New, and Some Not-so-New, Vaccines for Adolescents and Diseases They Prevent

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ABSTRACT
Adolescents in the United States now have the opportunity to receive new vaccines that prevent invasive meningococcal infections, pertussis (whooping cough), and cervical cancer. Except for their potential to cause serious illness, these infections could not be more different. Their incidence ranges from extremely low to quite high. Early clinical manifestations of infection range from none to life-threatening illness. Two of the vaccines are similar to those already in use, whereas 1 is completely new. In conjunction with the 4 vaccines previously recommended for adolescents (the tetanus and diphtheria booster, hepatitis B, measles-mumps-rubella, and varicella), the 3 new vaccines (meningococcal, human papillomavirus, and the tetanus-diphtheria-pertussis booster [which replaced the tetanus-diphtheria booster]) bring the number recommended for adolescents to 6. In this article, we describe key characteristics of the 3 new vaccines and infections they were designed to prevent. We also briefly discuss other vaccines recommended for all adolescents who have not already received them and new vaccines that are still under development.

BEFORE 2005, THE only vaccine routinely recommended for healthy adolescents who had received all recommended childhood vaccinations was the tetanus and diphtheria toxoids (Td) booster.1 Three other vaccines (measles-mumps-rubella [MMR], hepatitis B, and varicella) were used as “catch-up vaccinations” for adolescents who did not receive these vaccines as children (and, in the case of varicella, had not had chickenpox). The second dose of MMR vaccine was first recommended for adolescents by the American Academy of Pediatrics (AAP) in 1989,2 whereas hepatitis B and varicella vaccines were first recommended for this age group in 1995 and 1996, respectively.3,4 These recommendations were consolidated in 1996, when the Advisory Committee on Immunization Practices (ACIP), AAP, American Academy of Family Physicians, and American Medical Association harmonized their recommendations. These organizations suggested that the recommended immunizations and other preventive services be delivered at a routine preventive visit at 11 to 12 years of age.1

Three new vaccines intended primarily for adolescents are now available. The first of these, a new vaccine effective for the prevention of disease caused by Neisseria meningitidis, was licensed in the United States in 2005 and officially recommended for use when the ACIP recommendations were published in May of that year.5,6 Two vaccines for adolescents, both of which prevent infections with Bordetella pertussis, tetanus, and diphtheria, were licensed in May and June of 2005, respectively, and recommendations were published in early 2006.7 A vaccine that prevents human papillomavirus (HPV), the cause of cervical cancer, was licensed in May 2006, and recommendations for its use were published in March 2007.8

All the diseases against which these new vaccines offer protection are potentially serious, but the clinical course for each could hardly be more different. A fulminant life-threatening course is common with disease caused by N meningitidis but extremely rare among adolescents and adults infected with B pertussis and does not occur with HPV infection. Pertussis rarely causes serious complications in adolescents but does cause substantial morbidity. Moreover, adolescents may transmit pertussis to infants who are at risk for death if they develop pertussis. HPV infections can cause genital warts and abnormal Papanicolaou test results in adolescents and adults, and persistent HPV infection...
can result in cervical cancer, usually many years after the initial infection. Similarly distinct is the past and present incidence of the diseases that are prevented by these vaccines (Table 1).

In this article, we focus primarily on these new vaccines and discuss the diseases the vaccines prevent and the similarities and differences among the vaccines themselves. We also briefly discuss and compare these vaccines with the other vaccines (MMR, hepatitis B, and varicella) recommended for adolescents who have not previously received them and future vaccines that are still under development. A summary of vaccines in later stages of development as well as those recently licensed in the United States can be found at http://aapredbook.aappublications.org/news/vaccstatus.shtml.

