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# Rationale for Use of Tdap Booster Vaccines for Adolescent Immunization: Overview of Efficacy, Safety, and Clinical Use

William P. Hitchcock, MD

**Summary:** Pertussis is one of the only vaccine-preventable diseases with increasing incidence in the United States. The incidence of pertussis infection in adolescents is a growing concern; it can be a severe disease that may lead to significant morbidity and mortality when transmitted to susceptible populations (eg, infants). Experts have conceded that booster vaccination of adolescents may considerably decrease the incidence of pertussis infections in previously immunized, partially immunized, and nonimmunized populations. Studies in 2 tetanus, diphtheria, and acellular pertussis (Tdap) booster vaccines licensed by the Food and Drug Administration (FDA) have shown efficacy against pertussis disease and have demonstrated a safety profile comparable to tetanus and diphtheria vaccine (Td) in adolescents. Immunization schedules now include use of Tdap vaccines for preadolescent and adolescent populations to counter the increase in pertussis outbreaks. Challenges for clinicians include prompt recognition of pertussis symptoms, proper diagnosis using appropriate tools, and timely reporting of pertussis infections to surveillance bodies. Additional studies are needed to monitor trends of pertussis incidence after implementing the new vaccination schedule for adolescents. *Clin Pediatr.* 2006;45:785-794

## Introduction

**P**ertussis, caused by *Bordetella pertussis* and commonly known as whooping cough, is a highly contagious bacterial respiratory tract infection.<sup>1</sup> It is one of the only vaccine-preventable diseases with increasing

incidence in the United States. In the past century, pertussis infections were a major cause of mortality in children, with more than 200,000 cases of the illness reported each year. Following the introduction of acellular pertussis vaccines in the 1940s, the incidence of pertussis decreased dra-

matically to fewer than 5000 cases per year by 1968.<sup>2-4</sup> Despite high infant immunization rates, incidences of pertussis began to increase again in the 1980s in all age groups, with children and adolescents comprising the majority of cases.<sup>5,6</sup>

Reports of recent pertussis outbreaks have occurred mostly in middle- and high-school-aged children.<sup>7-10</sup> Thus, adolescents are now considered one of the main reservoirs of infection.<sup>1,11-13</sup> A consequence of pertussis outbreaks in the adolescent population is the infection of susceptible individuals who are either par-

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tially immunized against the disease or not vaccinated at all. Susceptible populations, such as infants, may experience severe symptoms, develop complications (eg, pneumonia or apnea), or require hospitalization.<sup>14</sup> In some situations, pertussis infections can lead to death in infants. Pertussis also appears to be a significant disease in the adolescent population, and the burden of the disease seems to increase with age.<sup>15</sup> In addition, pertussis in this population can be disruptive, and adolescents can experience se-

vere symptoms that may lead to insomnia and fainting from coughing fits.

To reduce this increasing epidemiologic trend, 2 pertussis booster vaccines (tetanus, diphtheria, and acellular pertussis [Tdap]) have been approved by the Food and Drug Administration (FDA);<sup>16,17</sup> their use may considerably decrease the number of pertussis infections.<sup>18</sup> In this article, an overview of pertussis incidence will be presented and a review of the efficacy and safety of acellular pertussis vaccines and

immunization recommendations for adolescents will be discussed.

### Increased Incidence of Pertussis

The incidence of reported cases of pertussis infection during the past 2 decades has been rising at a surprising rate (Figure 1).<sup>19,20</sup> The number of pertussis cases reported to the Centers for Disease Control and Prevention (CDC) in 2004 was 25,827.<sup>21</sup> Cases in adolescents comprised

