Indications for Acellular Pertussis Vaccines in Adults: The Case for Selective, Rather than Universal, Recommendations

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The availability of acellular pertussis vaccines, which appear to be both safe and immunogenic in adults, will require that vaccine advisory groups make recommendations regarding their use. Pertussis in adults has negligible mortality but is responsible for about one-quarter of cases of chronic cough syndrome in young adults. Parents and other infant caregivers are important transmitters of pertussis to infants, the group who have the highest morbidity and mortality. Assuming that further studies confirm the immunogenicity and safety profile of acellular pertussis vaccines in adults, recommendations can be made for its use for universal immunization of adolescents, epidemic control, and strongly considered targeted adults who give care to infants. Factors that mitigate against including acellular pertussis vaccine in the recommended decennial tetanus-diphtheria toxoids booster include the short duration of the immune response to the acellular pertussis vaccine, increased cost and reactogenicity, and the lack of vaccine delivery systems to most adults. The elderly and the infirm, who are the current focus of adult immunization programs, are unlikely candidates for pertussis immunization. Therefore, recommendations for use of acellular pertussis vaccine in adults should be selective, rather than universal.

The changes sweeping the health care system in the United States favor preventive measures, including immunization. The Childhood Immunization Initiative has resulted in record immunization levels among U.S. children. Polio has been eradicated from the Western Hemisphere, and <100 children die annually from vaccine-preventable diseases. Unfortunately, adult immunizations receive much less attention, although >99% of deaths from vaccine-preventable disease occur in adults [1]. In the United States, an estimated 50,000–70,000 persons die each year from pneumococcal infection, influenza, and hepatitis B–related illness (table 1). To put this in perspective, this is equivalent to the total U.S. death toll in the Vietnam War and exceeds the annual deaths from AIDS or automobile accidents in the United States. Even the modest goals of achieving 60% immunization levels for pneumococcal and influenza vaccines among the elderly by the year 2000 can have an important impact, and if adult levels were to reach the pediatric standard (>90% immunization rates), >25,000 deaths per year could be prevented, despite the fact that the current vaccines have only limited effectiveness. The proposal to immunize all adults with acellular pertussis vaccine will need to be evaluated in comparison with other adult vaccine priorities.

First Principles of Vaccine Policy

The primary principles of vaccine policy are summarized in table 2. The main benefit of an immunization is to protect the recipient from mortality and/or morbidity. In addition, many vaccines have a societal benefit in reducing transmission to others, particularly those at high risk. Cost-benefit studies have demonstrated, for most of the universally recommended vaccines, significant savings both to the individual and to society, especially if the indirect costs are included. In some instances (smallpox and soon polio), widespread immunization can lead to eradication of the disease.

Determinants of Vaccine Priority

The priority given to use of a particular vaccine is the result of many factors (table 3). Chief among these is the importance of the disease, both to the individual and to society. The enthusiasm that greeted effective polio vaccines stands in contrast to the tepid response in the United States to the recently developed vaccines to prevent diarrhea due to rotaviruses. The effectiveness of a vaccine in preventing or modifying the disease and reducing colonization and transmission, the duration of benefit, and the safety profile are other major considerations influencing policy. Particularly for a disease of low mortality (e.g., pertussis in adults), cost-benefit analyses are major determinants of recommendations for vaccine use.

Feasibility issues are also important. For example, can the vaccine be combined with other antigens in an already accepted schedule, without additional vaccine-related morbidity? Do delivery systems exist for getting the vaccine to the targeted populations?

