

Adolescent and adult pertussis vaccination: computer simulations of five new strategies

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Abstract

Approximately one million adult pertussis cases occur annually in the US, and infants still die from pertussis. Computer simulations were used to predict the impact of vaccination of children, adults and/or adolescents, and household members of newborns (cocoon strategy). Childhood vaccination greatly reduced cases in children, but increased the incidence in adolescents and adults. Routine adolescent and adult vaccination had a large direct effect, whereas the cocoon strategy had a predominantly indirect effect on young infants. The number needed to vaccinate (NNV) to prevent a case of typical pertussis in the entire population was lowest for the adolescent strategy. The cocoon strategy had the lowest NNV to prevent a case of typical pertussis in young infants. The current vaccination schedule, local epidemiological data, age-specific cost of pertussis cases, and accessibility of the target population will determine which strategy has the highest likelihood of success in achieving the public health goal.

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1. Introduction

The incidence of pertussis has decreased dramatically since the introduction of pertussis vaccination programs. Currently, reported pertussis incidence is 50-fold lower than in the pre-vaccine era, but a gradual increase in cases has been reported during the past two decades in most industrialized countries [1]. While pertussis was traditionally perceived as a childhood disease, most of the increase has been noted in adolescents and adults [2–5]. It has been estimated that 0.9–1.5 million cases of symptomatic pertussis occur annually in adults in the United States [1,6]. Physicians rarely diagnose pertussis in adults and adolescents, since they do not present with the characteristic whooping cough [7,8]. In most countries, the highest incidence rate occurs in young infants, in whom most of the morbidity, hospitalization and mortality occur [5,9–12]. Young infants often present with atypical symptoms, making early diagnosis and effective management difficult [13–15]. Of all infants diagnosed with pertussis and reported to surveillance systems, two-thirds are admitted to a hospital, and infants too young to be vaccinated still die from pertussis [16,17]. Experts have sug-

gested that young infants will continue to be at risk until adolescents and adults are immunized, thereby reducing the reservoir of pertussis [18–21]. Experience with the administration of whole cell pertussis vaccine in adults gave poor results [22]. New acellular pertussis vaccines have recently been developed which are safe and immunogenic in adolescents and adults, allowing expansion of pertussis vaccination beyond the routine childhood immunization program [23].

This study evaluated the impact of five adolescent/adult immunization strategies (Table 1) by the use of computer simulations of a deterministic, age-structured compartmental model, i.e. a model with a fixed set of baseline parameters, in which the population is divided into different compartments according to age category and further subdivided into distinct epidemiological classes (susceptible, infectious, immune). Evaluating new strategies to control pertussis requires an understanding of the likely effects on the transmission dynamics and epidemiology of pertussis. The burden of adolescent and adult pertussis and the risk of severe pertussis disease in infants under 6 months of age prompted us to not only evaluate the direct effect (protection of those vaccinated) of the new adolescent and adult vaccination strategies but also to evaluate the indirect effect on infant pertussis.

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Table 1
Six simulated vaccination strategies

Strategy 1	Current US childhood vaccination schedule: vaccination of all children at age 2, 4, 6, 12–15 months and at age 4–6 years	Current coverage
Strategy 2	Strategy 1 + routine vaccination of adolescents at age 12	75% coverage in adolescents
Strategy 3	Strategy 2 + routine vaccination of adults every 10 years starting at age 20	60% coverage in adults
Strategy 4	Strategy 1 + selective vaccination of household contacts of newborns	90% coverage in households
Strategy 5	Combination of strategy 2 + strategy 4	Coverage as above
Strategy 6	Combination of strategy 3 + strategy 4	Coverage as above

2. Methods

2.1. The compartmental model for pertussis transmission and vaccination (Fig. 1)

In the model shown in Fig. 1, adapted from previously published models [24,25], the population is distributed among distinct epidemiological compartments: S (susceptible), N4 (highest level of naturally acquired immunity), WN3-1 (three levels of waning of naturally acquired immunity), V4 (highest level of vaccine-induced immunity), V1-3 (children having received one to three doses of pertussis vaccine) and WV3-1 (three levels of waning of vaccine-induced immunity). Persons infected with pertussis can either be asymptomatic or subclinical, present with mild pertussis (i.e. less than 3 weeks of cough), or have typical pertussis (i.e. satisfying the World Health Organiza-

tion (WHO) definition of pertussis with at least 3 weeks of paroxysmal cough) [26]. The arrows in Fig. 1 indicate the transfers between compartments due to infection, recovery, waning of immunity, and vaccination.

As infection-acquired immunity wanes over time, people move from N4 through WN3 and WN2 to WN1. When infected or vaccinated, a person with pre-existing natural immunity (WN1, WN2, or WN3) moves up to the highest level of natural immunity (N4). Four doses of vaccine are required to obtain the highest level of vaccine-acquired immunity (V4). As vaccine-induced immunity wanes, people move from V4 through WV3 and WV2 to WV1. A single booster dose in individuals primed with at least two doses of pertussis vaccine produces a good immune response. This is consistent with several studies, which found that boosting after 1 year of age was equally efficacious after either two or three vaccine doses [27–30]. Hence, one vaccination moves

