REVIEW ARTICLE

Pediatr Drugs 2002; 4 (5): 299-313
1174-5878/02/0005-0299/$25.00/0

Which Strategy for Pertussis Vaccination Today?

Dorota Z. Girard

Department of Economics, University of Nantes, LEN-CEBS, Nantes, France

Contents

Abstract

Pertussis (whooping cough) remains an epidemic disease responsible for infant and child morbidity and mortality, and is perceived as a serious public health problem. Since the widespread use of whole-cell pertussis vaccines in the 1940s, vaccination programs have varied greatly between countries. National specificity is a function of several factors. The most important are: (i) vaccine efficacy and tolerability; (ii) vaccine coverage and distribution; and (iii) vaccine acceptance by parents and professionals. During the 1970s, Sweden, England, Wales and Japan provided contrasting examples of the attitude of health authorities to the use of whole-cell vaccines. The increase in pertussis incidence was noted as a consequence of active opposition to this vaccine.

The re-emergence of pertussis in the 1990s, in countries with high vaccination coverage and increased incidence of disease in individuals >15 years and <6 months of age, has drawn attention to the role of booster doses of pertussis vaccines and their introduction into regular vaccination programs. The use of acellular vaccines for booster doses for adolescents and adults would seem unambiguous because of their decreased reactogenicity, although the exact schedule has yet to be established. The choice between the two kinds of vaccines is more difficult for primary courses, where safety and efficacy profiles are similar, and the attitude towards acellular vaccines varies from country to country. In this case, the strategy adopted results from the national history of pertussis infection and from the quality of the available whole-cell vaccine. Two contrasting examples are the US, where acellular vaccines were licensed for the primary series in the 1990s, and the UK, where whole-cell vaccines are exclusively used for primary immunization.

The changing epidemiology of pertussis, and its local diversification, would suggest that at present it is difficult to define a single worldwide strategy with only one kind of vaccine and one schedule. In order to control pertussis incidence, each country should continue to determine the best national vaccination program established in very close relation to the past and present epidemiological situation and available healthcare resources.

The ability to control or eradicate an infectious disease is made possible by the use of a well tolerated and effective vaccine, and by institution of an adequate vaccination strategy which ensures that high vaccine uptake can be achieved and maintained with time. Three specific objectives may be sought by a vaccination program – eradication, elimination or control. The probability of achieving the objective depends on the characteristics of the infectious disease. Eradication of infection is more likely when there is no nonhuman host, the disease is easily diagnosed, there are no subclinical infections, transmissibility is low, and lifelong immunity is achieved following vaccination.[1]

Eradication occurs when the disease and its causal agent have been definitively removed from all human populations. Up to the present day, smallpox is the only disease to have been eradicated worldwide by vaccination. Poliomyelitis has also been suggested as a potential target for global eradication,[2] but only the elimination of this infection, i.e. regional eradication, has been achieved. Indeed, the World Health Organization (WHO) Western Pacific region has recently been certified free of indigenous polio transmission, after the WHO region of the Americas in 1994.[3]

Pertussis (whooping cough) eradication does not seem potentially feasible given the characteristics of the infection, and the fact that although pertussis vaccines are most effective in preventing severe disease they may have little impact on transmission of infection.[4-6] Two other options are then available for a pertussis vaccination program. Control, defined as the reduction of morbidity and mortality to levels which are no longer perceived to be a serious public health problem,[1] was considered during the 1980s as being already achieved. However, several outbreaks of pertussis infection during the 1990s in different age groups of an immunized population have called into question the feasibility of this goal using current vaccination programs.

The return of epidemic pertussis is a reminder that there are still many obstacles to overcome before the number of cases of this disease can be definitively reduced. It also suggests, after considering the development of acellular preparations, that pertussis control can at present only be the long-term objective for an optimal vaccination strategy.

In this article we discuss the characteristics of current immunization programs being undertaken by health authorities, focusing on the establishment of vaccination policies from historical and socioeconomic angles. We investigate the links between the choice of national strategies for particular pertussis vaccines and vaccination schedules, and past local experiences with routine use of whole-cell pertussis vaccine. We examine, in particular, the consequences of public and professional concerns about safety and efficacy of the whole-cell vaccine on the control of pertussis, and on the development of acellular pertussis vaccines.

In order to point out the impact over time of applied vaccination coverage on pertussis incidence, we restricted our analysis to industrialized countries where surveillance systems are uninterrupted. Data from these countries allow us to observe changes in the age distribution of pertussis morbidity. We focus on infant and child morbidity, although increasing incidence rates in adolescents and adults are highlighted because of the role of this population in the transmission of pertussis. Adverse events following the primary course of immunization with whole-cell and acellular pertussis vaccines are noted for infants and children. Available data on the safety of booster doses with pertussis acellular vaccines in adolescents and adults is still very limited.

1. Epidemiology of Pertussis

Pertussis has been and remains an epidemic disease responsible for significant widespread mortality and morbidity, mainly among infants and young children.[7-10] It is a highly infectious disease of the respiratory tract caused by the bacterium *Bordetella pertussis*, which was first isolated in 1906.[11,12] This bacterium is a pathogen for humans and no other reservoir is known. A second bacterium, *Bordetella parapertussis*, also causes the pertussis syndrome, but generally results in less clinically severe disease.[13,14] It shares surface antigens with *B. pertussis* but the two bacteria differ in many properties, including toxicity, growth rate, and biochemical activity. Distinction between pertussis and parapertussis is established on isolation of *B. pertussis* in laboratory culture. *Bordetella bronchiseptica* is the third species included in the genus *Bordetella*. This natural pathogen from the respiratory tract of animals is very rarely isolated from humans, but it causes pertussis-like disease in other mammals.

The most common complication of pertussis infection, and the cause of most pertussis-related deaths, is secondary bacterial pneumonia. Neurologic complications such as seizures and encephalopathy may occur as a result of hypoxia from coughing, or possibly from toxins. Other less serious complications of pertussis include otitis media, anorexia, and dehydration.

At the beginning of the 20th century, pertussis was one of the most common childhood diseases. In Britain, for example, it caused more deaths than any other infectious disease except measles,[15] and in the US only diphtheria and measles were substantially ahead of pertussis.[16] Regular statistics on pertussis have been available in a small number of countries since the 1920s. The systematic recording of epidemiological data adequate for comparative analysis has been possible for some countries only

since the 1940s, when statutory notifications were introduced for nations undertaking a pertussis immunization policy. This data provides the opportunity to examine the effect of pertussis vaccination on the epidemiology of pertussis infection, and the national specificity of applied vaccination programs.

In 1922, when pertussis became nationally notifiable in the US, 107 473 pertussis cases and 5099 pertussis deaths were reported.[16] During the period 1932 to 1941, the average reported annual incidence rate for pertussis was 157 cases per 100 000 population in the US,[17] and 153 cases per 100 000 population in Canada.[18] Pertussis incidence peaked in England and Wales in 1941 at 230 cases per 100 000 population (173 330 cases) and 2383 deaths.[19] The incidence rate for pertussis in Japan was approximately 185 cases per 100 000 population (152 072 cases) in 1947, with 17 001 deaths notified.[20]

1.1 Role of Vaccination

Significant reductions in pertussis incidence and mortality have been observed since the introduction of routine vaccination. The first standardized whole-cell pertussis vaccines had entered into widespread use by World War II (table I). Pertussis vaccines were subsequently combined with diphtheria and tetanus toxoids in DTP vaccines. Canada and the US were among the first countries to put pertussis vaccination into practice on a nationwide scale, in 1943 and 1944, respectively.[10,21,22] Use of the DTP vaccine was widespread in these countries in the late 1940s. New Zealand followed, introducing the pertussis vaccine in 1945.[23] Next came Japan where the pertussis vaccine was first made available in 1947, and was in general use in 1950.[24] For most European countries, the pertussis vaccination program began in the 1950s. In Finland, for instance, general vaccination with a whole-cell pertussis vaccine was recommended from 1952,[25] in Sweden from 1953,[26] and in England and Wales immunization was introduced on a national scale from 1957.[27,28]

In the years immediately following the start of widespread immunization, a substantial decline in pertussis incidence was reported by national disease surveillance systems. In England and Wales, the pertussis incidence rate fell by more than two-thirds during the period 1957 to 1961 (from 85 017 to 24 469 cases). Since then the decrease has continued more slowly, with outbreaks every 3 to 4 years, reaching, at the end of the 1960s, an average annual notification rate of approximately 35 cases per 100 000 population and an average of 23 deaths per year.[35,36] In Japan, a perceptible decline in pertussis incidence started in 1951. During the

Table I. Examples of current pertussis vaccination programs

Country	Introduction of pertussis vaccine	Immunization schedule primary course	Booster dose	Vaccine in use for primary course
Canada	1943[29]	2, 4 and 6 months of age	2 boosters; 1 dose at 18 months of age, 1 dose between 4 and 6 years of age	DTaP
USA	1944[16]	2, 4 and 6 months of age	2 boosters; 1 dose between 15 and 18 months of age, 1 dose between 4 and 6 years of age	DTaP
New Zealand	1945[23]	6 weeks, 3 and 5 months of age	Since 1996, 1 dose at 15 months of age	DTaP
Australia	1950[30]	2, 4 and 6 months of age	2 boosters; 1 dose at 18 months of age, 1 dose at 4 years of age	DTaP
Japan	1947[20] (discontinued in 1975)	Introduction of DTaP in 1981 for 2-year-old children. Currently 3 doses are recommended for children <12 months of age		DTaP
Finland	1952[25]	3, 4 and 5 months of age	1 dose at 2 years of age	DTwP
The Netherlands	1952[31]	3, 4 and 5 months of age	1 dose at 11 months of age	DTwP
Sweden	1953[32] (discontinued in 1979)	Between 1965 and 1979, 3 doses of DTwP at 2, 3 and 6 months of age. Currently DTaP vaccines are licensed and in routine or widening use		
England and Wales	1957[27]	2, 3 and 4 months of age	No booster	DTwP
France	1959[33]	2, 3 and 4 months of age	2 boosters; 1 dose between 16 and 18 months of age, 1 dose between 11 and 13 years of age	DTwP or DTaP
Russian federation	3 doses between 3 and 18 months of age, and 1 dose between 18 and 36 months of age (12-18 months after last infancy dose) with DTwP			
Italy	Facultative vaccination independently settled in each region at 3, 5, and 7 months with DTaP or DTwP. One booster dose during the third year of life is not necessarily included[34]			

DTaP = diptheria, tetanus and acellular pertussis; **DTwP** = diptheria, tetanus and whole-cell pertussis.

