

SYLVIA H. YEH, MD

Assistant Professor of Pediatrics, University of California, Los Angeles; Department of Pediatric Infectious Disease, Harbor-UCLA Medical Center; Los Angeles Biomedical Research Institute, Torrance, CA

JAY M. LIEBERMAN, MD*

Professor of Pediatrics, University of California, Irvine; Department of Pediatric Infectious Diseases, Miller Children's Hospital, Long Beach, CA

Update on adolescent immunization: Pertussis, meningococcus, HPV, and the future

ABSTRACT

Since January 2005, new vaccines against pertussis, meningococcal disease, and human papillomavirus (HPV) infection have been licensed. The target recipients are adolescents and preadolescents, who are at higher risk of these infections than other age groups. Routinely scheduled visits for 11- to 12-year-olds will allow for immunization against these and other diseases and give us an opportunity to provide anticipatory guidance against high-risk behaviors.

KEY POINTS

Two new combination vaccines against tetanus, diphtheria, and pertussis are approved for use in adolescents. They contain different amounts of the antigens than the vaccines used in infants.

A conjugate meningococcal vaccine is approved for people 11 to 55 years of age. It is recommended for preadolescents and others at risk, such as college freshmen and military recruits.

A newly approved vaccine covers the four serotypes of HPV that cause most cases of cervical cancer and genital warts. It should be given to all preadolescent girls before the onset of sexual activity and to other female patients up to 26 years of age who wish to reduce their risk.

PRETEENS AND TEENAGERS will be getting more shots as part of their routine immunization schedule now that new vaccines have been approved against:

- **Pertussis**—the only vaccine-preventable disease for which case numbers are rising (Children are already vaccinated against pertussis, but vaccinations during childhood alone will not control this disease.)
- **Meningococcal disease**—a disease with a peak incidence in adolescents and young adults and associated with a high risk of death in this age group
- **Human papillomavirus (HPV)**—a sexually transmitted infection often acquired in adolescence, a period of development marked by high-risk behaviors, including sexual activity.

BUILDING ON PAST SUCCESSSES

Vaccines have been one of the most successful means of preventing sickness and death worldwide. In the United States, cases of most of the diseases that are preventable by vaccines have been reduced by almost 99% from their incidence in the prevaccine era (**TABLE 1**).¹ Polio has been eradicated from the Western Hemisphere,² and indigenous measles transmission has been interrupted in the Americas.

Building on these successes, a number of new vaccines have been added to the US childhood and adolescent immunization



PATIENT INFORMATION

Why does my child need more shots?, page 728

*Dr. Lieberman serves on the speakers' bureaus of or as a consultant for the sanofi pasteur, GlaxoSmithKline, and Merck corporations.

TABLE 1

The resounding success of vaccination

DISEASE	CASES PER YEAR BEFORE VACCINES*	CASES IN 2005	% REDUCTION
Diphtheria	175,885	0	100
Measles	503,282	66	> 99.9
Mumps	152,209	314	99.8
Pertussis	147,271	25,616	82.6
Polio (wild)	16,316	0	100
Rubella	47,745	11	> 99.9
Tetanus	1,314	27	97.9
Invasive <i>Haemophilus influenzae</i> type b disease	20,000	9	> 99.9
Total	1,064,845	26,043	99.8

*Maximum cases reported in the prevaccine era

CENTERS FOR DISEASE CONTROL AND PREVENTION. SUMMARY OF NOTIFIABLE DISEASES—UNITED STATES 2005. MMWR 2006; 54(53):2–92.

schedule, so that children are now routinely vaccinated against up to 16 infectious diseases.³ The schedule also meshes with the need for those who provide routine health care to monitor growth and development and to provide anticipatory guidance. Indeed, the scheduled health care visits of the first year have been built around the vaccination schedule.

State laws that require children to be vaccinated before they enroll in school have helped boost coverage rates to a fairly high level in the last decade, although there is room for improvement.⁴ In contrast, coverage rates have been lower in adolescents and adults, due in part to fewer opportunities for health care visits.