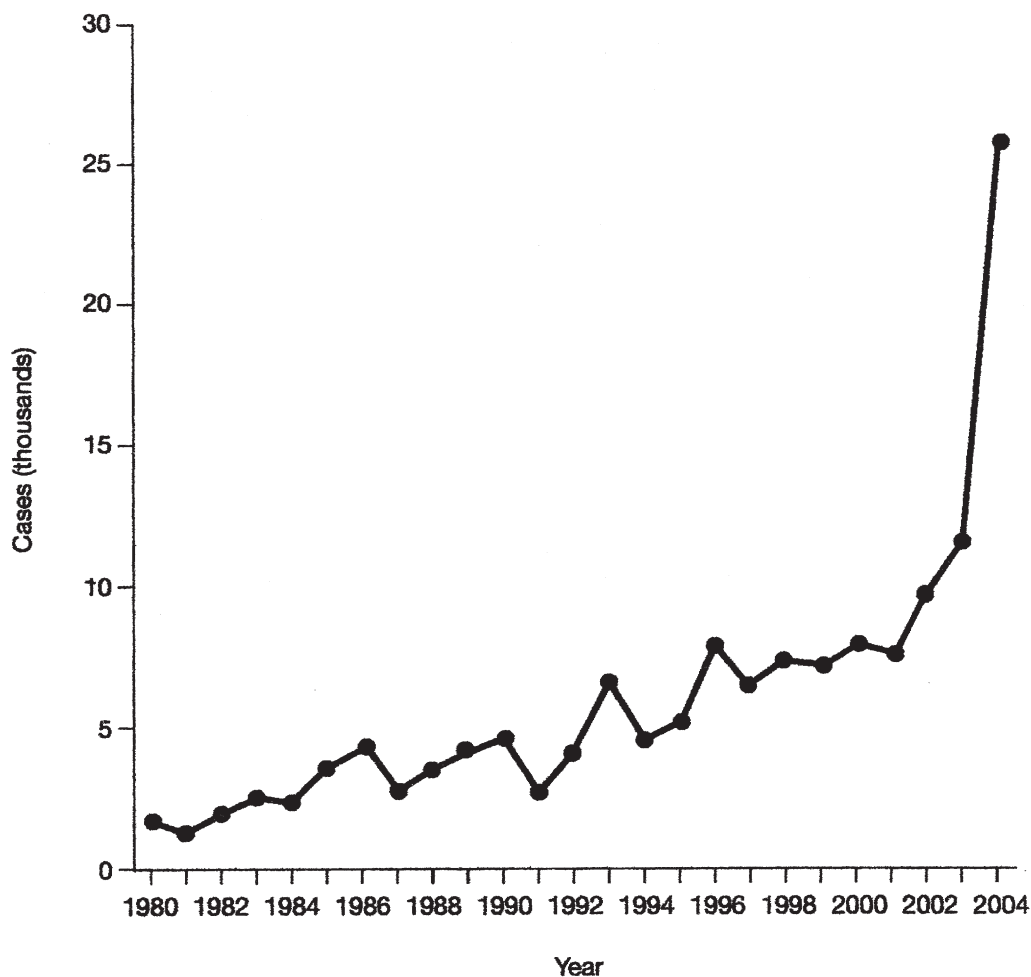


Figure 1. Reported cases of pertussis in the United States, 1980–2004.<sup>19–21</sup>

## Tdap Booster Vaccines for Adolescent Immunization

38% of pertussis reports, which translates into an incidence rate of 23.86 per 100,000 (Figure 2).<sup>22</sup> This rate in adolescents is higher than the rate in 1 to 4 year olds (1.4-fold higher), 5 to 9 year olds (nearly 2-fold higher), and in persons aged 20 years and older (almost 7-fold higher). In addition, the rate of pertussis occurrence among adolescents from 1997 to 2000 escalated 62% compared with rates reported from 1994 to 1996.<sup>23</sup> However, unlike the trend seen in adolescents, the incidence of pertussis has remained stable in children younger than 5 years, which may be the result of vaccine protection.<sup>4</sup>