5-year period following the widespread use of the pertussis vaccine, the disease incidence rate fell from 122 796 to 14 134 cases (from 147 to 16 cases per 100 000 population), and attained the level of 2 cases per 100 000 population at the end of the 1960s. At the end of the 1960s, an average of 11 deaths per annum were reported, while 1992 deaths per year were notified for the period 1951 to 1955.[20]

A significant but more gradual decline in pertussis morbidity and mortality has been observed in Canada and the US. After the introduction of the pertussis vaccine in the 1940s, pertussis incidence fell in the US from an average of 175 000 cases per year (157 cases per 100 000 population) to 15 000 reported cases (8 cases per 100 000 population) in 1960. During the 1970s, an average of 2300 cases per year, and an incidence rate of approximately 1 case per 100 000 population, were reported. Overall, by 1970, the average annual incidence of pertussis had been reduced by 99%.[21,37,38] In Canada, pertussis incidence decreased from an average of 17 000 cases (153 cases per 100 000 population) in the immediate pre-vaccine era to 2600 cases (10 cases per 100 000 population) at the end of the 1970s. This reflects a reduction of 93%.[22,29]

The causal relationship between the widespread use of whole-cell vaccine and the decline of pertussis incidence confirms that vaccination was the main explanatory variable for the decrease in disease incidence.[39] The contribution made by vaccination cannot, however, be dissociated from other surrounding factors. Increased standards of hygiene and health of newborn babies and older children, and technological advances in healthcare, making antibacterials and intensive care available, must also be taken into account.[15,40]

1.2 Controversy Surrounding the Safety of Whole-Cell Vaccines

In the mid-1970s, a considerable debate developed around the fundamental importance of mass immunization, compared with improved socioeconomic conditions, in contributing to the decline of pertussis and associated fatalities. The public controversy about pertussis vaccine and its adverse reactions arose within the context of low levels of pertussis mortality and morbidity obtained as a result of a high vaccine acceptance rate, and can be considered a predictable consequence of successful application of the pertussis control program.[41] In fact, due to epidemiological conditions, which were deemed satisfactory, critics of the vaccine did not believe that continuation of the immunization program on a national scale was necessary to control pertussis. In some countries, including Sweden, Japan and the UK, national discussions regarding the marginal protective effect of the vaccine, and the risk of serious neurological reactions after use of the DTP vaccine, gave rise to active movements against whole-cell pertussis vaccines. Attention has been shifted from complications of the disappearing disease to adverse effects of the whole-cell vaccine, considered potentially unsafe during the mid 1970s, and no longer justified in common use.

All whole-cell pertussis vaccines are composed of a suspension of formalin-inactivated *B. pertussis* cells, and they have a tendency to provoke transient local and systemic reactions.[42-45] Local sequelae such as redness, swelling and pain at the injection site, fever, and other mild systemic events are judged as undesirable, but generate little apprehension among parents of children being vaccinated. On the contrary, more severe systemic events including seizures, hypotonic hyporesponsive episodes and encephalopathic states, which can occur rarely after immunization, make these pertussis vaccines potentially unsafe.

A lack of faith in the safety and efficacy of the pertussis vaccines in use was induced by several reports published in Western Europe which have drawn attention to the appearance of alleged serious neurological complications following immunization against pertussis.[46-51] These reports, although based on uncontrolled data, were considered at the time to be important in medical circles and were taken up by the mass media as support for public anti-immunization campaigns, which claimed that the adverse effects of the vaccine posed a greater risk to the population than the disease itself.[52,53] The increasing distrust of parents towards pertussis whole-cell vaccines, heightened by the reluctance of family doctors to advise immunization, resulted in a general and progressive fall in vaccine coverage, and in a dramatic resurgence of pertussis in several industrialized countries. Indeed, in Japan, Sweden, and particularly England and Wales, which changed or interrupted their vaccination policies because of widespread adverse publicity for pertussis vaccines, significant epidemics were recorded during the 1970s. In Ireland, epidemics occurred during the 1980s, and in Australia during the 1990s. It should be noted that in the 1990s, as a result of the Expanded Program of Immunization initiated in the 1970s by the WHO, global use of the DTP vaccine increased from 5% to the current level of 80%.[54-56]

1.3 Drop in Vaccination Coverage

In England and Wales, a drop in the vaccination rate from 77 to 30% was followed by two of the most serious epidemics during the immunization period, which peaked with 65 956 cases of pertussis in 1978 and 65 810 in 1982 (approximately 133 cases per

100 000 population), and 12 and 14 deaths, respectively.[36] In Japan, the pertussis vaccine uptake decreased from 78% in 1974 to 14% in 1976. In 1979 there were 13 092 cases of pertussis in Japan (11 cases per 100 000 population) and 41 deaths.[57] In Sweden, the incidence of pertussis was already increasing from the beginning of the 1970s, despite a continuing high vaccination rate.[26] The outbreak which appeared in 1977 to 1978 while immunization coverage had stabilized at over 80%, suggested that the protective efficacy of pertussis vaccines had declined. The vaccination rate fell from 90% in 1974 to 12% in 1979, at which time the vaccine was withdrawn, and incidence rates rose from about 25 cases per 100 000 population in 1974 to 100 cases per 100 000 population in 1978.[32] The pertussis outbreak in 1982 occurred in a population in which the youngest age groups were unprotected.

Based on these epidemiological experiences, two points about the characteristics of the pertussis vaccine strategy can be noted. Firstly, significant pertussis epidemics occurred in countries which had had an excellent standard of hygiene for a considerable period of time. Given that socioeconomic conditions remained steady during the period of analysis, the drop in the level of vaccine uptake appears to be a major factor in the changes in pertussis incidence.[39,58] It therefore seems clear that containment of pertussis requires a systematic expansion of the vaccination program and maintenance of vaccination coverage at a high level, despite the positive effects obtained by improved social conditions.

Secondly, the mass media can influence the results of public health vaccination programs. The success of childhood immunization policy depends on parents' confidence in the pertussis vaccine. Health authorities can partly acquire trust by communicating in a convincing manner with the public. In order to avoid anti-vaccine publicity arising from isolated cases of severe systemic reactions, two conditions are required. Parents should be informed about both the risks of occasional adverse effects and the benefits of a widespread immunization strategy, and the consequences of an interrupted immunization program must be communicated. In addition, the mass media and physicians should be well informed and, therefore, have access to large-scale studies of the safety of pertussis vaccines.

It is important to mention that the results of quantitative controlled studies able to allay the suspicions of parents towards the use of whole-cell pertussis vaccine have only been available since the 1980s.[59-66] These studies have indicated that, contrary to an idea generally accepted in the 1970s, there is no causative role of pertussis vaccine in sudden infant death syndrome, and that whole-cell pertussis vaccines are not a proven cause of brain damage, infantile spasms, or Reye's syndrome.[8,9,67-69]

1.4 Attitude of Health Authorities

The fall in pertussis vaccination coverage resulted from active opposition to whole-cell vaccines and provoked differing reactions from health authorities in countries where an increase in pertussis incidence was reported. In England and Wales, the Department of Health and Social Security resisted pressure to remove the vaccine and tried successfully to reassure the public with the publication in 1981 of a report strongly recommending the advantages of pertussis immunization with whole-cell vaccines.[70,71] In Sweden, the Swedish Medical Society considered discontinuing general vaccination with whole-cell pertussis vaccines and waited for a new and safer vaccine. In 1979, pertussis vaccination was definitively interrupted in Sweden, mainly because the protective efficacy of the whole-cell vaccines was questioned.[32,72] In Japan, after the occurrence in 1975 of two fatalities in children given the DTP vaccine, the Ministry of Health and Welfare resolved to stop the program of vaccination with whole-cell vaccines. Later the program was reopened, but only for children >2 years of age.[20,57] To regain public confidence in pertussis vaccination, Japan introduced the acellular vaccine in 1981, and become the first country to use this new vaccine to control pertussis incidence.

Since the 1980s, the epidemiology of pertussis has continued to change as a function of the vaccine health policy undertaken in different countries. In England and Wales, for instance, regular progress in the uptake of whole-cell vaccine has been observed with an increase from 30% in 1978 to 91% in 1992, and this has resulted in a major decline in the incidence of pertussis.[73] Health authorities and general practitioners have actively contributed to this recovery. In Ireland and Australia, the opposition recorded in the UK to whole-cell vaccines directly influenced the epidemiology of pertussis.[74,75] In Ireland the vaccine coverage fell to 30% in 1976, then increased to 65% in 1990, but pertussis epidemics occurred in 1985 and 1989. Australia effectively controlled pertussis during the 1970s, then the information about neurological reactions to the vaccine gave rise to anti-vaccine movements. Consequently in 1994 the first large outbreak took place. In 1996, a pertussis epidemic caused the deaths of four infants in New South Wales, where vaccine uptake for the primary course was 87%.[30,76]

In countries where health authorities systematically maintained the use of whole-cell vaccines, a stable or increasing vaccination rate was observed, and until the 1980s the incidence of

pertussis seemed the lowest in the post-vaccine era. The US can be considered as an example of unchanging pertussis vaccination policy, strongly recommended by pediatricians and primary care organizations and supported by school-entry immunization requirements.[77,78] This policy made it possible to contain the pertussis infection rate, despite actions against whole-cell vaccines which grew in strength in the early 1980s. In fact, an all-time record low in the number of cases of pertussis was reached in 1976 with 1010 cases.

