

# Prevention of pertussis: Recommendations derived from the second Global Pertussis Initiative roundtable meeting

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## Abstract

The Global Pertussis Initiative (GPI) was established in 2001 to assess the global extent of the ongoing problem of pertussis and to evaluate and prioritize pertussis control strategies. Exchange of data, knowledge, and experience, facilitated by discussion and debate, resulted in the formulation, in 2002, of the following recommendation: all countries should consider expanding existing vaccination strategies to include adding pertussis booster doses to pre-school children (4–6 years old), to adolescents, and to those specific adults that have the highest risk of transmitting *Bordetella pertussis* infection to vulnerable infants. The GPI met again in 2005, where it reinforced its previous recommendation for universal adolescent immunization. Additionally, the GPI recommended implementation of the cocoon strategy (immunization of family members and close contacts of the newborn) in countries where it is economically feasible, and encouraged efforts toward global standardization of pertussis disease clinical definitions and diagnostics. Universal adult vaccination is a logical goal for the ultimate elimination of pertussis disease, but feasibility issues remain obstacles to implementation.

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## 1. Introduction

The Global Pertussis Initiative (GPI) was established in 2001 with three main objectives: to raise the profile of pertussis as an important and preventable disease that warrants greater global public health attention; to improve understanding of the increasing incidence of reported pertussis; and to develop effective immunization strategies for pertussis control. The GPI is composed of 37 experts in the field of pertussis from 17 countries worldwide and its work is supported by an unrestricted educational grant from sanofi

pasteur. After in-depth evaluation of the available data, prioritization of various immunization strategies, creation of a health economic model to study the cost effectiveness of the proposed strategies, and identification of potential barriers to implementation of the recommendations and possible solutions to these barriers, the GPI concluded that current vaccination strategies needed to be reinforced and expanded. Vaccination should include the addition of booster doses for adolescents in developed countries. Additionally, the group recommended that immediate universal adolescent vaccination and immunization of healthcare and childcare workers should be instituted. Australia introduced an adolescent booster in 2003, and the addition of an adolescent booster was suggested for Argentina and Japan [1]. Some other coun-

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tries, including, Austria, Canada, France, Germany, and the United States, have incorporated an adolescent booster dose into their current immunization schedules, as advocated by the GPI [2].

The GPI held its second roundtable meeting in December 2005 to re-evaluate previous recommendations and to discuss the progress made in pertussis control since their first meeting in 2002. Twenty-three members of the GPI, led by the Chairman, Professor Stanley Plotkin of the United States, met for 2 days to present the latest developments on the epidemiology and diagnosis of pertussis and to examine various vaccination strategies with the aim of proposing updated recommendations. This paper summarizes the key points derived from the meeting and presents the group's recommendations for adolescent and selective adult immunization.

## 2. Epidemiology of pertussis

Although progress has been made since the first GPI meeting in 2002 toward gaining a better understanding of the transmission and control of pertussis, in 2006 the disease remains an important public health concern. The World Health Organization (WHO) estimates that at least 27 million children did not receive DTP3 in 2004, and estimates that 294,000 deaths from pertussis in children under age 5 (2002 data) could have been preventable by vaccines [3]. It continues to be endemic worldwide, with an estimated 50 million cases occurring annually, 90% of which are in developing countries [4,5]. Infants remain the most vulnerable group. From 1997 to 2000 in the United States, 20% of all pertussis cases required hospitalization; 90% of those patients were infants <1 year old [6]. Incidence rates vary widely, but the general resurgence of reported pertussis, especially among the adolescent and adult populations, indicates that current immunization schedules, among other factors, inadequately protect against the disease.

In the pre-vaccine era, pertussis was universally present with cyclic peaks every 2–5 years. Reported cases averaged 157 per 100,000 in the United States and occurred almost exclusively in unvaccinated children [7,8]. The early use of whole-cell vaccines and the implementation of an immunization schedule in the United States were highly effective, reducing the incidence of reported pertussis to <1 case per 100,000 during the 1970s. Since 1984, there has been a modest increase, although some would say a resurgence, in reported pertussis, to 9 per 100,000, with cyclic peaks still occurring at 2–5-year intervals [7,9]. It is believed that endemic adolescent and adult disease is likely to be responsible for the cyclic pattern still seen in unvaccinated children.

