Potential Strategies to Reduce the Burden of Pertussis

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Abstract: Pertussis continues to be a significant cause of morbidity and mortality among nonimmunized young infants. Although the inception of childhood pertussis immunization programs has significantly reduced the occurrence of the disease in children, waning vaccine-induced immunity permits the disease to affect adolescents and adults, who in turn transmit the disease to unimmunized or incompletely immunized infants. The Global Pertussis Initiative brought together experts from 17 countries around the world to evaluate strategies to improve disease control. Seven strategies were considered: (1) universal adult immunization; (2) selective immunization of mothers and close family contacts of newborns; (3) selective immunization of health care workers; (4) selective immunization of child care workers; (5) universal immunization of adolescents; (6) preschool booster at 4-6 years of age; and (7) reinforcement and/or improvement of current infant and toddler immunization strategies. Because immunization programs vary widely from country to country, no single strategy is likely to be appropriate for all. Moreover it would be helpful to have additional data to support the strategies and provide a better understanding of the disease so that new approaches can be monitored effectively. However, certain steps can be taken now to reduce the incidence of pertussis.

Key Words: Bordetella pertussis, pertussis, immunization strategies

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Reductions in the incidence of pertussis disease in infants and children have been achieved through extensive childhood immunization programs. Nonetheless the disease remains endemic, even in countries with >90% immunization coverage, and herd immunity has not been complete. Pertus-

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sis remains the most common vaccine-preventable disease in children younger than 5 years of age in some countries and continues to pose a serious threat to infants, particularly those who are too young to be vaccinated or who have not completed the primary series.^{1,2}

Bordetella pertussis persists within communities, even those with successful immunization programs, because vaccine-induced immunity wanes \sim 5–6 years after immunization with either acellular pertussis (aP) or whole cell pertussis (wP) vaccines.^{3–10} Pertussis is therefore not uncommon in adolescents and young adults who have received the full course of childhood immunizations but whose immunity has declined.^{11,12} Adolescents and adults are a significant reservoir of infection and an important source of disease transmission to infants too young to be fully immunized.¹³

The Global Pertussis Initiative (GPI) brought together 37 experts from 17 countries to evaluate strategies to improve disease control. The process undertaken by the GPI is described in this supplement.¹⁴

The countries represented by the GPI all have pertussis immunization schedules that include 3-5 doses of vaccine administered between the ages of 2 and 34 months, followed, in some countries, by 1 dose at 4-6 years of age before starting school (see Table 1 of Tan et al¹⁵ in this supplement). Australia, Canada, France and Germany have recently begun to administer a booster to adolescents 11-18 years of age. Most countries immunize children with a combined diphtheria-tetanus-acellular pertussis (DTaP) vaccine. Some countries (France, United Kingdom) use diphtheria-tetanus-whole cell vaccine for the primary immunization course, followed by acellular pertussis boosters. Among the 17 countries represented by the GPI, only Finland (at 20–24 months) and Argentina (at 18 months and 4-6 years) use whole cell boosters after the primary DTwP course.

The GPI defined and evaluated 7 strategies to complement or improve current childhood immunization schedules (Table 1). These could apply either universally to a particular age group (ie, 4- to 6-year-olds, adolescents or adults) or selectively to a particular population subgroup (ie, new mothers and family and close contacts of newborns, such as health care or child care workers). Also considered was the need to

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ADDA 1. Initialization Strategies Assessed by GITT and parts		
Strategy	Primary Objectives	Secondary Objectives
1. Universal adult immunization	Reduce morbidity in adults Develop herd immunity	Reduce transmission to young infants Reduce morbidity in older children
2. Selective immunization of new mothers, family, and close contacts of newborns	Reduce transmission to infants	Reduce morbidity in adults, particularly young adults
3. Selective immunization of health care workers	Reduce transmission to patients	Reduce morbidity in health care workers
4. Selective immunization of child care workers	Reduce transmission to infants	Reduce morbidity in child care workers
5. Universal adolescent immunization	Reduce morbidity in adolescents and young adults Develop herd immunity	Reduce transmission to infants
6. Preschool booster at 4– yr of age	Reduce morbidity in 4- to 6-yr-olds Develop herd immunity	Reduce transmission to infants
 Reinforce and/or improve the current infant and toddler immunization strategy 	Reduce morbidity and mortality in infants, toddlers and children	Reduce overall circulation of pertussis

