes in the general patterns of the incidences and age distributions, but as shown in Sections 4.1 and 5.1, some parameter changes involving waning of immunity affect the magnitudes. This pertussis simulation study has several limitations that could influence the results. The compartmental models are reasonably simple, so that parameter estimation and computer simulations are possible, but this simplicity means that they only provide scenarios which are rough approximations to actual pertussis epidemiology. Here it is assumed that simple proportional mixing is adequate to describe the contact pattern between the 32 age groups, but actual contact patterns are more complicated and may depend on stochastic events, spatial factors, and complex social patterns involving people moving between homes, schools, workplaces, etc. Some parameter values are difficult to estimate, especially the relative infectivities of typical and atypical cases. Another limitation is that vaccination coverage for each age is assumed to be random, but compliance with vaccination recommendations at one age is probably related to compliance at another age. Despite these limitations, simulation modeling of pertussis epidemiology since 1940 is a useful exploratory tool. The modeling does not attempt to obtain accurate predictions, but seeks to obtain general estimates and new insights into the possible effects of pertussis vaccination programs. The two simulation models used here focus on estimating the potential effects of adding acellular pertussis vaccine to the current tetanus–diphtheria (Td) boosters used in adults.

As indicated in the Introduction, estimates by health economists of the average cost per typical and atypical pertussis case in the age groups could be combined with the reductions found in the simulations here as part of a complete cost-benefit analysis of an expansion of the current pertussis vaccination program to include booster vaccinations for adolescents and adults.

6.1. Comparisons with pertussis data

The results of the simulations using the first model have previously been compared with 1940–1995 pertussis data [29]. In the simulations with both

models, the incidence drops in children are roughly consistent with the observed drops in reported incidence between 1940 and 1995 (see Fig. 1 in [29]). The average ages of pertussis incidence in 1940 in the simulations with both models agree with the average age of attack of 5 yr in the prevaccine era [2]. Moreover, in both models as shown in Figs. 5–9, there are major shifts in the age distribution of pertussis cases towards older age groups after 1940 and this is consistent with the shifts in the distributions of reported pertussis cases [26,27]. In the simulations with both models as seen in Figs. 5 and 6, 9 and 10, the total incidence per adult per year of pertussis between 1940 and 2040 is between 0.0004 and 0.0008. These values are consistent with a recent estimate of the attack rate in German adults of 0.00052 per person per year [7] and an estimated attack rate of 0.00069 among university students in the United States [5], but they are less than the estimate of 0.00176 among members of a Kaiser health plan in San Francisco [25].

A study of pertussis reporting in 1985–88 [33] estimated that 46% of infected infants under 1 yr of age were hospitalized for pertussis and that 34% of the hospitalizations of those under age 1 yr were reported to CDC. These data suggest that at least 16% of pertussis cases in infants under 1 yr of age are reported. In 1996 there were 2370 reported pertussis cases in infants under age 1 yr. Assuming that at least 16% are reported, there would have been at most 15 000 pertussis cases in infants under age 1 yr in 1996. Let us compare the results of the simulations with this estimate. In the baseline simulations in both models, the yearly incidence after 1995 in those under age 1 yr is 6000–8000 severe, typical cases and about ten times as many less severe, atypical cases. Because the study [33] also found that severe cases, especially those with hospitalizations and complications, are more likely to be reported, the simulation results are compatible with the upper estimate of 15 000 pertussis cases in this age group.

Using a United States population size of 265 million, the 1995 values using the first model are about 35 000 typical (full-disease) cases in those under age 10 yr and about 560 000 typical cases in those at least age 10 yr. Using the second simulation model, these 1995 values are about 10 000 typical cases in those under age 10 yr and about 130 typical cases for those at least age 10 yr. The 1985–88 study [33] estimated that from 30 000 to as many as 125 000 cases of clinical pertussis disease may occur annually in the United States. Because clinical cases would include the typical (full-disease or highest-infectivity) cases in the simulations, the values of about 35 000 or 10 000 typical cases in children under age 10 yr are consistent with the estimated range of clinical cases in the study [33]. This study also found that reporting is strongly biased towards cases in younger children, especially those with hospitalizations or complications, so that many cases in adults are not reported. Nevertheless, the value in the first model of 560 000 typical cases per yr in those at least age 10 yr seems too high to be consistent with the study upper bound of 125 000 clinical cases

per year, so that the return of some people to the fully-susceptible S class in the first model may be unrealistic.

6.2. *Effects of the childhood vaccination program*

In both models childhood vaccinations reduce typical (full-disease or highest-infectivity) pertussis cases in children under 10 yr of age by at least 99%. This is seen in Figs. 5 and 9 for the two models, where the typical cases among young children decrease after 1940 as vaccination levels increase and are replaced after 1960 by less severe disease, atypical cases with lower infectivity occurring in the removed and vaccinated classes. Thus a major benefit of the vaccinations of children is that they prevent many severe pertussis infections in the very early years of life, when the rates of complications are highest. In the baseline simulations for both models, there are very modest (6–11%) reductions in the atypical (lower-disease or lower-infectivity) pertussis cases. This occurs because childhood vaccination prevents the early, typical, severe cases, but these children have less severe, atypical cases later when the vaccine-induced immunity wanes. Thus childhood vaccination tends to delay a person's first pertussis case and then this first case is less severe. The simulation results are consistent with the observation of epidemiologists that pertussis vaccination provides only short term protection from infection, but it does reduce the disease severity of a pertussis infection [14–16,24,25].