### 2.1. Evolution of *Bordetella pertussis*

To determine whether *B. pertussis* is polymorphic or evolving, members of the GPI roundtable agreed that the following must be accomplished: temporal analysis and com-

parison of clinical isolates in different parts of the world; analysis and comparison of clinical isolates collected before and after introduction of vaccination in the region of interest; and analysis of the epidemiology of the disease in the region of interest. The few studies that were conducted before the mid-1980s on the evolution of *B. pertussis* generally concluded that some strains were subject to rapid mutations and others were relatively stable [10,11]. Later analyses using typing techniques such as multi-locus enzyme electrophoresis (MLEE) to analyze proteins have indicated that *B. pertussis* exhibits very restricted genetic diversity compared with other bacterial species [12,13].

Results obtained with the use of more recent typing techniques that allow analysis of portions of the bacterial genome, such as restriction fragment length polymorphism (RFLP), multi-locus sequence typing (MLST), multiple antigen sequence typing (MAST), and multiple-locus-variable-number tandem repeat analysis (MLVA), have concurred that *B. pertussis* shows very restricted genetic diversity, but some differences are seen between vaccine strains and circulating isolates [14]. Small and seasonal differences are seen when typing techniques are used to analyze the whole genome [15]. In a study where pulsed-field gel electrophoresis was used to type *B. pertussis* strains isolated from children with severe versus mild illness, no significant differences in PFGE patterns were found between groups [16]. This indicates that variability in severity of pertussis could not be attributed to specific hypervirulent clones of *B. pertussis*.

Recent studies have indicated that in countries with a high rate of vaccination, polymorphism of *B. pertussis* is very limited and genetic diversity seems to decrease slowly over time, with differences in gene sequences of PT and PRN, two components included in several acellular component pertussis (aP) vaccines [15]. Data on duration of immunity in France after wP or aP vaccines show that the level of protection has not changed in the past 10 years although circulating isolates were shown to have changed [17,18]. Data on isolates collected in Japan, a country using aP vaccines for more than 20 years, indicate that the antigenic divergence found between *B. pertussis* vaccine strains and circulating strains have not affected the efficacy of pertussis vaccination in Japan [19].

### 2.2. New data on pertussis in Europe

The EUVAC-NET project comprised a 5-year surveillance period during which data were collected on the epidemiology and burden of reported pertussis in 16 European countries and to assess the burden of disease in adolescents and adults [20,21]. The study pooled national surveillance data from 1998 to 2002, and showed a wide variation in reported incidence, from 0.1 per 100,000 population for Portugal (a total of 47 reported cases) to 123.9 per 100,000 for Switzerland (a total of 845 reported cases). Countries north of Germany were shown to have a higher incidence of reported pertussis than countries in southern Europe. The incidence tended to

increase from 1998 to 2002 in adults and possibly in infants. Seasonality data suggest a synchronization of cases in children from 0 to 4 years old. Because there was no uniform case definition among the 16 participating countries, or stringent surveillance processes, there was likely significant under-reporting of cases and of deaths in many of the countries under study. The EUVAC-NET data did not include information on vaccination coverage for all the countries, but sub-analyses of the available data for Denmark (a total of 997 cases from 1998 to 2002), Italy (17,702 cases), The Netherlands (26,232 cases), and Norway (12,748 cases) indicated that one dose of aP protected against hospitalization, most notably in children less than 1 year of age [20].

