PREVENTION & CONTROL

ACELLULAR PERTUSSIS VACCINES

Prepared by

Dilşad Cebeci, M.D., MPH

Department of Public Health, School of Medicine. Marmara University, Istanbul, Turkey.

Pertussis is a dangerous infectious disease that is well controlled world-wide by widespread immunization. The major cause of the decline in the morbidity and mortality of the disease is the intensive World Health Organization's Expanded Program on Immunization. However, pertussis still remains one of major diseases because of its high morbidity; an estimated 40 million pertussis cases occurred worldwide in 1994, resulting in 5 million episodes of pneumonia, 360000 deaths, and 50000 neurological complications (including permanent brain damage).

Pertussis can be controlled only by immunization; other measures such as antimicrobial therapy offer negligible benefit. Pertussis vaccine has been available for more than 50 years. Despite nearly eliminating pertussis, the whole cell vaccines have been among the least satisfactory vaccines because of the adverse reactions they cause. They commonly cause reactions that are minor but burdensome (i.e. pain, redness, and swelling at the injection site, fever, drowsiness, anorexia), occasionally cause reactions that are transient but frightening (i.e., persistent inconsolable crying, high fever, hypnotic-hyporesponsive episodes), and, uncommonly, more severe adverse effects (i.e., febrile convulsions and acute encephalopathy).

Although whole-cell pertussis vaccine is 70-90 percent efficacious after the third dose, the efficacy of immunization apparently begins to wane over several years. Studies of whole cell vaccines indicate that protection typically decreases 79 percent in the first 3 years, 53 percent after 4 to 7 years, 35 percent after 8-11 years, and essentially nil 12 years after immunizations (1). The duration of protection is probably influenced by the vaccine used, the number of doses given, and the vaccination schedule. Currently in countries in which pertussis vaccination is common, the age distribution of pertussis has changed markedly. The increase in pertussis cases has been greatest among older children and adults, probably reflecting waning vaccine-induced immunity (2).

The identification and isolation of important constituents of B. pertussis led to the development in Japan of several purified component (acellular) vaccines. Early studies of extracted pertussis antigens demonstrated high level of immunogenicity with a low level reactogenicity (3). Current acellular pertussis vaccines contain one or more purified proteins of B. pertussis, including pertussis toxoid, filamentous hemagglutinin, pertactin, and fimbrial agglutinogens. The safety and immunogenicity of a number of acellular pertussis vaccines when administrated to infants have been demonstrated. These vaccines have been used extensively in Japan since 1981 and clearly have been efficacious. This Japanese experience stimulated the development of additional, more highly purified acellular pertussis vaccines (2).

The encouraging results of the Japanese experience stimulated vigorous efforts in other industrialized nations to evaluate further the Japanese acellular vaccines and to develop other acellular preparations. To date, nearly 24 acellular pertussis vaccines have been developed. After evaluation of immunogenicity and reactogenicity trials and some efficacy and safety field studies, seven acellular vaccines were licensed in North America and Europe.

In a large field study, different acellular pertussis vaccines and whole cell vaccines were evaluated for safety end efficacy when administrated to infants. Because of differences in study design, clinical case definition, and laboratory methods

used to confirm the diagnosis, comparison of efficacy estimates within types of acellular vaccines should be made with caution, but all the acellular vaccines evaluated were associated with fewer local and systemic adverse reactions than whole cell vaccines (4-6).

Similarly in a randomized double blind study (n= 2200 infants) of the adverse reactions following administration of 13 different acellular pertussis vaccines and one whole cell vaccine at 2,4, and 6 months of age, all the cellular vaccines were associated with substantially fewer local and systemic reactions than the whole-cell vaccine. The protective efficacy of the acellular vaccines against moderately severe pertussis disease ranged from 59-85 percent. Vaccine efficacy for the four whole cell vaccines ranged from 36 to 98 percent (7).

In addition, acellular vaccines have controlled pertussis in Japan at least as well as whole-cell vaccines ever did, and wide spread use of the acellular vaccine in the Göteborg area since mid-1995 has been associated with the near eradication of pertussis (8).

Thus all the licensed acellular vaccines seem to be more than good enough when used in a comprehensive immunization program. Program factors, such as immunization schedule and comprehensiveness of coverage, may be more important than vaccine efficacy.

Preliminary data indicate that protection by acellular pertussis vaccines lasts at least several years; long term efficacy is not yet defined. In the 1992 Stockholm trial the efficacy of acellular vaccine was sustained at more than 80% during 2 years of follow-up, whereas that of the control whole-cell vaccine declined sharply. When pertussis does occur in immunized persons, it tends to be milder, with coughing of shorter duration than in the unimmunized (9-10).

Use of acellular pertussis vaccine in adults

Although the occurrence of pertussis in adults and the role of adults in the transmission of pertussis have been recognized for many decades, immunization against pertussis has generally been restricted to children under the age of 7 years. Two prevailing attitudes that account for this practice can be gleaned from the literature. Immunization of adults was considered unnecessary, because the serious consequences of B. pertussis infections were rarely observed among older children and adults, most of whom had been infected during early childhood. In addition, immunization of adults with whole cell vaccine generally was perceived as too reactiogenic and the risk benefit ratio likely was considered too high to recommend immunization after childhood (11-12).

