MAJOR ARTICLE

New Pertussis Vaccination Strategies beyond Infancy: Recommendations by the Global Pertussis Initiative

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Background. The Global Pertussis Initiative, an expert scientific forum, was established to address the ongoing problems associated with pertussis disease worldwide.

Methods. The group analyzed pertussis disease trends, developed recommendations to improve disease control through expanded vaccination strategies, and proposed solutions to barriers to implementation and support of research activities.

Results. *Bordetella pertussis* infection is endemic and continues to be a serious problem among unvaccinated or incompletely vaccinated infants. In addition, the reported incidence of pertussis disease is increasing in adolescents and adults, who not only experience a considerable health burden themselves but also infect vulnerable infants.

Conclusions. Current vaccination strategies need to be reinforced. Expanded vaccination should include adding booster doses to existing childhood schedules (preschool or adolescent) and booster doses for those specific adult subgroups that have the highest risk of transmitting *B. pertussis* infection to infants (i.e., new parents, other contacts of newborns, and health care workers). More epidemiological studies and studies of disease transmission and the cost-effectiveness of vaccination would be valuable, and surveillance, diagnostic improvements, and educational campaigns are needed for implementation. However, as a prelude to universal adult vaccination, immediate universal adolescent vaccination should be instituted in countries in which it is economically feasible.

For more than 40 years, whole-cell pertussis (wP) vaccination of infants and toddlers has been highly effective, preventing ~760,000 deaths annually worldwide [1]. Nevertheless, there are an estimated 50 million cases of pertussis disease and 300,000 pertussis-related deaths every year globally, mostly among infants who are too young to have completed the primary vaccination series [2].

In response to the ongoing problem of pertussis, an international collaboration of multidisciplinary experts—the Global Pertussis Initiative (GPI)—was established in 2001 to examine the rationale for vaccination beyond childhood [3, 4] and to evaluate specific strategies, make recommendations for their implementation, and identify research needs to support their introduction. This article summarizes the findings and recommendations of the GPI.

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METHODS

The GPI was conducted in 3 stages: (1) international epidemiology, diagnosis, health and economic burden, and prevention and treatment of pertussis were assessed; (2) immunization strategies to address the problems identified were evaluated and prioritized; and (3) solutions to potential barriers to strategy implementation were identified. Exchange of data, knowledge, experience, and opinion was facilitated by discussion, debate, and voting through the use of a closed, interactive Web site, teleconferences, and a roundtable meeting.

PROBLEMS POSED BY PERTUSSIS

Bordetella pertussis *endemicity.* *B. pertussis* infection remains endemic, even in countries with a sustained high rate of vaccination coverage. Among the countries participating in the GPI, reported incidences ranged from 0.1 to 200 cases per 100,000 population [5–9].

Pertussis in adolescents and adults. Although pertussis is not generally perceived to be a serious problem beyond childhood, adolescents and adults experience a significant health burden from the disease [10]. Clinical manifestations are often atypical [11]. However, 21%–86% of adults have typical symptoms of paroxysmal cough, whoop, and posttussive vomiting, which can be severe [12]. Studies indicate that 12%–32% of adolescents and adults with a coughing illness lasting 1–2 weeks or longer are infected with *B. pertussis* [13]. Most (80%) of the adolescents and adults with pertussis disease have a cough lasting ⩾21 days [14], and many (27%) are still coughing at 90 days after onset [12, 15].

Pertussis-related complications, some of which may be serious [16], also occur fairly frequently in adolescents and adults [17]. Although hospitalization due to pertussis disease is most frequent among infants, it is not infrequent among adolescents and adults [18]. However, mortality is low among patients ⩾10 years of age who are hospitalized with cases of pertussis [19, 20].

Pertussis disease is increasing among adolescents and adults [15, 21]. This may be because of multiple factors, including waning vaccine-induced immunity and increased recognition, diagnosis, and reporting of pertussis disease. However, it is clear that adolescents and adults are commonly and regularly infected with *B. pertussis* and, therefore, are potentially a major source of pediatric infection [11, 22].

There is widespread agreement that parents are a common source of *B. pertussis* infection for infants [23, 24]. Grandparents, aunts, and uncles are also potential sources of infection [25, 26]. Although data reported from Germany have indicated similar levels of antipertussis toxin and other pertussis-related antibodies in pediatraic health care workers and non–health care workers [27], the increased risk of health care workers coming into contact with unprotected newborns makes this adult subgroup a focus when considering whom to vaccinate [28]. Adolescents are also an important reservoir of infection for infants and other household members [23].

