Chapter 4 — Use of Pertussis Vaccines in Outbreaks

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Routine immunization with pertussis vaccines has resulted in high coverage rates and greatly reduced morbidity from pertussis; however, outbreaks continue to occur. Because coverage is high among infants and preschool-aged children and because additional doses are not recommended for these or other age groups, pertussis vaccines play only a minor role as an outbreak control measure. In the future, licensure of pertussis vaccines for adolescents or adults may lead to new recommendations for the use of vaccines in outbreaks.

ROUTINE RECOMMENDATIONS FOR VACCINATION

Five doses of diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) are routinely recommended for children <7 years of age.[1]

- Three (primary) doses at ages 2, 4, and 6 months.
- Fourth (first booster) dose at 15-18 months of age. The fourth dose should be administered ≥6 months after the third. If the interval between the third and fourth doses is ≥6 months and the child is not likely to return for a visit at the recommended age, the fourth dose of DTaP may be administered as early as age 12 months.
- Fifth (second booster) dose at 4-6 years of age is given to confer continued protection against disease during the early years of school. A fifth dose is not necessary if the fourth dose in the series is administered on or after the fourth birthday.

Vaccination is not recommended for individuals ≥7 years of age, and no vaccine is currently licensed for use in persons aged ≥7 years.

AVAILABLE VACCINE PREPARATIONS

Whole-cell pertussis vaccines are killed bacterial vaccines, provided in combination with diphtheria and tetanus toxoids as DTP or with *Haemophilus influenzae* serotype b conjugate vaccine (DTP-Hib). Three combination diphtheria and tetanus toxoids and acellular pertussis vaccines (DTaP), Tripedia®, Infanrix™, and Certiva™, are currently licensed for use for the first four doses of the five-dose diphtheria, tetanus, and pertussis vaccination series. These three DTaP vaccines are not licensed for the fifth dose following four doses of the the same vaccine because data are insufficient to evaluate their safety in this situation; however, such data should be available before infants vaccinated with four doses of these vaccines require a fifth dose at 4-6 years of age. A fourth DTaP, ACEL-IMUNE®, is licensed for all five doses in the series. TriHIBit™ (ActHIB® reconstituted with Tripedia®) is licensed only for the fourth dose of the vaccination series and contains a Hib vaccine; TriHIBit™ can be used for the fourth dose following three doses of either DTaP or whole-cell DTP and a primary series of any Hib vaccine.

Because of the reduced frequency of adverse reactions and demonstrated efficacy, the ACIP recommends a licensed DTaP for all five doses of the routine diphtheria, tetanus, and pertussis vaccination series and for the remaining doses in the series for children who have started the vaccination series with whole-cell DTP vaccine. The ACIP considers the data to be insufficient in terms of safety and efficacy to express a preference between different acellular pertussis vaccine formulations. Whenever possible the same DTaP vaccine should be used throughout the entire vaccination series. No data exist on the safety, immunogenicity, or efficacy of different DTaP vaccines when administered as mixed sequences in the primary or booster vaccination of a child. However, if the vaccine provider cannot ascertain the type of DTaP vaccine the child to be vaccinated received previously or does not have the vaccine available, any of the licensed DTaP vaccines may be used to complete the vaccination series.

Estimates of the efficacy of immunization with pertussis vaccines are subject to wide variation due to variation in study design, including factors such as case definition, case ascertainment, and duration of followup. A recent study of reported cases in the United States in 1992 - 1994 estimated the effectiveness of whole-cell vaccine against culture-proven pertussis; the effectiveness of three doses among children aged 7-18 months was 79% and the effectiveness of 4 doses among children aged 19-47 months was 90%.[2] Estimates are also available from recent field trials that compared the efficacy of acellular and whole-cell pertussis vaccines.[3] In these trials, the efficacy of three doses of whole-cell pertussis vaccines from different manufacturers ranged from 83% to 98%, although the DTP vaccine from one manufacturer had a low efficacy in two trials (35% to 48%). In the field trials, the efficacy of the four licensed acellular vaccines ranged from 71% to 89%.

RECOMMENDATIONS FOR VACCINATION DURING OUTBREAKS

General

The immunization status of all contacts $\leq$6 years of age should be assessed. All contacts $\leq$6 years of age who are not up-to-date with DTaP/DTP should be brought up to date with doses of DTaP using the minimal recommended intervals (see **Table 4-1**). If the child has had three doses of DTaP or DTP, is $\geq$12 months of age, and $\geq$6 months have passed since the third dose of DTaP or DTP, then a fourth dose of DTaP should be given. If the child has had four doses of DTaP or DTP, is 4 - 6 years of age, and received the fourth dose before the 4th birthday, then the fifth dose of DTaP should be given.