Major factors contributing to increased cases reported in adoles-

cents are waning immunity from traditional early childhood vaccines (including whole-cell pertussis vaccines), presenting with atypical symptoms or subclinical infections that may go undiagnosed, and improving surveillance by health departments reporting pertussis infections.<sup>13,24-27</sup> The diminishing effects of immunity from previous infection or vaccination have triggered questions about the extent of protection from pertussis immunization.<sup>28</sup> Vaccination against pertussis was previously not reinforced after initial diphtheria, tetanus, acellular pertussis (DTaP) injections in early childhood.<sup>29,30</sup> It has been suggested that pertussis vaccine protection begins to decrease 1

year after the last injection is administered.<sup>29</sup> By the beginning of year 4, the vaccine's efficacy may not be adequate to provide protection from acquiring pertussis or passing the disease to more susceptible persons. In a study involving 824 adults, approximately one third of the study group no longer had pertussis antigens, also suggesting inadequate protection from pertussis vaccines administered during childhood.<sup>30</sup> In patients with pertussis who were previously vaccinated, the impending issue of revaccinating individuals to minimize epidemics or prevent transmission to vulnerable patients arises.<sup>12,28</sup>

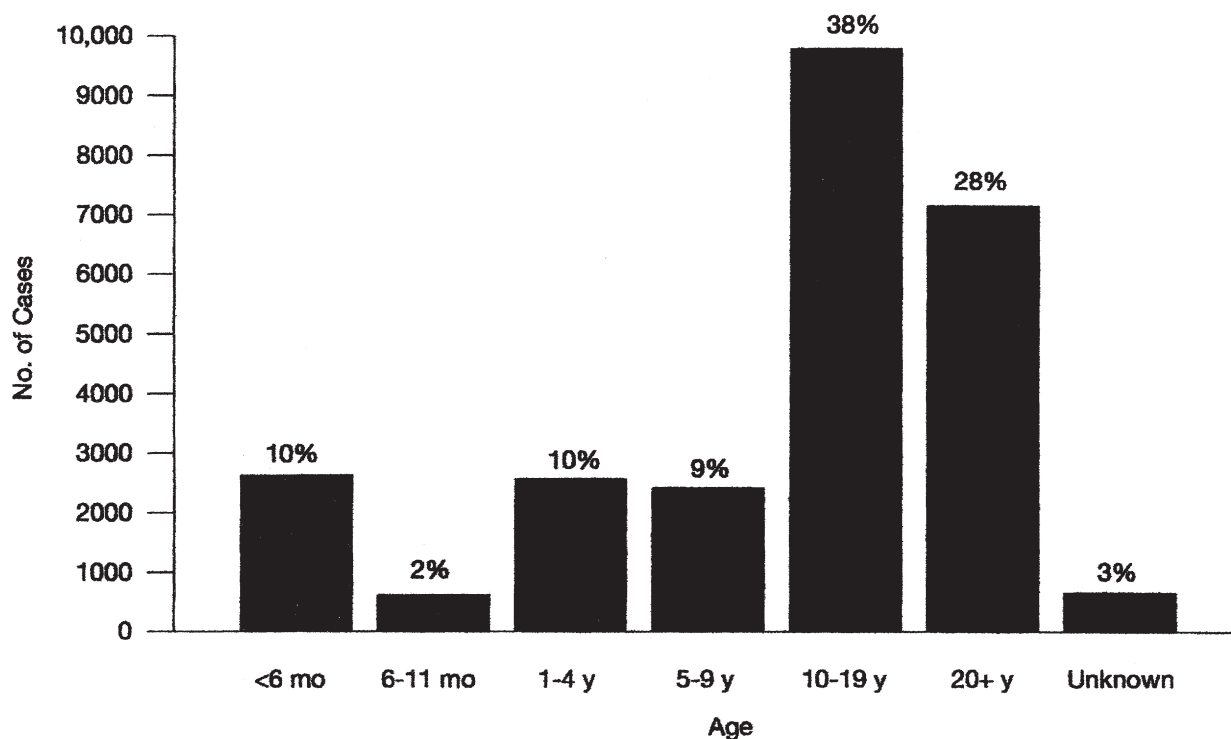


Figure 2. Percentage of reported cases of pertussis in 2004, according to age group.<sup>22</sup>