TABLE 1. Immunization Strategies Assessed by GPI Participants*

*Entries represent the consensus of opinion of the GPI participants.

TABLE 2. Advantages and Caveats for Various Immunization Strategies Assessed by the GPI

Advantages	Caveats Proceeding Implementation
1. Universal adult immunization Reduce transmission to nonimmune individuals, particularly infants Develop herd immunity	High level of coverage needed Evidence needed for reduced transmission to infants
Reduce morbidity among adults Easily included with dT boosters (dTaP)	Population difficult to access Poor compliance anticipated Availability of aP/dTaP vaccines Relatively expensive, no current proven health-economic benefits Data needed on reactogenicity after repeated aP immunizations
2. Selective immunization of new mothers, family, and close contacts of newborns	
New mothers are easy to access; family and close contacts of newborns are difficult to access Some target groups well-motivated Less expensive than universal adult immunization Targets high risk groups	Insufficient safety and effectiveness data on prenatal pertussis immunization Unknown effects of prenatal immunization on subsequent infant immunization Unlikely to affect morbidity among adult population
3. Selective immunization of health care workers	
Prevent pertussis spread within institutions Prevent spread to/from children and infants	No data on contribution of transmission from these workers to infants No efficacy data on the use of aP vaccines during outbreaks in this setting Poor compliance anticipated Availability of aP/dTaP vaccines More data needed on the duration of effect of multiple doses of aP vaccine
4. Selective immunization of child care workers	
Prevent pertussis spread within institutions Prevent spread to/from patients and infants	See point 3. Most children are vaccinated before entry to day care
5. Universal adolescent immunization	most emilien are vacentated before entry to day care
dTaP vaccine available for adolescents	More data needed on the morbidity of pertussis in adolescents to convince of need for booster
Target population easily identified Easy to administer immunization program but only if operated via schools	Lack of information of the reactogenicity of a sixth dose of aP vaccine Requires a monovalent aP vaccine to be available as well as a dTaP vaccine Possible shift in the disease curve to the child-bearing age group
 Preschool booster at 4–6 years of age Overcomes waning immunity in preschool children Booster fits well into many current immunization schedules Easy to replace a dT booster with a dTaP booster 	Inadequate availability of combination vaccines Reactogenicity of >4 doses of aP vaccine Data on duration of effect based mainly on wP vaccines
Easy to access the target group 7. Reinforce and/or improve the current infant and toddler immunization strategy	
Maximize current immunization programs	Current programs not sufficient even when well-implemented

reinforce or improve current infant and toddler immunization programs.

This article, which is based on the discussions of the GPI participants, describes the relative advantages and caveats for implementation for each strategy (Table 2). The specific strategies considered most appropriate in each GPI

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region are discussed later in this supplement, as are the plans that were suggested to effect the chosen strategies.^{16–18}

UNIVERSAL ADULT IMMUNIZATION

Universal immunization of adults 18 years of age and older would reduce pertussis incidence in adults. It could also

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contribute to the development of herd immunity to pertussis and therefore reduce disease transmission to infants, provided a high level of coverage was achieved. This strategy has only recently been implemented in Austria, so there are no data to confirm that it would meet these objectives.