Recent additions to the vaccination schedule are bundled in a preadolescent visit at 11 to 12 years of age (TABLE 2).^{5–7} However, the Society for Adolescent Medicine recommends that we bring adolescents into the office at least *three* times: at age 11 to 12, at age 14 to 15, and at age 17 to 18. These visits would give us the opportunity not only to vaccinate them but also to do comprehensive health screening and anticipatory care.⁵

Another advantage would be that they could be vaccinated while they are still covered by their parents' insurance or by the Vaccines for Children program.

■ **PERTUSSIS (WHOOPING COUGH)**

May be subtle in adolescents and adults

The clinical spectrum of pertussis ranges from an illness indistinguishable from a cold to classic whooping cough, depending on the degree of preexisting immunity. In people with preexisting immunity, such as adolescents and adults, the features of pertussis may be less severe and so it often goes unrecognized.

In children, classic whooping cough progresses through three phases:

- The catarrhal phase, characterized by rhinorrhea and mild cough. The severity of the cough increases over 1 to 2 weeks, leading to...
- The paroxysmal phase, in which patients go through repetitive series of 5 to 10 or more forceful coughs during a single expiration. The paroxysms may be followed by a massive inspiratory effort, producing the characteristic "whoop."

Most of the diseases that vaccines prevent have been reduced by almost 99%

TABLE 2

Immunization recommendations for preadolescent visit (11–12 years of age)**Varicella**

Give second dose if the patient previously received only one dose

Give two doses at least 4 weeks apart if the patient never previously received vaccine and if over 13 years of age

Hepatitis B

Requires receipt of three doses total during lifetime; complete series if incomplete

Hepatitis A

Give two doses 6 months apart if not previously immunized

Measles, mumps, rubella

Patient should have received two doses; give second dose if it was not given at 4 to 6 years of age

Influenza

Yearly for those with risk factors or those with contact with persons with risk factors

Tetanus, diphtheria, pertussis

Routine vaccination of adolescents 11 to 18 years of age (the preferred age of vaccination is 11 to 12 years)

Adolescents should receive a single dose of Tdap instead of Td

Adolescents age 11 to 18 years who received Td but not Tdap are encouraged to receive Tdap with an interval of at least 5 years between Td and Tdap

Vaccine providers should give Tdap and tetravalent meningococcal conjugate vaccine to adolescents age 11 to 18 years during the same visit if both vaccines are indicated and available

Meningococcus

Routine vaccination of preadolescents 11 to 12 years of age with tetravalent conjugate meningococcal vaccine (MCV4; Menactra)

Routine vaccination with MCV4 at high-school entry (approximately 15 years of age) of patients who have not yet received it

Elective vaccination with MCV4 of other adolescents who wish to decrease their risk for meningococcal disease

Other populations at increased risk of meningococcal disease: college freshmen who live in dormitories, microbiologists who are routinely exposed to isolates of *Neisseria meningitidis*, military recruits, people who travel or reside in countries with hyperendemic or epidemic *N meningitidis*, people with terminal complement component deficiencies, people with anatomic or functional asplenia

- For people 11 to 55 years of age, tetravalent conjugate meningococcal vaccine (MCV4) is recommended; for persons 2 to 10 years of age and >55 years of age, MSPV4 is recommended; MPSV4 is an acceptable alternative for persons 11 to 55 years of age

Human papillomavirus

Give three-dose series to all girls (at 0, 2, and 6 months)

DATA FROM AMERICAN ACADEMY OF PEDIATRICS. RECOMMENDATIONS FOR PREVENTIVE PEDIATRIC HEALTHCARE, COMMITTEE ON PRACTICE AND AMBULATORY MEDICINE. PEDIATRICS 2000; 105:645–646.
AMERICAN ACADEMY OF PEDIATRICS. IN PICKERING LK, BAKER CJ, LONG SS, MCMILLAN JA, EDITORS. RED BOOK. 2006 REPORT OF THE COMMITTEE ON INFECTIOUS DISEASE 27TH ED. ELK GROVE, IL: AMERICAN ACADEMY OF PEDIATRICS; 2006.

- The convalescent phase lasts from a few weeks to as long as 3 months and is characterized by decreasing frequency and severity of cough episodes.

In adults, the most commonly reported symptoms are protracted cough lasting 3 to 6 weeks (41%–52%), nighttime cough (56%–78%), and pharyngitis (31%–86%). Less frequent symptoms include post-tussive emesis (7%–45%), whoop (7%–35%), cyanosis (6%–12%), and apnea (15%–37%).^{8–12} Other reported complaints include cough exacerbated

by eating, drinking, exertion, or a change in climate. Differing from classic whooping cough in young children, lymphocytosis is often absent in adolescents and adults.

