

## Using computer simulations to compare pertussis vaccination strategies in Australia

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### Abstract

High levels of notified pertussis in adolescents and adults, persisting severe disease (hospitalization and deaths) in infants despite high childhood immunization coverage, together with the availability of adult-formulated pertussis vaccines, have made alternate strategies for vaccine control of pertussis an important issue in Australia. An age-structured computer simulation model was used to compare the likely effects of adopting different vaccination strategies in Australia on pertussis transmission by age group over a 50 year time period. Epidemiological parameters and vaccination coverage in Australia were estimated from previous pertussis modeling studies and existing data. In the simulations, replacing the pertussis booster at 18 months with a booster dose for adolescents at an age between 12 and 17 years, assuming 80% coverage, led to decreases in pertussis cases of 30% in children of ages 0–23 months (who have the highest complication rates) and of 25% in adolescents, but an increase of 15% in cases in 2–4-year-old children. The simulations did not suggest any shift of pertussis cases into the adult child-bearing years. Varying parameter values in the simulations in a series of sensitivity analyses showed the model predictions to be robust over a plausible range. The results of these simulations suggest that the recent change in the Australian pertussis vaccination schedule, replacing the 18 month dose with a pertussis booster in 15–17-year-old adolescents, is very likely to reduce overall pertussis incidence in Australia without increasing the cost of the current vaccine program.

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### 1. Introduction

Of all the diseases preventable by vaccines currently on the Australian Standard Vaccination Schedule, pertussis is the least well controlled. Despite a well-established immunization program that began in the 1950s, pertussis re-emerged in Australia in the 1990s following apparently good control in earlier decades. Pertussis now occurs in annual seasonal peaks with large epidemics every 4 years [1,2]. Moreover, the disease continues to cause significant complications and deaths in infants [2]. In contrast to the pre-immunization era, when pertussis was primarily recognized as a disease in children of primary school age, adolescents and adults now account for the majority of cases in well-immunized populations [3–6].

The main reason that pertussis is poorly controlled in older age groups, despite extensive immunization, seems to be related to waning vaccine-induced immunity. Both infection-acquired and vaccine-induced immunity to pertussis wane with time, so previously infected or vaccinated individuals slowly become more susceptible to pertussis. Pertussis infections in older children, adolescents, and adults are often atypical with milder symptoms [7–12] and so are frequently unrecognized, but they may be the source of pertussis in unimmunized children [5,6,13–20].

Combination vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens (DTaP) have been licensed in Australia for use in children since 1996. These acellular pertussis (aP) vaccines cause fewer adverse reactions than killed whole-cell pertussis vaccines. Although the protective efficacy of a primary course varies between different whole-cell and acellular pertussis vaccines [21–24], Salmaso et al. [25] recently demonstrated

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that three early doses of acellular pertussis vaccine at 2, 4, and 6 months conferred good protection against disease for at least 6 years. In Australia DTaP vaccinations are currently recommended at 2, 4, 6, 18 months, and 4 years. Unfortunately, the vaccines licensed for children are unsuitable for adolescents or adults because of the high rate of local reactions associated with the diphtheria and pertussis components. Combination diphtheria-tetanus-pertussis vaccines (dTpa) with reduced antigen and toxoid concentrations have been developed specifically for use in people over the age of 10 years [26,27]. The availability of these vaccines and the sub-optimal control of pertussis have led a number of groups to advocate the introduction of routine adolescent vaccination against pertussis [28]. Adolescent vaccination has the potential to reduce the burden of disease in the targeted age group and possibly also reduce transmission of pertussis in the community, providing indirect protection to unimmunized infants. However, developing policies to optimize control of pertussis requires an understanding of the likely impact on the long-term epidemiology of the disease of changes to the number and timing of doses.

Modeling has been used to study pertussis vaccination programs in the United Kingdom and the United States. Grenfell and Anderson [29] found that the force of infection for pertussis is age-dependent, and that pertussis incidence continues to oscillate as vaccination programs are introduced. Rohani et al. [30] found that the onset of pertussis vaccination led to a substantial reduction in pertussis transmission in England and Wales and to geographical synchronization of pertussis outbreaks with an almost 4-year inter-epidemic period. In a cost-effectiveness analysis Edmunds et al. [31] found greater reductions in pertussis morbidity and mortality in younger age groups in the UK with a booster at 4 years compared to 15 years.

In the United States, computer simulations using an age-structured epidemiological model for pertussis transmission and vaccination have been used to obtain estimates of the potential effects of the addition of adult pertussis booster vaccinations every 10 years on pertussis incidence in both adults and children in the USA [32–34]. Another simulation modeling study of adolescent and adult pertussis vaccination strategies in the USA considered vaccination of adolescents at age 12 years, young adults at age 20 years, adults at age 50 years, and combining the aP vaccine with the current Td (tetanus-diphtheria) booster that is recommended every 10 years [35].

In this paper computer simulations are used to explore the potential effect on pertussis epidemiology of changes to the pertussis vaccine schedule including introduction of a pertussis booster in adolescence in Australia. In view of the prolonged immunity demonstrated after an infant schedule, concerns about increased local reactions following multiple doses of DTaP, and the cost implications of adding another dose to the schedule, direct substitution of the fourth dose at 18 months with a dose in adolescence has been simulated.

2. Methods

Here we describe the compartmental model for pertussis and the age groups. Then the epidemiological literature and previous modeling studies are used to estimate parameter values. Australian data is used to estimate the demographic structure and both the current and historical pertussis vaccination coverage. All of these estimates are used in the computer simulation model to compare the effects of the current pertussis vaccination program and the effects of two changes in this vaccination strategy. Then the sensitivity of the results to changes in the parameter values and model structure are analyzed.

2.1. The age-structured pertussis model

The population is divided into sixteen distinct epidemiological classes as shown in Fig. 1, where the arrows indicate the transfers between classes due to infection, recovery, waning of immunity, or vaccination. In the model the letters S, I, R, V, and W correspond to the epidemiological states: susceptible, infectious, removed with infection-acquired immunity, vaccine-induced immunity, and waning of vaccine-induced immunity. The compartments in this model are S (fully susceptible), R4 (highest level of naturally acquired immunity), R3 (high level of naturally acquired immunity), R2 (intermediate level of naturally acquired

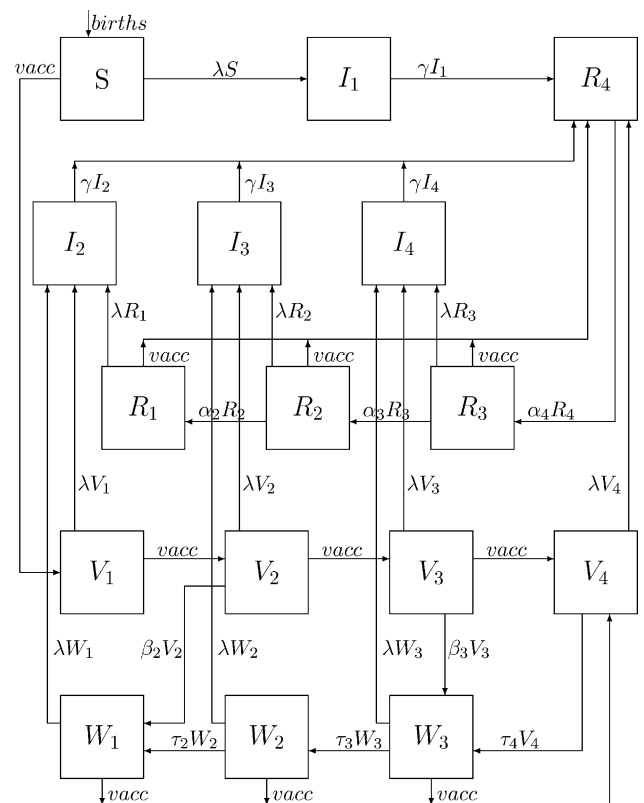


Fig. 1. Transfer diagram for the Australia pertussis model.