Children who have a history of well-documented pertussis disease (i.e. positive culture for *B. pertussis* or epidemiologic linkage to a culture-positive case) do not need to receive additional doses of pertussis-containing vaccine.[1] However, because at least one study found that infants (<12 months of age) may have a suboptimal immune response following *B. pertussis* infection,[4] some experts recommend including the pertussis

component for vaccination of infants who have had culture-proven pertussis.

Because currently there is no licensed product for use in persons 7 years of age and older, vaccination of persons in this age group should only be performed as part of a research study, with informed consent and approval of an institutional review board.

Infants - Accelerated Schedule

The use of an accelerated schedule of pertussis vaccination for infants (e.g., aged <2 months at initial vaccination) during pertussis outbreaks is considered an acceptable outbreak control measure but is usually not recommended because it would not match the schedule of other needed vaccinations (Table 4-1). While pertussis vaccine is usually given at 2, 4, and 6 months of age, the minimum acceptable age for initial vaccination is six weeks of age with subsequent doses recommended at ≥4 week intervals.[1] On this schedule, infants could complete their three-dose primary series by 14 weeks of age.

Immunologic Basis

Studies have found an immunologic basis for the use of an accelerated schedule beginning at 6 weeks of age (and possibly as early as 4 weeks of age) for whole-cell pertussis vaccines. Maternal antibody blocks development of a good antibody response to vaccination with whole-cell pertussis vaccine in the first weeks of life.[5] Vaccination of infants beginning at 1 week of age produces poor antibody results.[6-7] Vaccination beginning at ≥4 weeks of age produces antibody responses almost equal to vaccination beginning at 8 weeks of age.[8] Studies found that receipt of three doses at 1 month intervals gave a high degree of clinical protection against pertussis, even if begun at an early age.[9] High levels of agglutinating antibodies develop after the first two doses in up to 50% of recipients suggesting that some children may be protected after only 2 doses of whole-cell pertussis vaccines, although 3 doses are required for reliable antibody production.[10]

Some acellular pertussis vaccines are able to produce antibody responses that are less inhibited by maternal antibody than are the responses to whole-cell vaccines;[11] in addition, the antibody response to acellular vaccine seems to begin after the first dose as opposed to after the 2nd or 3rd dose for whole-cell pertussis vaccine.[11] The clinical importance of these differences in antibody kinetics is not clear, although some experts estimate that the effectiveness of one dose of acellular vaccine may be 20-40% with significant variation between different vaccines.[3]

Potential Difficulties with Implementation of an Accelerated Schedule in a Community

Implementation of an accelerated schedule might cause difficulties with achieving full coverage with other antigens. An accelerated schedule for pertussis vaccination could pose problems because administering vaccines against other antigens on this compressed schedule may not induce optimal antibody responses. Neither Hib nor IPV vaccine is

recommended at 4 weeks of age. Hib vaccines can be given as early as 6 weeks of age with a 4-week interval between subsequent doses; however, this schedule is not regarded as optimal. Vaccination with IPV is recommended to begin at 2 months of age with a minimum interval of 4 weeks between subsequent doses. In addition, it may be difficult to achieve high coverage with an accelerated schedule for pertussis vaccination because of the difficulty of implementing an alternative vaccination schedule for all infants.

Effectiveness of an Accelerated Schedule

The impact of implementing an accelerated schedule is likely to be modest, although it could result in some decrease in pertussis morbidity among infants between 14 weeks and 6 months of age. Well-documented experience is lacking on the use and effectiveness of accelerated immunization of infants. A recommendation was made during the 1993 outbreak in Cincinnati to vaccinate infants as young as 1 month of age with a minimum 1-month interval between doses. However, no published data are available as to the degree of implementation or impact of this recommendation on control of the outbreak.