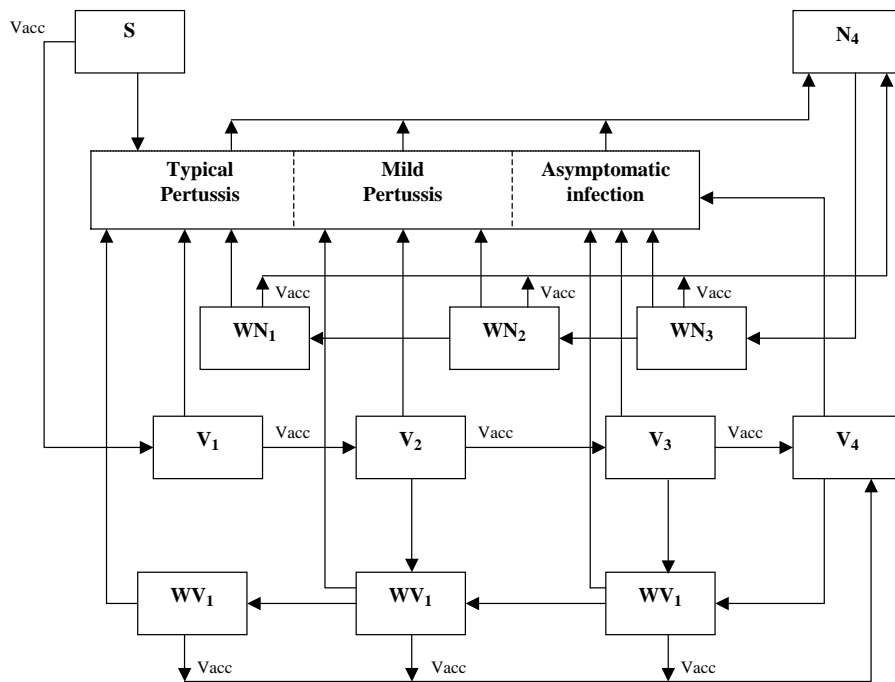


Fig. 1. Transfer diagram. The population is distributed among distinct epidemiological compartments: S, susceptible; N4, highest level of naturally acquired immunity; WN3-1, three levels of waning of naturally acquired immunity; V4, highest level of vaccine-induced immunity; V1-3, children having received one to three doses of pertussis vaccine; and WV3-1, three levels of waning of vaccine-induced immunity. Persons infected with pertussis can either be asymptomatic, present with mild or typical pertussis. Arrows indicate transfers between compartments due to infection, recovery, waning of immunity, and vaccination.

a previously vaccine-primed person to the highest level of vaccine-derived immunity (V4).

Infants in the V1 class never return to the class of fully susceptible individuals (S). Those who miss one of the 2-, 4- or 6-month dose, but receive a third dose after the age of 1 year, move up to the highest level of vaccine-induced immunity (V4). Infants who only received three initial doses move down to WV3, which has the same level of protection against typical pertussis. This is consistent with the data indicating that protection against typical pertussis after three childhood doses of acellular pertussis vaccine persists for 6 years [31].

Movement of individuals out of the compartments N4, WN2-3, V2-3 and WV2-3 is modeled by daily transfers of a fraction of the population in these compartments, where the fraction is the reciprocal of the average residence time in the compartment. Similarly, movements of individuals out of the three compartments of infectives (typical, mild, asymptomatic) are modeled by daily transfers of the fractions equal to the reciprocals of the average infectious periods. For example, if the average infectious period is 28 days, then 1/28th of infectives are transferred each day. The latent period is not included in the model. The force of infection on a susceptible is the summation of the number of infectives of the three types times their relative infectivities. Individuals who come into contact with an infectious person will develop typical, mild or asymptomatic pertussis depending on their level of pre-existing immunity. The incidence of pertussis in people in a compartment is the product of the force of infection and the number of people in that compartment.

Vaccination transfers fractions of the population, corresponding to the coverage rate at specific ages. Ages of vaccination represent the United States recommended vaccination schedule: DTaP at the ages of 2, 4, 6, 12–15 months and at age 4–6 years. The population is distributed among 50 age groups—months: 0–1, 2–3, 4–5, 6–11, 12–17, 18–23 months; years: 2, 3, . . . , 33, 34; 5-year intervals: 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84; and 85 years or older. Newborns enter the 0–1-month age group. In each age group there is a daily inflow from a previous age group, a daily outflow corresponding to aging, and a daily death rate.

2.2. Estimates of demographic and epidemiological parameter values

Recent fertility and death rates in the United States were used to obtain a theoretical population whose total size is constant and whose age distribution has reached a steady state. This is a reasonable assumption since US fertility and death rates have been nearly constant over the past 20 years [32].

The mean infectious periods for typical, mild, and asymptomatic pertussis are set at 4, 3, and 1 week, respectively, to account for the 1-week catarrhal stage and the duration of cough in the paroxysmal stage [33]. Although pertussis

transmission occurs primarily by aerosol droplets produced during a coughing episode, people with asymptomatic or subclinical infection could transmit during the 1-week period of the infectious catarrhal stage. The relative infectivities of typical, mild, and asymptomatic pertussis are chosen to be 1, 1, and 0.2, respectively. In this model, people with mild pertussis are assumed to have the same net infectivity as a typical case even though they probably cough less because they continue their daily activities and thus do not decrease their community contact patterns.

The median residence time in each of the naturally acquired immunity compartments (N4, WN3, and WN2) is 8 years. This value is consistent with the frequency of second infections [34], the observations that second episodes of pertussis in children rarely occur in preteens and similarity in attack rate in those with and without a history of pertussis after 20 years [35]. The median residence times in each of the vaccine-induced immunity compartments (V4, WV3, and WV2) is 4 years. This value is consistent with efficacy trials of 5-component acellular vaccine, which showed no decrease in vaccine efficacy during the first 2 years [36] and with data demonstrating good protection for a period of 6 years against disease following three infant doses of aP vaccine [31].