immunity), R1 (lowest level of naturally acquired immunity), V4 (highest level of vaccine-induced immunity), V3 (persons having received three doses of pertussis vaccine), V2 (persons having received two doses of pertussis vaccine), V1 (persons having received one dose of pertussis vaccine), W3 (high level of vaccine-induced immunity), W2 (intermediate level of vaccine-induced immunity), and W1 (lowest level of vaccine-induced immunity).

As disease-induced immunity wanes over time, people move down from R4 to R3 to R2 to R1. When people over 12 months of age with natural immunity (R1, R2, or R3) are vaccinated with one dose of acellular pertussis-containing vaccine, they are assumed to move back up to R4, the highest level of immunity. In infants, the immune system is immature, so that successive pertussis vaccine doses are required to move infants to the V1–V4 classes. As vaccine-induced immunity of people in V4 wanes, they move down from V4 to W3 to W2 to W1, but again one dose of vaccine is assumed to move a person back up to V4, the highest level of immunity. Because one pertussis vaccination is generally protective against severe disease, those in the V1 class never return to the class S of fully susceptible individuals. Those who miss one of the 2, 4 or 6 month doses, but get another dose after 1 year of age are also assumed to move up to the highest level of immunity. This is consistent with several studies, which found that boosting after 1 year of age was equally efficacious after a course of two or three doses [36–39]. Hence when immunity of those in the V2 class wanes, they move down to W1, which has a lower immunity level, but has the property that one dose moves them to V4. An Italian study [25] found that protection from the first three pertussis vaccinations persists for at least 6 years. Consequently, when those in the V3 class with three initial doses leave V3, they move down to W3, which has the same level of immunity.

The four types of infectives are I1, I2, I3, and I4. The I1 infectives have the highest average infectivity. The I1 infectives can have various disease severities, but since they come from the unvaccinated susceptible class, many of them have typical pertussis disease with a prolonged cough. The I2 infectives have a lower, but still high average infectivity; many of them have atypical pertussis disease with moderate severity. The I3 infectives have a medium average infectivity and often have atypical pertussis disease with mild symptoms. The I4 infectives have the lowest average infectivity and often have asymptomatic, subclinical pertussis disease. The residence times (i.e. the average infectious periods) of people in the compartments I1, I2, I3, and I4 have negative exponential distributions and mean residence times given by  $1/\gamma_1$ ,  $1/\gamma_2$ ,  $1/\gamma_3$ , and  $1/\gamma_4$ , respectively.

Individuals in many compartments in Fig. 1 become infected if they have sufficient contact with a person infected with the pertussis bacillus. The incidence of infection in the compartments is the product of the force of infection and the numbers of people in the compartments, where the force of infection ( $\lambda$ ) is the summation of the number of infectives

of the four types times their relative infectivities. The latent period, in which an individual is infected, but not yet infectious, is not included in the model, since it is only about one week for pertussis [40]. The residence times before moving to a different compartment of people in the compartments I1, I2, I3, I4, R4, R3, R2, V4, V3, V2, W3, and W2 have negative exponential distributions, so that the mean residence times are the reciprocals of the transfer rate constants. For example, the transfer rate of  $\gamma_1 I1$  from compartment I1 to R4 corresponds to an average infectious period for those in I1 of  $1/\gamma_1$ , the transfer rate of  $\alpha_4 R4$  for waning of immunity from R4 to R3 corresponds to an average residence time of people in R4 of  $1/\alpha_4$ , and the transfer rate of  $\tau_4 V4$  for waning of immunity from V4 to W3 corresponds to an average time in V4 of  $1/\tau_4$ . In the computer simulations, vaccination of a given fraction at specific ages is implemented by transferring the vaccinated people at the given vaccination ages.

The demographic part of the model uses year 2000 fertility and death rates in Australia to obtain a theoretical population whose total size is constant and whose age distribution has reached a steady-state age distribution. The 50 age intervals in the model are 0–1, 2–3, 4–5, 6–11, 12–17, 18–23 months, years 2, 3, ..., 33, 34, and the 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 outflow corresponding to aging into the next age group and a daily death rate. Because the average Australian woman has only 1.76 children, the fertilities are increased by 16% in the model to achieve a constant population size with a steady-state age distribution. The actual situation is slightly different, since the Australian population size is maintained by the immigration of people of various ages.

The pertussis model corresponding to the transfer diagram in Fig. 1 consists of nonlinear differential equations giving the rates of daily transfers among the 16 epidemiological classes and the 50 age groups. The computer simulations are the numerical solutions of these differential equations with vaccinations of specific age groups. The age distribution of pertussis cases starts at a pre-immunization steady-state. Then after the childhood vaccination program starts in 1953, the age distribution of cases changes in response to the vaccinations. More details about epidemiological models of this type are given in the related papers [32,34].

## 2.2. Estimates of the epidemiological parameter values

The average infectious period for typical pertussis is at least 21 days [40]. In the computer simulations the estimates for the average infectious periods are 28 days for those in the I1 and I2 classes, 21 days for those in the I3 class, and 7 days for those in the I4 class. Because the I3 and I2 infectives often continue their daily activities during their illness, their average effective infectivities may, overall, be similar to the I1 class. In the model, the average effective infectivities compared to those in the I1 class

are assigned as 1 for those in I2 and I3, and 0.2 for those in I4.

The median residence period (equal to  $\log 2$  times the mean residence time) before waning in classes R4, R3, and R2 is estimated to be 8 years. The median residence period in the vaccinated classes V3 and V2 is 2 years, and the median residence time before waning in the classes V4, W3, and W2 is estimated to be 4 years. It was shown in a previous study using a similar model [32] that these estimates are consistent with recent clinical pertussis data [7,17]. For those in V3 with three initial doses, the combined median residence time in V3 and W3 was modeled as 6 years, consistent with follow-up from an Italian vaccine trial [25]. Note that if the median residence time in a class is 4 years and the residence time has a negative exponential distribution, then 29% have moved after 2 years, 50% have moved after 4 years, 65% have moved after 6 years, and 75% have moved after 8 years.