**THE DISEASES AND THE VACCINES THAT PREVENT THEM**

### Invasive Meningococcal Infections

**Etiology, Pathogenesis, and Clinical Manifestations**

*N. meningitidis* is a Gram-negative diplococci that is classified antigenically into 13 distinct serogroups on the basis of their capsular polysaccharides. Worldwide, serogroups B, C, Y, and W-135 account for the majority of cases, although serogroup A disease is rare in the United States. Risk factors for infection include household exposure, crowding, concurrent upper respiratory tract infections, and active and passive smoking. *N. meningitidis* colonizes the nasopharynx in 5% to 10% of the population, but only a minority of strains are pathogenic, and fewer than 1% of carriers develop disease. Transmission occurs when close, mouth-to-mouth contact permits the exchange of salivary secretions. Although close contacts of people who are ill with meningococcal disease are at much higher risk, most people contract the bacteria from asymptomatic carriers. When *N. meningitidis* invades the bloodstream, it can cause a serious, rapidly progressing, and sometimes fatal disease. *N. meningitidis* can be isolated from the bloodstream in up to three fourths of patients, but meningococcal sepsis, which is also called meningococcemia, occurs in only 5% to 20% of patients. Meningeal infection results from hematogenous spread and occurs in approximately one half of patients. Pneumonia is the third most common presentation, occurring in 5% to 15% of patients. The onset of disease is often abrupt, and its course is rapid. The death rate is 10% to 14%, and an additional 11% to 19% of survivors suffer serious sequelae, including deafness, neurologic deficit, or limb loss.

**Epidemiology**

Annually, 1400 to 2800 cases of invasive meningococcal disease occur in the United States. In the past 5 years, serogroups B, C, and Y each caused approximately one third of disease cases. Disease is seasonal, with cases peaking in December and January. Most cases (97%) are sporadic; only a minority (3%) are associated with outbreaks. In 1990–2002, the incidence of invasive meningococcal disease in the United States ranged from 0.5 to 1.1 cases per 100,000 population. Disease rates among infants <1 year old (9.2 per 100,000); the rate for youth 11 to 19 years old (1.2 per 100,000) was also higher than that for the general population (Fig 1). College freshmen living in dormitories are at a higher risk than college students in general. Although the disease is quite rare, every case triggers a costly public health response.

**Vaccines**

The 2 vaccines available in the United States are derived from and protect against serogroups A, C, Y, and W-135 but not serogroup B, for which there is no licensed

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**TABLE 1**

Annual Reported Cases of Disease Occurrences in the United States in the 20th and 21st Centuries

<table>
<thead>
<tr>
<th>Disease</th>
<th>Maximum Reported Cases, 20th Century (All Ages)</th>
<th>Most Recently Reported Cases, 21st Century</th>
<th>NA</th>
<th>NA</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancella</td>
<td>4,000,000</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Measles</td>
<td>503,282</td>
<td>65</td>
<td>21</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>287,000</td>
<td>5119</td>
<td>11</td>
<td>514</td>
<td></td>
</tr>
<tr>
<td>Diphtheria</td>
<td>175,885</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mumps</td>
<td>152,209</td>
<td>314</td>
<td>75</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Pertussis</td>
<td>147,271</td>
<td>25,616</td>
<td>7028</td>
<td>3944</td>
<td></td>
</tr>
<tr>
<td>Rubella</td>
<td>47,745</td>
<td>11</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>NA</td>
<td>12,085</td>
<td>NA</td>
<td>115</td>
<td></td>
</tr>
<tr>
<td>Invasive meningococcal infection</td>
<td>3525</td>
<td>1245</td>
<td>140</td>
<td>261</td>
<td></td>
</tr>
<tr>
<td>Tetanus</td>
<td>1314</td>
<td>27</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

NA indicates not applicable.


b Unless otherwise noted, data are from Centers for Disease Control and Prevention. MMWR Recomm Rep. 2005;54:1–92.

¢ National surveillance for varicella cases remains incomplete, although active surveillance in limited geographic areas demonstrated that varicella cases decreased from 71% to 84% between 1995 and 2000.

d No historical data are available.

Table adapted from Centers for Disease Control and Prevention. Source: Active Bacterial Core surveillance data (adapted from Bilukha OO, Rosenstein N; National Center for Infectious Diseases, Centers for Disease Control and Prevention. MMWR Recomm Rep. 2005;54[RR-7]:1–21).
TABLE 2  Comparison of Menomune and Menactra Licensed for Use in Adolescents in the United States