## Clinical Presentation of Pertussis

Pertussis first clinically manifests after an incubation period of 7 to 10 days, and then usually progresses into 3 stages.<sup>1</sup> The first stage, the catarrhal stage, includes nonspecific symptoms similar to the common cold (eg, runny nose, sneezing, low-grade fever, mild occasional cough). After 1 to 2 weeks, the paroxysmal stage, named after the characteristic cough, begins. Heavy inspirations (whoops) and posttussive vomiting may also occur at this time. This cough can last up to 10 weeks, which is why pertussis is sometimes referred to as the "100-day cough." When the symptoms subside, the patient enters the convalescent stage and eventually returns to normal in a few weeks to months.<sup>1</sup>

The symptoms of pertussis can vary from infant to adolescent populations, making it difficult to diagnose (Table 1).<sup>32</sup> Infected infants typically display the classic symptoms described previously, but adolescents present with more atypical symptoms that may be indistinguishable from other respiratory tract infections (eg, pneumonia caused by *Mycoplasma* or *Chlamydia*; sinus, larynx, or bronchus infections).<sup>33</sup> Chronic respiratory infections, such as asthma, or co-infections with bacteria or viruses may also be confused with pertussis infection. The clinical presentation of pertussis in adolescents may range from mild cough illness (that lasts longer than 7 days) to classic pertussis.<sup>1</sup> However, the inspiratory whoop is commonly absent, which may be how this disease is silently transmitted to persons who are partially immunized or not immunized at all against *B. pertussis*.<sup>1</sup>

Table 1

### COMPARISON OF SYMPTOMS BETWEEN INFANT AND ADOLESCENT POPULATIONS

Infants	Adolescents
Paroxysmal cough (especially in infants <6 months old)	Cough
Inspiratory, high-pitched whoop	Inspiratory high-pitched whoop (frequently absent)
Appear extremely ill, distressed	Apnea
Cyanotic appearance	Vomiting
Vomiting	
Apnea	
Pneumonia	

See references 1,15,24,31.

Morbidity and mortality rates in adolescents, and especially infants, are another issue of concern. Infants account for the majority of hospitalizations and severe complications, including death.<sup>31,34</sup> However, the effect of pertussis in adolescents can lead to considerable parent/caregiver concern or distress, disruption of daily family life, and financial burden of medical costs (eg, physician visit or hospitalization) and nonmedical expenses, such as lost wages or days missed from school.<sup>34,35-38</sup> The morbidity of pertussis in adolescents can be substantial, with prolonged cough illness lasting weeks to months.<sup>39</sup> Hospitalization and complications (eg, pneumonia and rib fractures) occur in 2% or less of reported cases. Approximate societal costs of pertussis infection for an adolescent may reach as high as \$800 per case, with nonmedical costs (eg, time missed from work for caregivers and costs associated

from other non-healthcare expenditures) accounting for nearly one third of total expenditures.<sup>34</sup> Complications from pertussis in adolescents are estimated to account for 46% of pertussis-related hospitalizations.<sup>40</sup> In 2002, adolescents in whom complications developed were estimated to incur \$1746 in hospitalization costs.

## Challenges in Diagnosing Pertussis Infection

A history of present illness and physical examination are normally used in identifying possible pertussis illness.<sup>1</sup> However, the gold standard in pertussis diagnosis is via culture of respiratory secretions. Although considered the preferred method, several factors contribute to proper isolation of the bacteria. Culture sensitivity depends on transportation, methodology, culture media, and storage of the acquired speci-

men.<sup>41</sup> Other problems that may affect results when culturing for the organism include a medical history of treatment with antibiotics that are effective against pertussis (eg, trimethoprim/sulfamethoxazole, erythromycin), prior vaccination, or specimen acquisition after the catarrhal stage of infection.<sup>1,41</sup>