An innovative feature of the pertussis model used in this study is that the distribution of severity of disease depends on the immune status of the person infected (Table 2). The S distribution is based on historical data on the presentation of pertussis in children in the prevaccine era. V1 and V2 percentages are based on a Swedish surveillance study, which demonstrated a decrease in hospitalization rate and duration of hospitalization but minimal efficacy in protection against disease after the first dose [37]. The largest decrease in incidence of severe pertussis occurred after the second dose. V3 and V4 percentages are based on an efficacy trial with the 5-component acellular vaccine [36]. WV3, WV2, and WV1 percentages are based on data of disease presentation at different ages during outbreak and household contact studies

Table 2
Distributions (in %) of distinct outcomes of contact with an infectious person according to immune status

	Typical pertussis	Mild pertussis	Asymptomatic infection	Not infected
S	73	25	2	0
V1	65	20	5	10
V2	20	10	20	50
V3	15	7	7	71
V4	10	5	5	80
WV3	15	15	30	40
WV2	20	20	35	25
WV1	25	25	40	10
N4	0	0	0	100
WN3	0	10 (5)	30	60 (65)
WN2	5 (1)	15 (10)	35 (45)	45 (44)
WN1	10 (2)	30 (15)	45 (60)	15 (23)

Values in parentheses are used in the sensitivity analysis (Section 3.10.4).

[35,37–55]. The N4 distribution is based on the assumption that natural infection provides temporary protection against infection and disease. Due to the paucity of data, the remaining distribution values are educated estimates. The percentages in parentheses are the values used in a sensitivity analysis (Section 3.10.3).

Historical data are used to estimate vaccination coverage between 1940 and 2002, as described previously [34]. Strategy 1 assumes that the childhood vaccination levels in 2002 are continued through 2040. For strategy 2, 75% coverage in adolescents represents the coverage obtained in the USA for adolescent hepatitis B vaccination [56]. The aP vaccination for adults would probably be combined with the tetanus–diphtheria (Td) booster. The 60% coverage in adults for strategy 3 is consistent with the level of decennial coverage with the currently recommended tetanus–diphtheria booster among US adults [57]. Strategy 4 provides a protective household cocoon for an infant by vaccinating all household members (including parents and siblings) who have not been vaccinated in the past 5 years. A high compliance rate of 90% is expected, since parents on the day of birth would be motivated to be vaccinated to protect their newborn baby. Different levels of vaccination coverage were investigated in sensitivity analyses.

Estimates of forces of infection for pertussis in the prevaccine era are based on those available in the literature [58–60] and were set at 0.11 for 4–23 months, 0.32 for 2–4 years, 0.35 for 5–10 years, 0.21 for 11–17 years, 0.04 for 18–24 years and 35–64 years, and 0.03 for >65 years. The force of infection in infants 0–3 months who have few daily contacts was set at 0.05, about half of that of 4–23 month old infants. The force of infection for the 25–34-year-old age group was set slightly higher (0.05) compared to other adults to reflect the higher incidence found in this age group [37].

The prevaccine steady state prevalences in the infectious classes and the estimated forces of infection were used to determine the entries in the contact matrix. The 9×9 mixing matrix is a larger version of widely used Who Acquires Infection From Whom (WAIFW) matrices [59,61,62]. The nine age groups in the WAIFW mixing matrix correspond to newborn babies (0–3 months), infants (4–23 months), preschool children (2–4 years), elementary school children (5–10 years), secondary school children (11–17 years), college-age adults (18–24 years), young adults (25–34 years), older adults (35–64 years), and senior citizens (>65 years).

In order to simulate strategy 4 (the cocoon strategy), newborn infants are divided into those who are protected by vaccination of household members and those who are not. It is assumed that the children born into vaccinated households have the same transmission rate from the community, but only 10% of the baseline transmissions from within the household, corresponding to a vaccine efficacy of 90% for household members. Any benefit from this household cocoon protection disappears after age 5 years when the immunity of the household members wanes and children have

increasing contacts outside their household. Data on the proportion of children infected by household members are limited. The results of the French RENACOQ Study (Bonmarin, personal communication) indicate that the fractions of children of ages 0–1, 2–3, 4–5, 6–11, 12–17, 18–23 months and 2, 3, 4, and 5 years with known source of infection infected by a parent or sibling are 0.87, 0.78, 0.82, 0.67, 0.74, 0.88, 0.72, 0.85, 0.74 and 0.50, respectively. Similar proportions for infants less than 12 months of age were observed in the United States [63], where out of 174 cases with known source, the source was a mother in 31%, father in 13%, siblings in 11%, grandparents in 9%, and non-household members in 27%.

Data on child spacing and multiple births in the United States were used to estimate the number of parents to be vaccinated in the cocoon strategy [64]. Women who deliver more than 5 years after the last vaccination receive a booster dose. The fractions of delivering women to be vaccinated in years 2003, 2004, 2005, 2006, and 2007–2040 are 0.90 (reflecting the 90% participation) times 0.88, 0.87, 0.77, 0.65, and 0.57, respectively. The ages of vaccination of the mothers correspond to the age-specific fertility data. Based on data in the United States, 74% of mothers have a male partner living in the same household who is on average 3 years older [65]. For every woman vaccinated in the simulation model, 0.74 men who are three years older were also vaccinated in the simulations.

3. Results

3.1. Prevaccine era

Most of the typical pertussis cases in the prevaccine steady state occur in children (Table 3), consistent with historic observations. In the prevaccine steady state cohort, people have an average of 0.68 mild pertussis episodes and 0.95 asymptomatic pertussis infections during their lifetime, and 83% have at least one episode of typical pertussis.