Comparison of the data between the EUVAC-NET countries may not be appropriate due to the high variability of the surveillance systems and diagnostic and reporting methods, but EUVAC-NET was the first pertussis surveillance study that might allow for an examination of incidence data between European countries. In contrast, there is a serious lack of information regarding the incidence of pertussis in the developing world, including Latin America, Africa, Asia, and India. Better diagnostic tools and better reporting will likely prove that current numbers grossly underestimate the true incidence. For epidemiologically and clinically valuable data to be collected, there is a need to enhance and harmonize surveillance systems among countries worldwide, using standard clinical and microbiological definitions of pertussis. Availability of single-sample serology using anti-PT IgG and anti-PT IgA may provide a better approximation of true rates of infection in adolescent and adult populations.

Clearly, there are different surveillance systems, different diagnostic protocols, even different clinical definitions of pertussis disease worldwide. The GPI recognizes these problems and seeks to find some process to enhance standardization globally. Policy issues around infectious disease and immunization are handled differently in different jurisdictions. The GPI would consider convening a pertussis standardization summit to begin a process of harmonization of pertussis protocols internationally. Only then can true comparisons be undertaken and better understanding of pertussis disease be gleaned.

### 3. Differential diagnosis

Correct diagnosis of pertussis can be a challenge because of the overlap of symptoms with other respiratory infections caused by viruses and other bacteria. Differential diagnosis of prolonged cough, even with paroxysms, may include *Bordetella parapertussis*, *Bordetella bronchiseptica*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, adenoviruses, respiratory syncytial virus (RSV), human parainfluenza viruses, influenza viruses A and B, rhinovirus, and human metapneumovirus [22].

Although culture is now less frequently used than in years past for laboratory confirmation of causative pathogens, bac-

terial isolates are still needed for genotypic and phenotypic analysis. Real-time PCR is being increasingly used; its advantages include offering a result within a few hours, and no requirement for samples to be handled post-amplification, which will reduce the risk of contamination. The European Research Programme for Improved Pertussis Strain Characterization and Surveillance (EUpertstrain) published a consensus paper in 2005 that addressed the methodology and the application of real-time PCR for detecting *Bordetella* DNA [23]. It concluded that real-time PCR is more sensitive than culture for the detection of *B. pertussis* and *B. parapertussis*, especially after the first 3–4 weeks of coughing and after antibiotic therapy has been started. There are still problems with quality control and standardization; a good working model for global use is still 2–4 years away from being available.

There is good evidence that PT IgG geometric mean titre correlates with severity of symptoms [24], and that an IgG–PT cut-off of 100 U/ml for serodiagnosis is reliable in all age groups. Furthermore, an IgG–PT of <10 U/ml is associated with increased risk of re-infection [25]. Serology is therefore a reliable test for clinicians to diagnose *B. pertussis* infection, but it should be further improved and standardized, primarily in relation to anti-PT IgG. A reference serum prepared by the FDA is currently generally accepted, but a new one being tested is expected to become the WHO reference serum. The serological cut-off for confirmation of diagnosis will probably be similar worldwide.

### 4. Prevention of pertussis: vaccination strategies

Since it was established in 2001, GPI members have reviewed the international literature and exchanged data, knowledge, experience, and opinion through teleconferences, a password-protected interactive Web site, and the two roundtable meetings. With the goal of identifying and addressing potential barriers to pertussis control, they evaluated a number of immunization strategies, including universal immunization of adolescents; universal immunization of adults; selective immunization of new mothers, and family and close contacts of newborns (cocoon strategy); selective immunization of healthcare workers; selective immunization of childcare workers; implementation of a fourth or fifth booster dose for all pre-school children (4–6 years of age); and improvement of current infant and toddler immunization strategies. An outcome of the first major GPI symposium was a clear recognition that adolescent vaccination was an important additional step to help control pertussis disease in the adolescent populations. This second GPI symposium has expanded on this earlier recommendation, in that the ongoing problems of severe pertussis disease in the neonatal and infant populations have been better clarified and understood, with a particular focus on possible intervention strategies to address this problem.