Other laboratory tests used to diagnose pertussis infection include polymerase chain reaction (PCR) testing, direct fluorescent antibody (DFA) testing, serological testing, or complete blood count (CBC). PCR testing is a quick, precise technique, but drawbacks include unstandardized assays and the probability of receiving a false-positive result.<sup>1,42</sup> If PCR testing is used, it must be accompanied by a positive bacteria culture. DFA testing is useful in diagnosing pertussis, but should not be considered standard practice because of its unpredictable specificity and low precision. Serological testing may be useful in diagnosing pertussis, but it is not linked to disease immunity or levels of antibodies. Therefore, results from serology tests are complex to interpret. An elevated CBC with an increased lymphocyte count over 20,000 (lymphocytosis) is characteristically associated with typical pertussis infection, which may be problematic in patients with milder versions of the disease.<sup>1</sup> Possible inaccessibility and higher costs are caveats to consider for these laboratory tests.

Another obstacle for diagnosing pertussis is presentation of atypical symptoms during visits to clinics or physicians' offices. In 2 retrospective cohort studies, investigators assessed physician abilities to diagnose pertussis infections in 8235 children.<sup>43</sup> Results showed that consideration for

possible pertussis infection was significantly higher among pediatricians than general practitioners, but the percentage diagnosed by pediatricians was similar to that of general practitioners. In children older than 6 years, variables that affected diagnosis included parent awareness of pertussis exposure history, more symptoms, and longer duration of cough. Results from the merged data also showed fewer than half of the children in the study diagnosed for pertussis infection were reported to the surveillance body (24% met the surveillance pertussis case definition; 26% met the World Health Organization's [WHO's] pertussis case definition). Heininger and colleagues<sup>44</sup> conducted a 6-year, prospective, multicenter surveillance study of patients with confirmed pertussis diagnoses to assess clinical presentation in an outpatient setting. One sixth of patients presented with an uncharacteristically short duration (3 weeks) of cough symptoms. The study concluded that these patients would not be diagnosed as having pertussis according to the definition outlined by the WHO.

As with the WHO's definition, the CDC's current case definition of pertussis is not universally practical and may cause pertussis infections to be misdiagnosed or undiagnosed.<sup>33</sup> Patients who present with "mild pertussis" symptoms usually do not meet sign and symptom criteria described in the definition of classic pertussis infection. Current case definitions also do not allow for comparison of cases in multiple countries or evaluation of global epidemiology. In other instances, more than 1 visit is needed to correctly diagnose pertussis infection. Results from an outpatient study showed 42% of patients who visited local

public health units did not have a pertussis infection correctly diagnosed (according to surveillance case definition) by clinicians on the first visit.<sup>15</sup>

Finally, the adolescent population generally underutilizes physicians' offices for multiple reasons, including added autonomy, decreased access to medical care, and inadequate or no health insurance.<sup>45</sup> In 1994, adolescents (11–21 years old) accounted for less than 10% of total office visits. This challenge increases the probability that pertussis infections are less likely to be diagnosed by clinicians in the first place.

### **Strategies for Reducing the Incidence of Pertussis**

The key to preventing recurrence of pertussis infection and sustaining high rates of vaccine coverage is compliance with the recommended childhood and adolescent schedule.<sup>46</sup> Previous recommendations for pertussis vaccination consisted of a primary series of DTaP (5 injections), in which 4 doses were administered prior to the second birthday and the fifth dose is administered between 4 and 6 years of age. Despite these guidelines, coverage rates with 4 or more doses of DTaP remained below those of other vaccines, with the exception of pneumococcal vaccination.<sup>47</sup> In 2004, 85.5% of children received at least 4 doses of DTaP according to the CDC, which is lower than coverage rates for polio (91.6%), mumps, measles, rubella (MMR) (93%), hepatitis B (93.5%), and varicella (87.5%).

A promising method for controlling pertussis outbreaks is to reinoculate adolescents, frequently the source of epidemics.

In 2004, an expert scientific forum, the Global Pertussis Initiative,<sup>48</sup> analyzed trends in pertussis disease. The group suggested expanding the current vaccination schedule to include booster injections against pertussis in adolescents. Administering a pertussis booster vaccine in adolescents may help to manage rates of pertussis infections in this age group and minimize exposure of the disease in young infants. In addition, the booster vaccine may significantly counter the effects of waning immunity and spread of pertussis from close contact with peers.