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Menomune (MPSV4)</th>
<th>Menactra (MCV4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year licensed</td>
<td>1981</td>
<td>2005</td>
</tr>
<tr>
<td>Age indication, y</td>
<td>≥ 2</td>
<td>11–55</td>
</tr>
<tr>
<td>Private-sector cost per dose, US dollarsa</td>
<td>86</td>
<td>82</td>
</tr>
<tr>
<td>Route/dose</td>
<td>Subcutaneous/single</td>
<td>Intramuscular/single</td>
</tr>
<tr>
<td>Immunogenicity/efficacy</td>
<td>Good short-term (3–5 y) protection (85%) in older children and adults; antibody levels after 3 y are lower than those for MCV4.</td>
<td>Higher antibody levels after 3 y than those for MPSV4; potential for induction of T-cell memory on subsequent boosting potential, reduction of immune tolerance induction on repeated exposure, and reduction of nasal carriage</td>
</tr>
<tr>
<td>Adverse events after vaccination</td>
<td>Severe allergic and neurologic reactions in &lt;0.1 per 100 000 population; systemic adverse events are similar to those with MCV4; local adverse events (redness, swelling, induration, and pain) are significantly less common than with MCV4.</td>
<td>Small increased risk of Guillain-Barré syndrome after receipt of MCV4. Systemic adverse events are similar to those with MPSV4; local adverse events (redness, swelling, induration, and pain) are significantly more common than with MCV4</td>
</tr>
<tr>
<td>ACIP recommendations</td>
<td>Groups increasingly at risk for meningococcal diseaseb</td>
<td>Children 11–12 y old at the recommended health care visit; previously unvaccinated persons 11–18 y old at the earliest possible health care visit; college freshmen living in dormitories and other groups increasingly at risk for meningococcal diseaseb</td>
</tr>
</tbody>
</table>

a Based on order of 100 doses, as of March 2006.
b Other persons at high risk include microbiologists who are routinely exposed to isolates of N meningitidis, military recruits, those who travel to or reside in countries in which N meningitidis is hyperendemic or epidemic (particularly if contact with the local population will be prolonged), and those who have anatomic or functional asplenia or terminal complement component deficiencies.

vaccine. Table 2 highlights the difference between these 2 vaccines. The older vaccine is a meningococcal polysaccharide vaccine (MPSV4), known by its trade name Menomune (sanofi pasteur: Swiftwater, PA). The newer vaccine, a meningococcal polysaccharide-protein conjugate vaccine (MCV4; trade-named Menactra [sanofi pasteur: Swiftwater, PA]), is similar to Haemophilus influenzae type b conjugate vaccine, pneumococcal conjugate vaccine, and the serogroup C meningococcal conjugate vaccines, which have been used routinely in the United Kingdom since 2001. Menactra was created by bonding the polysaccharide, which normally induces a weak antibody response, to diphtheria protein, which is a more potent source of antigen stimulation. Improved immunologic priming and antibody persistence are important aspects of long-term protection induced by conjugate vaccines, as is their ability to prevent nasal carriage. On the basis of evaluation of other conjugate vaccines, we hope that MCV4 will have a longer duration of protection than that of MPSV4. In times of MCV4 shortages, MPSV4 can be substituted for the vaccination of persons who have brief elevations in their risk for meningococcal disease (eg, travelers to areas in which meningococcal disease is hyperendemic or epidemic). In January 2005, the ACIP recommended routine vaccination with MCV4 for children who were 11 to 12 years old and catch-up vaccination of adolescents who have not already been vaccinated when they enter high school (ie, at ~15 years old) or as college freshmen (if they live in dormitories). Vaccination was also recommended for other persons at increased risk for meningococcal disease (ie, military recruits, travelers to areas in which meningococcal disease is hyperendemic or epidemic, microbiologists who are routinely exposed to isolates of N meningitidis, persons with anatomic or functional asplenia, and persons with terminal complement component deficiencies). ACIP recommendations and similar ones by the AAP and American Academy of Family Physicians have been published. These recommendations have now been expanded to include previously unvaccinated children who are 11 to 18 years old.

The public health community faced a number of challenges in the first 18 months after ACIP recommendations were published. Shortly after the recommendations were published, demand outpaced supply and led to temporary shortages of the vaccine. The demand seems to have been caused by vaccination of adolescents of all ages during to the seasonal increase of visits to health care providers that occurs each summer. During the summer of 2005 and again in 2006, the CDC recommended that providers defer vaccination of 11- to 12-year-olds but continue to vaccinate adolescents at high school entry who had not previously received MCV4 and college freshmen living in dormitories. Routine recommendations for adolescent vaccination with meningococcal conjugate vaccine were reinstated in November 2006 when supply improved. In October 2005, reports that indicated a possible association between receipt of MCV4 and Guillain-Barré syndrome (GBS) were made to the Vaccine Adverse Event Reporting System. Available data suggest a small increased risk for GBS after vaccination, but the inherent limitations of the passive reporting system and the uncertainty regarding background incidence rates for GBS require that these findings be viewed with caution. Because of the ongoing risk
for meningococcal disease and limitations of the risk data, the CDC continues to recommend routine vaccination with meningococcal conjugate vaccine for persons in target groups described by the ACIP, but persons with a history of GBS should not receive meningococcal conjugate vaccine unless they are at a substantially elevated risk for meningococcal disease.21