The rate of movement from susceptible, removed, and vaccinated classes into the infective classes is the product of the force of infection ( $\lambda$ ) on an age group times the number in that age group in these classes. These incidences are shown as  $\lambda R_1$ ,  $\lambda R_2$ ,  $\lambda R_3$ ,  $\lambda V_1$ ,  $\lambda V_2$ ,  $\lambda V_3$ ,  $\lambda W_1$ ,  $\lambda W_2$ , and  $\lambda W_3$  in Fig. 1. The force of infection ( $\lambda$ ) on an age group is the summation of adequate infectious contacts with infectives in all other age groups, where an adequate infectious contact is one that is sufficient for transmission of an infection from an infective to a susceptible person during the contact. Note that an adequate infectious contact depends on how close together people come during their daily activities and the likelihood of transmission (depending on the infectivity of the infective) during these encounters.

Mixing patterns and contact behaviors vary with age. For example, school age children mix more with other school age children than they do with adults. The matrix of transmission coefficients where each matrix entry depends on the mixing between two age groups and the probabilities of transmission is called a who acquires infection from whom (WAIFW) matrix [41–43]. Here we cluster the age groups into nine age intervals. Since the age-dependent transmission coefficients cannot be measured directly, they must be estimated from data on seroprevalence or disease incidence in the pre-vaccination period [44]. Once the values of the force of infection are known for the nine age groups in the pre-vaccination era and the epidemiological parameters have been estimated, then simulations can be used to determine the prevalences in the nine age groups. Then we solve nine simultaneous equations for the nine forces of infection in terms of the nine unknown transmission coefficients in the WAIFW matrix and the prevalences in the nine age groups.

The WAIFW matrix calculated in this way is then assumed to remain constant throughout the time period in the simulation modeling. The underlying assumption in this method is that age dependent mixing patterns and contact behavior have not changed significantly since the pre-vaccination estimates of force of infection were made. Although this seems likely for school age children, it is possible that contact be-

tween pre-school age children has increased as a result of increased use of childcare with a resulting decline in the contact between parents and pre-school age children. Therefore, transmission estimates between young adults and pre-school children are probably over estimates. Also the increasing age of parents and the increasing use of grandparents for care of young children in Australia may mean that mixing between older adults and young children has increased.

Based on case reports of whooping cough in England and Wales during 1956 (before widespread vaccination), Anderson and May [41,45] estimated that the forces of infection are about 0.09 for less than 1 year, 0.11 for 1–2 years, 0.21 for 2–5 years, 0.47 for 5–10 years, 0.25 for 10–15 years, and 0.06 for 15–25 years. Based on similar data in 1980 after pertussis vaccination began, they estimated the forces of infection to be about 0.11 for less than 1 year, 0.16 for 1–2 years, 0.32 for 2–5 years, 0.35 for 5–10 years, 0.12 for 10–15 years, and 0.07 for 15–25 years. Using the age distribution of whooping cough notifications in England and Wales in 1944–1946, Grenfell and Anderson [29] estimated pertussis forces of infection of 0.22 for 0–5 years, 0.43 for 5–10 years, 0.19 for 10–15 years, and 0.04 for 15–20 years, and 0.04 for >20 years. A personal communication (Nigel Gay, Health Protection Agency, London) suggests that values from 0.03 to 0.06 are plausible for ages over 15 years. Because 4–23-month-old children have more contacts outside the home at play groups, babysitters, and preschool than 0–3-month-old infants, the force of infection in 0–3 month babies is assumed to be about half of the force of infection of 4–23 month children. Based on all of the data available, we use the force of infection values of 0.05 for 0–3 months, 0.11 for 4–23 months, 0.32 for 2–4 years, 0.35 for 5–10 years, 0.21 for 11–17 years, 0.05 for 18–34 years, 0.04 for 35–64 years, and 0.03 for >65 years.

### 2.3. Estimates of pertussis vaccination coverage in Australia

The estimates of pertussis vaccination coverage are based on vaccination data in Australia between 1950 and 2000. Because future pertussis vaccination strategies are compared in the computer simulation modeling, good estimates of the current pertussis vaccination coverage are needed, while estimates of the historical vaccination coverage are less crucial.

#### 2.3.1. Current pertussis vaccination coverage

Immunization coverage data on a three month (1 January 2000 to 31 March 2000) birth cohort derived from the Australian Childhood Immunization Register (ACIR) indicate that 0.871 of 2–3-month-old children had at least one pertussis dose, 0.793 of 4–5 month children had at least two doses, 0.870 of 6–11 month children has at least three doses, 0.928 of 12–17 month children had at least three doses, and 0.810 of 18–23 month children had at least four doses. These estimates and other estimates derived from the ACIR have

been used to estimate vaccination rates in age groups. The fractions receiving no doses are chosen to be consistent with data from Australian Bureau of Statistics (ABS) surveys in 1977, 1983, and 1989, which show that about 3–5% of Australian children never receive any pertussis-containing vaccinations.

In the model no infants of age 0–1 months are vaccinated. The first vaccination dose is given to 87% of those in the S class. Thus the fractions of 2–3-month-old infants in the epidemiological classes are 0.13 in S and 0.87 in the V1 class. The vaccination coverage for the dose given at 4–5 months is 30% for those in S and 91% for those in V1, so that 0.091 are still in S, 0.117 are in the V1 class, and 0.792 are in the V2 class. In the 6-month period corresponding to 6–11 months of age, 30% of those in S and 98% of those in the V2 class are vaccinated. Because those in the V1 class at 4–5 months have missed a previous dose, there is the regularly scheduled vaccination of 90% between 6 and 11 months plus an extra catch-up vaccination of 90%. Thus for infants in V1 at 4–5 months, 1% remain in V1 at 6–11 months, 18% move to V2, and 81% move to V3, so that the fraction in V3 is 0.871.

Although no vaccination is scheduled in the 12–17 month age group, there is a catch-up vaccination of 20% of those in the S class, and a catch-up vaccination of 95% of those in the V2 class. Because those in the V1 class at 6–11 months have missed two previous doses, there is vaccination of 90% at 12–17 months plus an extra catch-up vaccination of 90%. Thus for those in V1 at 6–11 months, 1% remain in V1 at 12–17 months, 18% move to V2, and 81% move to V3, so that the fraction in V3 is 0.929.

Finally, during the age 18–23 months, 20% of those in the S class and 90% in the V1, V2, and V3 classes receive vaccine, so that the fraction in V4 is 0.836. This vaccination coverage of 90% for the fourth dose is consistent with the 89% coverage from ACIR derived data on the 3-month birth cohort born in 1998 receiving the 4th dose at 18–23 months. Because vaccination data show consistent increases in vaccination coverage between 1995–1996 and 2000, it is assumed that the vaccination coverage for the fifth dose at age 4–6 years is 85% in year 2000.