As 10-yearly low dose diphtheria and tetanus (dT) boosters are already recommended to adults in many countries, a switch to a dTaP vaccine, if available locally, would be relatively simple, although a stand alone aP vaccine would also be beneficial for a catch-up program for individuals recently immunized against diphtheria and tetanus. However, where they do exist, dT immunization programs have generally achieved poor coverage (eg, only 30-60% in Germany, 40-60% in the United States and 30% in Spain).¹⁹⁻²¹ Higher levels of coverage are unlikely to be achieved by the addition of pertussis immunization, especially given that pertussis is not generally perceived to be a serious problem in adults. Moreover without data to confirm the duration of pertussis immunity conferred by initial or booster immunization in adults, it is not certain whether 10-year intervals between boosters would be sufficient, and it is not possible to devise an appropriate immunization schedule. In addition, where appropriate dT immunization programs do not exist, a new delivery infrastructure would have to be created.

Another obstacle lies in poor access to the young adult population. Young adults generally do not have routine preventive health care, although some countries have excellent school-based immunization programs. Immunization of adults is therefore unlikely to achieve sufficiently high levels of coverage to develop herd immunity. Moreover since adolescents are a significant reservoir of pertussis,^{13,22,23} there is little point in implementing universal adult immunization without also immunizing all adolescents.

Effective, safe and well-tolerated vaccines formulated for adults would be required. The vaccines of choice would be an aP and a dTaP vaccine, because they provide similar levels of effectiveness to those of wP vaccines but are better tolerated.^{24–26} Available data suggest that stand alone or combination aP vaccines have good immunogenicity, efficacy, and safety profiles in adolescents and adults.^{27–36} Suitable dTaP vaccines have only recently been licensed in some countries for use in adolescents and adults, and further investigation is needed regarding concerns about the potential reactogenicity after >5 doses.³⁷

A universal program of immunization would require significant investment and resources to pay for the volume of vaccine needed and the delivery infrastructure, and to support the public health education campaigns required to convince adults of the need for immunization. Such high costs in the absence of demonstrable health benefits could hinder the implementation of universal adult immunization. Health economic analyses are being performed to analyze the potential cost effectiveness of adult immunization.

SELECTIVE IMMUNIZATION OF NEW MOTHERS AND FAMILY AND CLOSE CONTACTS OF NEWBORNS

Pertussis is a highly contagious disease and an important source of infection for unimmunized or incompletely immunized infants in the immediate family.^{13,38,39} Therefore selective immunization of new mothers, family members and close contacts of unimmunized or incompletely immunized young infants would be a logical strategy. Two immunization schedules were considered by GPI participants: prenatal immunization of mothers during the third trimester of pregnancy; or perinatal immunization of mothers, family members and other close contacts before the infant reaches 4 weeks of age. Individuals would be immunized with either an aP vaccine or a combined dTaP vaccine, depending on their immunization history.

The primary objective of this strategy is to reduce transmission of pertussis to unimmunized or partially immunized infants. The secondary objective is to reduce morbidity among adults, particularly young adults, although this strategy is unlikely to have an impact on overall pertussis morbidity in adults, as the target population is relatively small. *Prenatal Booster*. Prenatal booster immunization against diseases other than pertussis has been successfully implemented in many developing countries, where women are often inadequately immunized. For example, prenatal administration of tetanus toxoid in such countries has proven to be safe and effective. Similarly, in the United States, dT immunization is recommended for all pregnant women who have not been completely immunized, and the safety of this approach has been confirmed.

Immunization of mothers during pregnancy would have the potential advantage of transferring antibodies to the infant via the placenta, although prenatal pertussis immunization has not yet been shown to protect infants from infection; indeed studies with wP vaccines were inconclusive in this regard.⁴⁰ Moreover neither the duration of effect of passively acquired antibodies nor the extent of potential interference with the infants' response to subsequent immunizations is known. It is therefore currently not possible to define the timing of prenatal and subsequent infant immunizations.

Although vaccination in the third trimester would circumvent some of the safety and teratogenicity concerns, coincidental premature birth or stillbirth may cause medical legal problems. *Postnatal Booster*. As there are insufficient data on the safety of pertussis immunization during pregnancy, the safest option would be to immunize mothers just after they have given birth. Other close family contacts could be vaccinated during the prenatal period or at the same time as the mother.