1.5 Re-Emergence of Pertussis

A resurgence of pertussis was recorded for the first time in the US in 1983, with 2463 cases, despite vaccination coverage of approximately 70% having been maintained since 1962.[79-82] Subsequently, epidemics occurred at regular time intervals in 1986, 1990 and 1993, but the number of reported cases increased; the 5457 cases reported in 1993 exceeded the number notified for any year since 1969.[38,83-85] It is important to note that the incidence based on reported cases increased among all age groups; however, the most striking rate of increase occurred among adolescents and adults. During 1992 and 1993, 23 deaths attributed to pertussis were recorded and pertussis became the most common vaccine-preventable childhood disease in the US.[10,86-89] The next outbreak occurred in 1996, with 7796 cases, despite the vaccine coverage rate which had been 95% since 1995.

The increasing trend in pertussis mortality and morbidity has also been observed in other countries where high levels of immunization with whole-cell vaccines have been maintained. For instance, in Finland an outbreak was notified in 1992, when about 97% of children were immunized with at least three doses of vaccine.[25,90] In The Netherlands, despite a vaccination coverage which remained stable at 96%, a sudden increase in pertussis incidence occurred in 1996. At that time, 4231 pertussis cases were reported, compared with 341 cases in 1995 and 4 cases in 1976. Five deaths caused by pertussis were notified from 1976 to 1996; however, two of these occurred in 1996.[31,91] A resurgence of pertussis has been also noted in Canada since 1991,[92,93] and an epidemic without any deaths from pertussis was observed in New Zealand in 1996.[94]

In some other countries such as France, a resurgence of pertussis is also suspected, but can not be formally confirmed because of the absence of national surveillance data. There was no anti-vaccine campaign in France during the 1970s,[15,28] and vaccination coverage estimated at about 95% has been maintained continuously for 30 years. In 1985 only 85 pertussis cases were reported and routine notification systems were broken off. With no surveillance data being available, recent studies have estimated that the current annual incidence of pertussis, identified by hospital practitioners in children younger than 1 year, is 95 cases per 100 000 population.[33,95]

The re-emergence of pertussis, which has manifested itself in countries with high vaccination coverage, has led to the suggestion that the current prevention and control strategies for pertussis have to be improved. In order to define components missing from vaccination programs, it is necessary to examine potential reasons for pertussis outbreaks. A sudden increase in incidence might be attributed to different factors if it could not be explained by a fall in vaccination coverage. For example, improvements in diagnosis and better surveillance data support, use of an ineffective vaccine, waning vaccine-induced immunity, antigenic changes in *B. pertussis*, and increased awareness of pertussis among healthcare providers and parents, are all factors which could be taken into consideration.[7,91,96-98]

2. Populations Susceptible to Pertussis

Although pertussis mortality and morbidity remain at its highest level among infants and young children, changes in the age distribution of notified cases related to the use of pertussis vaccine have been observed. After the vaccine came into widespread use, infants <1 year of age of age have remained the most susceptible to pertussis morbidity,[99-101] while in the pre-vaccine era the pertussis rate was highest among children aged between 1 and 5 years. This age group still accounts for the highest number of reported pertussis cases in some countries including Italy, Sweden and the former West Germany, where immunization is limited.[10,26,102,103]

2.1 Modifications in Age Distribution

In recent years, two significant modifications in age distribution have to be considered. First, an upward shift in the age distribution of pertussis morbidity has been demonstrated, characterized by an increased incidence in adolescents and adults, and explained, in part, by a better recognition and reporting of pertussis in this population. The proportion of pertussis cases occurring in individuals ≥15 years of age increased in the US from 15.1% of the total number of cases in 1977 to 28% in 1994,[78,104] while only 3% of the cases were reported in this age group before widespread immunization. In England and Wales, the proportion of notified pertussis cases in patients >15 years of age rose from 4.4% in 1990 to 9.3% in 1997.[105] In 1998, a total of 47% of 7405 reported pertussis cases which occurred in the US were in persons aged >10 years, while this age group accounted only for 29 and

45% of the cases, respectively, in the periods 1993 to 1995 and 1996 to 1997.[106] In Canada, children aged <10 years are by far the most affected group, but the proportion of older patients has also increased during the 1990s. The average annual incidence rate was 24.3 per 100 000 population for persons aged between 10 and 19 years, and 2.75 per 100 000 population for those aged >19 years. In Canada, between 10 and 25% of adults and adolescents are considered as being susceptible to pertussis.[107] They are thought to provide a potential source for transmitting infection to close contacts. It has been estimated that the pertussis incidence rate among household members exposed to the disease could range from 11 to 18% in contacts aged between 18 and 29 years, and from 8 to 33% in adults aged >30 years.[107-109]

Second, pertussis cases among infants <6 months of age is increasing, although the highest number of reported cases continues to be among children aged <1 year. In England and Wales, the proportion of cases among children <6 months of age rose from 6.2 to 19.3% between 1990 and 1997.[105] In the US, 24% of reported cases in 1998 were among children aged <7 months.[106] Infants who are too young to have completed primary immunization are at highest risk of severe pertussis-associated complications, mainly related to the effects of paroxysms. The incidence of bronchopneumonia during pertussis appears to be similar for all children <5 years of age, but may be more severe in infants. According to US data from 1989 through 1991, 70% of pertussis infections occurring among infants <6 months of age result in hospitalization, compared with approximately one-third of the total patient population.[10] Approximately 16% of infected infants had secondary pneumonia and 1.8% had neurological complications, mostly seizures, compared with 11 and 1.6%, respectively, of the total pertussis patient population. In Canada, 75% of infants with pertussis infection <6 months of age were hospitalized during the last decade, and 20% of these cases were admitted to an intensive care unit. Overall, 10% of infants <6 months of age with pertussis had secondary pneumonia, and 5% had neurologic complications, mostly seizures.[110]

These modifications in age distribution seem to have consequential effects for the epidemiology of pertussis. It has been confirmed that infection with *B. pertussis* is the usual cause of a persistent cough among adolescents and adults. However, as pertussis is often unrecognized in this population, adolescents and adults should be considered as the potential source of an outbreak of pertussis in a family with a neonate, or an unprotected infant for whom the morbidity and mortality are very high.

2.2 Immunization Schedules

The changes in age distribution of pertussis incidence are closely related to the characteristics of applied vaccination programs. In fact, widespread immunization has reduced the possibility of individuals acquiring infection-induced immunity, and current vaccination strategies do not provide the opportunity to prolong vaccine-induced immunity. Immunization schedules with whole-cell pertussis vaccines consist of three doses of primary series injected before the sixth month of life. Completion of the primary course early in life is essential because of the major risks of pertussis complications. Booster doses are also recommended at age 2 and 4 to 6 years.[7] A fifth dose of DTP vaccine is given in the US and Canada; however, in most industrial countries four-dose schedules are routine because local reactions occur more frequently with a greater number of doses. In some countries including the UK, Ireland, Denmark and Spain, no booster doses are used after 1 year of age,[111] while in developing countries, the WHO Expanded Program on Immunization schedule calls for only three doses injected in the first year of life, with no boosters. According to these immunization practices, two population groups seem to be particularly susceptible to disease: infants with an uncompleted primary course of vaccination, and previously vaccinated individuals. Indeed, the protection ensured by whole-cell vaccines has to be considered as only short-lived because vaccine-induced immunity wanes 5 to 10 years after the last injection, and is almost nonexistent after 12 years.[67,112-115] This means that even in communities with high vaccine uptake for the primary course, vaccinated children aged >14 years became vulnerable and potentially infectious adults.[116-118]

Therefore, adults and adolescents, especially females, with vaccine-associated or naturally acquired[119,120] waning immunity and mild atypical disease, have been suggested as an important reservoir for transmission of pertussis to under-immunized infants.[9,10,25,99,113,118-130] Epidemiological studies indicate that the infection rate of adults in the same household as children with pertussis could reach 83%,[131,132] but only a small proportion of these adults would be recognized as clinically ill. The main reason for underdiagnosis of pertussis in older patients is its atypical presentation in these populations, characterized by a persistent cough without whoop and lymphocytosis.[105,133-142] Another reason is the persistence of a common perception among physicians that pertussis is exclusively a disease of children. In order to reduce the incidence of pertussis among unvaccinated or incompletely vaccinated young children, it could be necessary to limit the exposure of this age group to pertussis through prevention of disease among older individuals. It would then appear that the only strat-

egy to prevent the transmission of pertussis from adults to infants might be to give booster doses of pertussis vaccine to all adolescents and adults.[9,123,143-145]

Booster immunizations with the present whole-cell vaccines have not been recommended for persons ≥7 years of age,[80,146] because pertussis is considered as being less severe in older children and adults, and at the same time, the adverse effects of whole-cell vaccines have been perceived as more common and more serious in these age groups. The availability of a safer and less reactogenic acellular vaccine provides an opportunity to consider adult booster immunizations.