The simulations show that vaccination programs do lead to some reduction in the reservoir of pertussis infection in the community, but they not lead to herd immunity. Thus the primary benefit of pertussis vaccination is to provide direct, temporary protection for vaccinated individuals against pertussis infections with more severe disease. Both before and after the pertussis vaccination program in the simulations with both models, adults typically have several less severe-disease pertussis infections with lower infectivity during their lifetime. This adult reservoir of infection occurs before vaccination starts in 1940 and continues as the vaccination coverage increases. As the childhood reservoir of infection decreases due to vaccination of children, the adult reservoir of infection becomes more important in transmission of pertussis. This is consistent with the observation that atypically infected mothers (or fathers) are now frequently the source of infections in babies and young children [13,15–17,8]. A pertussis infection with a less severe-disease case boosts the immunity of the person, so that a case with more severe-disease is less likely. The simulations show that the pertussis vaccination program has not eliminated this community-exposure type of pertussis boosting, which in the past was sometimes called 'streetcar boosting'. The computer simulations using both pertussis models with continued vaccination at the 1995 level show that the incidences might change slightly in some age groups, but no large changes occur in the incidences after 1995. This suggests that the observed trend of increasing re-

ported pertussis cases since 1976 may be due to some other factor such as an increase in the fraction of pertussis cases being reported.

6.3. *Effects of adding an adult pertussis booster program*

In the baseline-parameter simulations with the first model, giving booster vaccinations to all adolescents and adults every 10 yr starting at age 10 yr reduces the severe, full-disease cases by 66% in those at least 10 yr old and by only 3% in those less than 10 yr old. Thus adult boosting prevents typical, full-disease cases in adults, but has very little impact on these severe cases in children. The 20% reduction in the less-severe, atypical cases suggests that the community reservoir of infection is reduced somewhat, but not nearly enough for herd immunity.

For the second model simulations with baseline parameters, complete adult boosting reduces severe, typical cases by nearly 100% in those at least 10 yr old and by 28% in those under age 10 yr. These larger decreases are due to the more optimistic modeling of adult boosting in this model. The 36% reduction in the less-severe, atypical pertussis cases suggests that there is a somewhat larger reduction in the community reservoir of pertussis infection, but herd immunity is not attained. In the second model, people who have been vaccinated or had pertussis never lose all of their immunity and become fully susceptible, so that typical, severe cases in adults are rare in the simulations.

In simulations with both models, when complete adult boosting is suddenly added in the year 2000, the incidence jumps down from being almost at equilibrium and has a damped oscillatory approach to a new lower equilibrium. In the first model simulations, complete adult boosting leads in 40 yr after initiation to a 9% reduction in typical and atypical cases in children under age 10 yr and a 26% reduction in these cases in those at least 10 yr of age. In the second model simulations, complete adult boosting leads to a 20% reduction in all cases in children under age 10 yr and a 42% reduction in all cases in those at least 10 yr of age. These larger reductions using the second model are consistent with the more optimistic boosting used in it. The addition of adult boosting slightly decreases the significance of the adult reservoir of infection. In simulations with the first (second) model, the percentage of cases due to adults over age 18 drops from 45% (43%) with only vaccination of children to 37% (33%) with the addition of adult boosting every 10 yr, but these values are still above the 26% (34%) of cases due to adults in the prevaccine era.

What are the practical implications of the simulations of adult booster vaccinations? National Health Interview Survey estimates of the percentages of adults in the age groups 18–64 and over 65 yr, who received a tetanus-diphtheria (Td) booster within the past ten yr, are 56% and 29% in 1991, 61% and 34% in 1993, and 56% and 28% in 1994. One goal of the Healthy People 2000 project is to have at least 62% of adults receive a Td booster within the last 10 yr [34]. Because the acellular pertussis booster vaccinations would be combined

with the Td boosters, it is likely that only about 60% of adults would receive these acellular pertussis booster vaccinations. Thus the assumption in the simulations that adult boosting every 10 yr would be complete in the sense that 100% of adults would receive these booster doses is probably not realistic. When the simulations use 60% adult boosting every 10 yr instead of complete (100%) adult boosting, the effects are approximately 60% as large. Thus in the first (respectively, second) model, 60% adult pertussis boosting leads in 40 yr after initiation to a 6% (12%) reduction in typical and atypical cases in children under age 10 yr and a 13% (23%) reduction in these cases in those at least 10 yr of age. For the first (respectively, second) model, 60% adult pertussis boosting leads to a 2% (17%) reduction in the typical cases in children under age 10 yr and a 12% (22%) reduction in atypical cases overall. Thus these simulations are consistent with the basic concept that adult booster vaccinations provide direct temporary protection of those vaccinated and do reduce atypical cases in adults, but the modest reductions in cases in children suggests that booster vaccination programs do not cause a significant reduction in the pertussis reservoir of infection. Indeed, in simulations of the first (respectively, second) model with 60% adult pertussis boosting, the percentage of cases due to adults drops slightly from 45% (43%) with vaccination of children to 40% (37%) with the addition of adult boosting every 10 yr.

If the goal of adult boosting is to reduce the number or severity of atypical cases in adults, then the simulations suggest that adult boosting is moderately successful. In simulations with both models, the addition of an adult booster vaccination program leads to fewer atypical cases in adults and those atypical cases that do occur are more likely to be less severe-disease cases. But if the goal is to reduce the pertussis incidence in infants and children, then the simulations warn that adult boosting may be relatively unsuccessful. Because epidemiologists have been hoping that adult booster doses would have a large impact on pertussis incidences in young children, the relatively minor impact in the simulations is disappointing. However, an adult vaccination program focused on parents and grandparents of young children, schoolteachers, and pediatric health-care workers might be more effective in preventing cases in children than estimated in the simulations here. These simulations reinforce the insight that when the vaccine used gives only temporary immunity, a vaccination program does not have much effect on transmission in the population. Hence the primary benefit of pertussis vaccination of children or adults is the direct, temporary protection of those vaccinated.

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