Pertussis is increasing in incidence, shifting to infants, adolescents, adults

Worldwide, an estimated 20 to 40 million cases of pertussis occur each year.¹³ In the United States, the number of cases reported to the US Centers for Disease Control and Prevention (CDC) has increased markedly

Pertussis is shifting to infants, adolescents, and young adults

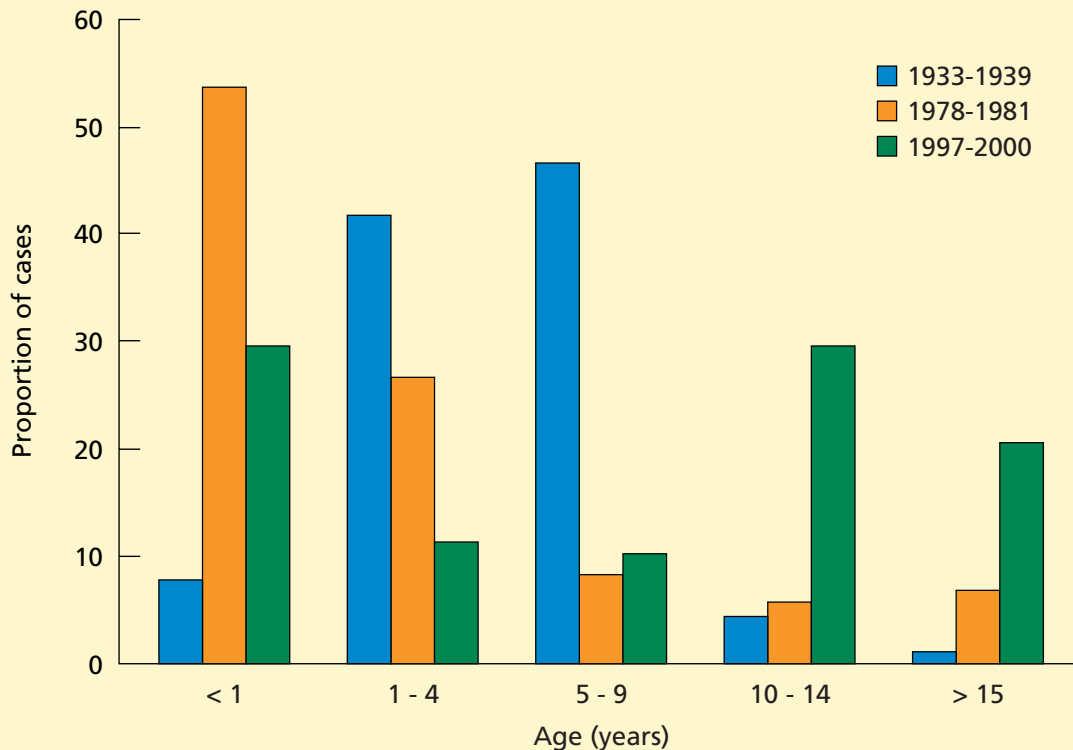


FIGURE 1. Age distribution of reported pertussis cases, United States, prevaccine and postvaccine eras. The 1933–1939 data are from Massachusetts; the other data are national. The 1933–1939 and 1978–1981 data are from Cherry,¹⁴ and the 1997–2000 data are from the Centers for Disease Control and Prevention.¹⁵

FROM YEH SH, MINK CM. SHIFT IN THE EPIDEMIOLOGY OF PERTUSSIS INFECTION: AN INDICATION FOR PERTUSSIS VACCINE BOOSTERS FOR ADULTS? DRUGS 2006; 66:731–741. USED WITH PERMISSION.