3. Pertussis Vaccines in Current Use

The first acellular vaccines, which contain purified and inactivated components of *B. pertussis* cells, were licensed in Japan for immunization of children aged ≥2 years in 1981, and for infants from the age of 3 months in 1989. These new vaccines entirely replaced the whole-cell preparations and were reported to have low reactogenicity and satisfactory control of pertussis incidence in Japan.[24,57] However, the lack of formal evaluation of vaccine efficacy in randomized controlled trials delayed the approval of acellular vaccines in most other countries,[147] where successful whole-cell vaccination programs have been carried on.

3.1 Efficacy of Acellular Vaccines

During the 1990s, several large trials were set up in Sweden, Italy, Germany and Senegal in order to measure and compare the efficacy and adverse event rate of different whole-cell and acellular pertussis vaccines. However, these studies varied in type and number of vaccines, case definition, and the laboratory method used to confirm the infection, therefore comparison between studies is not necessarily relevant.

In the Swedish prospective clinical trial, designed to provide precise efficacy estimates, whole-cell vaccines were compared with three acellular vaccines containing two, three and five components, given to babies at 2, 4 and 6 months.[148] The whole-cell vaccine produced in the UK had the highest efficacy against culture-confirmed pertussis, with at least 21 days of paroxysmal cough.[149,150] The five-component acellular vaccine containing inactivated pertussis toxin, filamentous hemagglutinin, pertactin, and fimbriae 2 and 3 was more protective against pertussis infection than the three-component vaccine containing inactivated pertussis toxin, filamentous hemagglutinin and pertactin. In contrast, the whole-cell vaccine licensed in the US and tested in trials in Italy and Sweden, and a two-component acellular vaccine with antigens pertussis toxin and filamentous hemagglutinin, had inadequate efficacy.[151,152] The efficacy of European whole-cell vaccines compared with two- and three-component acellular vaccines was confirmed in case-control studies in Germany and Senegal.[153,154] These results suggest that the addition of fimbriae in the multicomponent acellular vaccines has an apparently significant role in protection against less severe infection,[54,148,149,155] and has stimulated discussion about which components should be included in acellular vaccines. The optimal composition of acellular vaccines is still debated, and it is not known which antigens are essential in order to ensure optimal efficacy.

The choice of antigen content for acellular pertussis vaccines is of crucial importance because a reduction in the number of components could decrease the excessive cost of acellular vaccines and make them more affordable. It could also, however, diminish their protective efficacy and make the new vaccines less competitive with whole-cell vaccines. At present it is recognized that the best whole-cell and acellular vaccines are both highly efficacious in preventing typical mild pertussis.[54,156-160] Acellular vaccines were estimated to provide approximately 85% protection in field trials, and whole-cell vaccines that have been used around the world and in field studies of efficacy have been shown to be 85 to 95% protective against pertussis infection.[97,161] It is important to note that efficacy may vary considerably within these two groups of pertussis vaccine, depending on the components involved and the study design.[147,151,162-165]

3.2 Choice Between Acellular and Whole-Cell Vaccines

Assuming that the efficacy of whole-cell and acellular vaccines is similar in preventing pertussis infection, the choice between these two types of vaccines for public health immunization programs involves essentially a trade-off between safety and cost. In industrialized countries, which have faced difficulties in the control of pertussis outbreak because of adverse effects following whole-cell vaccination, safety would appear to be the priority. Decreased reactogenicity of acellular vaccines is likely to improve public acceptance of pertussis vaccination and to maintain vaccination coverage at a high and stable level. However, given that acellular vaccines are not as efficacious as the best current whole-cell vaccine,[149] exclusive use of acellular vaccines might result in less successful pertussis control at significantly higher cost. It seems, nevertheless, that currently the most important aspect of acellular vaccines is their safety rather than efficacy.

The reduced reactogenicity of acellular vaccines compared with whole-cell vaccines was first established in Japan from their extensive use in that country, and confirmed in recent safety and efficacy trials.[24,147,151,155,166-187] Data from studies comparing

various diphtheria-tetanus vaccines containing an acellular pertussis component (DTaP) and a whole-cell pertussis component (DTwP) have established that the DTaP vaccines have produced significantly fewer and less severe adverse events during the primary course.[148,150,187,188] Indeed, local and systemic vaccine-associated adverse events, including injection site erythema, swelling, tenderness, fever and crying occurred less frequently among infants given the new vaccines, and with a similar frequency to rates observed with diphtheria and tetanus toxoid vaccines. A large, multicenter trial reported that 20 to 33% of infants had a high temperature after administration of DTaP vaccines compared with 60% after DTwP injections.[181] Redness was observed in 47 and 73% of children who received the DTaP compared with the DTwP injection, respectively, swelling in 34 and 61%, and pain in 11 and 40%. The incidence of serious adverse events, for example high fever, persistent crying and hypotonic hyporesponsive episodes, has also been reported to be lower with DTaP vaccines. However, this finding could be considered a debatable point, because data from other studies have shown that there is no significant difference in the occurrence of severe reactions after DTaP compared with DTwP vaccination.[54,163,189]

Adverse events have been reported to be, in general, significantly less common and less reactogenic after DTaP vaccines, compared with DTwP vaccines, when given as a booster dose in 18-month-old children.[171,188,190] For example, fever was observed in 5% of children vaccinated with DTaP compared with 85% of those given DTwP.[171] Respective rates of other adverse events are as follows: tenderness, 22 and 100%; swelling, 10 and 35%; anorexia, 2.5 and 35%; and vomiting, 0 and 10%. DTaP vaccines given as a booster dose at preschool age have also been shown to have a good safety profile and to be immunogenic, but they did result in a higher frequency of local reactions compared with primary immunization with DTaP and booster with DT.[191,192]

Decreased reactogenicity has been considered in several developed countries, in which reactions to whole-cell vaccines have caused problems, as the main achievement of pertussis acellular vaccination, and despite a high cost, the new vaccine has been recommended for booster doses or primary courses. It is important to emphasize that the current attitude of national health authorities towards acellular vaccines differs from country to country, and that the strategy adopted for pertussis vaccination is a factor of the national history of pertussis infection and the quality of whole-cell vaccines (table I). For example in the US, where the efficacy of whole-cell vaccines has been questioned by recent trials, acellular vaccines were licensed in 1991 for the fourth and fifth doses of the pertussis series and in 1996 for the primary series.[193] A diametrically opposed situation can be observed in the UK where booster doses for infants and children have never been recommended, and where a highly effective whole-cell vaccine is exclusively used for the primary immunization course with an accelerated schedule.[58,194-196] This vaccination strategy is unlikely to be modified at present because of the high acceptance rate for the current vaccine, its lower cost, the high coverage level which can generate herd immunity, and very low pertussis incidence in England and Wales.[197] However, it is envisaged that a booster dose of pertussis vaccine could be recommended in the near future in order to confer continued and adequate immunity against pertussis in preschool years. After an evaluation of its acceptability at this age, the use of acellular vaccines with reduced reactogenicity could then be justified for booster doses.[108,147,198-202]

The intermediate current vaccination strategy applied in most European countries consists of the use of highly potent whole-cell vaccines in primary immunization schedules for infants, and the potential application of less reactogenic acellular vaccines for booster doses. However, in most Eastern European countries, only whole-cell vaccines are used for all doses of the vaccination schedule because of the deterioration of healthcare resources secondary to the economic transition.[203] In developing countries, the WHO does not recommend the choice of acellular vaccines as these are considerably more expensive than current vaccines. In such countries whole-cell vaccines, highly effective in preventing pertussis, should remain the choice for public health pertussis immunization programs.[204] However, the WHO approves the use of acellular vaccines in countries where pertussis vaccination has been questioned because of adverse effects of whole-cell vaccines.

3.3 Clinical Use of Acellular Vaccines

The use of acellular vaccines for primary immunization and for booster doses seems to be promising for effective control of pertussis. The lower reactogenicity of acellular vaccines appears to be a deciding factor in their use. Firstly, the safety profile of acellular vaccines could improve acceptance of wide application of pertussis vaccination in infants, and decrease the risk of sudden interruption of the vaccination program.

Secondly, public confidence in new vaccines could also make the introduction of additional booster doses of pertussis vaccine into regular vaccination programs easier. The use of well tolerated vaccines in adolescents and adults could significantly reduce disease transmission. However, the age at which the booster dose is given, considered to be an important point of the

strategy, remains undetermined because the duration of protection after primary immunization with acellular vaccines has not yet been established. Currently, the routine use of acellular pertussis vaccines for adolescents and adults is not recommended. France is the only country where the official schedules include a booster dose of pertussis acellular vaccine for teenagers. This second booster dose has been applied since 1998 at 11 to 13 years of age.[205]

Several clinical trials and other studies have been undertaken to determine the safety and efficacy of acellular vaccines used for adolescents and adults, but additional data on the potential benefit of booster doses in this population are needed. Some preliminary results have already reported that the acellular vaccines are immunogenic and are associated with relatively limited local adverse effects, including erythema, swelling or induration, while previous experiences with whole-cell vaccines among adults had demonstrated an unacceptable rate of adverse effects. A Canadian clinical trial evaluating the frequency of adverse events after vaccination with the DTaP vaccine licensed for use in people aged between 12 and 54 years, found that the most frequent local reaction was pain (89% of vaccinated adolescents and adults), followed by swelling (17%) and erythema (12%). Systemic adverse events such as headache (39%), generalized bodyache (20%) and fever (9%) were also reported.[205] Adverse reactions after vaccination of adults with whole-cell vaccines were observed in a hospital outbreak in Cincinnati in 1974. The results indicated that among vaccinated hospital staff, erythema occurred in 45% of adults, 29% had swelling or induration, 27% had limitation of motion in the inoculated arm, and 10% had fever.[206]

Thirdly, acellular pertussis components are likely to be more suitable than whole-cell composition for inclusion in combination vaccines. The use of these vaccines could increase ease of administration, reduce the number of injections required, and could lead to extended vaccination coverage. Currently, all types of pertussis vaccines can be successfully combined with diphtheria and tetanus vaccines. Whole-cell pertussis vaccines can also be combined with hepatitis B, inactivated polio and *Hemophilus influenzae* type b (Hib) vaccines. Such combinations are licensed in some countries. At present, acellular pertussis vaccines can be combined with inactivated poliovirus vaccine and Hib vaccines. Combinations with hepatitis B are under development. However, not all pertussis acellular vaccines are at present available in multicomponent form because of a reported reduction in the antibody response to one or more antigens in the combined product. Combinations of diphtheria, tetanus, acellular pertussis and Hib vaccines have indeed led to a decrease in the immunogenicity of the Hib component.[54,163]

The main obstacle to wider application of acellular vaccines, apart from their high price, is uncertainty about the magnitude of the protection against severe disease, duration of effect, and effect on transmission. Other questions regarding an association between acellular vaccines and serious adverse events, and the safety of repeated booster doses, still remained unresolved. Postlaunch monitoring and studies of effectiveness of acellular vaccines in a large population, including adults, are required to evaluate the role of the new vaccines in the epidemiology of pertussis. Analysis of accumulated pertussis surveillance data would determine whether or not widespread use of acellular vaccines should be encouraged in the long term.