Pertussis

Etiology, Pathogenesis, and Clinical Manifestations

B pertussis is a fastidious Gram-negative coccobacillus that has no known animal or environmental reservoir20 or clinically significant carrier state.21 However, B pertussis infections are highly communicable, especially during the catarrhal and early paroxysmal phases of illness, and attack rates can be as high as 80% to 90% among nonimmune household contacts. Young infants (<6 months old) have the highest incidence of pertussis and are the most likely age group to have hospitalizations, complications, or death related to the disease.22 In contrast, hospitalization and deaths related to pertussis are rarely reported for adolescents and adults.7

The clinical presentation of pertussis is influenced by a number of factors including age, level of immunity, and use of antimicrobial agents early in the course of the illness.23,24 After an incubation period of 7 to 10 days, the disease sometimes progresses through 3 classic phases: catarrhal, paroxysmal, and convalescent. Illness often begins with mild cold-like symptoms that include coryza and a mild cough.24 It may progress over a period of 1 to 2 weeks to classic paroxysmal spasms of coughing, posttussive vomiting, and whooping.20,24 Among adolescents reported to have pertussis, the most common serious manifestations include pneumonia (2%), rib fractures (1%), and loss of consciousness (1%). A prolonged cough is a common feature of pertussis in adolescents, whereas a classic whoop is much less common. In Massachusetts, 38% of adolescents with pertussis had been coughing for at least 1 month at the time of diagnosis.7 In a Canadian study, 47% of adolescents with pertussis reported a cough duration of >9 weeks.25 Adolescents with pertussis and the people who care for them frequently miss school or work; for instance, in a study performed in Massachusetts, 83% of adolescents missed a mean of 5.5 days of school, and 43% of their parents missed a mean of 2.4 days of work.26 Unfortunately, there are few distinguishing epidemiologic or clinical characteristics of pertussis in adolescents or adults except for prolonged illness with cough.24 Diagnosis, therefore, relies on culture and single serologic testing but limited availability and lack of sensitivity, specificity, or both. Recently, polymerase chain reaction, in combination with cultures (to determine antibiotic susceptibility), has proven to be useful for appropriate clinical management and public health response.27 The use of improved diagnostic tests, in conjunction with surveillance, antibiotic prophylaxis, isolation of infected cases, and enhanced communication and education, offers the prospect of better control of pertussis outbreaks.28

Epidemiology

Pertussis vaccines administered to infants and young children in the United States have been effective at reducing the incidence of childhood pertussis cases and deaths. After the introduction of routine childhood immunization against pertussis in the 1940s and 1950s, the number of reported cases fell to a nadir of 1010 (0.5 per 100 000 population) in 1976 (Fig 2).29,30 Since then, the number of reported cases has increased, reaching 8.9 per 100 000 population in 2004 and 2005.31 Of the 25 827 cases of pertussis reported in the United States in 2004, 8897 (34%) were in adolescents 11 to 18 years old.7

It is unclear as to what proportion of the increase is attributable to an actual increase in cases and how much is attributable to better recognition, wider availability of diagnostic tests, or a higher proportion being reported to public health authorities.32 At least part of the increase is attributable to waning immunity, which leads to increased susceptibility to pertussis ~5 to 10 years after completing childhood vaccination,33 and there is also little doubt that there are many more cases than reported. For example, a study with careful follow-up revealed the incidence of pertussis among persons who were ≥15 years old ranged from 370 to 450 cases per 100 000 person-years.29 Data from Massachusetts are likely to provide a more accurate picture of the epidemiology of the disease, because the state has especially good pertussis surveillance and uses a validated serology test to confirm cases in adolescents and adults. In 2004, Massachusetts reported 10% of the total adolescent pertussis cases in the United States, although it accounted for only 2% of the adolescent population (CDC, unpublished data, 2006). During 1996–2004, the rate of pertussis among adolescents 11 to 18 years old in Massachusetts was 93 per 100 000. By contrast, the incidence among adolescents in the rest of the United States (excluding Massachusetts) was 7.3 per 100 000 population.7