### 2.3.2. Historical pertussis vaccination coverage

Vaccination with three early doses began in the Australian states/territories in 1953. The vaccination coverage increased, so that it was between 66 and 96% in the 1970s and 1980s. Vaccination coverage values were chosen to match reported coverage in 1962, where 0.44 of 2–3 month children received a first dose, 0.35 of 4–5 month children received a second dose, and 0.28 of 6–11 month children received a third dose [46]. Then it was assumed that the percentage of eligible children vaccinated with each of the first three doses increased linearly from 1953 to 1962 values to a level in 1985 that was 0.09 below the year 2000 levels. Thus in 1985 the percentage of 2–3-month-old infants vaccinated was 78%, the percentage of those in V1 at 2–3 months vac-

inated at 4–5 months was 82%, and the percentage of those in V2 at 4–5 months vaccinated at 6–11 months was 89%. The percentage of those in V1 at 4–5 and 6–11 months was 81% for the regular and the catch-up vaccinations, so that 4% remained in V1, 30% moved to V2, and 66% moved to V3. Finally in 1985, 86% of those in V2 at 6–11 months were vaccinated at 12–17 months. Then it was estimated that these percentages vaccinated with the first three doses increased linearly up to the coverage levels in year 2000 and remained constant between years 2000 and 2050.

Because its effects after the year 2000 are negligible, the transient introduction between the 1960s and 1977 of the fourth dose given at 18–23 months is not included in the simulation modeling. When the fourth dose was restarted in 1985, the coverage was assumed to be about 60%, because similar or higher coverage was being obtained for other pertussis vaccinations (ABS). The percentage receiving the fourth dose in 1995 was estimated at about 78% [47]. Thus in the computer simulation modeling, the percentage receiving the fourth dose increased linearly from 60% in 1985 up to 80% in 1995, then increased linearly up to 90% in year 2000, and remained constant after year 2000. The estimate of the vaccination coverage for the fifth dose at ages 4–6 years was about 68% in 1995 (ABS), so that the percentage receiving the fifth dose when it was started in August 1994 was 70%. In the computer simulation modeling, the percentage receiving the fifth dose increased linearly from 70% in August 1994 up to 85% in year 2000 and is constant after year 2000.

## 3. Results

### 3.1. Pre-immunization era

Using the parameter values in Section 2, the simulation model is run until a pre-immunization steady-state epidemiological age distribution is reached. Table 1 shows the I1, I2, I3, and I4 cases per 100,000 in age groups in the pre-immunization era (1950) based on the computer simulations. Note that most of the I1 pertussis cases with highest average infectivity occur in children, which is consistent with the concept that most children had a typical case of pertussis in the pre-immunization era. For a birth cohort in the simulations for the pre-immunization era steady-state before 1953, 99.75% of them have an I1 pertussis infection (which is often a typical case) during their lifetime. Each individual in this steady-state cohort also has an average of 0.5 cases of I2 pertussis with high average infectivity (often with moderate symptoms), 0.5 cases of I3 pertussis with medium average infectivity (often with mild symptoms), and 1.2 cases of I4 pertussis with low average infectivity (often asymptomatic) during their lifetime.

As explained in Section 2.2 the forces of infection and prevalences in the infectious classes at the pre-immunization steady-state are used to determine the entries in a  $9 \times 9$  con-

Table 1  
Computer simulations of incidences in age groups (entries are given as cases per 100,000)

	Age group (years)								
	0–3 months	4–23 months	2–4 years	5–10 years	11–17 years	18–24 years	25–34 years	35–64 years	>64 years
Pre-immunization era (1950)									
I1 (highest infectivity) cases	4937	9660	15517	4982	622	64	43	15	5
I2 (high infectivity) cases	0	0	17	9	207	186	518	966	1022
I1 and I2 cases	4937	9660	15534	4991	829	250	561	981	1027
I3 (medium infectivity) cases	0	5	160	600	854	472	768	678	484
I4 (low infectivity) cases	1	81	1586	4055	3872	1353	1457	983	647
2002 with childhood vaccination									
I1 (highest infectivity) cases	847	153	156	167	128	6	4	2	1
I2 (high infectivity) cases	650	106	143	314	1152	168	295	489	489
I1 and I2 cases	1497	259	299	481	1280	174	299	491	490
I3 (medium infectivity) cases	0	285	265	489	1262	192	289	243	156
I4 (low infectivity) cases	0	1516	1068	1483	3084	426	446	270	160
2050 with childhood vaccination									
I1 (highest infectivity) cases	1107	189	177	162	130	8	5	2	1
I2 (high infectivity) cases	848	130	162	320	1267	249	462	740	736
I1 and I2 cases	1955	319	339	482	1397	257	467	742	737
I3 (medium infectivity) cases	0	352	315	575	1582	252	356	286	169
I4 (low infectivity) cases	0	1866	1282	1743	3630	533	542	315	175
2050 with no 18 month boosting									
I1 (highest infectivity) cases	1194	207	214	174	117	7	5	2	1
I2 (high infectivity) cases	913	167	409	438	1267	255	474	766	765
I1 and I2 cases	2107	374	623	612	1384	262	479	768	766
I3 (medium infectivity) cases	0	419	721	701	1528	266	383	310	186
I4 (low infectivity) cases	0	2791	3950	2069	3638	578	591	347	196
2050 with adolescent boosting									
I1 (highest infectivity) cases	776	121	132	139	79	11	8	4	1
I2 (high infectivity) cases	597	98	259	361	361	193	409	632	595
I1 and I2 cases	1373	219	391	500	440	204	417	636	596
I3 (medium infectivity) cases	0	245	449	542	514	210	265	184	107
I4 (low infectivity) cases	0	1643	2382	1474	1419	399	352	188	103

tact matrix between age groups. Using the prevalence in the age groups from the pre-immunization era computer simulations and the forces of infection values in Section 2, the nine unknowns in the matrix are determined. This contact matrix is used in all subsequent computer simulations to determine the forces of infection, which change as vaccination occurs in the population. Other initial forces of infection and other forms of the contact matrix are investigated in the sensitivity analysis.

### 3.2. Childhood vaccination between 1950 and 2050

The pre-immunization epidemiological steady-state is used as a starting point for the simulations between 1950 and 2050 using the estimates of childhood vaccination coverage. Fig. 2 shows the incidences of the four types of pertussis as the Australian childhood vaccination programs are phased in over time. After 2000 the solid curves correspond to continuation of the year 2000 childhood vaccination at constant levels until year 2050. Note that after the introduction of vaccination in 1953 and after other vaccination changes, there is a damped oscillation towards a steady-state. This

oscillatory behavior with a period of about 4 years has occurred in previous pertussis models and is consistent with the 4-year periods that are observed in pertussis incidence data in many countries [33]. The incidences are close to a steady-state when the 18-month vaccination introduced in 1985 causes a rapid decrease in the incidence. When vaccination of 4-year-old is introduced in August 1994, there is another drop followed by a damped oscillatory approach to a steady-state. Note that the solid curves in Fig. 2 are close to a steady-state equilibrium by 2050.