Pertussis in neonates and infants. Infants, particularly those who are not fully vaccinated, continue to experience the greatest pertussis disease burden [2]. In Finland, a 5-fold increase in the reported incidence of pertussis disease among those <1 year old occurred between 1995 and 1999, and in the United States, the mean annual incidence among infants ⩽4 months old increased from 63.4 cases per 100,000 population in the 1980s to 88.7 cases per 100,000 population in the 1990s; the mean annual incidence of pertussis disease among infants aged ⩽2 months increased by 49%, from 72.1 cases per 100,000 population in the 1980s to 107.3 cases per 100,000 population in the 1990s [29].

Mortality due to pertussis disease is highest among infants [30]. Moreover, the number of infant deaths due to pertussis may be underreported because of misdiagnosis of pertussis as other respiratory illnesses or sudden infant death syndrome [31–34].

Economic burden of pertussis. The economic burden of pertussis is significant. A US study estimated the direct costs of pertussis disease at $2822 (€2209) for infants, $308 (€241) for children, $254 (€199) for adolescents, and $181 (€142) for adults [35]. For infants, hospitalizations accounted for two-thirds of medical costs [35]. German data on children aged ⩽6 years estimated the direct costs of an uncomplicated case of pertussis at ~€110 (~$141). If a case involved hospitalization, pneumonia, or encephalopathy, the costs were €1700 ($2171), €3940 ($5033), and €5170 ($6604), respectively [36]. For children, adolescents, and adults, most direct costs are incurred through physician office visits, but antibiotic treatment and hospitalization also contribute to the expense [12]. The indirect costs of pertussis disease also appear to be substantial, particularly among adults, for whom personal illness or child care responsibilities frequently result in absenteeism or reduced productivity [12].

Problems with pertussis diagnosis and surveillance. Reported cases of pertussis disease are estimated to be 1%–36% of the true number of cases [8, 37]. Underrecognition, underreporting, and misdiagnosis are widespread, and they are a particular problem with adolescent and adult disease.

Intercountry comparisons and global evaluations are difficult to perform, because countries use different pertussis disease case definitions, diagnostic techniques, surveillance methods, and reporting regulations [38, 39]. Laboratory diagnosis of *B. pertussis* infection is also problematic. Culture and PCR are difficult to perform and of low sensitivity if the patient's disease has progressed beyond the catarrhal phase of the illness. Although there are numerous PCR and antibody

Table 1. Immunization strategies assessed by the Global Pertussis Initiative.

Immunization strategy	Potential schedule	Primary objectives	Secondary objectives
Universal adult immunization	All adults aged ⩾18 years at regular intervals (possibly coinciding with diphtheria, tetanus, and polio[a] boosters)	Reduce morbidity in adults; develop herd immunity	Reduce *Bordetella pertussis* transmission to young infants
Selective immunization of new mothers, family, and close contacts of newborns	Either prenatally during the third trimester or perinatally before the newborn reaches 4 weeks of age	Reduce disease transmission to young infants	Reduce morbidity in adults, especially young adults
Selective immunization of health care workers	On entry into the profession (regardless of diphtheria, tetanus, and polio[a] vaccination status), followed by administration of booster doses, as appropriate	Reduce disease transmission to susceptible patients (including young infants)	Reduce morbidity in health care workers
Selective immunization of child care workers	On entry into the profession (regardless of diphtheria, tetanus, and polio[a] vaccination status), followed by booster doses, as appropriate	Reduce disease transmission to young infants	Reduce morbidity in child care workers
Universal adolescent immunization	Age 11–12 years (depending on the recommended age for administration of diphtheria, tetanus, and polio[a] booster doses), with catch-up until age 18 years	Reduce morbidity in adolescents and young adults; develop herd immunity	Reduce disease transmission to young infants
Universal preschool booster doses at 4–6 years of age	All preschool or early school children 4–6 years of age	Reduce morbidity in school-aged children; develop herd immunity	Reduce disease transmission to young infants
Reinforce and/or improve current infant and toddler immunization strategies	As per current recommendations, which vary from country to country	Reduce morbidity and mortality in infants, toddlers, and children	Reduce overall circulation of *B. pertussis*

[a] Polio booster doses are administered to children >5 years old in some, but not all, countries.

assays available, PCR assays must be standardized, and experienced individuals are needed to accurately interpret pertussis antibody concentrations.