#### 4.1. Adolescent vaccination

The GPI previously noted that the incidence of pertussis in adolescents appears to be increasing, as shown in studies from regions as diverse as Canada, Poland, and the United States [26–29]. Pertussis is a particularly serious illness among unvaccinated or incompletely vaccinated infants, and adolescents have been shown to be an important source of infection for young infants. A recent Centers for Disease Control and Prevention (CDC) study of 774 infant cases of reported pertussis from four states showed that among 264 infants for whom a source could be identified, 56% were adults  $\geq 20$  years of age and 20% of the sources were 10–19 years of age [30]. Adding boosters to existing childhood schedules (pre-school or adolescent) and boosters for specific adult subgroups at highest risk of transmitting *B. pertussis* infection to infants were expanded immunization strategies recommended previously by the GPI.

Pertussis continues to be a worldwide problem even though immunogenic and effective vaccines are available and can be safely administered beyond childhood [31–33]. A study in Prince Edward Island in Canada explored the immunogenicity of Tdap after different vaccination intervals (2–9 years) in cohorts who had previously been vaccinated with DTwP, DTaP, and/or Td (depending on their age) [34,35]. The results showed that Tdap was well tolerated by adolescents who were immunized after intervals of 2 to  $\geq 10$  years after receiving a previous DTwP/DTaP/Td-containing vaccine and that it can be safely administered at intervals as short as 18 months after prior tetanus, diphtheria, or pertussis vaccination. A more recent study to assess the safety and immunogenicity of a sixth dose of Tdap vaccine in adolescents showed that, regardless of the prior DTaP/DTwP vaccination history, a sixth sequential dose of Tdap appears safe and immunogenic [36].

The Advisory Committee on Immunization Practices (ACIP) of the CDC has recently recommended routine Tdap vaccination for adolescents, based on the following: “evidence regarding the burden of pertussis among adolescents; negative effects of pertussis outbreaks involving adolescents on the community and the public health system; studies suggesting use of Tdap among adolescents will likely be safe, effective, and economical; and the established infrastructure for adolescent vaccination” [37]. Other countries, including Canada, Austria, Australia, France, and Germany, have introduced universal immunization of adolescents; early evidence suggests that they are effective, but surveillance will be required to confirm this [38]. The duration of protection (and need for an adult booster after the adolescent one) is not known. Some studies indicate that antibody levels may decrease after 3 years, but they remain significantly higher than pre-booster immunization levels [39]. As more data from vaccinated cohorts become available, it will be clearer whether a decennial adult booster will be needed. The GPI recommendation of universal adolescent immunization programs is still valid based on the continued high rates of

adolescent pertussis in regions that do not have booster doses after school entry.

#### 4.2. Adult vaccination

There are two potential approaches to vaccinating adults: universal adult vaccination to build up herd immunity and eradicate *B. pertussis* infection; and selective vaccination of those adults who are at highest risk of transmitting *B. pertussis* infection to vulnerable infants to minimize the incidence and impact of disease in these infants. Currently, in the United States and elsewhere, disease prevention in adults is not widely practiced: for example, although annual flu vaccination is recommended for healthcare workers, CDC survey data for 2004 indicated a vaccination coverage level of only 42% [40]. Experts and supporting models support the notion that universal vaccination would markedly reduce the incidence of pertussis disease among all ages [32,41,42]. In the past, pertussis did not have a sufficiently high profile to drive a change in preventive medicine practices. However, some recent events have led to an increased public awareness of adolescent and adult pertussis and also the need for a more universal approach to adult immunization. Specifically, the dramatic increase in reported pertussis in adolescents and adults has resulted in extensive media coverage and dissemination of the information that new vaccines are available [43,44]. In the opinion of the GPI, the concern about avian influenza and the publicity surrounding new human papillomavirus (HPV) vaccines that can prevent cervical cancer have led to an increased general awareness about vaccines for adolescents and adults, and increasingly our public health policy bodies are advocating ‘whole-of-life’ immunization strategies.