### Tdap Booster Vaccination in Adolescents

In June 2005, a panel of immunization experts voted to propose use of newly licensed Tdap booster vaccines to address the issue of the rising pertussis incidence among adolescents in the

United States.<sup>49</sup> The Advisory Committee on Immunization Practices (ACIP) to the CDC now recommends that clinicians administer Tdap to patients at the 11- to 12-year visit and as "catch-up" for patients aged 13 to 18 years. The committee encourages adolescents who received the tetanus and diphtheria vaccine (Td) booster to further protect themselves by asking their clinicians to receive a dose of Tdap. In addition, in October 2005, the ACIP recommended that adults receive Tdap as the adult booster vaccine in place of Td booster vaccination.<sup>50</sup>

The FDA recently licensed 2 Tdap vaccines: Boostrix<sup>®</sup> (Glaxo-SmithKline Biologicals, Rixensart, Belgium) and Adacel<sup>®</sup> (Sanofi-Pasteur, Toronto, Ontario, Canada). Both products contain the same ingredients as their infant vaccine counterparts, but in reduced doses, and do not contain a preservative ingredient (Table 2).<sup>51,52</sup>

### Efficacy and Immunogenicity of Tdap Booster Vaccines

At this time, there are no head-to-head clinical trials comparing the efficacy of the 2 licensed booster vaccines. However, separate clinical trials comparing the booster vaccines with the Td vaccine have shown noninferiority in immunogenicity. In a study involving 2043 adolescents randomized to Tdap or Td vaccine, results showed similar immunogenicity (antibody geometric mean titers [GMTs]) for patients in both groups for diphtheria and tetanus toxins.<sup>53</sup> The Tdap vaccine administered to adolescents showed high pertussis efficacy compared with infants who received DTaP (pertussis GMTs were 3- to 6-fold higher in adolescents versus infants). In a subanalysis of a prospective acellular pertussis vaccine efficacy trial, results showed that GMTs remain detectable for 4 to 13 years in adolescents and adults after administration of acellular pertussis vac-

Table 2

#### COMPONENTS OF TDAP VACCINE PRODUCTS FOR ADOLESCENTS

Antigen	Boostrix <sup>®</sup> (3-component vaccine)	Adacel <sup>™</sup> (5-component vaccine)
T (Lf)	5.0	5.0
D (Lf)	2.5	2
ap (µg)	8 (PT)	2.5 (PT)
	8 (FHA)	5 (FHA)
	2.5 (PRN)	3 (PRN)
		5 (FIM 2 and 3)

See references 51 and 52.

ap = acellular pertussis; D = diphtheria; FHA = formaldehyde-treated filamentous hemagglutinin; FIM = fimbriae types 2 and 3; Lf = flocculation units; PRN = pertactin; PT = inactivated pertussis toxin; T = tetanus toxoids.

cine.<sup>54</sup> These data also suggested sustained levels of antibodies with the assay's limit of quantitation (LOQ) lasting for 2 to 9 years. The authors concluded that the booster vaccine provides adequate protection against *B. pertussis*.

Minh and colleagues<sup>55</sup> evaluated 510 adolescents (aged 10–13 years) in Finland who were assigned to receive either Tdap or Td vaccine. Results revealed that those who received Tdap showed significant increases in GMTs of antidipteria (100% of subjects in both groups with concentrations .1 IU/mL) and antitetanus (100% of subjects in both groups with concentrations .1 IU/mL) antibodies compared with those who received the Td vaccine (100% of subjects in both groups with concentrations .1 IU/mL), suggesting similar protection against diphtheria and tetanus. Immune responses for pertussis were comparable to infants who received DTaP. In another study, 4114 adolescents (aged 10–18 years) were randomized to receive Tdap or Td.<sup>56</sup> Similar to the Finland study,<sup>55</sup> the Tdap vaccine administered to adolescents had similar efficacy against diphtheria and tetanus compared with Td vaccines (>99.9% of subjects in both groups with concentrations .1 IU/mL).<sup>56</sup> In addition, efficacy against pertussis was comparable to infants who received DTaP.