Vaccines

During 2005, 2 tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (TdaP) products formulated for use in adolescents (and, for 1 product, use in adults) were licensed in the United States. Table 3 high-
TABLE 3  Comparison of Boostrix and Adacel, Adsorbed Products Licensed in the United States

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Boostrix</th>
<th>Adacel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic name</td>
<td>Tdap</td>
<td>Tdap</td>
</tr>
<tr>
<td>Pertussis antigens&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Pertussis toxoid, μg</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>Filamentous hemagglutinin, μg</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>Pertactin, μg</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>Fimbriae (types 2 and 3), μg</td>
<td>—</td>
</tr>
<tr>
<td>Year licensed</td>
<td>2005</td>
<td>2005</td>
</tr>
<tr>
<td>Age indication, y</td>
<td>10–18</td>
<td>11–64</td>
</tr>
<tr>
<td>Private-sector cost per dose, US dollars</td>
<td>34.00</td>
<td>33.50</td>
</tr>
<tr>
<td>Route/dose</td>
<td>Intramuscular (preferably into the deltoid muscle)/0.5 mL</td>
<td>Intramuscular (preferably into the deltoid muscle)/0.5 mL</td>
</tr>
<tr>
<td>Immunogenicity/efficacy</td>
<td>Tetanus and diphtheria: seroprotective and booster response rates after Tdap were noninferior to Td; pertussis: immune responses to vaccine pertussis antigens in adolescents vaccinated with a dose of Tdap were noninferior to responses in infants vaccinated with 3 doses of DTaP with the same antigens during clinical efficacy trial; adolescent booster responses were adequate</td>
<td>Tetanus and diphtheria: seroprotective and booster response rates after Tdap were noninferior to Td; pertussis: immune responses to vaccine pertussis antigens in adolescents vaccinated with a dose of Tdap were noninferior to responses in infants vaccinated with 3 doses of DTaP with the same antigens during clinical efficacy trial; adolescent booster responses were adequate</td>
</tr>
<tr>
<td>Adverse events after vaccination</td>
<td>Pain at the injection site is more common (75%) than with Td (71%); grade ≥2 headache (16%) more frequent than with Td (13%); comparable rates for other systemic events</td>
<td>Pain at the injection site is more common (78%) than with Td (71%); fever of ≥100.4°F (5%) is more frequent than with Td (3%); comparable rates for other systemic events</td>
</tr>
<tr>
<td>Recommended (routine use)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Adolescents 11–18 y old should receive a single dose of Tdap; the preferred age is 11–12 y</td>
<td>Adolescents 11–18 y old should receive a single dose of Tdap; the preferred age is 11–12 y</td>
</tr>
</tbody>
</table>


<sup>b</sup> Both vaccines contain the same amount of tetanus toxoid (5 limits of flocculation [Lf] per unit). Adacel contains 2 Lf of diphtheria toxoid, whereas Boostrix contains 2.5 Lf of diphtheria toxoid.

<sup>c</sup> A single dose of Adacel is also recommended for adults <65 years old. Boostrix is not licensed for those who are >19 years old.

lights the differences between these 2 vaccines. Boostrix (GlaxoSmiithKline, Philadelphia, PA) was licensed on May 3, 2005, for use in children 10 to 18 years old, and Adacel (sanofi pasteur, Swiltwater, PA) was licensed on June 10, 2005, for use in children and adults from 11 to 64 years old. The 2 vaccines contain similar tetanus, diphtheria, and pertussis components to those included in the childhood diphtheria and tetanus toxoids and acellular pertussis vaccines (DTaP), although some antigens are present in reduced amounts. The tetanus and diphtheria toxoid composition of Tdap are both lower than that of childhood DTaP but similar to that of licensed adult formulations of Td. A single Tdap booster was recommended to replace the Td booster previously recommended for all adolescents.<sup>7,34</sup> The preferred age for this booster is 11 to 12 years; however, all 11- to 18-year-old adolescents who have not received Td or Tdap should receive a single dose of Tdap. Among adolescents who already received Td, Tdap is encouraged 5 or more years after the Td dose to reduce the risk for local and systemic reactions after Tdap vaccination. However, vaccine providers can administer Tdap after Td at shorter intervals, particularly when the benefit of protecting against pertussis is likely to be increased (eg, during outbreaks or periods of increased pertussis activity in the community). The safety of an interval as short as ~2 years between Td and Tdap is supported by a Canadian study among children and adolescents.<sup>2,35</sup> Providers should administer Tdap and MCV4 to 11- to 18-year-old adolescents during the same visit if both vaccines are indicated and available.<sup>3</sup>