DTaP is for infants and small children, Tdap is for teens and adults

over the last several years, although the disease is still significantly underreported. An average of 6,000 to 8,000 cases per year were reported in the 1990s, but in 2004 and 2005 more than 25,000 cases were reported each year, which is the highest level since the nadir of pertussis cases in the 1970s.¹

Before pertussis vaccine was widely used, pertussis mostly affected school-age children, but now it has shifted to very young infants who have not received their full course of vaccinations and to adolescents and adults (FIGURE 1).^{14–16} Almost 40% of reported cases in 2004 and 2005 were in the 10-to-19-year-old age group. A recent prospective study estimated the incidence of pertussis in the 15-to-64 age group to be 3 to 4 cases per 1,000 persons per year in the United States—

almost 1 million cases per year.¹⁷

In states with enhanced surveillance for pertussis, adolescents have one of the highest incidence rates of pertussis of all age groups.^{18,19} Furthermore, adolescents and adults are important reservoirs and sources of *Bordetella pertussis* transmission and infection for unimmunized or partially immunized infants and children.^{20–24}

New pertussis vaccines for adolescents and adults

The first vaccines against pertussis consisted of killed *B pertussis* organisms, and in 1914 a licensed whole-cell pertussis vaccine became available.²⁵ The whole-cell vaccine was then combined with diphtheria and tetanus toxoids in a vaccine (DTwP) that became widely

available in 1948. However, whole-cell pertussis vaccines were associated with unfavorable reactions²⁵ and the unproven perception that they might cause rare, but serious, adverse reactions.

Acellular pertussis vaccines, containing purified components associated with the bacteria's pathogenesis, were first developed in Japan, where two deaths following pertussis vaccination in the mid-1970s led to low public acceptance of whole-cell vaccines.²⁶ In the United States, combination vaccines that contain diphtheria toxoid, tetanus toxoids, and acellular pertussis (DTaP) have been available and in use for children since the 1990s.²⁵ Available products are Daptacel, Infanrix, Pediarix, and Tripedia.

In 2005, two combination vaccines that contain the same ingredients but in different amounts were licensed for use in adolescents and adults in the United States.^{27,28} These are abbreviated as "Tdap" rather than DTaP because they contain less diphtheria toxoid and acellular pertussis—capital letters indicate more antigen.

Boostrix (GlaxoSmithKline) is licensed for use in people 10 through 18 years of age.

Adacel (sanofi pasteur) is licensed for use in people 11 through 64 years of age.

Both Boostrix and Adacel were approved on the basis of safety and immunogenicity assessments, without any data about clinical efficacy.^{27,28} However, most adults and adolescents who received a single booster dose of Tdap achieved higher antibody levels than infants who had received three doses of comparable DTaP vaccines,¹⁸ suggesting that these vaccines should be protective in these age groups. In a study in people 18 to 64 years of age,¹⁷ an acellular pertussis vaccine demonstrated up to 92% protective efficacy, supporting the concept that vaccinating adolescents and adults should provide them with significant protection. Postlicensure studies are necessary to determine the duration of protection after vaccination and whether there is a need for further booster doses.

Acellular pertussis vaccines are generally safe and well tolerated. Both of the US Tdap vaccines had acceptable profiles for local and systemic events, comparable with those with Td vaccines, which contain only tetanus tox-

oid and reduced-dose diphtheria toxoid. Injection site pain was the most frequent adverse event reported with Boostrix, Adacel, and the Td vaccines. However, Adacel recipients experienced more fever (temperature > 100.4°F; [38.0°C]) than Td recipients (5% vs 2.7%, respectively).^{18,28}

In general, Tdap is recommended for all adolescents 11 to 18 years of age (TABLE 2), with a preferred age of immunization of 11 to 12 years of age.²⁹ An interval of at least 5 years between Td and Tdap immunization is suggested. However, intervals as short as 2 years between Td and Tdap have been studied and determined to be safe and should be considered during pertussis outbreaks or if adolescents have contact with young infants.

■ MENINGOCOCCUS

Even more fatal in adolescents than in infants and children

Invasive meningococcal disease, caused by *Neisseria meningitidis*, is infrequent (approximately 1,400 to 3,000 cases occur in the United States annually) but has high morbidity and mortality rates and often has a fulminant course leading to death within hours.³⁰ The most common clinical forms are meningitis (47% of cases), bacteremia and sepsis (43%), and pneumonia (6%).³¹

The case fatality rate is 10% to 14%, and 11% to 19% of survivors suffer serious sequelae such as deafness, neurologic deficit, or limb loss.^{32–35} Despite major advances in medical and supportive care, the mortality rate in invasive meningococcal disease has not declined over the past 20 or 30 years.

Meningococcal disease is often accompanied by a petechial rash.