Table 1 shows the cases per 100,000 people, in the I1, I2, I3, and I4 classes for the age groups in 2002 and in 2050 based on the computer simulations when the current childhood vaccination is extended out to 2050. Childhood vaccination leads to a 97% reduction in I1 highest infectivity cases, a 25% reduction in I2 high infectivity cases, a 43% reduction in I3 medium infectivity cases, and a 45% reduction in I4 low infectivity cases in year 2002 compared to 1950. Continuation of the current childhood vaccination out to 2050 leads to a 97% reduction in I1 highest infectivity cases, a 3% increase in I2 high infectivity cases, a 31% reduction in I3 medium infectivity cases, and a 45% reduction

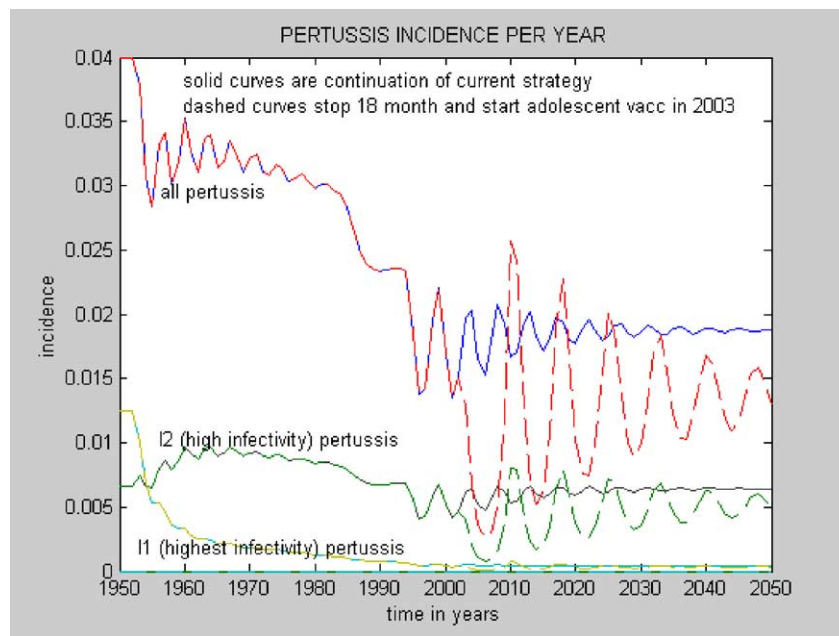


Fig. 2. The incidence curves up to 2003 correspond to the historical childhood vaccination program. After 2003 the solid curves are the incidences if the current childhood vaccination program is continued, and the dashed curves correspond to stopping the 18-month vaccination and adding vaccination of 80% of 12-year-old adolescents in 2003.

in I4 low infectivity cases in year 2050 compared to 1950. Note that childhood vaccination greatly decreases the I1 (often typical) pertussis cases occurring in children but causes an increase in I2 cases in children up to age 17 years. The computer simulations lead to I1 and I2 pertussis incidences in adults in 2002 that are consistent with a recent United States estimate from active surveillance of 507 cases per 100,000 adults per year [4].

Note that the current strategy has reduced the I1 + I2 case rate out to about age 10 years, but then as immunity wanes after vaccination at age 4 years, the case rate increases up to a maximum in the 11–17-year-old age group. The I1 + I2 case rate drops in the 18–24-year-old age group, partly due to immunity from their infections as 11–17-year-old and partly due to the decreased contact rate of 18–24-year-old as they leave secondary school. Beyond age 25 years the I1 + I2 case rate per 100,000 increases as the immunity wanes in these adults.

### 3.3. Effects of eliminating the 18-month booster vaccination in 2003

If the pertussis vaccination at 18 months is removed from the current childhood vaccination schedule, then the general level of immunity in children 19–47 months of age would be predicted to decrease. The model estimates that this change leads to an increase of about 13% in total pertussis cases in 2050 in this age group compared to the number predicted with continuation of the current childhood vaccination program (Table 1). This increase in total 19–47 month cases in 2050 comprises mostly the lowest infectivity (I4) cases with

a 21% increase, but also includes a 4% increase in highest infectivity (I1) cases, a 6% increase in I2 cases, and a 9% increase in I3 medium infectivity cases. Most of the increase occurs in cases in 2–4-year-old children, with some increases in adjoining age groups. This is expected because this 2–4-year-old age group will be the one primarily affected by lower immunity without the 18-month vaccination.

### 3.4. Effects of replacing the 18-month booster with an adolescent booster in 2003

In the computer simulations the adolescent vaccinations are given at age 12 years, but results would be similar for adolescent vaccinations at any age between 10 and 17 years, with 15–17 years being the age group for a pertussis booster recommended in Australia in September 2003. Based on recent experience with hepatitis B immunization, compliance with recommendations is anticipated to be relatively good at ages 10–17 years in a school-based program, so, it is assumed that 80% coverage would be obtained for a recommended adolescent pertussis booster.

The results of computer simulations in which the vaccination at 18 months is replaced by vaccination of 80% of adolescents at age 12 years at the beginning of 2003 are shown in Fig. 2 and in Table 1. This schedule is estimated to lead to a 23% reduction in I1 highest infectivity cases, a 25% reduction in I2 high infectivity cases, a 39% reduction in I3 medium infectivity cases, and a 34% reduction in I4 low infectivity cases in year 2050. Note that adolescent vaccination leads to decreases in cases in the 11–17-year-old age group to about 1/3 of the values estimated for the year 2050

with continuation of the current schedule. But the elimination of the 18-month vaccination still leads to increases of 15% in I1 and I2 cases, 43% in I3 medium infectivity cases, and 85% in I4 low infectivity cases in the 2–4 year age group. The incidences in most other age groups are predicted to be slightly lower than expected with the current schedule.

In Fig. 2 each change in the vaccination strategy causes a sudden change in the incidence, followed by damped oscillations towards a new steady-state. Note that all of the damped oscillations have a period of about 4 years, which is consistent with the period of the observed oscillations in reported cases of pertussis [32]. Although the predicted incidence with adolescent boosting is still oscillating in 2050, the new steady-state value is below the steady-state value in 2050 using the current childhood vaccination program. Thus replacing the booster at 18 months with an adolescent booster in 2003 is predicted to lead to fewer total pertussis cases, especially in adolescents, but with more cases in 2–4-year-old children. Importantly, the change from 18-month boosters to adolescent booster doses is estimated to cause about a 30% decrease in cases in children of ages 0–23 months, who have high complication rates.

### 3.5. Sensitivity to changes in parameter values and model assumptions

#### 3.5.1. Changing the forces of infection and the contact matrix

Because there is some uncertainty about the values of the forces of infections in adults, the effects of increasing the forces of infection by 50% in adults over age 18 years are explored with computer simulations. These values lead to an increase in cases in adults of about 50% in the simulations, but the comparisons between the vaccination strategies are similar. For other types of WAIFW matrices [43] the incidences change, but the comparisons of the vaccination strategies are similar. For example, typical I1 cases decreased by 16% in 2–4-year-old children and by 37% in 11–17-year-old adolescents, when boosters were given to adolescents instead of 18 month children. A proportionate mixing matrix is based on the assumption that each age group has a mixing activity level defined as the average number of adequate contacts per day in that age group. Then each entry is the product of the activity levels of the two interacting groups [32]. With a proportionate mixing matrix the incidence of infection decreases by a factor of up to 3, but the comparisons of vaccination strategies are similar. When boosters were given to adolescents instead of 18 month children, typical I1 cases decreased by 16% in 2–4-year-old children and by 13% in 11–17-year-old children.