Infections Caused by HPV

**Epidemiology**

HPV is the most common sexually transmitted infection in the United States and around the world.<sup>36,37</sup> HPV acquisition often occurs within the first few years after sexual debut. In 15- to 24-year-olds, the average annual incidence of HPV infection is ~12 000 per 100 000, with prevalence reaching ~25 000 per 100 000 for young adults in their early 20s.<sup>37</sup> The total number of new infections in the United States among those who are 15 to 44 years old is estimated to be ~6.2 million, with 4.6 million of these (74%) occurring in those who are 15 to 24 years old. Modeling estimates suggest that up to 80% of women will acquire HPV infection by the age of 50.<sup>38</sup> Increased risk of infection is associated with early initiation of sexual activity and multiple sex partners.

The time between initial HPV infection and cervical cancer can be several decades. Cervical cancer was once one of the most common causes of cancer death for American women, and it remains the second most common cancer in women in less-developed countries, where cervical cancer screening and treatment are not widely available. Worldwide, there are an estimated 274 000 deaths per year.<sup>39</sup> In the United States, primarily because of the screening that detects precancerous le-
TABLE 4  Comparison of Gardasil and Cervarix (HPV Vaccines)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Gardasil (Merck, Whitehouse Station, NJ)a</th>
<th>Cervarix (GlaxoSmithKline)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbreviated name</td>
<td>Quadrivalent HPV</td>
<td>Bivalent HPV</td>
</tr>
<tr>
<td>Types</td>
<td>6, 11, 16, 18 adjuvanted with alum (aluminum hydroxide phosphate sulfate)</td>
<td>16, 18 adjuvanted with aluminum hydroxide and monophosphoryl lipid A</td>
</tr>
<tr>
<td>Year licensedc</td>
<td>2006</td>
<td>Not yet applied for</td>
</tr>
<tr>
<td>Age indication, y</td>
<td>9–26</td>
<td>NA</td>
</tr>
<tr>
<td>Private-sector cost per dose, US dollars</td>
<td>120</td>
<td>NA</td>
</tr>
<tr>
<td>Route/dose</td>
<td>3 intramuscular doses/second and third doses to be given 2 and 6 mo, respectively, after the first</td>
<td>3 intramuscular doses/second and third doses to be given 1 and 6 mo, respectively, after the first</td>
</tr>
<tr>
<td>Efficacy</td>
<td>100% against HPV 16- or 18-related CIN and two thirds against AIS, 98.9% against HPV 6-, 11-, 16-, or 18-related genital wartsa</td>
<td>100% against HPV 16- or 18-related CIN</td>
</tr>
<tr>
<td>Adverse events after vaccination</td>
<td>Vaccine-related adverse effects were seen in &gt;1% of females and significantly more common than in the placebo group include pain, swelling, erythema, pruritis, and fever</td>
<td>Injection-site symptoms systemic reactions: no significant difference between the vaccine and placebo groups</td>
</tr>
<tr>
<td>ACIP recommendations</td>
<td>Girls 11–12 y old at the time of the early adolescent visit (as young as 9 y old, if desired); catch-up recommended for those 13 to 26 y old who have not been previously vaccinated or who have not completed the full vaccine series</td>
<td>NA</td>
</tr>
</tbody>
</table>

CIN indicates cervical intraepithelial neoplasia; AIS, adenocarcinoma in situ.

a Adapted from the Food and Drug Administration. Gardasil, Merck. Available at www.fda.gov/cber/label/gardasilLB.pdf.
c Ages for which vaccine is indicated in the biological license application and the year the application was approved.

sions and allows for treatment before they can progress to cancer, deaths decreased from 10 to 3 per 100 000 during the last half of the 20th century.40 In 2002, the age-standardized cervical cancer incidence in the United States was 8.7 per 100 000.41 In part, however, because of differences in cervical cancer screening, there are substantial racial and ethnic differences in the incidence of cervical cancer in the United States.42