The Adult Pertussis Trial (APERT), sponsored by the National Institutes of Health (NIH), has demonstrated the efficacy of acellular pertussis vaccines in preventing pertussis disease in adolescents and adults [45,46]. Subjects who received either a dose of a tricomponent acellular vaccine ( $n = 1391$ ) or a hepatitis A vaccine (controls,  $n = 1390$ ) were monitored for 2.5 years. Nine cases of pertussis in the control group and one case in the group that received the acellular pertussis vaccine met the primary case definition (culture, PCR, and serological case criteria), yielding an overall vaccine efficacy of 92% (95% confidence interval, 32–99%). Among cases that were confirmed by culture or PCR assay, five were in the control group and none were in the vaccine group. The duration of protection and prevention of secondary disease were not assessed in this study.

The safety of vaccination in adolescents and adults is well documented, but more data are needed on the safety of repeat doses of Tdap. Pertussis prevention advocacy will be key to overcoming implementation issues, but payment will be an issue in many countries (particularly developing countries). For an adult vaccination program to be successful, key components must include education and public awareness. Advocacy among healthcare providers is important

in driving vaccine coverage and needs to be emphasized in most countries. Because there is a moral imperative for healthcare workers to protect themselves and those in their care, hospitals might consider mandatory vaccination of their employees. With education, childcare workers and parents and families of neonates may accept the rationale for vaccination more quickly than the general population. Furthermore, adults with chronic underlying lung disease, such as chronic obstructive pulmonary disease (COPD), may also benefit from pertussis immunization. Findings from one study in patients with COPD indicated that as much as 31% of acute exacerbations might be caused by *Bordetella* infections [47]. The new ACIP recommendations to replace Td with Tdap among adults in the United States are highly significant. This indicates a policy shift to adult pertussis disease prevention, and although it may not have an immediate effect, the leadership in immunization provided by the ACIP will likely lead to increased adult immunization uptake over time [48]. Twelve European countries currently recommend Td vaccination every 10 years.

#### 4.3. Cocoon strategy

Several recent studies indicate that adults – mothers, in particular – are an important source of *B. pertussis* infection to unvaccinated or incompletely vaccinated infants. A national active monthly surveillance program of child health specialists conducted in 2001 in Australia revealed that 140 infants (median age at diagnosis, 8 weeks) were hospitalized with pertussis and 4 infants (<6 weeks old) died [49]. Of 97 (69%) infants who had not been vaccinated for pertussis, 63 (65%) were under the age of the first scheduled dose of DTPa vaccine (<8 weeks old). A coughing contact was identified for half the cases, and 68% of those were adults, usually one of the infant's parents. Other studies have confirmed these results and indicate that parents act as primary vectors in 30–57% of infant cases [9,30,50,51].

Vaccination of household members (including parents and siblings) of newborns, known as the cocoon strategy, should be considered as a first step toward (or a component of) universal adult vaccination. A study designed to evaluate the impact of five adolescent/adult immunization strategies showed that although the cocoon strategy leads to only a 9–17% reduction in typical adult cases, there is a strong indirect effect on infants and young children: a decrease by 70%, 65%, and 69% was noted in cases among the 0–3-month-old, 4–23-month-old, and 2–4-year-old groups, respectively [52]. If universal adult vaccination is not yet a feasible option, the cocoon strategy should be recommended, even though it can only reduce (but not eliminate) the risk of infants acquiring severe pertussis disease. Although targeted immunization strategies have not been successful for the control of other infectious diseases, it is considered that the cocoon strategy is worthy of implementation for pertussis [53,54]. Even protecting just some infants would be considered a success. The cocoon strategy is recommended in Australia, France, Ger-

many, and Austria, although there are no requirements in these countries to enforce this policy, and vaccine coverage is currently low [38,55].

#### 4.4. Maternal vaccination

Neonates are uniquely at risk for many different infections that cause substantial morbidity and mortality worldwide. The immune system of neonates is immature and relatively ineffective, and a US study by Healy et al. has shown that babies born during recent years have low levels of pertussis-specific antibody [56]. They found that although placental transfer of pertussis antibodies is efficient, low maternal levels and their rapid decay in infant sera leave infants with little protection against life-threatening pertussis in early infancy. Although Healy's data provide some support for the rationale of maternal immunization with acellular pertussis vaccines, there is clearly a role for cellular immunity in pertussis prevention, and given the relative cellular paresis of the infant and the resistance to injecting the pregnant human with any biological agent, it is unlikely maternal immunization alone will significantly reduce the incidence of *B. pertussis* infection in infants; it needs to be part of a broader vaccination strategy, including adolescents and at least those adults who pose the biggest threat of infection to unprotected infants.