WANING IMMUNITY AND THE NEED TO EXPAND EXISTING VACCINATION STRATEGIES

The key factor underlying the continuing endemicity of *B. pertussis* infection in countries with high rates of vaccination is that both vaccine-induced and naturally acquired immunity wane without boosting. Although the precise time frame remains unresolved, immunity provided by wP vaccines appears to persist for at least 3–5 years and then to progressively decline 6–10 years after vaccination [40]. The limited data on acellular pertussis (aP) vaccines suggest that, in most cases, protective immunity persists for ⩾6 years after primary vaccination with 3 or 4 doses [41–43]. A study conducted in Senegal [44] has shown that even partially vaccinated patients with breakthrough cases of pertussis are less contagious than unvaccinated patients with cases of pertussis.

VACCINATION STRATEGIES: GENERAL CONSIDERATIONS

The GPI defined and evaluated 7 strategies to complement or improve current childhood vaccination schedules (table 1). Several countries already have a preschool pertussis booster. Australia, Austria, Canada, France, Germany, and Switzerland have an adolescent booster. In Switzerland, catch-up vaccination for adolescents who have missed the fourth and/or fifth dose at preschool age is recommended. Recently, Austria and Canada recommended routine aP boosters in adults.

Universal adult vaccination. In countries where low-dose diphtheria and tetanus (dT) or dT–inactivated polio vaccine (dT-IPV) boosters are already recommended for adults every 10 years, a switch to a dTaP vaccine or dTaP-IPV would be relatively simple and inexpensive. However, a massive educational effort would be required to maximize uptake. The highest coverage possible would be necessary for optimal levels of protection and herd immunity; an epidemiological model suggested that a coverage of >85% would be needed to ef-

fectively reduce the number of cases of infant pertussis [45]. Where appropriate dT vaccine or dT-IPV programs do not exist, a new delivery infrastructure would be needed. In the absence of research indicating otherwise, vaccination every 10 years is a reasonable frequency to recommend for universal adult vaccination.

The vaccines of choice would be acellular vaccines (combination dTaP vaccine or dTaP-IPV, or stand-alone aP vaccine), which have been shown to have good immunogenicity, efficacy, and safety profiles in adolescents and adults [46]. Protection of ~80% has been reported [47], but further efficacy data are needed. Suitable dTaP vaccines and dTaP-IPVs are now licensed for adults and adolescents in many countries, including Australia, Canada, and most European countries. To avoid gaps in protection for individuals who have recently received a dT or dT-IPV booster dose, a stand-alone aP vaccine should be made available to complement the current combined vaccines. Because adolescents are a significant reservoir of *B. pertussis* [48], universal adult vaccination would have to be accompanied by universal adolescent vaccination.

Universal adolescent vaccination. Because vaccine-induced immunity to *B. pertussis* infection is likely to have decreased significantly by adolescence, and because the reported incidence of *B. pertussis* infection is increasing in this group [49], an adolescent booster dose will prolong immunity and reduce disease prevalence (and thereby transmission) in this age group, indirectly reducing transmission to vulnerable infants. However, in the absence of universal adult vaccination, adolescent vaccination will not sufficiently control *B. pertussis* circulation and transmission to infants.

In many countries, dT or dT-IPV booster doses are given in early adolescence (generally before 16 years of age) through school-based programs, so switching to a dTaP vaccine would be simple. All individuals <18 years of age (or younger than the nationally defined upper age range for adolescence) who have already received a dT or dT-IPV booster dose could be given a stand-alone aP vaccine, if available, to ensure adequate protection. For countries not operating school vaccination programs, an extensive education program will be required to encourage uptake.

Universal preschool booster doses at 4–6 years of age. Randomized trials have reported increased antibody titers after receipt of pertussis booster doses at 4–7 years of age [50, 51], and health-economic models have indicated potential health benefits and cost-effectiveness with this strategy [52, 53]. After the introduction of a booster dose for 4–6-year-old children, the disease burden in US preschool and school children decreased [7].

With administration of a booster dose at 4–6 years of age, it is expected that immunity will be extended into adolescence. The possibility of moving administration of the adolescent booster dose from early adolescence to mid-adolescence could be explored.

Administration of a pertussis booster dose at 4–6 years of age is already included in the vaccination schedules of some countries. In others, this strategy would require the introduction of a fourth or fifth booster dose for this age group.