3.2. Strategy 1: Maintaining the current childhood vaccination program

Childhood vaccination led to a 65% reduction in typical, 44% reduction in mild cases and 28% reduction in asymptomatic infections in the year 2002 compared to 1940. The results are consistent with the concepts that pertussis vaccination has a higher efficacy against typical disease compared to mild pertussis disease and vaccination protects against disease but not infection [44,47,66]. Childhood vaccination increased the average age of infection and thus increased the burden of pertussis in adolescents, in whom the incidence rate of typical pertussis doubled from 575 in 1940 to 1202 in 2002 (Table 3). This is similar to the estimated pertussis incidence rate of 997 among adolescents in Massachusetts and confirms the high rates in adolescents reported in the

Table 3
Computer simulations of age-specific pertussis incidences (per 100,000 population)

	Age group									
	0–3 months	4–23 months	2–4 years	5–10 years	11–17 years	18–24 years	25–35 years	35–64 years	>64 years	All ages
Prevaccine era (1940)										
Typical cases	3604	7059	11327	3705	575	95	163	181	158	1072
Mild cases	1235	2423	4109	2034	1054	306	554	603	521	885
Asymptomatic cases	99	221	986	2278	2359	702	1169	1135	930	1231
Strategy 1 (2002)										
Typical cases	1491	706	965	1497	1202	118	160	129	97	380
Mild cases	488	406	724	1257	1424	189	308	337	292	498
Asymptomatic cases	74	596	1174	2149	2775	383	599	588	483	891
Strategy 1 (2040)										
Typical cases	1524	678	924	1471	1271	127	179	159	118	400
Mild cases	497	397	693	1215	1471	195	318	341	294	502
Asymptomatic cases	76	581	1112	2060	2843	393	614	602	493	897
Strategy 2 (2040)										
Typical cases	1260	550	761	1339	940	129	186	155	105	347
Mild cases	411	322	569	1098	912	167	277	295	254	403
Asymptomatic cases	63	471	914	1850	1666	327	521	513	421	701
Strategy 3 (2040)										
Typical cases	992	476	682	1263	920	87	118	79	39	281
Mild cases	324	279	510	1035	880	99	151	128	88	278
Asymptomatic cases	50	409	818	1735	1598	189	288	245	175	495
Strategy 4 (2040)										
Typical cases	456	237	290	1484	1451	118	154	132	107	363
Mild cases	148	135	217	1211	1591	165	237	265	262	440
Asymptomatic cases	24	194	349	2027	3015	328	459	483	439	793
Strategy 5 (2040)										
Typical cases	366	185	228	1291	1064	121	165	130	93	307
Mild cases	119	106	170	1049	987	144	215	228	221	344
Asymptomatic cases	19	152	273	1752	1769	276	400	408	367	602
Strategy 6 (2040)										
Typical cases	301	165	207	1213	1043	84	111	75	37	257
Mild cases	98	94	154	987	961	90	129	113	81	252
Asymptomatic cases	16	135	248	1649	1713	169	242	216	161	450

US, Canada and Australia [4,5,67,68]. The simulations predicted a decrease in the adult incidence of mild and typical pertussis from 702 cases per 100,000 adults per year in 1940 to 438 in 2002. The 2002 incidence in adults is comparable to the recent estimate of 337 cases per 100,000 adults (age 20–49) per year based on surveillance data and the estimated incidence of symptomatic disease of 400–700 per 100,000 person years based on active case finding during a vaccine efficacy trial [6,67]. When the current childhood vaccination program was continued until year 2040, the pertussis incidence remained stable for most age groups, suggesting that significant changes would not be expected if the current pertussis vaccination program remained unchanged.

3.3. Strategy 2: Routine adolescent vaccination

Routine adolescent vaccination leads to a 19% overall reduction in pertussis burden, a 13% reduction in typical

cases, 20% reduction in mild cases, and a 22% reduction in asymptomatic infections in the year 2040 compared to the predicted values in 2040 with the current childhood vaccination strategy (strategy 1). Most of this reduction in incidence is due to the direct effect in the 11–17-year-old age group with reductions in typical and mild pertussis of 26 and 38%, respectively (Table 3). The adolescent vaccination program leads to some herd immunity, so that there are decreases in the pertussis burden in the 0–3-month, 4–23-month and 2–4-year age groups (Tables 3 and 5).

3.4. Strategy 3: Routine adolescent and adult vaccinations

Strategy 3 leads to a 30% reduction in typical cases, and 45% reductions in mild and asymptomatic infections in the overall population in 2040 compared to the 2040 childhood vaccination values (Table 3). This vaccination program not

only has a substantial direct effect in the adolescent and adult population, but also has a sizeable indirect effect with 35, 30 and 26% reductions in mild and typical cases in the 0–3-month, 4–23-month and 2–4-year age group, respectively, when compared to the 2040 childhood vaccination values (Table 5).

3.5. Strategy 4 or cocoon strategy: Vaccinations of household members for the protection of newborns

The cocoon strategy leads to a 9% overall reduction in typical cases, and 12% reductions in mild and asymptomatic cases in year 2040 compared to the 2040 childhood vaccination values. This vaccination strategy has only a moderate direct effect with 9–17% decreases in typical cases and 11–25% decreases in mild pertussis cases in the adult population. The indirect effect on young children is very strong: typical cases decrease by 70, 65 and 69% in the 0–3-month-old, 4–23-month-old, and 2–4-year-old age groups, respectively, when compared to the 2040 childhood vaccination values. The cocoon strategy has no effect on the 5–10 year age group, but does cause a 14% increase in the incidence of typical pertussis in adolescents.

3.6. Strategy 5: Combination of routine adolescent and cocoon vaccination strategies

This combination strategy leads to a 23% overall reduction in typical cases, and 31 and 33% reductions in mild and asymptomatic cases, respectively, in year 2040 compared to the 2040 childhood vaccination values (Table 3). These percentage decreases are approximately equal to the sum of the percentage decreases with the two separate strategies. Similar to the cocoon strategy, the largest impact is in the youngest age groups, with reductions in typical pertussis cases of 76% in the 0–3-month-old, 73% in the 4–23-month-old, and 75% in the 2–4-year-old age groups, when compared to the 2040 childhood vaccination values. Because of the additional effect of the adolescent vaccination, there is now a reduction of 16% in typical pertussis in adolescents instead of an increase of 14% using the cocoon strategy alone.