During the 1930s and 1940s, the possibility of protecting newborns against pertussis by immunizing their mothers during pregnancy was investigated, but no further work in that area was published until recently. Some animal and human studies have provided limited but promising data on maternal pertussis immunization as a basis for future immune response [57–59]. The ACIP recently stated that pregnancy is not a contraindication to Tdap or Td vaccination, and guidance on the use of Tdap during pregnancy is currently under consideration [48]. Immunization during pregnancy has the potential to protect both mother and infant during a vulnerable period in their lives. Transplacental transfer of antibodies is safer and less expensive than administration of immunoglobulin preparations to the infant. There is proven antibody transfer from vaccinated women to their unborn infants, but more data are needed on whether the levels of transferred antibodies are sufficient to protect the neonate from *B. pertussis* infection. There is also uncertainty about whether maternal immunization could affect the immunogenicity and efficacy of primary and/or booster vaccination in infants/children [60–62].

#### 4.5. Neonatal vaccination

In the United States from 1938 to 1940, there were more than 10,000 recorded pertussis deaths, 70% of which occurred in infants (most were younger than 4 months) [63]. In recent years, there has been a resurgence of reported pertussis in infant populations, as demonstrated by studies in Canada, France, Germany, and the Netherlands [9,64–66]. In Australia over the past 20 years, hospitalization rates for

infants <5 months have remained unchanged despite extensive immunization coverage [49].

Several studies conducted during the past decade have confirmed earlier findings of acceptable safety, efficacy, and immunogenicity of pertussis vaccination (DTwP), in full-term and pre-mature infants [67,68]. A study by Englund et al. showed that there was no suppression of subsequent vaccine immunogenicity in infants born to mothers with high antibody levels after primary immunization with Tdap (although after whole-cell pertussis vaccine, higher levels of pre-existing antibody were associated with substantial (28–56%) reductions in the subsequent antibody response to pertussis toxin) [69]. Neonatal and maternal vaccinations are similar ways to achieve the same goal, but maternal vaccination has fewer implementation issues, although will not give cellular immunoprotection for the infant. The issues surrounding neonatal vaccination are complex. It is practice in some countries to give hepatitis B vaccine at birth. However, the uptake is relatively low, partly because the immunization delivery infrastructure has not traditionally included midwives. It is unclear if newborn pertussis immunization will induce sufficient and timely immunity. Clearly further trials are needed, and the GPI strongly endorses such trials to be undertaken.

## 5. Utilization of Tdap in 4–6 year olds

Booster doses of DTaP vaccines given at 4–6 years of age are commonly followed by large injection site reactions, with an increase in redness, swelling, and pain compared to previous reactions [70]. Several studies have shown that the adolescent/adult formulation diphtheria, tetanus, and acellular pertussis combination vaccine with lower pertussis and diphtheria antigen content (Tdap) was significantly less reactogenic and slightly less immunogenic than the pediatric formulation combination vaccine (DTaP) when given as a booster to 4–6-year-old children [71–73].

As booster responses to all antigens appear adequate with Tdap, it might be preferable to use Tdap or Tdap-IPV (inactivated poliomyelitis viruses vaccine) from mid-childhood onwards. Where both Tdap and DTaP are licensed, countries need to determine which vaccine to use. Australia and Switzerland currently use DTaP for primary immunization and the pre-school booster. Germany has recently introduced Tdap as a fifth dose, given at 5–6 years of age, while continuing to recommend Tdap-IPV at 9–17 years (previously the fifth dose, but now the sixth dose).

Further studies would be useful to confirm that Tdap ( $\pm$ IPV) vaccines are not inferior in immunogenicity and are less reactogenic compared to full-content DTaP ( $\pm$ IPV) vaccines. Because Tdap vaccines may be significantly better tolerated, more studies are warranted on their routine use for children 4–6 years of age. These studies should be done with vaccines from both major manufacturers (sanofi pasteur and Glaxo SmithKline).