Vaccines
A quadrivalent vaccine has been licensed for use in the United States,4 and a bivalent vaccine is in the final stages of clinical development (Table 4). Both the licensed and candidate vaccines are made from noninfectious HPV-like particles composed of the L1 major capsid protein. The quadrivalent vaccine is directed against HPV types 16 and 18, which are responsible for ~70% of cervical cancers, and HPV types 6 and 11, which cause ~90% of genital warts; the bivalent vaccine contains types 16 and 18 only. In clinical trials among adolescent girls and young women without evidence of the relevant HPV infection at enrollment, these vaccines have demonstrated 100% efficacy in preventing clinical HPV infection.43–46 In addition to preventing cervical cancer, HPV vaccines will reduce the risk of, and, therefore, the economic burden of disease. Chronically infected persons are also the source of most transmissions. Cirrhosis and hepatocellular carcinoma are responsible for an estimated 5000 deaths per year among persons with chronic hepatitis B infection.49 Before childhood hepatitis B vaccination programs became routine in the United States, an estimated 30% to 40% of chronic infections resulted from perinatal or early childhood transmission. As of 2004, among US children aged 19 to 35 months, >92% had been fully vaccinated with 3 doses of hepatitis B vaccine.50 Vaccination coverage among adolescents has also increased substantially. Preliminary data demonstrate that 50% to 60% of adolescents aged 13 to 15 years have records indicating that they have completed hepatitis B vaccination. The effectiveness of these childhood and adolescent vaccination efforts seem primarily responsible for a 75% decrease in the incidence of acute hepatitis B in the United States during 1990–2004 and the low number of cases of hepatitis B among adolescents (Table 1).51 The greatest decline in cases has occurred among children and adolescents, coincident with an increase in hepatitis B vaccine coverage.52,53 Nonetheless, coverage

Hepatitis B

Etiology, Pathogenesis, Clinical Manifestations, and Epidemiology
The hepatitis B virus is a member of the Hepadnavirus family of double-stranded DNA viruses. Although acute infection in adolescents can be temporarily incapacitating, chronically infected people remain responsible for a majority of the morbidity and mortality and, therefore, the economic burden of disease. Chronically infected persons are also the source of most transmissions. Cirrhosis and hepatocellular carcinoma are responsible for an estimated 5000 deaths per year among persons with chronic hepatitis B infection.49 Before childhood hepatitis B vaccination programs became routine in the United States, an estimated 30% to 40% of chronic infections resulted from perinatal or early childhood transmission. As of 2004, among US children aged 19 to 35 months, >92% had been fully vaccinated with 3 doses of hepatitis B vaccine.50 Vaccination coverage among adolescents has also increased substantially. Preliminary data demonstrate that 50% to 60% of adolescents aged 13 to 15 years have records indicating that they have completed hepatitis B vaccination. The effectiveness of these childhood and adolescent vaccination efforts seem primarily responsible for a 75% decrease in the incidence of acute hepatitis B in the United States during 1990–2004 and the low number of cases of hepatitis B among adolescents (Table 1).51 The greatest decline in cases has occurred among children and adolescents, coincident with an increase in hepatitis B vaccine coverage.52,53 Nonetheless, coverage
among adolescents who were born in the 1990s varies considerably depending primarily on the state of implementation of childhood vaccination programs, the presence and enforcement of primary and middle school–entry laws,54–56 and the presence of Health Plan Employer Data and Information Set requirements.57

**Vaccine**

A serum-based vaccine was licensed in 1981 and became available in 1982. The current recombinant hepatitis B vaccine is safe and confers a protective immune response in >95% of infants, children, and adolescents. Vaccination provides long-term protection, with breakthrough infections being extremely rare and usually transient and asymptomatic. Vaccination was first recommended by the ACIP in 1982 for adults who had a high risk of infection (eg, health care workers, men who have sex with men, injecting drug users).58 Routine maternal screening for hepatitis B surface antigen (HBsAg) and immunization of infants born to HBsAg-positive mothers was recommended in 1988.59 Difficulties in implementing targeted recommendations for adults and recognition of the substantial burden of hepatitis B–related disease resulting from infections during childhood led to the development of a new strategy. In 1991, a comprehensive strategy to eliminate hepatitis B transmission was implemented with a recommendation to vaccinate all infants.60 A primary focus of this strategy, which was updated in 2005, is the universal vaccination of infants, beginning at birth, to prevent early childhood hepatitis B infection and to eventually protect adolescents and adults from infection.61 Other components include routine screening of all pregnant women for HBsAg and postexposure immunoprophylaxis of infants born to HBsAg-positive women, vaccination of children and adolescents who were not previously vaccinated, and vaccination of unvaccinated adults who are at increased risk for infection. This strategy led to a recommendation for vaccination of adolescents 11 to 12 years old in 19952 and all adolescents in 1999.63 Despite these recommendations, the success of catch-up vaccination efforts during childhood and middle school has been inconsistent, particularly among children and teens not covered by the recommendation for universal infant immunization against hepatitis B. Most of the success has been the result of primary and middle school vaccination requirements.64