3.7. Strategy 6: Combination of routine adolescent, routine adult, and cocoon vaccination strategies

This combination strategy leads to a 36% overall reduction in typical cases and 50% reductions in mild and asymptomatic cases in year 2040 compared to the 2040 childhood vaccination values (Table 3). Compared to strategy 5, there is a small additional indirect effect of 2–4% decrease in typical cases in children of all age groups. The direct effect on adolescents is approximately equal to that of strategy 5. The direct effect on adults is comparable to that seen in strategy 3 (routine adolescent and adult vaccination).

3.8. Comparisons of impact of the five new strategies on age-specific pertussis incidences

The incidence of typical pertussis in young children (age 0–23 months) decreases with all five strategies when compared to the current childhood vaccination strategy (Fig. 2). A large decrease occurs with those strategies that contain a “cocoon” component (strategies 4, 5 and 6). Among older children and adolescents, all strategies except for strategy 4 (cocoon) provide a small additional protection against typical pertussis as compared to the current childhood vaccination program (Fig. 3). The effect on adult pertussis is the largest with strategies 3 and 6, strategies that include vaccinating all adults every 10 years (Fig. 4). A smaller effect on adult pertussis is seen with those strategies that selectively vaccinate adults in contact with newborns (strategies 4, 5). Adolescent vaccination has no significant effect on the incidence of typical pertussis in adults.

3.9. Comparisons of the number needed to vaccinate to prevent one case of typical pertussis

The cocoon strategy (strategy 4) was the most efficient strategy per dose administered for the prevention of typical pertussis in young infants. As shown in Table 4, the number needed to vaccinate (NNV) to prevent one case of typical (severe) pertussis in infants age 0–3 months was 444 for the cocoon strategy, compared to NNVs of 605 for strategy 5 (adolescent + cocoon), 853 for strategy 2 (adolescent), 1340 for strategy 6 (adolescent + adult + cocoon), and 2325 for strategy 3 (adolescent + adult). The adolescent vaccination strategy was the most efficient strategy per dose in preventing typical pertussis in the entire population. The NNV to prevent one case of typical pertussis in all age groups was 20 for strategy 2 (adolescent) compared to 35 for strategy 5 (adolescent + cocoon), 49 for strategy 3 (adolescent + adult), 59 for strategy 4 (cocoon), and 56 for strategy 6 (adolescent + adult + cocoon).

3.10. Sensitivity to changes in parameter values and model assumptions

3.10.1. Changes in forces of infection and contact matrix (Table 5)

Although the values of the force of infection used in the simulations were consistent with surveillance data given by a cumulative infection curve, it was difficult to evaluate the precision of the forces of infection used for the very young infants, adolescents, and adults. When the force of infection in 0–3-month-old children was increased from 0.05 to 0.11 (equal to the value for the 4–23-month age group), the relative effects of the new strategies on typical pertussis in infants remained unchanged. Halving the force of infection in adolescents to 0.105 led to similar mixing rates of adolescents with children under 2 years of age but lower mixing rates with other younger children. In this case, the rela-

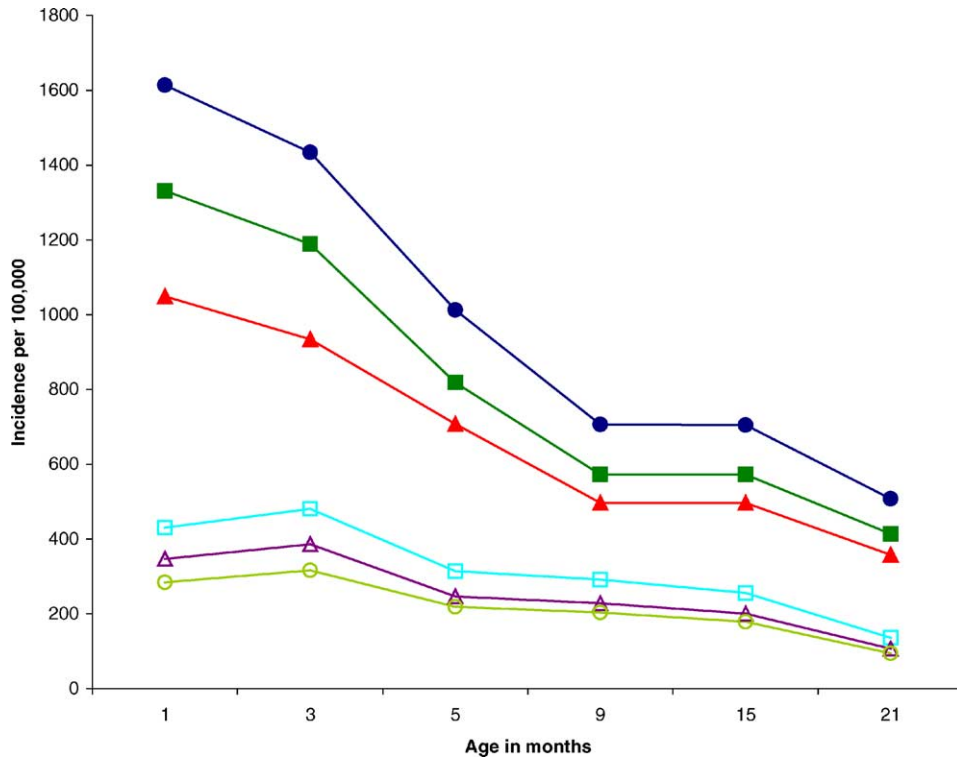


Fig. 2. Incidence of typical pertussis in infants in 2040 with six strategies: childhood vaccination only (filled circle), routine adolescent vaccination (filled square), routine adolescent and adult vaccination (filled triangle), household cocoon vaccination (open square), routine adolescent and cocoon vaccination (open triangle), routine adolescent + routine adult + cocoon vaccination (open circle).