Pertussis Epidemiology in Adults

Factors involved in the epidemiology of pertussis in adults are summarized in table 4. Mild or asymptomatic infections
Table 1. Estimates of the impact of full utilization of the vaccines currently advocated for adults.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Estimated annual deaths*</th>
<th>Estimated vaccine efficacy²</th>
<th>Current vaccine utilization¹</th>
<th>Additional preventable deaths/y³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>20,000[^1]</td>
<td>70%</td>
<td>59%</td>
<td>5,740</td>
</tr>
<tr>
<td>Pneumococcal infection</td>
<td>40,000</td>
<td>60%</td>
<td>37%</td>
<td>15,120</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>5,000</td>
<td>90%</td>
<td>10%¹</td>
<td>4,050</td>
</tr>
<tr>
<td>Tetanus/diphtheria</td>
<td>&lt;25</td>
<td>99%</td>
<td>40%**</td>
<td>&lt;15</td>
</tr>
<tr>
<td>Traveler’s diseases (cholera, typhoid, Japanese encephalitis, yellow fever, poliomyelitis, rabies)</td>
<td>&lt;10</td>
<td>...</td>
<td>...</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Adult measles, mumps, and rubella</td>
<td>&lt;30</td>
<td>95%</td>
<td>Variable</td>
<td>&lt;30</td>
</tr>
</tbody>
</table>

NOTE. Adapted from [1].

* From [1–3].

² These composites from [1–3] indicate efficacy in immunocompetent adults. In the elderly and immunocompromised, efficacy estimates are lower.

¹ Percentage of targeted groups who are in compliance with current recommendations. These are overall composite rates from [2–4]. Rates are variable among different targeted groups.

³ (Potential additional vaccine utilization) × (estimated vaccine efficacy) × (estimated annual deaths).

[^1] Variable (range, 0–40,000).

[^2] Highly variable (1%–60%) among different target groups.

** Estimate based on seroprevalence data.

Table 2. First principles of vaccine policy.

- Protection of the individual
  - Mortality
  - Morbidity
- Societal benefit
  - Reduce transmission to others, particularly those at high risk
  - Reduce costs
  - Possibly eradicate disease

Table 3. Factors determining the priority of use of a particular vaccine.

- Importance of the disease
  - Individual
    - Incidence
    - Severity
  - Societal costs
    - Direct
    - Indirect
- Effectiveness of the vaccine
  - Prevention or modification of disease
  - Prevention of colonization/transmission
  - Duration of benefit
  - Vaccine safety and costs
  - Cost-benefit analyses
- Feasibility issues
  - Vaccine issues
    - Combination with other antigens
  - Ease of administration
  - Access to targeted populations

Table 4. Epidemiological factors involved in pertussis in adults.

- Limitations of case ascertainment
  - Culture is not sensitive; serodiagnosis is not standardized
  - Clinical definitions probably overlook milder cases
  - Studies of carriage (even transient) or mild disease are very limited and hard to do
- Parents and other caregivers are key in transmission to infants
- Adults are important transmitters in certain closed settings (e.g., colleges, nursing homes)
- The relative role of adults versus children in transmission is not well defined, but children appear to be most important in community outbreaks with AIDS in the early 1980s, before the availability of serotesting for HIV allowed a broader case definition and established more precise means of defining cases.

Settings in which adult transmission of pertussis is clearly important include the infection of infants by parents and other caregivers (because of the severity and mortality of infant pertussis, reduction of pertussis among infant caregivers deserves the highest priority when considering the use of acellular pertussis vaccines in adults) and outbreaks in closed adult populations (e.g., college students, nursing home residents).

In the general population, the relative role of adults versus children in transmission of pertussis is not well defined, but children appear to be more important in community outbreaks [6].

Clinical Significance of Pertussis in Adults

Although mortality from pertussis is a significant issue in infants, it is essentially nil in adults [8] (table 5). Pertussis in adults is a nuisance disease whose morbidity has been measured by the prolonged cough syndrome. This can occur at any age but has been best evaluated in young adults, among whom...
pertussis accounts for about one-fourth of those with cough lasting >2 weeks [6]. There is a paucity of data regarding the impact of adult pertussis on hospitalization, absenteeism, and costs (both medical and indirect). Other potential pertussis morbidity in adults (e.g., exacerbations in patients with chronic obstructive pulmonary disease) has not been well evaluated.

Goals of Pertussis Immunization of Adults

The primary benefit of immunizing adults is to reduce their risk of transmitting pertussis to infants (table 6), for whom the disease has significant morbidity and mortality, especially in the early months of life before active immunization is complete [8].

Another benefit of adult immunization (table 6) is to reduce the individual’s own risk of developing persistent cough syndrome. In addition, reducing transmission to older children or young adults (persons who should have been actively immunized per the standard pediatric schedule) will contribute to herd immunity as part of the overall reduction in and eventually eradication of pertussis.