In practical terms, this strategy would be easier to implement than universal adult immunization given that at least some of the target population, mothers, are easy to access via their

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regular contact with gynecologists, obstetricians, midwives, primary care physicians and other health care workers.

Other close contacts of newborn infants are more difficult to target because there is no current immunization schedule that requires such a disparate group of individuals to be immunized. However, it is hoped that close contacts would be motivated to take up the vaccine for altruistic reasons. Moreover in countries with private health care systems, insurance companies would have to be convinced of the effectiveness of such a strategy as families would be unlikely to pay for pertussis immunization. Although there is considerable evidence that close contacts are a primary source of disease transmission to these infants,^{13,41} there are no data to confirm that immunization of close family members will prevent pertussis in young infants.

SELECTIVE IMMUNIZATION OF HEALTH CARE AND CHILD CARE WORKERS

Selective immunization of health care and child care workers would require workers to be immunized when they enter the profession or training and to receive regular boosters throughout their employment. The objectives of the strategy are to reduce transmission to susceptible groups (patients or infants in child care) and to reduce morbidity among these workers.

There are no data currently available on the transmission of pertussis from children to child care workers. Moreover most children do not enter day care until after the primary immunization series is complete, although in the United States, infants as young at 6-8 weeks routinely enter child care.^{7,42} Immunization of child care workers is therefore unlikely to make a significant contribution to infant morbidity and mortality. However, pertussis is known to spread from patients to health care workers who in turn transmit the disease to susceptible patients,^{26,43-47} although it is not known whether this type of transmission is a major contributor to adult pertussis disease or infant morbidity.

Both the target populations are easy to access, although the strategies have practical difficulties in that the timing of pertussis immunization would be different for all workers, because some will already have a full immunization history before starting work or training. The duration of effectiveness of the aP vaccine is also unknown, but it is at least 5 years.^{9,10} Moreover published experience with influenza immunization programs in health care workers in Canada, Germany and Switzerland suggests that they are reluctant to comply with immunization programs, although they are generally convinced of the advantages of being immunized.^{48–50} Additionally enforced immunization as a condition of employment could not be sanctioned in the absence of strong data to confirm its effectiveness.

A pragmatic approach would be to combine pertussis immunization with the 10-yearly dT immunization program

that is available in some countries, although this would inevitably leave gaps in protection.

European Union countries are now required to offer health care workers who are at risk with defined infectious agents an immunization against those diseases for which a vaccine is available. The employer has to bear the cost, but individual health care workers are not required to undergo immunization. As a result of EC Directive 2000/54/EC,⁵¹ German health care workers who work in pediatrics and infectious diseases should now receive routine pertussis boosters to protect them from infection. However, this program began only in 2001, and no data on its effectiveness are yet available. Until such data do become available, this strategy is unlikely to be taken up by many countries.

UNIVERSAL ADOLESCENT IMMUNIZATION

The highest antibody titers for pertussis toxin and filamentous hemagglutinin are observed in adolescents, which suggests a high level of natural infection.²¹ This population is also known to be a significant source of infection for young infants and others.^{23,38} Universal immunization of adolescents (at 11 or 12 years of age with catch-up immunization until the age of 18 years) therefore aims to reduce pertussis morbidity among adolescents and young adults, develop herd immunity and reduce transmission to unimmunized or incompletely immunized infants.

Because immunity to pertussis is known to wane with time (over \sim 5–6 years),^{7,42,52} it is reasonable to presume that an adolescent booster will reduce morbidity and prolong immunity. The target population is easy to access in most countries through schools. Indeed in many countries early adolescent dT boosters are already offered, so a switch to a dTaP vaccine would be relatively simple, with a stand alone aP vaccine, if available, for those who have already received the dT vaccine. Thus far, only Australia, Canada, France, Austria and Germany have implemented this strategy, and data on its effectiveness, tolerability and effects on infant morbidity and mortality are awaited. For countries or regions that do not operate immunization programs via schools, extensive educational programs would be required to encourage primary care physicians to undertake immunization programs and to encourage parents to immunize older children and adolescents.