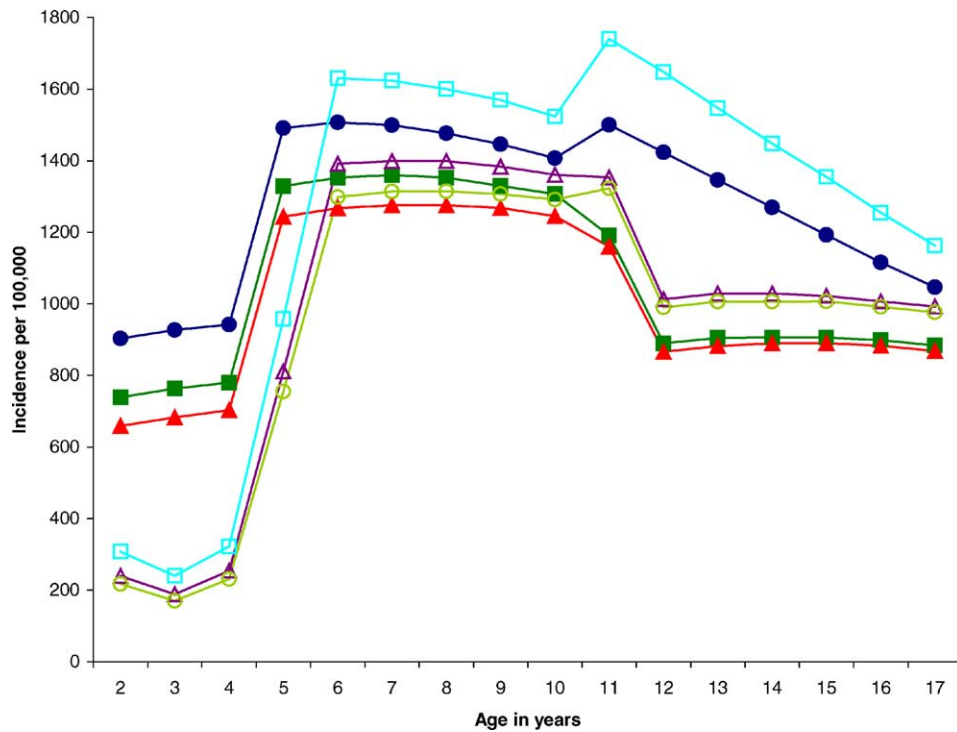


Fig. 3. Incidence of typical pertussis in children and adolescents with six strategies: childhood vaccination only (filled circle), routine adolescent vaccination (filled square), routine adolescent and adult vaccination (filled triangle), household cocoon vaccination (open square), routine adolescent and cocoon vaccination (open triangle), routine adolescent + routine adult + cocoon vaccination (open circle).

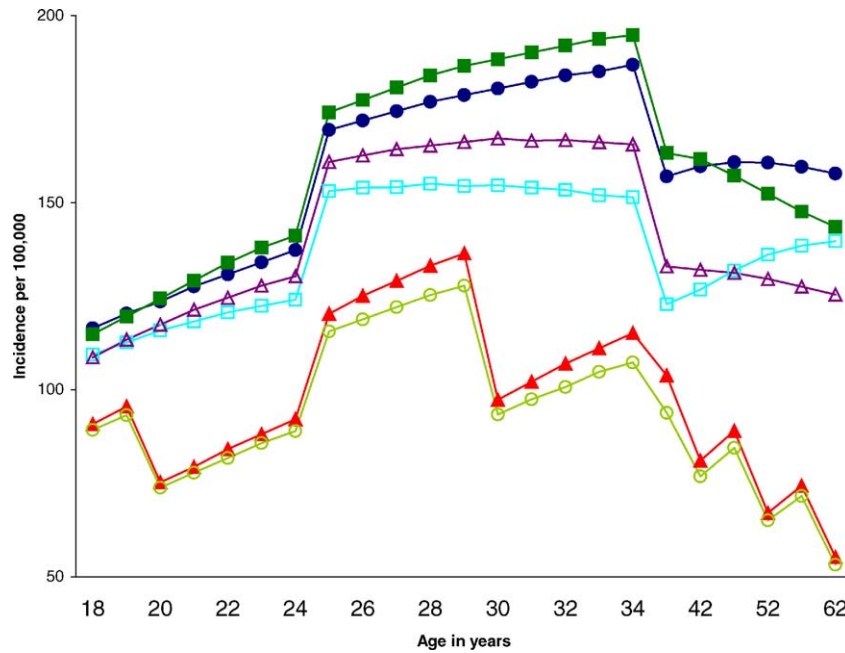


Fig. 4. Incidence of typical pertussis in adults with six strategies: childhood vaccination only (filled circle), routine adolescent vaccination (filled square), routine adolescent and adult vaccination (filled triangle), household cocoon vaccination (open square), adolescent and cocoon vaccination (open triangle), routine adolescent + routine adult + cocoon vaccination (open circle). The incidence in adults with routine adolescent and adult vaccination looks erratic, because the simulation assumes that 60% of adults are vaccinated at ages 20, 30, 40, 50, 60, 70, and 80 years.

tive effectiveness of the new vaccination strategies was also preserved. Doubling the forces of infection in adults caused small increases in the incidence in children and substantial increases in the adult incidence. In this situation, strategies 2 and 3 were about equally effective per dose in reducing typical cases in infants, and the cocoon strategy was about five times as effective as them. For the baseline analysis and sensitivity analysis described above, the probability of contact between individuals was age-dependent, derived from data obtained by serological studies and expressed by a 9×9 WAIFW matrix. Switching to a commonly used alternative, the proportionate mixing matrix, where the probability of contact between individuals is proportionate to the product of activity levels of the two interacting age groups [34], changed the pertussis incidence, but the relative indirect effect of the five new strategies on infant pertussis remained similar.