Strategy Options to Prevent Infant Pertussis

Active immunization of infants, beginning at 2 months of age, remains the cornerstone of prevention of pertussis in infants. Unfortunately, the three-dose schedule (diphtheria-pertussis-tetanus, with whole cell or acellular pertussis vaccine) is not complete until age 6 months, leaving infants susceptible during their period of maximal risk for severe morbidity and mortality [5, 8]. Boosters for older children in their second year of life and at age 4–6 years are part of the standard pediatric schedule and are requirements for school entry in most states. The immunogenicity and good safety profile of acellular pertussis vaccines in older children and adults has led to strong consideration of additional boosters beyond school entry to further reduce transmission [6, 9]. Pertussis immunization of adolescents has the dual advantages of boosting individual protection at a time when immunity from preschool pertussis immunization has largely waned and enhancing immunity of persons as they enter the decades in which they are likely to become parents.

Pregnant women deserve special consideration for pertussis immunization, not only to reduce the risk of transmitting pertussis to their infants but also to boost maternal antibodies that might benefit their infants during the early months of life. Earlier studies of maternal pertussis immunization with whole cell pertussis vaccines were inconclusive regarding benefit [10–14], but these bear repeat study with the acellular pertussis vaccines. The reluctance to immunize pregnant women is waning in the face of accumulated evidence of safety, and the Advisory Committee on Immunization Practices now recommends that pregnant women receive a variety of killed antigens (tetanus-diphtheria toxoids, hepatitis B, influenza, and inactivated polio vaccines) for indicated reasons [15]. The acellular pertussis vaccines should be evaluated for safety and benefit in this population.

The exposure of infants to adults is primarily to parents and other providers of infant care, predominantly young adults, rather than to the elderly (the group targeted for influenza and pneumococcal vaccines). To reduce infant risk, it would seem prudent and more cost-effective to focus efforts of pertussis immunization on targeted young adult groups rather than to attempt to immunize all adults. Unfortunately, the duration of the antibody response to the acellular pertussis vaccines is short (~1–2 years), although it is hoped that protective efficacy will be of longer duration. However, it appears that repeated boosters will be necessary to ensure maximal protection. The feasibility of repeatedly immunizing young adults is a serious problem. An adolescent immunization visit is becoming a standard of pediatric practice, but there are no well-developed delivery systems to give boosters to older adults. Because new parents and their families are highly attuned to (and motivated to prevent) environmental risks to newborns, obstetrics caregivers and infant caregivers are the most obvious candidates among which to promote immunization of providers of infant care.

Impediments to Recommending Universal Acellular Pertussis Immunizations for Adults

Current morbidity and mortality data do not support a universal stand-alone recommendation for acellular pertussis vaccine in adults. There is need for more detailed information regarding age-specific incidence of disease in adults of all ages, together with an analysis of health care costs and epidemiological impact. There is also an important feasibility problem in that young adults, the most important group in terms of preventing transmission to children, do not get routine preventive care.

Table 6. Goals of pertussis immunization of adults.

| Primary goal: reduce transmission to infants who bear the brunt of pertussis mortality and morbidity |
| Secondary goals: |
| • Reduce morbidity in older children and young adults |
| • Reduce morbidity in all adults |
| • Develop herd immunity to reduce transmission |
with the notable exception of pregnant women. Therefore, to achieve universal immunization of adults with acellular pertussis vaccines, a major new delivery system would need to be implemented. This is unlikely, given the fact that adult pertussis has negligible mortality and does not command a high priority among adult preventive medicine practices.