**Varicella**

**Etiology, Pathogenesis, and Clinical Manifestations**

Like other members of the herpesvirus group, varicella zoster virus manifests first as a primary infection (chickenpox) and has the capacity to persist in the body (latent infection) and recur (shingles).3 It is transmitted through respiratory contact and the conjunctiva, replicating at the site of entry and the lymph nodes. A primary viremia follows, but it is not until a secondary viremia that skin infection manifests. Although considered by many to be a benign disease, varicella can result in serious complications, sequelae, and death.

**Epidemiology**

In the prevaccine era, virtually all people in the United States acquired varicella by adulthood, with the highest age-specific incidence in children 1 to 4 years old.65 During 1990–1994, before implementation of the varicella vaccination program, an estimated 4 million cases, 11,000 hospitalizations, and 100 deaths were attributed to varicella disease each year in the United States.66 After recommendation of the vaccine for children 12 to 18 months old in 1996, vaccine-coverage rates increased from 26% in 1997 to 87% in 2004.67 Although national surveillance for varicella cases remains incomplete, active surveillance in limited geographic areas and national mortality data revealed marked decreases in varicella incidence, varicella-related hospitalizations, and deaths in all age groups.68-70 Varicella cases decreased 71% to 84% and mortality decreased by 66%.70 Cases among vaccinated individuals are now increasing, which is believed to be happening because of waning immunity.58

**Future Vaccines**

Of the >80 known infectious agents that are pathogenic to humans, there are now >30 vaccines against 26, mainly viral and bacterial infections.80,81 Many important vaccines that would likely be recommended for administration during adolescence remain elusive, in part because these vaccines need to stimulate both cell-mediated and humoral immune responses. Such vaccines...
include ones against herpes simplex, cytomegalovirus, chlamydia, group B streptococcus, tuberculosis, and HIV.

Herpes simplex type 2 may cause lifelong infection and significant medical and psychosocial morbidity. Vaccines that prevent herpes simplex virus infection may not only decrease acquisition but also disease severity, neonatal herpes, and the transmission of HIV. Cytomegalovirus has also been the target of vaccine-development efforts. Cytomegalovirus is the most common intrauterine infection in the United States. A vaccine targeting it would decrease both morbidity and mortality, primarily by preventing congenital infection. By 2015, it is possible that vaccines against HIV and tuberculosis will be introduced; at least some of these will be intended primarily for adolescents. Although most of these vaccines are the subject of active research, it is likely that the majority may not be clinically available until the middle of the next decade.

CONCLUSIONS
Vaccines and vaccination programs are among the greatest public health accomplishments of the 20th century. Decades of efforts have been needed to realize these achievements. With the development of new vaccines, new diseases in adolescents have become vaccine-preventable, and the burden of these vaccine-preventable diseases is substantial.

A number of factors will make delivery of these vaccines a challenge. The high cost of the vaccines and the difficulty in reaching adolescents for vaccination and other health care issues (see Szilagyi et al, Broder et al, and Sneller et al) have suggested that a new paradigm may be necessary. We must be able to explain to adolescents, their parents, and public health decision-makers the special place that vaccines hold among clinical preventive services (see Broder et al). Unlike many other clinical preventive services that are recommended for adolescents, their effectiveness is not in doubt. However, immunization advocates need to concede that numerous other clinical and community preventive services are of tremendous value in reducing the burden of disease and injury among adolescents. Furthermore, the challenge of implementing even the most strongly recommended preventive services cannot be underestimated. Analyses of the cost-effectiveness of mature vaccination programs and comparisons between vaccines and other preventive services continue to be conducted and are essential to guiding public policy.

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REFERENCES


New, and Some Not-so-New, Vaccines for Adolescents and Diseases They Prevent
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