4. Conclusions

The current strategy for successful control of pertussis infection, which is the common goal of many national public health policies, requires the realization of two conditions. Increased vaccination coverage has to be achieved among young children, and this must be maintained at a high level over time. In addition, an immunization program for adolescents and adults has to be introduced, with periodic booster doses to extend immunity effects.

If the optimal strategy is defined as a health policy providing the best possible control of pertussis infection within a given set of circumstances, the changing epidemiology of pertussis would suggest that at present it seems difficult to define a single worldwide optimal strategy for pertussis vaccination.

In fact, the manner in which the common goal could be achieved is determined in each country by a proper national vaccination program established in very close relation to the past and actual epidemiological situations and available healthcare resources. Programs could involve two kinds of vaccines and different immunization schedules. The use in several countries of whole-cell vaccines for the primary course should remain the appropriate choice for immunization programs focused on lower cost, better protection and proven high efficacy. However, vaccination programs in other countries could be based on the sole use of acellular vaccines because of reduced reactogenicity and consequently better acceptance in a population, despite high cost. Recommendations for the use of each kind of pertussis vaccine for the primary course could take into consideration local risk-benefit and cost-benefit analyses based on the price of two vaccines, and the evaluation of direct and indirect costs of disease and adverse events following immunization.

If the safety and efficacy of acellular vaccines are confirmed in the long term for use among children and adults, and if these vaccines become less costly, widespread replacement of whole-

cell pertussis vaccines with acellular vaccines might lead to more standardized conditions for the realization of vaccination programs. The idea of a single optimal strategy for pertussis vaccination could then be taken into consideration. However, it does not seem likely that a single optimal strategy could result in pertussis elimination or eradication in the near future.

References

1. Begg N, Cutts FT. The role of epidemiology in the development of a vaccination programme. In: Cutts FT, Smith PG, editors. Vaccination and world health. Chichester: John Wiley & Sons, 1994: 123-44
2. Centers for Disease Control and Prevention. Achievements in public health, 1900-1999: control of infectious diseases. MMWR Morb Mortal Wkly Rep 1999; 48 (29): 621-9
3. Centers for Disease Control and Prevention. Certification of poliomyelitis eradication: the Americas, 1994. MMWR Morb Mortal Wkly Rep 1994; 43: 720-2
4. Preston NW. Pertussis today. In: Wardlaw AC, Parton R, editors. Pathogenesis and immunity in pertussis. Chichester: John Wiley & Sons, 1988: 1-18
5. Fine PEM. Epidemiological considerations for whooping cough eradication. In: Wardlaw AC, Parton R, editors. Pathogenesis and immunity in pertussis. Chichester: John Wiley & Sons, 1988: 451-67
6. Centers for Disease Control and Prevention. Fact sheets for candidate disease for elimination or eradication. MMWR Morb Mortal Wkly Rep 1999; 48 (SU01): 154-203
7. Cherry JD. Historical review of pertussis and the classical vaccine. J Infect Dis 1996; 174 Suppl. 3: S259-63
8. Hodder SL, Mortimer Jr EA. Epidemiology of pertussis and reactions to pertussis vaccine. Epidemiol Rev 1992; 14: 243-67
9. Cherry JD, Baraff LJ, Hewlett E. The past, present, and future of pertussis: the role of adults in epidemiology and future control. West J Med 1989; 150: 319-28
10. Black S. Epidemiology of pertussis. Pediatr Infect Dis J 1997; 16 (4 Suppl.): S85-9
11. Bordet J, Gengou O. The microbe of whooping cough [in French]. Ann Inst Pasteur 1906; 20: 731-41
12. Bordet J, Gengou O. The coquelucheuse endoxine [in French]. Ann Inst Pasteur 1909; 23: 415-9
13. Heininger U, Cherry JD, Eckhardt T, et al. Clinical characteristics of illness caused by Bordetella parapertussis compared with illness caused by Bordetella pertussis. Pediatr Infect Dis J 1994; 13: 306-9
14. Goldman WE. Tracheal cytotoxin of bordetella pertussis. In: Wardlaw AC, Parton R, editors. Pathogenesis and immunity in pertussis. Chichester: John Wiley & Sons, 1988: 231-46
15. Miller DL, Alderslade R, Ross EM. Whooping cough and whooping cough vaccine: the risks and benefits debate. Epidemiol Rev 1982; 4: 1-24
16. Centers for Disease Control and Prevention. Achievement in public health, 1900-1999: impact of vaccines universally recommended for children, United States, 1990-1998. MMWR Morb Mortal Wkly Rep 1999; 48 (12): 243-8
17. Hutchins SS, Cochi SL, Brink EW, et al. Current epidemiology of pertussis in the United States. Tokai J Exp Clin Med 1988; 13: 103-9
18. Pertussis incidence in Canada. Can Dis Wkly Rep 1985; 11: 33-5
19. Cherry JD. The epidemiology of pertussis and pertussis immunization in the United Kingdom and the United States: a comparative study. Curr Probl Pediatr 1984; 14: 3-77
20. Kanai K. Japan's experience in pertussis epidemiology and vaccination in the past thirty years. Jpn J Med Sci Biol 1980; 33: 107-43
21. Centers for Disease Control and Prevention. Annual summary 1983: morbidity and mortality tables. MMWR Morb Mortal Wkly Rep 1984; 32: 115-20
22. Pertussis consensus conference. Can Commun Dis Rep 1993; 19 (16): 124-35
23. Dow DA, Mansoor O. New Zealand immunization schedule history. NZ Med J 1996; 109: 209-12
24. Sato Y, Kimura M, Fukumi H. Development of pertussis component vaccine in Japan. Lancet 1984; I: 122-6
25. He Q, Viljanen M, Nikkari S, et al. Outcomes of Bordetella pertussis infection in different age groups of an immunized population. J Infect Dis 1994; 170: 873-7
26. Isacson J, Trollfors B, Taranger J, et al. How common is whooping cough in a nonvaccination country. Pediatr Infect Dis J 1993; 12: 284-8
27. Pollard R. Relation between vaccination and notification rates for whooping-cough in England and Wales. Lancet 1980; I: 1180-2
28. Griffiths E. Efficacy of whole-cell pertussis vaccine. In: Wardlaw AC, Parton R, editors. Pathogenesis and immunity in pertussis. Chichester: John Wiley & Sons 1988: 353-74
29. Canadian National Report on Immunization 1996. Can Commun Dis Rep 1997; 23: S4
30. Williams GD, Matthews NT, Choong RKC, et al. Infant pertussis deaths in New South Wales, 1996-1997. Med J Aust 1998; 168: 281-3
31. De Melker HE, Conyn-van Spaendonck MAE, Rümke HC, et al. Pertussis in The Netherlands: an outbreak despite high level of immunization with whole-cell vaccine. Emerg Infect Dis 1997; 3: 175-8
32. Romanus V, Jonsell R, Bergquist SO. Pertussis in Sweden after the cessation of general immunization in 1979. Pediatr Infect Dis J 1987; 6: 364-71
33. Baron S, Njamkepo E, Grimprel E, et al. Epidemiology of pertussis in French hospitals in 1993 and 1994: thirty years after a routine use of vaccine. Pediatr Infect Dis J 1998; 17: 412-8
34. Beutels PH, Bonanni P, Tormans G. An economic evaluation of universal pertussis vaccination in Italy. Vaccine 1999; 17: 2400-9
35. Public Health Laboratory Service. Whooping cough surveillance. CDR Wkly 1982; 82: 3-6
36. PHLS Communicables Disease Surveillance Centre. Whooping cough: annual notifications and vaccine uptake rates for England and Wales. London. PHLS Communicables Disease Surveillance Centre, 1992
37. Centers for Disease Control and Prevention. Diphtheria, tetanus, and pertussis: recommendations for vaccine use and other preventives measures recommendations of the immunization practices advisory commitee (ACIP). MMWR Morb Mortal Wkly Rep 1991; 40 (RR10): 1-28
38. Centers for Disease Control and Prevention. Pertussis: United States, Jan 1992-Jun 1995. JAMA 1995; 274: 450-1
39. Girard DZ. Intervention times series analysis of pertussis vaccination in England and Wales. Health Policy 2000; 54: 13-25
40. Mortimer Jr EA, Jones PK. An evaluation of pertussis vaccine. Rev Infect Dis 1979; 1: 927-32
41. Fine PEM, Clarkson JA. Individual versus public priorities in the determination of optimal vaccination policies. Am J Epidemiol 1986; 124: 1012-20
42. Cody CL, Baraff LJ, Cherry JD, et al. Nature and rates of adverse reactions associated with DTP and DT immunization in infants and children. Pediatrics 1981; 68: 650-60
43. Baraff LJ, Manclark CR, Cherry JD, et al. Analysis of adverse reactions to diptheria and tetanus toxoids and pertussis vaccine by vaccine lot, endotoxin content, pertussis vaccine potency and percentage of mouseweight gain. Pediatr Infect Dis J 1989; 8: 502-7
44. Baraff LJ, Cody CL, Cherry JD. DTP-associated reactions: an analysis by injection site, manufacturer, prior reactions, and dose. Pediatrics 1984; 73: 31-6
45. Chen RT, Rastogi SC, Mullen JR, et al. The vaccine adverse event reporting system (VAERS). Vaccine 1994; 12: 542-50
46. Ström J. Is universal vaccination against pertussis always justified. BMJ 1960; II: 1184-6
47. Kulenkampff M, Schwartzman JS, Wilson J. Neurological complications of pertussis inoculation. Arch Dis Child 1974; 49: 46-9