In a study that included 466 adolescents (aged >12 years), results showed those who received a single dose of Tdap had lower antibody titers versus adolescents who received 1 dose of Td and acellular pertussis vaccine separately, but a vigorous response was observed in all patients.<sup>57</sup> The authors concluded similar efficacy of Tdap when compared with Td and acellular pertussis vaccines administered separately.

### *Safety and Reactogenicity of Tdap Booster Vaccines*

Before acellular vaccines, whole-cell pertussis vaccines were used to prevent serious pertussis illness.<sup>1</sup> Concerns over decreasing efficacy and incidence of adverse reactions (injection-site reaction, fever, convulsions, and encephalopathy) led to development of acellular pertussis vaccines in the 1990s. Acellular vaccines are not associated with the same degree of adverse reactions as whole-cell vaccines. Clinical trials have demonstrated Tdap vaccines to be similar in safety when used in combination with or as an alternative to Td vaccines.<sup>55–59</sup> Halperin and colleagues<sup>59</sup> studied 749 healthy adolescents and adults who received a 5-component acellular pertussis vaccine in combination with Td vaccine in a randomized, double-blind, controlled clinical trial. Results showed tolerability to the acellular pertussis vaccine with no increase in reported adverse event rates. Another study that included adolescents and adult participants (aged 18–64 years) also demonstrated a similar safety profile in patients receiving Tdap vaccine compared with patients in the Td vaccine group.<sup>58</sup> Similar safety profiles of Tdap booster vaccine compared with Td vaccine are supported by other studies.<sup>55–57</sup>

### **Implementation of Tdap Into an Adolescent Immunization Program**

Studies have shown that Tdap booster vaccines can provide additional protection against pertussis disease in addition to protection from tetanus and diphtheria.<sup>55–57,60</sup> Purdy and colleagues<sup>40</sup> suggested that vaccinating adolescents

(aged 10–19 years) would save \$0.3 to \$1.6 billion over a 10-year period, preventing 0.4 to 1.8 million cases of pertussis infection. In a literature review, Pichichero and Casey<sup>61</sup> also concluded that Tdap vaccines administered to adolescents would be a cost-effective strategy and provide cost-benefit rationalization to society.

Based on the epidemiologic changes in pertussis and these cost-benefit analyses, the ACIP has recommended booster vaccination against pertussis infection.<sup>46</sup> Implementing Tdap booster vaccines into the adolescent immunization schedule is not expected to further complicate it.<sup>46</sup> Tdap vaccine can easily replace administration of Td vaccine in the adolescent immunization schedule (Figure 3) and also would be administered with other routine vaccinations. For adolescents, the ACIP recommends administration of Tdap booster vaccine starting at 11 years of age<sup>49</sup> and that adolescents who received the Td vaccine booster receive Tdap booster vaccine for added protection preferable with a 5-year interval.<sup>62</sup> The role of clinicians in the pertussis crisis may need to be adjusted to better address increasing pertussis outbreaks. It is necessary for clinicians to actively educate adolescents and their parents about pertussis and booster vaccines. In addition, clinicians should take a larger role in incorporating the ACIP's recommendations into their standards of care by reviewing immunization records and administering Tdap booster vaccines if indicated.