Children 1-6 Years of Age

Vaccination of children who are not up-to-date for age for pertussis *is* recommended. Administration of the 4th and 5th doses is recommended for children who are eligible for these doses but have not yet received them; however, other supplemental vaccination *is not* recommended for children who are up-to-date for age. Catch-up vaccination of children 1-6 years of age is likely to play a minor role in controlling outbreaks, because coverage with >3 doses of DTP/DTaP is high among children $\geq$19 months of age; in 1997 coverage of 19-35 month-olds was $\geq$95% and coverage with 4 doses was $\geq$81%.[12] In community outbreaks involving preschool-aged children, additional vaccination among undervaccinated children may provide some benefit. In the 1993 Chicago outbreak, a coverage survey showed that 17% of children 19 to 47 months of age in the community had received <3 doses whereas 25% of case-patients in this age group had received <3 doses; case-patients who had received <3 doses had more severe disease than children who received $\geq$3 doses.[13] Efforts to bring children up-to-date in this outbreak could not have prevented the majority of cases in this age-group but could have decreased the severity of the cases that did occur. Efforts to enhance coverage may be difficult; a campaign to recall and immunize children who were not up-to-date during a pertussis outbreak in Oklahoma in 1983 appeared to fail to reach 82% of the targeted population.[14]

In most outbreaks among children attending day care or school, coverage is usually very high due to state laws requiring vaccination for children attending school and day-care institutions. In an analysis of pertussis containment measures employed in the 1993 Cincinnati outbreak, only 6 of 233 schoolchildren who were exposed to pertussis were not up-to-date for DTP vaccination.[15] Outbreaks in unvaccinated children under the age of 7 years do occasionally occur among groups opposed to vaccination. Parents in some of these groups will allow vaccination of their children under outbreak conditions;

however, reliable protection of these children requires at least three doses of vaccine and three provider visits over a two-month period.

Older Children, Adolescents, and Adults

Currently, vaccination of children ≥7 years of age, adolescents, and adults is not recommended either routinely or as an outbreak control measure. Experience with whole- cell vaccine demonstrated that pertussis vaccination of adults was associated with an unacceptable frequency of side effects among adults. Vaccination of older children, adolescents, and adults may play a role in outbreak control when acellular pertussis vaccines are licensed for these age groups. Clinical trials to assess safety and efficacy are underway among adults using acellular pertussis vaccines; preliminary results show the vaccines to be immunogenic and associated with relatively limited local side effects including local pain, redness, and induration.[16,17,18] Optimal strategies to use such a vaccine, once one is licensed, still need to be developed. Factors to consider include the health burden among adolescents and adults and the expected impact of vaccination of these age groups on disease among infants.

Hospital outbreaks are a special situation in which multiple cases of pertussis may be recognized among adults and the risk of transmission to children without immunity or with compromised health status is high. In a hospital outbreak in 1974, >800 staff at a large Cincinnati hospital were vaccinated with a whole-cell pertussis vaccine.[19] Of 119 nurses followed prospectively, 45% had erythema >6cm and 29% had swelling or induration >6 cm; 27% had limitation of motion of the inoculated arm and 10% had fever. In the remaining vaccinees, passive surveillance found fewer local side effects; however, 2 individuals had generalized rashes, one of which required epinephrine, diphenhydramine, and steroids. Vaccination of these persons was found to be immunogenic; 77% of tested employees who had been vaccinated had a ≥4-fold rise in pertussis antibody titers. However, the effectiveness of the intervention was not formally assessed.

More recently, an acellular pertussis vaccine (half-doses of pediatric formulation DTaP) was used to vaccinate 630 hospital staff during a hospital outbreak of pertussis in 1993.[20] A retrospective study using a questionnaire found that local side effects were reported by 29% of survey respondents, but were mild. Only 5% had limitation of arm movement and <1% had documented fever. Although 11% of vaccinees who responded reported some systemic symptoms, 22% of unvaccinated hospital staff who were surveyed at the same time also reported systemic symptoms. This experience may not be applicable to results from use of monovalent acellular pertussis vaccines due to the reactogenic diphtheria and tetanus components contained in the pediatric formulation. The investigators were not able to evaluate the clinical effectiveness of the intervention. Currently, vaccination of adults is not recommended for control of hospital outbreaks; no product is currently licensed for use among persons ≥7 years of age, and studies of the

use of acellular pertussis vaccine for this purpose are needed.

Table 4-1. Routine and Outbreak Control Recommendations for the use of Pertussis Vaccines (DTaP† or DTP‡)

Dose	Customary age for routine administration	Minimum age or interval during outbreaks
Primary 1	2 months	6 weeks of age
Primary 2	4 months	4 weeks after first dose
Primary 3	6 months	4 weeks after second dose
First booster	15-18 months	6 months after third dose but not before 12 months of age
Second booster	4-6 years¶	same as customary
Additional doses	Not recommended	Not recommended
Doses for individuals ≥ 7 years of age	Not recommended	Not recommended

† Diphtheria and tetanus toxoids and acellular pertussis vaccine.
‡ Diphtheria and tetanus toxoids and whole-cell pertussis vaccine.
¶ Second booster not needed if first booster administered on or after fourth birthday.

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