48. Aicardi J, Chevrie JJ. Neurologic manifestations following pertussis vaccination [in French]. Arch Fr Pediatr 1975; 32: 309-17
49. Bassili WR, Steward GT. Epidemiological evaluation of immunization and other factors in the control of whooping cough. Lancet 1976; I: 471-4
50. Steward GT. Vaccination against whooping cough: efficacy versus risk. Lancet 1977; I: 234-7
51. Steward GT. Whooping cough in relation to other childhood infections in 1977-79 in the United Kingdom. J Epidemiol Community Health 1981; 2: 481-7
52. Gangarosa EJ, Galazka AM, Wilfe CR, et al. Impact of anti-vaccine movements on pertussis control: the untold story. Lancet 1998; 351: 366-1
53. McKinnon JA. The impact of the media on whooping cough immunization. Health Educ J 1979; 37: 198-202
54. Halperin SA. Developing better pediatric vaccine: the case of pertussis vaccine. BioDrugs 1999; 12: 175-91
55. Kim-Farley R, The Expended Programme on Immunization Team. Global immunization. Ann Rev Public Health 1992; 13: 223-8
56. Bernier R, Orenstein W, Hutchins S, et al. Do vaccines reach those who most need them. In: Cutts FT, Smith PG, editors. Vaccination and world health. Chichester: John Wiley & Sons, 1994: 213-25
57. Kimura M, Kuno-Sakai H. Developments in pertussis immunization in Japan. Lancet 1990; 336: 30-2
58. Miller E, Gay NJ. Epidemiological determinants of pertussis. Dev Biol Stand 1997; 89: 15-23
59. Broome CV, Fraser DW. Pertussis in the United States, 1979: a look at vaccine efficacy. J Infect Dis 1981; 144: 187-90
60. Pollock TA, Morris J. A 7 year survey of disorders attributed to vaccination in north west Thames region. Lancet 1983; I: 753-7
61. Miller DL, Ross EM, Alderslade R, et al. Pertussis immunization and serious acute neurological illness in childhood. BMJ 1981; 282: 1595-9
62. Miller DL, Wadsworth J, Diamond J, et al. Pertussis vaccine and whooping cough as risk factors in acute neurological illness and death in young children. Dev Biol Stand 1985; 61: 389-94
63. Bellman MH, Miller DL, Ross EM. Infantile spasms and pertussis immunization. Lancet 1983; I: 1031-4
64. Walker AM, Jick H, Perera DR, et al. Diphtheria-tetanus-pertussis immunization and sudden infant death syndrome. Am J Public Health 1987; 77: 945-51
65. Alderslade R, Bellman MH, Rawson NSB, et al. The childhood encephalopathy study. In: Whooping cough: report from the Committee on Safety of Medicines and the Joint Committee on Vaccination and Immunization. London. London Department of Health and Social Security, 1981: 79-154
66. Fine PEM, Chen RT. Confounding in studies of adverse reactions to vaccines. Am J Epidemiol 1992; 136: 121-35
67. Cherry JD, Brunell PA, Golden GS, et al. Report of the task force on pertussis and pertussis immunization, 1988. Pediatrics 1988; 81: 939-84
68. Committtee on Infectious Disease. The relationship between pertussis vaccine and central nervous system sequelae: continuing assessment. Pediatrics 1996; 97: 279-81
69. Centers for Disease Control and Prevention. Update: vaccine side effects, adverse reactions, contradications, and precautions after DTP vaccination. Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 1996; 45 (RR-12): 22-35
70. Department of Health and Social Security. Whooping cough: report from the Committee on Safety of Medicines and the Joint Committee on Vaccination and Immunization. London: Her Majesty's Stationery Office, 1981
71. Public Health Laboratory Service Epidemiological Research Laboratory. Efficacy of pertussis vaccination in England. BMJ 1982; 285: 357-9
72. Trollfors B, Rabo E. Whooping cough in adults. BMJ 1981; 283: 696-7
73. Miller E, Vurdien JE, White JM. The epidemiology of pertussis in England and Wales. Commun Dis Rep 1992; 13: R152-4
74. Howell F, Jennings S. The epidemiology of pertussis in the Republic of Ireland. Commun Dis Rep 1992; 2: R31-3
75. McIntyre CR, Nolan T. Attitudes of Victorian vaccine providers to pertussis vaccine. Med J Aust 1994; 161: 295-9
76. Andrews R, Herceg A, Roberts C. Pertussis notifications in Australia, 1991-1997. Commun Dis Intell 1997; 21: 145-8
77. Onorato IM, Wassilak SG, Mead B. Efficacy of whole-cell pertussis vaccine in preschool children in the United States. JAMA 1992; 267: 2745-9
78. Centers for Disease Control and Prevention. Reported vaccine-preventable diseases: United States, 1993, and the childhood immunization initiative. MMWR Morb Mortal Wkly Rep 1994; 43: 57-60
79. Centers for Disease Control and Prevention. Resurgence of pertussis: United States 1993. JAMA 1994; 271: 340-1
80. Centers for Disease Control and Prevention. Summary of notifiable diseases: United States 1991. MMWR Morb Mortal Wkly Rep 1991; 40: 12
81. Bass JW, Wittler RR. Return of epidemic pertussis in the United States. Pediatr Infect Dis J 1994; 13: 343-5
82. Marchant CD, Loughlin AM, Lett SM, et al. Pertussis in Massachusetts, 1981-1991. J Infect Dis 1994; 169: 1297-305
83. Centers for Disease Control and Prevention. Resurgence of pertussis: United States, 1993. MMWR Morb Mortal Wkly Rep 1993; 42: 952-60
84. Centers for Disease Control and Prevention. Pertussis surveillance: United States, 1986-1988. MMWR Morb Mortal Wkly Rep 1990; 36: 57-65
85. Sutter RW, Cochi SL. Pertussis hospitalizations and mortality in the United States, 1985-1988. Evaluation of the completeness of national reporting. JAMA 1992; 267: 386-91
86. Wortis N, Strebel PM, Wharton M, et al. Pertussis deaths: report of 23 cases in the United States, 1992 and 1993. Pediatrics 1996; 97: 607-12
87. Shaikh R, Guris D, Strebel PM, et al. Under-reporting of pertussis deaths in the United States: need for improved surveillance [letter]. Pediatrics 1998; 101: 323
88. Centers for Disease Control and Prevention. Pertussis: United States, Jan 1992-Jun 1995. MMWR Morb Mortal Wkly Rep 1995; 44: 525-9
89. Christie CD, Marx ML, Marchant CD, et al. The 1993 epidemic of pertussis in Cincinnati: resurgence of disease in a highly immunized population of children. N Engl J Med 1994; 331: 16-21
90. Mestrola J, Viljanen MK, Ruuskanen O. Current status of pertussis and pertussis vaccination in Finland. Ann Clin Res 1982; 14: 253-9
91. De Melker HE, Schellekens JFP, Neppelenbroek SE, et al. Reemergence of pertussis in highly vaccinated population of The Netherlands: observations on surveillance data. Emerg Infect Dis 2000; 6: 348-57
92. De Serres G, Bouliane N, Douvulle-Fradet M, et al. Pertussis in Quebec: ongoing epidemic since the late 1980s. Can Commun Dis Rep 1995; 15: 45-8
93. Milord F. Resurgence of pertussis in Monteregie, Quebec: 1990-1994. Can Commun Dis Rep 1995; 21: 40-4
94. Mansoor O, Reid S. The future of the immunisation schedule: recommendation of a workshop. NZ Med J 1999; 112: 52-5
95. Grimpel E, Baron S, Lévy-Bruhl D, et al. Influence of vaccination coverage on pertussis transmission in France. Lancet 1999; 354: 1699-700
96. Mooi FR, van Oirschot H, Heuvelman K, et al. Polymorphism in the Bordetella pertussis virulence factors P.69/pertactin and pertussis toxin in The Netherlands: temporal trends and evidence from vaccine-driven evolution. Infect Immun 1998; 66: 670-5
97. Eskola J. Childhood immmunization today. Drugs 1998; 55: 759-66
98. Halperin SA, Bortolussi R, McLean D, et al. Persistence of pertussis in an immunized population: results of the Nova Scotia enhanced pertussis surveillance program. J Pediatr 1989; 115: 686-93
99. Farizo KM, Cochi SL, Zell ER, et al. Epidemiological features of pertussis in the United States, 1980-1989. Clin Infect Dis J 1992; 14: 708-19
100. Brooks GF, Buchanan TM. Pertussis in the US. J Infect Dis 1970; 122: 123-5