Selective vaccination of new mothers, family, and close contacts of newborns. Two main vaccination schedules were considered for this strategy: vaccination of mothers prenatally (during the third trimester) and vaccination of mothers, fathers, family members, and other close contacts perinatally (before the infant reaches 4 weeks of age). Maternal vaccination during pregnancy might reduce transmission of *B. pertussis* infection from mother to newborn and have the advantage of transferring antibodies to the infant via the placenta. However, studies of prenatal vaccination using wP vaccines have been inconclusive in this regard [54].

Given the general public concern about vaccinations in pregnancy, postnatal vaccination of mothers may be a more acceptable option than prenatal vaccination. Other family members and close contacts would also be vaccinated, preferably during the prenatal period but, failing this, within the first 4 weeks of the newborn's life. This strategy would be easier to implement than universal adult vaccination, because mothers are easy to access via their contact with health care services and are motivated to protect their infants. Access to other family members and other potential close contacts would be more difficult to achieve, but education on the potential risks of transmitting *B. pertussis* to a young infant should motivate them to be vaccinated.

Selective vaccination of child care and health care workers. In many countries, few infants <6 months of age attend day care, so vaccinating child care workers may not contribute significantly to reducing infant morbidity and mortality. However, infants and children who are exposed to child care workers infected with *B. pertussis* are at particular risk of infection because of the greater chance of prolonged and close contact. Preventing and diagnosing *B. pertussis* infection among health care workers is also important.

A European Union directive specifies that all persons at occupational risk from infectious agents should be offered vaccination at the employer's expense if an effective vaccine is available [55]. Currently, Austria and Germany are the only countries implementing this directive. Experience with influenza vaccination suggests that some health care workers are reluctant to be vaccinated [56], but education of this target group should maximize compliance.

Selective vaccination of health care and child care workers would require vaccination on entry into the profession and

Table 2. Research needs identified by the Global Pertussis Initiative to facilitate implementation of expanded immunization schedules.

Epidemiology and transmission
Information on the correlation between seropositivity and disease presentation
The influence of vaccination policy and natural boosting on the age-related incidence of symptomatic versus asymptomatic infection
Monitoring of emerging antigenic variants that might compromise vaccine efficacy
Further studies to establish whether there is a reduced opportunity for natural boosting among populations where uptake of childhood pertussis vaccination is high
Surveillance and diagnosis
Enhanced surveillance methods are needed to collect accurate epidemiological and vaccine coverage data
Clinical case definitions of pertussis disease should be standardized, particularly for mild disease
Rapid, reliable, widely available, easy-to-use, and inexpensive laboratory diagnostic techniques are needed, as are the standardization and increased use of PCR and antibody testing techniques
Vaccines
Further data on the effectiveness and reactogenicity of adolescent/adult acellular pertussis vaccines
Determine the duration of vaccine-induced immunity
Maternal and neonatal vaccination
Data on the safety of pertussis vaccines administered during the last trimester of pregnancy
Further research on whether high titers of antibodies induced in mothers before delivery confer protection on the infant, and also whether high titers of antibodies, if passed to the infant, interfere with active immunization in infancy
Cost-effectiveness: cost-effectiveness studies of recommended strategies
Enhancing program implementation
Simple, effective educational campaigns are needed for health care professionals and the public
Political will needs to be raised
All countries must ensure that they have effective vaccines, delivery infrastructures, and appropriate diagnostic techniques and surveillance systems
Additional research into public perceptions and understanding of pertussis disease and vaccination in adults

regular booster doses throughout employment. Health care workers are easy to access, although the timing of vaccination would depend on their vaccination history before starting work. A pragmatic approach would be to combine pertussis vaccination every 10 years with dT or dT-IPV booster doses.

Reinforce and/or improve current infant and toddler vaccination strategies. To ensure that current infant and toddler vaccination strategies are reinforced and/or improved, public health education, particularly for parents, is important. Efforts are needed to ensure that vaccinations are not missed or delayed, because study data indicate that even a single vaccination may protect against severe disease and hospitalization [43, 57].

STRATEGY RECOMMENDATIONS BY THE GPI

GPI participants agreed that any changes in pertussis vaccination strategies should be underpinned by improved vaccine coverage of infants and toddlers, particularly in impoverished and deprived populations, for whom coverage rates may be poor. However, it was universally acknowledged that, even if 100% coverage of infants and children was achieved, infants too young to be vaccinated would still be vulnerable. Booster vaccination of groups who are currently beyond the recommended age range is therefore needed.