### **Conclusions**

The incidence of pertussis infection in the adolescent popula-

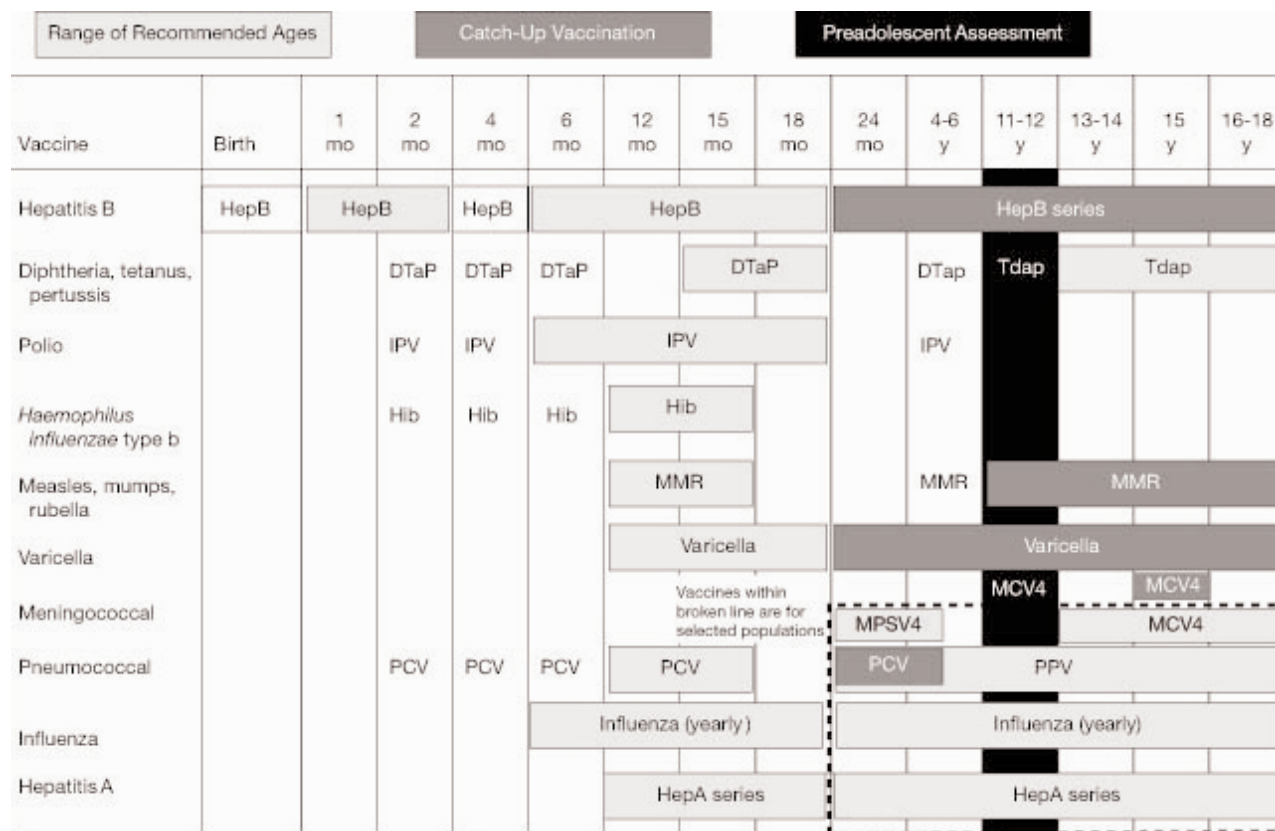


Figure 3. Preadolescent and adolescent immunization schedule with proposed Tdap placement in adolescents aged 11 to 18 years (adapted from reference 46).

tion is of growing concern. In addition to medical and nonmedical costs that are an economic burden affecting society, the seriousness of the disease and the insidious transmission from adolescents to susceptible populations such as infants can lead to serious complications, including death. Challenges for clinicians include recognizing and diagnosing symptoms of pertussis, reporting pertussis infections to surveillance bodies, and minimizing spread of infection. A booster vaccination with Tdap can have a major impact on reducing contraction of the illness, diminishing reservoirs of pertussis, and minimizing trans-

mission of the disease to partially immunized or unimmunized populations. Tdap booster vaccines are generally well tolerated and have comparable efficacy to Td vaccines. The use of the Tdap booster vaccine can be easily incorporated into the adolescent immunization schedule by having it replace the Td vaccine. Using the Tdap booster vaccine would not result in additional visits, because it would be included with other scheduled immunizations. Further studies are needed to monitor trends in pertussis incidence after implementing a new vaccination schedule.

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