101. Pollock TM, Miller E, Lobb J. Severity of whooping cough in England before and after the decline of pertussis immunisation. Arch Dis Child 1984; 59: 162-5
102. Stroffolini T, Giammanco A, de Crescenzo L, et al. Prevalence of pertussis IgG antibodies in children in Palermo, Italy. Infection 1989; 17: 280-3
103. Binkin NJ, Salmaso S, Tozzi AE, et al. Epidemiology of pertussis in a developed country with low vaccination coverage: the Italian experience. Pediatr Infect Dis J 1992; 11: 653-61
104. Wright W, Edwards KM, Decker MD, et al. Pertussis infection in adults with persistent cough. JAMA 1995; 273: 1044-6
105. Van Buynder PG, Owen D, Vurdien JE, et al. Bordetella pertussis surveillance in England and Wales: 1995-1997. Epidemiol Infect 1999; 123: 403-11
106. Guris D, Strebel PM, Bardenheier B, et al. Changing epidemiology of pertussis in the United States: increasing reported incidence among adolescents and adults, 1990-1996. Clin Infect Dis 1999; 28: 1230-7
107. National Advisory Committee on Immunization. Statement on adult/adolescent formulation of combined acellular pertussis, tetanus, and diphtheria vaccine. Can Commun Dis Rep 2000; 26 (ACS-1): 1-7
108. Halperin SA, Bartolussi R, Langley JM, et al. A randomized, placebo-controlled trial of erythromycin estolate chemoprophylaxis for household contacts of children with culture-positive Bordetella pertussis infection. Pediatrics 1999; 104: E42
109. De Serres G, Boulianne R, Duval B. Field effectiveness of erythromycin prophylaxis to prevent pertussis within families. Pediatr Infect Dis 1995; 14: 969-75
110. Gold R, Dery P, Halperin S, et al. Pertussis in children hospitalised at five Canadian pediatric tertiary care centres. Can Commun Dis Rep 1994; 20: 31-4
111. Ranganathan S, Tasker R, Booy R, et al. Pertussis is increasing in immunised infants: is a change in policy need? Arch Dis Child 1999; 80: 297-9
112. Jenkinson D. Duration of effectiveness of pertussis vaccine: evidence from 10-year community study. BMJ 1988; 296: 612-4
113. Lambert HJ. Epidemiology of a small pertussis outbreak in Kent County, Michigan. Public Health Rep 1965: 80; 365-9
114. Long SS. Pertussis. In: Behrman RE, editor. Nelson textbook of pediatrics. 15th ed. Philadelphia (PA): WB Saunders, 1996: 779-84
115. Grimpel E, Begue P, Anjak I, et al. Long-term human serum antibody responses after immunization with whole-cell pertussis vaccine in France. Clin Diagn Lab Immunol 1996; 3: 93-7
116. Cattaneo LA, Reed GW, Haase DH, et al. The seroepidemiology of Bordetella pertussis infections: a study of persons ages 1-65 years. J Infect Dis 1996; 173: 1256-9
117. Fine PEM, Clarkson JA. Distribution of immunity to pertussis in the population of England and Wales. J Hyg (Lond) 1984; 92: 21-36
118. Mink CM, Sirota NM, Nugent S. Outbreak of pertussis in fully immunized adolescent and adult population. Arch Pediatr Adolesc Med 1994; 148: 153-7
119. Cherry JD, Beer T, Chartrand SA, et al. Comparison of antibody values to Bordetella pertussis antigens in young German and American men. Clin Infect Dis 1995; 20: 1271-4
120. Nelson JD. The changing epidemiology of pertussis in young infants: the role of adults as reservoirs for infection. Am J Dis Child 1978; 132: 371-3
121. Baron S, Begue P, Grimpel E. Epidemiology of pertussis in industrialized countries. Santé 1994; 4: 195-200
122. Christie CD, Baltimore RS. Pertussis in neonates. Am J Dis Child 1989; 143: 1199-202
123. Izurieta HS, Kenyon TA, Strebel PM, et al. Risk factors for pertussis in young infants during an outbreak in Chicago in 1993. Clin Infect Dis 1996; 22: 503-7
124. Mink CM, Cherry JD, Christenson P, et al. A search for Bordetella pertussis infection in university students. Clin Infect Dis 1992; 14: 464-71
125. Mortimer EA. Pertussis and its prevention: a family affair. J Infect Dis 1990; 161: 473-9
126. Wirsing von Köning CH, Postels Multani S, Bock HL, et al. Pertussis in adults: frequency of transmission after household exposure. Lancet 1995; 346: 1326-9
127. Siegel C, Davidson A, Kafadar K, et al. Geographic analysis of pertussis infection in an urban area: a tool for health services planning. Am J Public Health 1997; 87: 2022-6
128. Biellik RJ, Patriarca PA, Mullen RJ, et al. Risk factors for community-and household-acquired pertussis during a large-scale outbreak in central Wisconsin. J Infect Dis 1988; 157: 1134-41
129. Linnemann Jr CC, Nasenbeny J. Pertussis in the adult. Annu Rev Med 1997; 28: 179-82
130. Schmitt-Grohé S, Cherry JD, Heininger U, et al. Pertussis in German adults. Clin Infect Dis 1995; 21: 860-6
131. Mertsola J, Ruuskanen O, Eerola E, et al. Intrafamilial spread of pertussis. J Pediatr 1983; 103: 359-63
132. Long SS, Welkon CJ, Clark JL. Widespread silent transmission of pertussis in families: antibody correlates of infection and symptomatology. J Infect Dis 1990; 161: 480-6
133. Robertson PW, Goldberg H, Jarvie BH, et al. Bordetella pertussis infection: a cause of persistent cough in adults. Med J Aust 1987; 146: 522-5
134. Herwaldt LA. Pertussis in adults: what physicians need to know. Arch Intern Med 1991; 109: 1510-2
135. Herwaldt LA. Pertussis and pertussis vaccine in adults. JAMA 1993; 269: 93-4
136. Cromer BA, Goydos J, Hackell J, et al. Unrecognized pertussis infection in adolescents. Am J Dis Child 1993; 147: 575-7
137. Deville JG, Cherry JD, Christenson PD, et al. Frequency of unrecognized Bordetella pertussis infection in adults. Clin Infect Dis 1995; 2: 639-42
138. Heininger U, Cherry JD, Eckhardt T, et al. Clinical and laboratory diagnosis of pertussis in the regions of a large vaccine efficacy trial in Germany. Pediatr Infect Dis J 1993; 12: 504-9
139. Aoyama T, Takeuchi Y, Goto A, et al. Pertussis in adults. Am J Dis Child 1992; 146: 163-6
140. Postels-Multani S, Schmitt HJ, Wirsing von König CH, et al. Symptoms and complications of pertussis in adults. Infection 1995; 23: 13-6
141. Aoyama T, Harashima M, Nishimura K, et al. Outbreak of pertussis in highly immunized adolescents and its secondary spread to their family. Acta Paediatr Jpn 1995; 37: 321-4
142. Rosenthal S, Strebel P, Cassiday P, et al. Pertussis infection among adults during the 1993 outbreak in Chicago. J Infest Dis 1995; 171: 1650-2
143. Hewlett EL. Pertussis in adults: possible use of booster doses for control. Tokai J Exp Clin Med 1988; 13: 125-8
144. Edwards KM, Decker MD, Grahams BS, et al. Adult immunization with acellular pertussis vaccine. JAMA 1993; 269: 53-6
145. Onorato IM, Wassilak SG. Laboratory diagnosis of pertussis: the state of the art. Pediatr Infect Dis J 1987; 6: 145-51
146. Englund JA, Decker MD, Edwards KM, et al. Acellular and whole-cell pertussis vaccines as booster doses: a multicenter study. Pediatrics 1994; 93: 37-43
147. Miller E. Acellular pertussis vaccines. Arch Dis Child 1995; 73: 390-1
148. Olin P, Rasmussen F, Gustafsson L, et al. Randomised controlled trials of two-component, three-component, and five-component acellular pertussis vaccine compared with whole-cell pertussis vaccine. Lancet 1997; 350: 1569-77
149. Preston NW, Matthews RC. Acellular pertussis vaccines: progress but déjà vu. Lancet 1998; 351: 1811-2
150. Plotkin S, Cadoz M. The acellular pertussis vaccine trials: an interpretation. Pediatr Infect Dis 1997; 16: 508-17
151. Greco D, Salmaso S, Mastrantonio P, et al. Clinical efficacy, immunogenicity and safety of two acellular and one whole-cell pertussis vaccines: results from the Italian trials. N Engl J Med 1996; 334: 341-8
152. Olin P. The best acellular vaccines are multi-component. Pediatr Infect Dis 1997; 16: 517-9
153. Simondon F, Preziosi M-P, Yam A, et al. Randomized double-blind trial comparing a two-component acellular to whole-cell pertussis vaccine in Senegal. Vaccine 1997; 15: 1606-12