North America. For North America, it was agreed that the overall objective should be to develop lifelong immunity to *B. pertussis* infection. This would best be achieved by introducing universal adolescent and adult vaccination.

All North American participants agreed that adolescent vaccination should be introduced. Although adult vaccination is the logical eventual goal, the group was divided on whether there are sufficient data to support its introduction. More research is needed, particularly on the duration of immunity conferred by aP vaccines in adults. A minority in the group strongly believed that universal adult vaccination is justified by the available data and urged its immediate introduction. The remainder proposed a step-wise approach and recommended initially focusing on vaccination of all adolescents, supplemented by vaccination of specific adult subgroups (including, but not limited to, young adults and new parents, close contacts of newborns, health care workers, and child care workers). Although this would be unlikely to have any significant overall effect on extending herd immunity or reducing pertussis cir-

culation, the approach acknowledges the likely logistical and economic barriers to introducing a program of regular adult pertussis booster doses.

Europe. Three strategies were proposed for the European region. First, adherence to current national schedules should be reinforced through improved education for the public and health care workers. Second, the best pan-European strategy would be for most countries to add a dose to the existing schedule by introducing universal preschool or adolescent booster doses. Selective vaccination of health care workers should be implemented in all countries, in line with the European Community directive [55].

International. Because of a wide spectrum of epidemiological conditions, vaccination requirements, and health care resources in the international region, consistent proposals for all participating countries were not possible. Nevertheless, primary objectives were deemed similar in Argentina, Australia, and Japan—to reduce morbidity in adolescents and young adults and to develop herd immunity. The following strategies were considered important in meeting these objectives.

- For Australia, Argentina, and Japan, universal vaccination of adolescents was recommended. Australia has recently removed the 18-month DTaP vaccine dose from the vaccination schedule and replaced the dT vaccine given to adolescents 15–19 years old with a dTaP vaccine.
- For Australia, selective vaccination of new mothers, family, and close contacts of newborns and selective vaccination of health care workers was recommended.
- For Japan, a fourth booster dose for all preschool children (which is already given in Australia and Argentina) was recommended.

Brazil is unlikely to expand pertussis vaccination without further data on health benefits and cost-effectiveness because of a current focus on controlling tuberculosis and malaria.

ADDITIONAL RESEARCH AND IMPLEMENTATION REQUIREMENTS

The introduction and refinement of expanded vaccination strategies should be supported by a range of research efforts and common measures (table 2).

SUMMARY

Although pertussis epidemiology and health care priorities vary worldwide, all countries should ensure the highest possible coverage rates among infants and children and should consider expanding existing vaccination strategies with the goals of reducing transmission to young infants, developing herd immunity, and reducing morbidity in children, adolescents, and adults. Complete protection against pertussis, particularly against serious disease in young infants, will require lifelong universal vaccination. However, recognizing the unfeasibility of immediate implementation of this approach, most GPI members recommended that countries with high levels of infant vaccination first consider administration of booster doses to 4–6-year-old children at school entry, to adolescents, and to specific adult groups (such as young adults and new parents, other contacts of newborns, and child care and health care workers), with concurrent accumulation of data on the safety and effectiveness of those programs. Universal adult vaccination is the logical goal in countries in which it is economically feasible.

MEMBERS OF THE GPI

Chairman: S.P. (United States). Steering Committee: K.F. (Australia), T.T. (United States), C.-H.W.K. (Germany), and J.C. (United States). European participants: Lieven Annemans (Belgium), M.C.-M. (Spain), Ron Dagan (Israel), Adam Finn (United Kingdom), Emmanuel Grimprel (France), N.G. (France), Hans Hallander (Sweden), U.H. (Switzerland), Luc Hessel (France), Friedrich Hofmann (Germany), Henri Laurichesse (France), Johannes Liese (Germany), Jussi Mertsola (Finland), Stefania Salmaso (Italy), J.S. (The Netherlands), Claire-Anne Siegrist (Switzerland), and Jim Van Steenbergen (The Netherlands). International participants: Alejandro Lepetic (Argentina), Masaaki Nagai (Japan), and Evelinda Trindade (Brazil). North American participants: J.D.C. (United States), Michael Decker (United States), Kathryn Edwards (United States), Janet Englund (United States), Stanley Gall (United States), Pierce Gardner (United States), Paul Glezen (United States), D.G. (United States), Scott Halperin (Canada), Mark Miller (United States), Peter Neumann (United States), Edward Rothstein (United States), Danuta Skowronski (Canada), and Annelies Van Rie (United States).

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