#### 3.5.2. Changing the infectivities and average residence times in compartments

If the average effective infectivities are changed to 0.75 for those in I2, 0.5 for those in I3, and 0.25 for those in I4, the values of the cases per 100,000 are reduced in 2002

and 2050 by factors ranging from 2 to 8, but again relative differences between program options do not change. The pre-immunization forces of infection and the contact matrix are strongly affected by the number of I1 cases with full infectivity. After vaccination there are not as many I1 cases with full infectivity and there are many more atypical cases with lower infectivities, so that the new forces of infection and the resulting incidences are much lower. In this case replacing the 18-month booster by a 12-year booster causes more dramatic reductions in the incidences than using the baseline parameter set; e.g., typical I1 cases decreased by 75% in both 2–4-year-old and 11–17-year-old.

If the average infectious periods are changed to 4 weeks for those in the I1 class, 3 weeks for those in the I2 class, 2 weeks for those in the I3 class, and 1 week for those in the I4 class, then the incidences in 2050 are about 20–50% lower. However, 12-year boosters are still more effective than 18-month boosters and cause decreases of 53% in 2–4-year-old and 56% in 11–17-year-old. If the median residence times in R4, R3, and R2 are changed from 8 to 4 or 16 years, then boosting at age 12 years is still better than boosting at 18 months of age. Changing the median residence times in the V2 and V3 compartments from 2 to 1 or 4 years causes only small changes in the incidences in 2002 and 2050, so that the improvement of the 12-year boosting over the 18 month boosting is about the same as in the baseline simulations. For the four changes in the median residence times above, typical I1 cases decreased by at least 20% in 2–4-year-old and by at least 22% in 11–17-year-old, when boosters were given to adolescents instead of 18 month children.

Changing the median residence times in the V4, W3, and W2 compartments from 4 to 2 years causes large increases in the incidences. In this situation people move down through the V4–W3–W2 chain of compartments much faster, so there are more people in the W2 compartment where they get I2 infections. However, vaccination at age 12 years is still better than vaccination at 18 months, but the reductions are less dramatic than with the baseline parameter set with decreases of only 4% in 2–4-year-old and 21% in 11–17-year-old in typical I1 cases. When the median residence times in V4, W3, and W2 are changed from 4 to 8 years, then there are large decreases in the incidences. With this new value people move down through the V4–W3–W2 chain of compartments much slower, so there are more people in the V4 and W3 compartments with high immunity and the 2050 incidences in the I2 compartment age groups are up to 1/12 of those in the baseline simulations. In this case the 12-year boosters are much better than the 18-month boosters.

#### 3.5.3. Changing the new vaccination coverage

If the adolescent boosting is given to 70% of 12-year-old instead of 80%, then the incidences in 2050 are higher by about 20% than when using the baseline parameter set, but the boosting of 12-year-old is still better than boosting of 18-month-old children. In the simulations vaccination of

70% at age 12 years leads to an 11% overall reduction in I1 highest infectivity cases (reductions of 12% in 2–4-year-old and 26% in 11–17-year-old), a 14% reduction in I2 high infectivity cases, a 27% reduction in I3 medium infectivity cases, and a 21% reduction in I4 low infectivity cases in year 2050 compared to the values in year 2050 using the current childhood vaccination strategy. Boosting at least 20% of adolescents leads to lower 0–23 month and total I1 highest infectivity cases in 2050 than the current 18 month boosting.

#### 3.5.4. Changing to different models

The sensitivity of the simulation results to changes in the model structure in Fig. 1 is now examined by looking at three model variations. The first revised model assumes that a booster after 1 year of age does not induce the highest immunity level in children who have only received two doses of the primary series, so that children in V2 go back to V1 instead of W1 when their immunity wanes. This change leads to only small changes in the results. For example, typical I1 cases decreased by 29% in 2–4-year-old and by 41% in 11–17-year-old, when boosters were given to adolescents instead of 18 month children. If the three initial doses do not give as much immunity as found in the Italian study [25], then those who leave the V3 class would go to the W2 class instead of the W3 class. In the simulations with this second revised model, the boosters at 12 years and 18 months are about equally effective overall in controlling pertussis; however, there were increases of 54% in 2–4-year-old and decreases of 45% in 11–17-year-old in typical I1 cases.

If a vaccination at or after 1 year of age of a partially vaccinated child does not give a high level of immunity, then a child who moves out of the V2 or V3 class due to waning of immunity would move down to a lower V class instead of going to a W class. In this third revised model, children in the V2 and V3 classes move back down through the V classes as immunity wanes and move back up one class when they are vaccinated. As in the base model, children who do reach the V4 class move down through the W classes. In simulations with this third revised model, the incidences increase significantly when the 18-month booster is eliminated. This is expected since many children would get at most three initial doses and the third revised model requires four initial doses to achieve high immunity. When the vaccination at 18 months is replaced by vaccination of adolescents, there is still a 15% overall increase in I1 highest infectivity cases, a 23% increase in I2 high infectivity cases, a 46% increase in I3 medium infectivity cases, and a 29% increase in I4 low infectivity cases in year 2050 compared to the values using the current childhood vaccination. For typical I1 cases there are increases of 32, 40, 71, and 17% in the 0–3 month, 4–23 month, 2–4 year, and 5–10 year age groups, but respectively; there is a decrease of 59% in the 11–17-year-old age group. Thus using this third revised model, boosting of 80% of 12-year-old children is worse than the current boosting of 18-month-old children. The important model change is that children in V3 are moved to

V2 instead of going to W3 or W2 when immunity wanes. This change reverses the comparison conclusion in all of the previous simulations, and thus identifies the crucial model assumption that a single booster dose after 1 year of age, in a child who has had three initial doses, induces a high level of immunity with good protection [36–39].

## 4. Discussion

This paper describes the results of using computer simulation modeling to compare new pertussis vaccination strategies in Australia. Although, as with most models, there is some uncertainty in the model formulation and in the parameter estimates, the comparisons are consistent over a wide range of parameter values, so that the vaccination strategy comparisons seem robust.

In the computer simulations, the historical childhood pertussis vaccination program between 1953 and 2002 in Australia reduced the I1 highest infectivity cases (often with typical, severe symptoms) by 97%. Thus the model simulations predict that the current pertussis vaccination program is very effective in reducing the I1 highest infectivity cases of pertussis in children. Moreover, I1 and I2 cases decreased by 60–70% in the 0–3 month age group, and by about 97% in the 4–23 month and 2–4 year age groups. Thus a major benefit of the current pertussis vaccination program is that it provides direct, temporary protection for vaccinated children against I1 and I2 pertussis infections, which are often associated with more serious disease symptoms, higher complication rates, and higher mortality rates. The I1 (often typical) cases among young children in the pre-immunization era are replaced by atypical I2, I3, and I4 cases occurring in the removed and vaccinated classes, which often have moderate, mild, and asymptomatic disease symptoms.

Replacing the current pertussis booster at 18 months in 2003 with a booster for 80% of those who are 12 years of age leads to reductions of 2–39% in total cases at the various infectivity levels in year 2050. In the simulations vaccination of adolescents instead of 18 month children reduced I1 and I2 cases by 69% in the 11–17-year-old age group, but increased the I1 and I2 cases by 15% in the 2–4 year age group. Overall the increase in cases when the 18-month vaccination is eliminated is more than counterbalanced by the addition of the booster vaccinations at 12 years of age. It is significant that cases in children of ages 0–23 months, who have high complication rates, decrease by about 30%.