## 6. Economic assessment

An understanding of the impact of vaccination on disease transmission (i.e., capturing herd immunity) is a key to being able to assess the economic value of adult strategies. A modeling study conducted by Drs. A. Van Rie and J. Caro was designed to provide transmission probabilities data to better assess the impact of the following adolescent and adult vaccination strategies in the United States: routine adolescent vaccination; the cocoon strategy; and routine adult vaccination every 10 years (unpublished data presented at the GPI Roundtable Meeting, December 9, 2005, Paris, France). Preliminary results of that study, using an updated computer simulation incorporating the most current US epidemiological information, indicate the following:

- If vaccinations were introduced using any of the three strategies above, the overall incidence of infection would decrease.
- Routine adolescent vaccination would have an important effect on the incidence of pertussis in the 0–19 year olds, reducing infection to 40% of its current level.
- The cocoon strategy plus routine adolescent vaccination would effect a further 50% reduction in infant pertussis, but would have no substantial additional impact on the incidence of pertussis infection in the general population.

Morbidity and societal costs (especially absenteeism from school or work) associated with reported pertussis in adolescents and adults have been shown to be increasing [74]. When the infected adults are healthcare workers, serious adverse health (transmission to patients, colleagues, and family) as well as economic consequences can result [75]. Although there are limited new data examining both direct and indirect costs associated with immunization, investigators have begun to use models to examine adolescent and adult vaccination strategies, and utility estimates have also been developed. Computer simulations predict that the cocoon strategy will be cost effective (if assumptions on incidence, costs per case, and extent of herd immunity are accurate, and implementation of the vaccination schedule is feasible), although the relative ranking of the various adolescent/adult vaccination strategies remains unclear [42,76]. A number of limitations to these models persist: cost data are scanty, especially for mild cases; the extent of herd immunity is unknown; no data exist from outside Europe, North America, and Australia; and the long-term effectiveness of the vaccines is uncertain.

## 7. Conclusions and recommendations

Since 2001, there has been notable progress in the understanding of *B. pertussis* disease, but it continues to affect millions of people worldwide and is a major cause of infant mortality, especially in developing countries. Previously, the GPI recommended that an acellular pertussis vaccine be incorporated into the current dT vaccine schedule for adoles-

cents, either as dTaP or as a stand alone aP booster, and several countries have incorporated that recommendation into their immunization schedule [77]. The GPI also recommended increased and improved surveillance, improved detection, and greater awareness of pertussis as a major public health problem in order to arrive at a measure of the true incidence of the disease and the effectiveness of any immunization strategy. At their second meeting, the GPI acknowledged the continuing need for improved surveillance and diagnosis, and reinforced their previous recommendations for expanding pertussis vaccination to adolescents. They emphasized the importance of each country ensuring that current pertussis immunization schedules are implemented and enforced. This second meeting addressed quite specifically the problems of neonatal and infant pertussis disease, and after reviewing and discussing available data the GPI has further endorsed implementation of the cocoon strategy in countries where it is economically possible, as well as selective vaccination of healthcare workers and childcare workers. Universal adult vaccination may be justified by the available epidemiological data, but its feasibility is currently in question. As new data continue to support the immunogenicity and safety of Tdap vaccines in adolescents and adults, an efficient way to immunize these populations would be to substitute Tdap or Tdap–IPV vaccines for the Td vaccine boosters currently recommended in many countries. Standardization of diagnostic tests, reagents and clinical criteria are urgently required; the GPI is willing to support or generate such a process.

Ongoing research and discussion among the GPI members will focus on issues that must be resolved with the aim of preventing infant morbidity and mortality from pertussis and tailoring strategies to fit the needs of each country. The GPI members concurred that there is a vital need for adequate pertussis surveillance and reporting systems in all countries, and that feasibility issues are assuming a major role in the design and implementation of vaccination strategies.

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