In view of these attitudes, it is interesting that most of the early studies were conducted among adults. The safety and immunogenicity of a number of acellular pertussis vaccines were documented in phase I evaluations of candidate preparations conducted in healthy adults before their administration to infants and children. These studies paved the way for their consideration as candidates for booster immunization of older children and adults to control pertussis effectively. Booster immunization after childhood is now regarded as an important component of programs designed to control pertussis in populations. Several common themes have emerged from the collected experience gained during clinical trials of AC pertussis vaccine in adults. All vaccines were well tolerated and systemic symptoms occurred no more frequently among subjects given vaccine than among those given placebo. Acellular pertussis vaccines are generally highly immunogenic when administrated to healthy adults (12).

The frequency and magnitude of serum antibody responses are related to the dose and source of antigen. The occurrence of late-onset or biphasic local reactions is associated with higher post immunization antibody levels. Antibody responses may develop to antigens not known to be in the vaccine; their significance is uncertain (2).

Use of Acellular Pertussis vaccine in outbreaks

Limitations of both whole-cell and acellular pertussis vaccines restrict their usefulness in

controlling outbreaks among unvaccinated children. A single dose of DTP and DTaP vaccine does not confer protection, three or more doses are believed necessary to reliability confer protection (2).

Conclusion

Although whole-cell pertussis vaccines have been highly effective in preventing whooping cough, their common and burdensome adverse reactions and age limitations in administration led to the development of safer alternatives. Japan was the first country to develop and use acellular vaccine. Today it is used in different countries. According to the Advisory Committee on immunization Practices, The American Academy of Family Physicians, and the American Academy of Pediatrics, diphtheria and tetanus toxoids and acellular pertussis vaccine absorbed (DTaP) is the preferred vaccine formulation for all doses in vaccination series; DTP is acceptable only if no DTaP is available (13). Although DTP will likely disappear from the market in some countries within the next few years, whole cell vaccines will remain the most widely used globally for some time to come. Whole cell vaccines are produced locally in many regions of the world, are generally efficacious, and are inexpensive to produce. Each country will have to evaluate, based on its own circumstances, the relative virtues of the cost, efficacy, and adverse reactions of available whole-cell and acellular vaccines.

REFERENCES

1. *Strebel PM, Guris D, Wassilak SGF. Pertussis. In: Maxcy-Rosenau-Last, eds. Public Health â Preventing Medicine. 14th ed. Connecticut: Appleton and Lange, 1998; 98-101.*
2. *Decker MD, Edwards KM. Acellular pertussis vaccines. Pediatr Cli North Am 2000; 42: 309-335.*
3. *Cherry JD, Mortimer EA Jr, Hackell JG and the Multicenter Vaccine Study Groups: Clinical Trials in the United States and Japan with the Lederla-Takeda and Takeda acellular pertussis-diphtheria-tetanus (APDT) vaccines Dev Biol Stand 1991;73:51-??*
4. *Gustafsson L, Hollander HO, Olin P, Reizenstein E, Storsaeter J. A controlled trial of a two-component acellular, a five component acellular, and a whole cell pertussis vaccine. N Eng J Med 1996; 334: 349-355.*
5. *Greco D, Salmaso S, Mastranonio P, Giuliano M, Tozzi AE, Anemona A. A controlled trial of two acellular vaccines and one whole cell vaccine against pertussis. N Eng J Med 1996; 333: 1045-1050.*
6. *Schmitt HJ, Wirsing Von Konig CH, Neiss A, et al. Efficacy of acellular pertussis vaccine in early childhood after household exposre. JAMA 1996; 275: 37-41.*
7. *Decker MD, Edwards KM, Steinhoff MC, Rennels MB, Pichichero ME, Enflung JA. Comparison of 13 acellular pertussis vaccines: adverse reactions. Pediatrics 1995: 96 (Suppl): 557-566.*
8. *Taranger J, Trollfors B, Lagergard T. Mass vaccination with a monocomponent pertussis toxoid vaccine in a defined geographic area (abstract G-8). In Programs and Abstracts of the 37 th Interscience Conference of Antimicrobial Agents and Chemotherpy 1997, Toronto, Ontario, Canada.*
9. *Taranger J, Trollfors B, Lagergard T. Unchanged efficacy of a pertussis toxoid vaccine throughout the two years after the third vaccination of infants. Pediatr Infect Dis J 1997;16: 180-??*
10. *Ad hoc Group for the Study of Pertussis Vaccines: Placebo-controlled trial of two acellular pertussis vaccines in Sweden: Protective efficacy and adverse events. Lancet 1988; 1: 955-*
11. *Edwards KM, Decker MD, Barney S. Adult immunization with acellular pertussis vaccine JAMA 1993; 269: 53-56.*
12. *Keitel WA. Cellular and acellular pertussis vaccines in adults. Clin Infect Dis 199; 28(Suppl 2): S118-23.*
13. *Centers for Disease Control and Prevention: Diphteria, tetanus and pertussis: Recommended childhood immunization Schedule-United States. Recommendations for vaccine use and other preventive measures. Recommendations of the advisory committee on Immunization Practices (ACIP).MMWR Morb Mortal Wkly Rep1999; 48: 12s.*