A general concern about the introduction of adolescent pertussis boosters is the possibility that the peak age of pertussis susceptibility and infections might shift from adolescents to young adults, who may have greater contact with infants than adolescents. But Table 1 shows that the I1 + I2 case rates increase after age 18 years in simulations of the three vaccination strategies. Thus in the simulations of adolescent vaccination, an additional shift to higher case rates from adolescents to young adults does not occur. Indeed,

adolescent vaccination seems to lower the community reservoir of infection, so that case rates are lower in both adolescents and adults.

A follow-up study of the Italian acellular pertussis vaccine trial [25] found that protection from the first three pertussis vaccinations persists up to 6 years, a crucial finding in determining that the fourth dose at 18 months could be postponed. The duration of immunity following five doses of either acellular pertussis vaccines or a combination of acellular and whole cell vaccines is unknown, but it is likely that by 12–15 years of age many adolescents will have low immunity since the last dose was at least 7 years earlier. This would result in vaccination of these adolescents having a larger marginal effect, as reflected in the computer simulations.

The sensitivity analysis shows that the comparisons are not sensitive to assumptions about the force of infection, form of WAIFW matrix, relative infectivity of infectious classes, average duration of infectious period, average duration of natural immunity or average duration of vaccine derived immunity. Reduction of vaccine coverage at age 12–15 years from 80 to 70% increased estimated cases by 20% at steady-state, but an advantage for the adolescent strategy remained. However, should much lower coverage be achieved, such as might be anticipated with a private sector rather than school-delivered program, this advantage could be lost. Thus program measures to ensure high adolescent coverage are important.

The comparison results are, however, sensitive to model assumptions about the immune response to boosting doses. Using the second and third revised models in Section 3.5.4 we saw that if three primary doses do not give good protection, then loss of the 18 month dose could lead to more cases in 2–4-year-old children. While it is generally accepted that for a child whose immunity has waned after two or three doses, a pertussis booster dose at or beyond age 1 year of age leads to high immunity; if this is not the case, then advantages of an adolescent schedule are not realized. Because of the differences between the results using the original model, compared to the sensitivity analysis models 2 and 3, future experimental studies should be designed to verify the results of the Italian study [25] and the serologic response studies [36–39] regarding the level and duration of immunity after 2 or 3 primary doses and a booster dose.

The computer simulations, which are based on the best data and information available at this time, suggest that substituting the 18 month booster with a booster in adolescence will result in improved control of pertussis in Australia. Epidemiological, economic, and logistic factors that need to be considered when developing policy in Australia or other countries include the current vaccination program, the local epidemiological situation, the costs of pertussis cases in various age groups, and the accessibility and vaccination costs for the target population. Since we are proposing direct substitution of one booster dose for another, the cost-effectiveness of this schedule change is likely to be

favorable, particularly since dT is already recommended for adolescents in Australia. However, high coverage of the adolescent age group is best achieved through school-based programs and the costs of establishing and maintaining a school-based program where none currently exists would have to be included in any economic analysis.

In this paper we have only considered the impact on pertussis epidemiology. It is possible that removing the 18 month booster may have important implications for immunity to diphtheria and tetanus, although the evidence indicates that the 18 month booster is not needed to maintain diphtheria immunity into the school years. Italy recommends the first diphtheria booster at 5–6 years and the UK at 3–5 years, and seroprevalence data show that in both these countries greater than 90% of children aged between 2 and 5 years have protective levels of anti-diphtheria antibodies [48]. In addition, the risk that schedule changes either at 18 months or in adolescence might adversely impact the future delivery of other vaccines that may be considered for inclusion in the schedule must be taken into account. Nevertheless, the simulation results of the effects on pertussis transmission over time suggest that the recent replacement of the 18 month dose with a pertussis booster in 15–17-year-old adolescents is likely to reduce overall pertussis incidence in Australia without increasing the cost of the current vaccine program.

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## References

- [1] Cordova SP, Gilles MT, Beers MY. The outbreak that had to happen: *Bordetella pertussis* in north-west western Australia in 1999. *Commun Dis Intell* 2000;24:375–9.
- [2] McIntyre P, Gidding H, Gilmour R, Lawrence G, Hull B, Horby P, et al. National Centre for Immunization Research and Surveillance of Vaccine Preventable Diseases. Vaccine preventable diseases and vaccination coverage in Australia, 1999 to 2000. *Commun Dis Intell* 2002;(Suppl i–xi):1–111. [http://www.health.gov.au/pubhlth/cdi/pubs/pdf/vpd99\\_00.pdf](http://www.health.gov.au/pubhlth/cdi/pubs/pdf/vpd99_00.pdf).
- [3] Guris D, Strebel PM, Bardenheier B, Brennan M, Tachdjian R, Finch E, et al. Changing epidemiology of pertussis in the United States: increased reported incidence among adolescents and adults, 1990–1996. *Clin Infect Dis* 1999;28:1230–7.
- [4] Strebel P, Nordin J, Edwards K, Hunt J, Besser J, Burns S, et al. Population-based incidence of pertussis among adolescents and adults, Minnesota, 1995–1996. *J Infect Dis* 2001;183:1353–9.