3.10.2. Changing the relative infectiousness of typical, mild and asymptomatic pertussis

There are no reliable data on the relative infectiousness of persons with typical, mild and asymptomatic or subclin-

ical pertussis. Sensitivity analysis was performed by changing the relative infectiousness from 1, 1, and 0.2 to 1, 0.5, and 0.01 for typical, mild, and asymptomatic pertussis, respectively. With these values childhood vaccination led to greater decreases in pertussis incidence in 2002 and 2040. Moreover, the additional percentage reductions in pertussis incidence were somewhat greater for strategies 2, 3, and 5. However, the indirect effect on the infant pertussis remained the greatest with the cocoon strategy.

3.10.3. Changing the median residence times in compartments

Even though most experts believe that vaccine-induced immunity wanes faster than infection-acquired immunity, there is uncertainty in the waning rates of immunity with time. In a sensitivity analysis, the median residence times for infection-acquired immunity were set at 4 years (equal to those for vaccine-acquired immunity). The impact of the different vaccination strategies on the pertussis incidence was sensitive to these changes. However, the cocoon strategy was still more effective in reducing infant pertussis. Changes in the median residence times in the infectious classes and in

Table 4
Numbers needed to vaccinate (NNV) (adolescent and adult doses) to prevent one typical pertussis case

Population in which 1 case of typical pertussis is prevented	Number of adolescents/adults needed to vaccinate				
	Strategy 2	Strategy 3	Strategy 4	Strategy 5	Strategy 6
In infants age 0–3 months	853	2325	444	605	1340
In infants age 0–23 months	250	804	146	194	453
In total population	20	49	60	36	57

the vaccine-acquired immunity classes V2 to V4, WV3 and WV2 altered the incidences slightly, but the relative impact of the five new strategies remained approximately the same.

3.10.4. Changing the distributions of the severities of disease

The proportions of people in WN3, WN2, and WN1 that develop typical, mild, and asymptomatic pertussis following infection were assessed using the values in parentheses in Table 1. This reduced the typical and mild pertussis incidence and increased the occurrence of asymptomatic cases in those over 2 years of age. However, the incidences in those less than 2 years of age were similar to those with the baseline parameter set. The relative impact of the different strategies on infant pertussis therefore remained unchanged. Likewise, there were only minor changes in incidence in infants when different proportions of those in V1–V4 and WV1–WV3 moving into typical, mild, and asymptomatic disease categories were simulated.

3.10.5. Changes in vaccination coverage levels

Changes in vaccination coverage levels for the childhood vaccination program and for the new vaccination strategies did not lead to substantive changes in the relative impact on infant pertussis of the five new vaccination strategies. For example, if for strategy 4 (cocoon) only 70% (instead of 90%) of households participate, then strategy 4 remains the most efficient in reducing pertussis in young children age 0–4 years (Table 5).

3.10.6. Changing the fraction of children infected by parents and siblings (Table 5)

For the baseline analysis, the fractions of infants infected by household members were derived using a subgroup of infants in whom a suspected source of *Bordetella pertussis* was reported. This might overrepresent the importance of household members in the transmission to infants as household members are more likely to be reported as the sus-

pected source. Using all infant pertussis cases reported to the French RENACOQ surveillance study, including those with unknown sources of infection, the fractions of children of ages 0–1, 2–3, 4–5, 6–11, 12–17, and 18–23 months and 2, 3, 4, and 5 years infected by a parent or sibling (0.60, 0.49, 0.41, 0.34, 0.39, 0.42, 0.38, 0.41, 0.40, and 0.20) are lower. These lower values most likely underestimate household transmissions, since parents and siblings could be the source of cases with unknown source of infection. When the lower estimates were used in a sensitivity analysis simulation, the cocoon strategy led to a 7% overall reduction in typical cases, and 10% reductions in mild and asymptomatic cases in year 2040 compared to the 2040 childhood vaccination values. Thus, with these lower estimates, the indirect effect on young children was not as strong. As shown in Table 5, typical cases decreased by 48, 36, and 38% (instead of 77, 65, and 69%) in the 0–3-month-old, 4–23-month-old, and 2–4-year-old age groups, respectively, when compared to the 2040 childhood vaccination values. However, the cocoon strategy was still the most effective strategy to reduce cases in infants with 644 vaccinations needed to prevent one case of typical pertussis in infants of age 0–3 months.

3.10.7. Changing to different models

Mathematical models have played an important role in the analysis of complex and varied epidemiological trends of many infectious diseases. While most models used in the study of pertussis share common features (e.g. have a deterministic, compartmental structure and incorporate waning immunity), there is substantial variation in the degree of complexity with which population contact patterns, the natural history of infection, and changes in immunity is described by the different models [24,25]. The sensitivity of the simulation results to changes in the model structure in Fig. 1 was examined by looking at two model variations. The first new model assumed that immunity wanes faster when children do not receive the first three doses of infant vaccination, so that they move from V2 to WV1, which has

Table 5
Sensitivity analysis and reductions in typical pertussis cases in young children for three new vaccine strategies compared to the current childhood vaccination (strategy 1)

Age of pertussis case	Strategy	Baseline values (%)	Sensitivity analysis (%)					
			Higher λ in infants 0–3 months	Lower λ in adolescents	Higher λ in adults	Proportionate WAIFW	Lower transmission from household contacts	Lower (70%) coverage rate for strategy 4 (cocoon)
0–3 months	2	–17	–18	–16	–5	–29	–17	–17
	3	–35	–29	–33	–45	–45	–35	–35
	4	–70	–70	–70	–71	–86	–48	–39
4–23 months	2	–19	–18	–18	–9	–29	–19	–19
	3	–30	–29	–28	–36	–45	–30	–30
	4	–65	–66	–64	–65	–84	–36	–29
2–4 years	2	–18	–16	–13	–9	–28	–18	–18
	3	–26	–25	–35	–31	–43	–26	–26
	4	–69	–69	–77	–69	–84	–38	–31

a lower immunity level than WV2. The second new model assumed that immunity also wanes faster when children do not receive the fourth dose at the age of 12–17 months. These children move from V3 to WV2, which has a lower level of immunity than WV3. With both of these new models, there was very little change in the incidences and the percentage reductions with the new strategies were almost the same as with the model in Fig. 1. Thus the results were insensitive to these two changes in the structure of the model.