An important potential disadvantage of this strategy, if implemented in isolation, is that it might lead to a peak in pertussis incidence in the group in their mid- to-late 20s, which is the peak childbearing age. Were this to occur, it would be important to ensure effective booster vaccination of these groups, either by a selective close contact strategy or by universal adult vaccination.

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INTRODUCE OR MAINTAIN UNIVERSAL PRESCHOOL BOOSTER AT 4–6 YEARS OF AGE

A fourth or fifth pertussis preschool booster to reduce morbidity among school age children is included in some countries' immunization schedules (see Table 1 of Tan et al¹⁵ in this supplement). In others, this strategy would require the introduction of a booster dose for this age group.

Most studies have followed up children immunized with wP vaccine and, depending on the type of wP used, the protection was found to be very variable. Some studies have demonstrated that aP vaccines provide immunity for 5–6 years.^{9,10,53} Data from the United States (DTaP vaccine) do appear to confirm the effectiveness of preschool boosters and have shown that pertussis rates declined in preschool children in the period 1997–2000 after the introduction of these boosters in 1997.² Similar reductions were also observed in Australia (DTaP),⁵⁴ where children also receive preschool boosters.

aP vaccines provide relatively constant immunity for at least 5–6 years.^{9,10} If this proves to be the case, a different immunization schedule with preschool boosters might be more effective in reducing overall pertussis morbidity and in developing herd immunity. However, a preschool booster fits well into most countries' current immunization schedules and, with the use of combined vaccines, prevents children from undergoing an excessive number of injections. Increased local reactogenicity after the fourth or fifth dose of aP vaccine is a concern and could be a barrier to the widespread introduction of aP immunization until further data on the optimum interval between aP immunizations become available.³⁷ One possibility to reduce the number of doses might be to eliminate the fourth toddler booster dose of DTaP vaccine.

REINFORCE AND/OR IMPROVE THE CURRENT INFANT AND TODDLER IMMUNIZATION STRATEGY

The obvious way to reduce the incidence of pertussis in children is to ensure that, at the very least, high coverage of the primary immunization schedule with an effective vaccine is achieved and a fourth dose is in place in all countries. Such a strategy requires effective pertussis surveillance and immunization monitoring systems to continually assess the effectiveness and coverage of immunization programs. Programs vary from country to country, and future improvements may depend on data concerning the recently introduced aP vaccines. General improvements should include efforts to increase the coverage of current programs through health education, to provide effective delivery infrastructures and to improve diagnosis and surveillance to ensure that the data on which the programs are based are accurate.

CONCLUSION

Despite widespread childhood immunization programs in the countries represented in the GPI, pertussis continues to pose a significant threat to public health, in particular to unimmunized or incompletely immunized infants. Universal adult immunization is possibly the ultimate solution to this problem but is difficult to achieve given the high costs involved, the anticipated low levels of compliance among adults and the current lack of widely available aP vaccines. Universal adolescent immunization is likely to be more successful, particularly in terms of vaccine coverage. A more efficient approach would be to target high risk groups. Such an approach would include the maintenance of current childhood immunization schedules, with additional doses where necessary to ensure the continued protection of children. Perinatal immunization of parents and other close family contacts may be another way to protect vulnerable infants, although more research is needed to confirm the effects of such a strategy on the incidence of pertussis in young infants.

None of the strategies discussed by GPI participants is, on its own, appropriate for all countries because approaches to pertussis immunization vary widely, as does vaccine availability. Indeed all the strategies are limited by the duration of immunity following natural infection or immunization. Strategies thought most appropriate for each of the regions represented by the GPI are discussed in this supplement.^{15–17}

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