- [5] Yih WK, Lett SM, des Vignes FN, Garrison KM, Sipe PL, Marchant CD. The increasing incidence of pertussis in Massachusetts adolescents and adults, 1989–1998. *J Infect Dis* 2000;182:1409–16.
- [6] Centers for Disease Control and Prevention. Pertussis—United States, 1997–2000. *Morbidity Mortality Weekly Rep* 2002;51(4):73–6.
- [7] Mink CAM, Cherry JD, Christenson P, Lewis K, Pineda E, Shlian D, et al. A search for *Bordetella pertussis* infection in university students. *Clin Infect Dis* 1992;14:464–71.
- [8] Long SS, Welkon CJ, Clark JL. Widespread silent transmission of pertussis in families: antibody correlations of infection and symptomatology. *J Infect Dis* 1990;161:480–6.
- [9] Wright SW, Edwards KM, Decker MD, Zeldin MH. Pertussis infection in adults with persistent cough. *J Am Med Assoc* 1995;273:1044–6.
- [10] Nanning ME, Shinefield HR, Edwards KM, Black SB, Fireman BH. Prevalence and incidence of adult pertussis in an urban population. *J Am Med Assoc* 1996;275:1672–4.
- [11] De Serres G, Shadmani R, Duval B, Boulianne N, Déry P, Fradet MD, et al. Morbidity of pertussis in adolescents and adults. *J Infect Dis* 2000;182:74–9.
- [12] Thomas PF, McIntyre PB, Jalaludin BB. Survey of pertussis in adults in western Sydney. *Med J Aust* 2000;173:74–6.
- [13] Cherry JD. Epidemiological, clinical, and laboratory aspects of pertussis in adults. *Clin Infect Dis* 1999;28:S112–7.
- [14] Edwards KM, Decker MD, Graham BS, Mezzatesta J, Scott J, Hackell J. Adult immunization with acellular pertussis vaccine. *J Am Med Assoc* 1993;269:53–6.
- [15] Deen JL, Mink CAM, Cherry JD, Christenson PD, Pineda EF, Lewis K, et al. Household contact study of *Bordetella pertussis* infections. *Clin Infect Dis* 1995;21:1211–9.
- [16] Farizo KM, Cochi SL, Zell ER, Brink EW, Wassilak SG, Patriarca PA, et al. Epidemiological features of pertussis in the United States, 1980–1989. *Clin Infect Dis* 1992;14:708–19.
- [17] Deville JG, Cherry JD, Christenson PD, Pineda E, Leach CT, Kuhls TL, et al. Frequency of unrecognized *Bordetella pertussis* infections in adults. *Clin Infect Dis* 1995;21:639–42.
- [18] He Q, Viljanen MK, Nikkari S, Lyytikäinen R, Mertsola J. Outcomes of *Bordetella pertussis* infection in different age groups of an immunized population. *J Infect Dis* 1994;170:873–7.
- [19] van Boven M, de Melker HE, Schellekens JF, Kretzschmar M. Waning immunity and sub-clinical infection in an epidemic model: implications for pertussis in The Netherlands. *Math Biosci* 2000;164:161–82.
- [20] Campins-Marti M, Cheung HK, Forsyth K, Guiso N, Halperin S, Huang L-M, et al. Recommendations are needed for adolescent and adult pertussis immunization: rationale and strategies for consideration. *Vaccine* 2002;20:641–6.
- [21] Greco MD, Salmaso D, Mastrantonio P, Giuliani M, Tozzi A, Anemona A, et al. A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis. *N Engl J Med* 1996;334:341–8.
- [22] Trollfors B, Taranger J, Lagergard T, Lind L, Sundh V, Zackrisson G, et al. A placebo-controlled trial of a pertussis-toxoid vaccine. *N Engl J Med* 1995;333:1045–50.
- [23] Gustafsson L, Hallander HO, Olin P, Reizenstein E, Storsaeter J. A controlled trial of a two-component acellular, a five-component acellular, and a whole-cell pertussis vaccine. *N Engl J Med* 1996;334:349–55.
- [24] Lugauer S, Heining U, Cherry JD, Stehr K. Long-term clinical effectiveness of an acellular pertussis component vaccine and a whole cell pertussis component vaccine. *Eur J Pediatr* 2002;161:142–6.
- [25] Salmaso S, Mastrantonio P, Tozzi AE, Stefanelli P, Anemona A, Ciofi ML, et al. Sustained efficacy during the first 6 years of life of 3-component acellular pertussis vaccines administered in infancy: the Italian experience. *Pediatrics* 2001;108:e81. <http://www.pediatrics.org/cgi/content/full/108/5/e81>.
- [26] Halperin SA, Smith B, Russell M, Hasselback P, Guasparini R, Skowronski D, et al. An adult formulation of a 5-component acellular pertussis vaccine combined with diphtheria and tetanus toxoids is safe and immunogenic in adolescents and adults. *Vaccine* 2000;18:1312–9.
- [27] Turnbull FM, Heath TC, Jalaludin BB, Burgess MA, Ramalho AC. A randomized trial of two acellular pertussis vaccines (dTpa and pa) and a licensed diphtheria-tetanus vaccine (Td) in adults. *Vaccine* 2000;19:628–36.
- [28] Halperin SA. Pertussis immunization for adolescents: what are we waiting for? *Paediatr Child Health* 2001;6(4).
- [29] Grenfell BT, Anderson RM. Pertussis in England and Wales: an investigation of transmission dynamics and control by mass vaccination. *Proc R Soc London B* 1989;236:213–52.
- [30] Rohani P, Earn DJD, Grenfell BT. Opposite patterns of synchrony in sympatric disease metapopulations. *Science* 1999;286:968–71.
- [31] Edmunds WJ, Brisson M, Melegaro A, Gay NJ. The potential cost-effectiveness of acellular pertussis booster vaccination in England and Wales. *Vaccine* 2002;20:1316–30.
- [32] Hethcote HW. An age-structured model for pertussis transmission. *Math Biosci* 1997;145:89–136.
- [33] Hethcote HW. Oscillations in an endemic model for pertussis. *Can Appl Math Q* 1998;6:61–88.
- [34] Hethcote HW. Simulations of pertussis epidemiology in the United States: effects of adult booster vaccinations. *Math Biosci* 1999;158:47–73.
- [35] Hethcote HW. New vaccination strategies for pertussis. In: Castillo-Chavez C, Blower S, van den Driessche P, Kirschner D, Yakubu AA, editors. *Mathematical approaches for emerging and reemerging infectious diseases*. Part I. An introduction to models, methods, and theory. Berlin: Springer-Verlag; 2001. p. 97–118.
- [36] Tomoda T, Ogura H, Kurashige T. Two primary doses of diphtheria-tetanus-acellular pertussis vaccine induce immunological responses to *Bordetella pertussis* as strong as those induced by three primary doses. *Vaccine* 1997;15:1955–8.
- [37] Blennow M, Granstrom M. Adverse reactions and serologic response to a booster dose of acellular pertussis vaccine in children immunized with acellular or whole-cell vaccine as infants. *Pediatrics* 1989;84(1):62–7.
- [38] Blennow M, Granstrom M. Long term serologic follow-up after pertussis immunization. *Pediatr Infect Dis J* 1990;9(1):21–6.
- [39] Tindberg Y, Blennow M, Granstrom M. A ten year follow-up after immunization with a two component acellular pertussis vaccine. *Pediatr Infect Dis J* 1999;18(4):361–5.
- [40] Chin J, editor. *Control of communicable diseases manual*. 17th ed. Washington, DC: American Public Health Association; 2000.
- [41] Anderson RM, May RM. *Infectious diseases of humans: dynamics and control*. Oxford: Oxford University Press; 1991.
- [42] Brisson M, Edmunds WJ, Gay NJ, Law B, DeSerres G. Modelling the impact of immunization on the epidemiology of varicella zoster virus. *Epidemiol Infect* 2000;125:651–69.
- [43] Edmunds WJ, Gay NJ, Kretzschmar M, Pebody RG, Wachmann H. The pre-vaccination epidemiology of measles, mumps, and rubella in Europe: implications for modeling studies. *Epidemiol Infect* 2000;125:635–50.
- [44] Grenfell BT, Anderson RM. The estimation of age related rates of infection from case notifications and serological data. *J Hyg* 1985;95:419–36.
- [45] Anderson RM, May RM. Age-related changes in the rate of disease transmission: implications for the design of vaccination programmes. *J Hyg Camb* 1985;94:365–436.
- [46] Graydon JJ. Whooping-cough vaccination. *Med J Aust* 1964;15(33):251–4.
- [47] Jalaludin B, Chow C. Western Sydney survey of long day care centers April 1995: receipt of 4 DTP doses by age 2. *NSW Public Health Bull* 1996;7–10:118.
- [48] Edmunds WJ, Pebody RG, Aggerback H, Baron S, Berbers G, Conyn-van Spaendonck AE, et al. The sero-epidemiology of diphtheria in western Europe. ESEN project. European sero-epidemiology network. *Epidemiol Infect* 2000;125:113–25.