154. Liese JG, Meschievitz CK, Harzer E, et al. Efficacy of a two-component acellular pertussis vaccine in infants. Pediatr Infect Dis J 1997; 16: 1038-44
155. Gustafsson L, Hallander HO, Olin P, et al. A controlled trial of a two-component acellular, five-component acellular, and a whole-cell pertussis vaccine. N Engl J Med 1996; 334: 349-55
156. Ivanoff B, Robertson SE. Pertussis: a worldwide problem. Dev Biol Stand 1997; 89: 3-13
157. Hewlett EL, Cherry JD. New and improved vaccine against pertussis. In: Levine MM, Woodrow GC, Kaper JB, et al., editors. New generation vaccines. 2nd ed. New York: Marcel Decker, 1997: 387-416
158. Schmitt HJ, von Koning CHW, Neiss A, et al. Efficacy of acellular pertussis vaccine in early childhood after household exposure. JAMA 1996; 275: 37-41
159. Edwards KM, Decker MD. Acellular pertussis vaccines for infants. N Engl J Med 1996; 334: 391-2
160. Cherry JD. Comparative efficacy of acellular pertussis vaccines: an analysis of recent trials. Pediatr Infect Dis J 1997; 16 (4 Suppl.): S90-6
161. National Advisory Committee on Immunization. Statement on pertussis vaccine. Can Commun Dis Rep 1997; 23 (ACS-3): 1-12
162. De Serres G, Boulianne N, Duval B, et al. Effectiveness of whole cell pertussis vaccine in child-care centers and schools. Pediatr Infect Dis 1996; 15: 519-24
163. Lopez AL, Blumberg DA. An overview of the status of acellular pertussis vaccines in practice. Drugs 1997; 54: 189-96
164. Fine PE. Implications of different study designs for the evaluation of acellular pertussis vaccines. Dev Biol Stand 1997; 89: 123-33
165. Poirier MK, Poland GA, Jacobson RM. Parameters potentially affecting interpretation of immunogenicity and efficacy data in vaccines trials: are they adequately reported. Vaccine 1996; 14: 25-7
166. Aoyoma T, Hagiwara S, Murase Y, et al. Adverse reactions and antibody responses to acellular pertussis vaccine. J Pediatr 1986; 109: 925-30
167. Aoyama T, Murase Y, Gonda T, et al. Type-specific efficacy of acellular pertussis vaccine. Am J Dis Child 1988; 142: 40-2
168. Edwards KM, Lawrence E, Wright PF. Diphtheria, tetanus, and pertussis vaccine: a comparison of the immune response and adverse reactions to conventional and acellular pertussis components. Am J Dis Child 1986; 140: 867-71
169. Nobel GR, Bernier RH, Esber EC, et al. Acellular and whole-cell pertussis vaccine in Japan: report of a visit by US scientists. JAMA 1987; 257: 1351-6
170. Blennow M, Granström M. Sixteen-month follow-up of antibodies to pertussis toxin after primary immunization with acellular or whole cell vaccine. Pediatr Infect Dis 1989; 8: 621-5
171. Lewis K, Cherry JD, Holroyd J, et al. A double-blind study comparing an acellular pertussis-component DTP vaccine with a whole-cell pertussis-component DTP vaccine in 18-month-old children. Am J Dis Child 1986; 140: 872-6
172. Edwards KM, Bradley RB, Decker MD, et al. Evaluation of a new highly purified pertussis vaccine in infants and children. J Infect Dis 1989; 160: 832-7
173. Anderson EL, Belshe RB, Bartram J, et al. Clinical and serologic responses to acellular pertussis vaccine in infants and young children. Am J Dis Child 1987; 141: 949-53
174. Anderson EL, Belshe RB, Bartram J. Differences in reactogenicity and antigenicity of acellular and standard pertussis vaccines combined with diphtheria and tetanus in infants. J Infect Dis 1988; 157: 731-7
175. Aoyama T, Murase Y, Kato M, et al. Efficacy and immunogenicity of acellular pertussis vaccine by manufacturer and patient age. Am J Dis Child 1989; 143: 655-9
176. Granstrom M, Thoren M, Blennow M, et al. Acellular pertussis vaccine in adults: adverse reactions and immune response. Eur J Clin Microbiol 1987; 6: 18-21
177. Pichichero ME, Bagdett JT, Rodgers GC, et al. Acellular pertussis vaccine: immunogenicity and safety of an acellular pertussis vs a whole cell pertussis vaccine combined with diphtheria and tetanus toxoids as a booster in 18- to 24-month old children. Pediatr Infect Dis J 1987; 6: 352-63
178. Morgan CM, Blumberg DA, Cherry JD, et al. Comparison of acellular and whole-cell pertussis-component DTP vaccines: a multicenter double-blind study in 4- to 6-year old children. Am J Dis Child 1990; 144: 41-5
179. Edwards KM, Meade BR, Decker MD, et al. Comparison of 13 acellular pertussis vaccines: overview and serologic response. Pediatrics 1995; 96 (3 Pt 2): 548-57
180. Schmitt HJ, Schuind A, Knuf M, et al. Clinical experience of a tricomponent acellular pertussis vaccine combined with diphtheria and tetanus toxoids for primary vaccination in 22,505 infants. J Pediatr 1996; 129: 695-701
181. Decker MD, Edwards KM, Steinhoff MC, et al. Comparison of 13 acellular pertussis vaccines: adverse reactions. Pediatrics 1995; 96: 557-66
182. Schmitt HJ, Beutel K, Schuind A, et al. Reactogenicity and immunogenicity of a booster dose of a combined diphtheria, tetanus, and tricomponent acellular pertussis vacccine at fourteen to twenty-eight months of age. J Pediatr 1997; 130: 616-23
183. Pichichero ME, Deloria MA, Rennels MB, et al. A safety and immunogenicity comparison of 12 acellular pertussis vaccines and one whole-cell vaccine given at a fourth dose in 15- to 20-months-old children. Pediatrics 1997; 100: 772-88
184. Cassone A, Ausiello CM, Urbani F, et al. Cell mediated and antibody responses to Bordetella pertussis antigens in children vaccinated with acellular or whole cell vaccines. Arch Pediatr Adolesc Med 1997; 151: 283-9
185. Halperin SA, Barreto L, Eastwood BJ, et al. Safety and immunogenicity of five-component acellular pertussis vaccine with varying antigen quantities. Arch Pediatr Adolesc Med 1994; 148: 1220-4
186. Pichichero ME. Acellular pertussis vaccines: towards an improved safety profile. Drug Saf 1996; 15: 311-24
187. Centers for Disease Control and Prevention. Pertussis vaccination: use of acellular pertussis vaccine among infants and young children. Recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep 1997; 46 (RR-7): 1-25
188. Blennow M, Granström 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: 62-7
189. Patel SS, Wagstaff AJ. Acellular pertussis vaccine (InfanrixTM-DTPa; SB-3): a review of its immunogenicity, protective efficacy and tolerability in the prevention of Bordetella pertussis infection. Drugs 1996; 52: 254-75
190. Pichichero ME, Francis AB, Marsocci SM, et al. Safety and immunogenicity of an acellular pertussis vaccine booster in 15- to 20-month-old children previously immunized with acellular or whole-cell pertussis vaccine as infants. Pediatrics 1993; 91: 756-60
191. Tozzi AE, Anemona A, Stefanelli P, et al. Reactogenicity and immunogenicity at preschool age of a booster dose of two three-component diphtheria-tetanus-acellular pertussis vaccines in children primed in infancy with acellular vaccines. Pediatrics 2001; 107: E25
192. Pichichero ME, Edwards KM, Anderson EL, et al. Safety and immunogenicity of six acellular pertussis vaccines and one whole-cell pertussis vaccine given as a fifth dose in four- to six-year-old children. Pediatrics 2000; 105: E11
193. Centers for Disease Control and Prevention. Use of diphtheria toxoid-tetanus toxoid-acellular pertussis vaccine as a five-dose series: supplemental recommendations of the Advisory Committee on Immunization practices (ACIP). MMWR Morb Mortal Wkly Rep 2000; 49 (RR-13): 1-8
194. Booy R, Aitken SJM, Taylor S, et al. Immunogenicty of combined diphteria, tetanus and pertussis vaccine given at 2, 3, and 4 months versus 3, 5, and 9 months of age. Lancet 1992; 339: 507-10
195. White JM, Fairley CK, Owen D, et al. The effect of an accelerated immunisation schedule on pertussis in England and Wales. Commun Dis Rep CDR Rev 1996; 6: R86-91
196. Ramsay MEB, Farrington CP, Miller E. Age-specific efficacy of pertussis vaccine during epidemic and non-epidemic periods. Epidemiol Infect 1993; 111: 41-8
197. Miller E. Public health implications: United Kingdom. Dev Biol Stand 1997; 89: 367-8

198. Miller E, White JM, Fairley K. Pertussis vaccination. Lancet 1994; 344: 1575-6
199. Noveli V, Al-Ansari H, Mok Q, et al. Pertussis vaccination: is there a need for a booster dose. Lancet 1994; 344: 1225-6
200. Edmunds WJ, Brisson M, Melegaro A, et al. The potential cost-effectiveness of acellular pertussis booster vaccination in England and Wales. Vaccine 2002; 20: 1316-30
201. Beard SM, Finn A. Do we need to boost pertussis immunization within the existing UK vaccination schedule. J Public Health Med 2000; 22: 349-56
202. Stevenson M, Beard S, Finn A, et al. Estimating the potential health gain and cost consequences of introducing a pre-school DTaP pertussis booster into the UK child vaccination schedule. Vaccine 2002; 20: 1778-86
203. Balinska MA. Warsaw conference on emerging infections in central and eastern Europe. Lancet 2000; 355: 1246
204. Pertussis vaccines: WHO position paper. Wkly Epidemiol Rec 1999; 74 (18): 137-42
205. Grimprel E, Baron S, Lévy-Bruhl D, et al. Influence of vaccination coverage on pertussis transmission in France. Lancet 1999; 354: 1699-700
206. Linnemann C, Ramundo N, Perlstein P, et al. Use of pertussis vaccine in an epidemic involving hospital staff. Lancet 1975; II: 540-3

Correspondence and offprints: *Dorota Z. Girard*, Faculté des Sciences Economiques, Université de Nantes, Chemin de la Censive du Tertre, 44 322 Nantes, BP 52241, France.
E-mail: girard@sc-eco.univ-nantes.fr