4. Discussion

Reemergence of pertussis in highly immunized countries over the past decade has raised concerns about the current pertussis control strategy. The advent of safe acellular pertussis vaccines has triggered considerable interest in adolescent and adult pertussis vaccination as this might not only reduce the pertussis burden in adolescents and adults, but also reduce pertussis morbidity and mortality in young infants in whom pertussis is often severe and life threatening. There is, however, a great amount of uncertainty surrounding the epidemiological impact of new vaccination strategies in already highly vaccinated communities. Mathematical modeling is a scientific method that allows one to assess the impact of new vaccination strategies prior to implementation. The main aim of this analysis was to evaluate and compare the impact of five different adolescent and adult vaccination strategies on the burden of pertussis disease and circulation of *B. pertussis*.

The computer simulation results indicate that *B. pertussis* cannot be eradicated by the current childhood pertussis vaccination program or by any of the five new strategies evaluated. This confirms the observation that, while childhood pertussis vaccination programs have been highly successful in controlling pertussis disease, they have not been able to stop the circulation of *B. pertussis* in the community. Overall reductions of 36% in typical cases and 50% in mild and asymptomatic cases, obtained with the most extensive vaccination strategy (the adolescent–adult–cocoon combination), was the most that could be achieved with any of the new strategies.

Results of the analysis also indicate that there is no one single strategy that is superior in all respects. Different vaccination strategies have diverse direct and indirect (herd immunity) effects on specific age groups. Furthermore, reduction of the burden of pertussis in one age group can lead to a rise in the incidence of pertussis in an older age group. The routine adolescent and adult vaccination strategies had mainly a large direct effect, reducing the burden in those who received the vaccine, whereas the strategies involving vaccination of household members of newborns (cocoon strategy) had a large indirect effect on young infants. Based on the number needed to vaccinate to prevent one case of typical pertussis in the entire population, adolescent vaccination was 1.8 times as effective as the adolescent–cocoon com-

bination strategy, and about 2.5–3 times as effective as the other strategies. Similarly, based on the number needed to vaccinate to prevent a case of typical pertussis in infants age 0–3 months, the age group with the highest hospitalization, complication and mortality rate, the selective vaccination of household members of newborns strategy was about 1.3 times as effective as the adolescent–cocoon combination, and about 2–5 times as effective as the other strategies. According to these results, adolescent vaccination seems to be the most dose-effective strategy of those evaluated in reducing typical cases in the entire population, while the cocoon strategy seems to be an effective program for reducing pertussis in infants. Preventing typical cases of pertussis in young infants would have a critical impact on pertussis deaths and hospitalizations as more than 90% of pertussis deaths and more than 80% of pertussis hospitalizations occur in this age group [5,17,69,70]. Although the adolescent–cocoon combination strategy was not the most effective strategy per vaccine dose in reducing typical cases in either infants or all age groups, it was reasonably effective in both groups, so that it could be a very effective overall policy.

As in all simulations using mathematical models, there is the limitation of the uncertainty in the model formulation and parameter estimates. In this study, we have attempted to account for these limitations by validating the model output against available data, by exploring the sensitivity of the model to changes in key input parameters over a wide range of values, and by exploring the model sensitivity to changes in model structure. Simulations of the current childhood vaccination program resulted in a large reduction of childhood cases and a shift of pertussis cases towards older age groups, consistent with epidemiological observations. The predicted 2002 pertussis incidence of 438 per 100,000 adults was similar to the recent estimate of 337–507 cases per 100,000 adults (age 20–49 years) per year based on surveillance data and consistent with the incidence of symptomatic adult pertussis of 400–700 cases per 100,000 person years as estimated in a vaccine efficacy trial [6,60]. The predicted 2002 incidence of all pertussis, symptomatic and asymptomatic, of 1799 per 100,000 population is consistent with the 1000–5000 per 100,000 estimate obtained by seroepidemiological studies [71].

Changes in forces of infection, relative values for and type of contact matrix, relative infectiousness of typical, mild and asymptomatic pertussis, duration of vaccine-induced and natural immunity, relative infectiousness of asymptomatic, mild and typical pertussis, vaccination coverage levels and model structure affected the magnitude of changes in pertussis incidence following the introduction of a new vaccination strategy. The comparisons of the relative impact on typical pertussis of the different strategies however remained consistent over a plausible range of parameter values and model assumptions. The parameter to which the model was the most sensitive was the proportion of infants and young children infected by parents and siblings. When the proportions of young infants infected by household members were

reduced in a sensitivity analysis, the cocoon strategy was still 1.3 times as effective in the protection of young infants as the adolescent vaccination strategy. The results of an ongoing study designed to obtain more robust data on household transmissions will allow more definite predictions on the indirect effect of the various adolescent and adult vaccination strategies.

In conclusion, using a modeling approach, we have been able to demonstrate that, in the United States, the adolescent strategy, cocoon strategy and adolescent-cocoon combination strategy seem to be the more promising policies to further reduce the morbidity and mortality of pertussis, realizing that other important factors such as the age-specific cost of pertussis cases and accessibility of the target population also need to be taken into account when determining which strategy has the highest likelihood of success in achieving the public health goal.

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