The initially attractive idea of combining acellular pertussis vaccine with the adult tetanus-diphtheria toxoids vaccine has a number of drawbacks that would be difficult to reconcile. These include the following. First, the duration of serological immunity following immunization with acellular pertussis vaccine is very short relative to immunity to tetanus or diphtheria and would probably require boosters more often than the 10-year interval for tetanus-diphtheria toxoids recommended by most advisory groups. Second, toxicity issues of tetanus-diphtheria toxoids vaccine related to “over-immunization” include more severe local reactions and rare neurological complications (Guillain-Barré syndrome and brachial plexus neuritis) [16]. In addition, the recommendation for decennial boosters of tetanus-diphtheria toxoids vaccine has had low compliance and is not well supported by epidemiological data [17]. Cost-benefit studies suggest that a single midlife booster with tetanus-diphtheria toxoids is preferable, and several advisory groups (American College of Physicians and the American Academy of Family Practice) have recommended this as an alternative. If a single midlife booster becomes the standard, the need for frequent boosters with acellular pertussis vaccine will not be served by combining it with tetanus-diphtheria toxoids vaccine. Finally, it is estimated that about one-half of the use of tetanus-diphtheria toxoids vaccine is in the management of tetanus-prone wounds rather than as a result of the routine booster recommendation. The addition of diphtheria toxoid to tetanus toxoid was made at a negligible cost increment. The addition of acellular pertussis vaccine to tetanus-diphtheria toxoids is likely to result in a significant cost increase and may result in mild incremental toxicity. Currently, the level of awareness and concern about adult pertussis is low, both in the medical profession and in the populace. Acceptance of a more expensive (and possibly more reactogenic) combined vaccine will require favorable cost-benefit studies, as well as a major educational effort to inform the public and the medical community about adult pertussis and its consequences.

What Adult Uses of Acellular Pertussis Vaccine Can Be Recommended Now?

Assuming that studies confirm the immunogenicity and good safety profile of acellular pertussis vaccine in adults, current data support its use in the universal immunization of adolescents, presumably with tetanus-diphtheria toxoids and acellular pertussis vaccine (an adolescent immunization visit is becoming a standard of pediatric practice and will also focus on “catch-up” immunization against hepatitis B and varicella), and in epidemic control, presumably with an acellular pertussis stand-alone vaccine (state and local health departments will have a central role). Acellular pertussis vaccine should be strongly considered for targeted adults who give care to infants. The high annual rate of pertussis seroconversion among health care workers [6] suggests that they may be candidates for regular boosters.

What Do We Need to Know?

Studies that are needed to inform recommendations for pertussis immunization among other adult groups include age-specific morbidity data and vaccine efficacy studies with cost-benefit analyses; safety studies in pregnant women, together with an evaluation of maternal antibody protection of infants in the first months of life; evaluation of the importance of adult immunization in creating herd immunity; and evaluation of the role of certain subgroups, such as health care workers, day care staff, and teachers, in the epidemiology of pertussis.

Summary

The availability of acellular pertussis vaccines, which appear to be both safe and immunogenic in adults, will require that vaccine advisory groups make recommendations regarding their use. Pertussis in adults has negligible mortality but is responsible for about one-quarter of cases of chronic cough syndrome in young adults. Parents and other infant caregivers are important transmitters of pertussis to infants, the group who have the highest morbidity and mortality.

Assuming that further studies confirm the immunogenicity and safety profile of acellular pertussis vaccine in adults, recommendations can be made for its use for universal immunization of adolescents with a combined acellular pertussis vaccine and tetanus-diphtheria toxoids preparation and for epidemic control with acellular pertussis vaccine alone. It should be strongly considered for targeted adults who give care to infants (either acellular pertussis vaccine alone or in combination with tetanus-diphtheria toxoids). Factors that mitigate against including acellular pertussis vaccine in the recommended decennial booster with tetanus-diphtheria toxoids include the short duration of the immune response to acellular pertussis vaccine; increased cost and reactogenicity; further reduction in the already poor compliance with the recommendation for the decennial tetanus-diphtheria toxoids booster; and the lack of vaccine delivery systems to most young adults. Studies of pregnant women are strongly recommended, not only to evaluate the benefit of protecting the most important infant caregivers but also to evaluate maternal antibody protection of infants during their most vulnerable months. Other recommendations for adult uses of acellular pertussis vaccine will await cost-benefit studies. It is unlikely that the elderly and the infirm, who are the current focus of adult immunization programs, will be important targets for adult pertussis immunization. Therefore, the
recommendations for acellular pertussis vaccine use should be selective, rather than universal.

References