Meningococcemia can be a fulminant illness characterized by a nonspecific febrile illness followed by rapid deterioration. Many deaths occur within 12 hours of the onset of illness and almost all within 48 hours. Adolescents 15 years or older are more likely than infants and children to have meningococcemia without meningitis (40% vs 20%, respectively), shock at presentation (69% vs 27%, respectively), and a fatal outcome (22.5% vs 4.6%).^{36,37}

Outbreaks of invasive meningococcal disease have occurred in military recruits and college freshmen in dormitories

Meningococcal disease by age

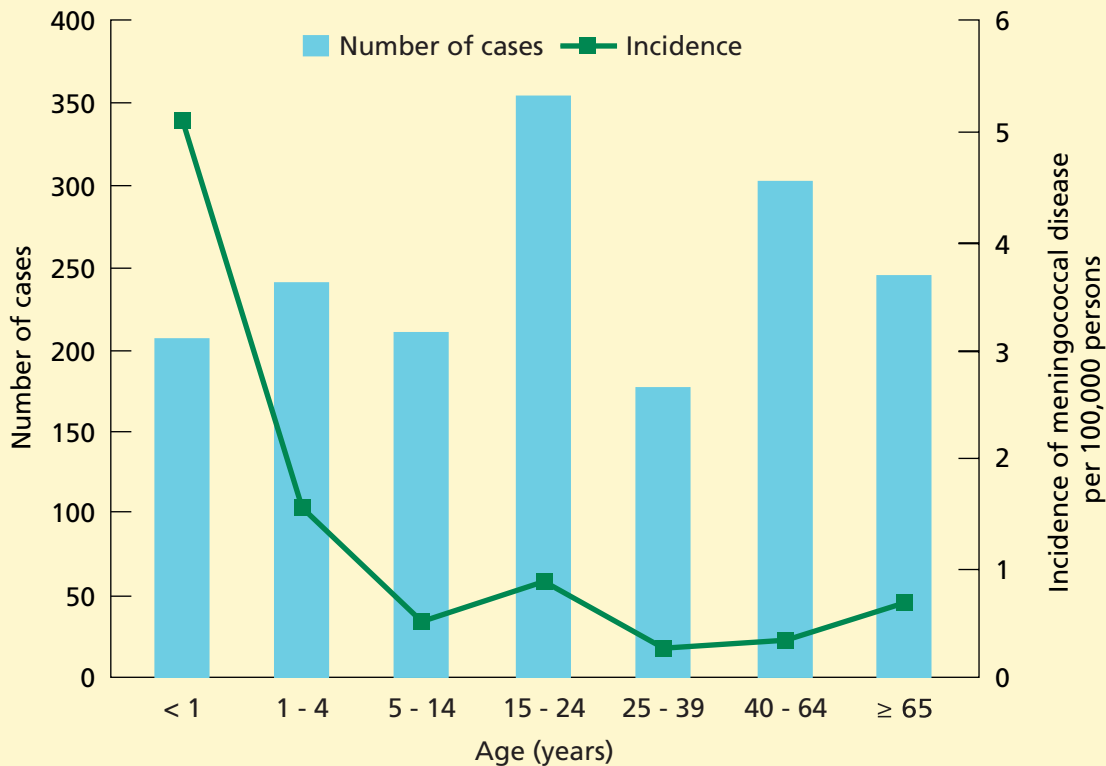


FIGURE 2. Meningococcal disease and incidence by age group—United States, 2003.

US CENTERS FOR DISEASE CONTROL AND PREVENTION. SUMMARY OF NOTIFIABLE DISEASES—UNITED STATES, 2003. MMWR 2003; 52:28.

Two peaks in incidence

The annual incidence of invasive meningococcal disease in the United States is approximately 1 per 100,000 population. The incidence is highest in infants younger than 12 months, and 35% to 40% of cases are in children younger than 5 years, but there is a second, smaller peak in adolescents (FIGURE 2).³⁸ In the United States, 16% of cases are among infants younger than 1 year, and 20% of cases are in adolescents and young adults 14 to 24 years of age.³²

N meningitidis is transmitted by respiratory droplets, requiring direct, close contact. However, carrier rates of disease-associated meningococcal strains in the general public are usually less than 5%.³⁰

Risk factors for invasive meningococcal disease, in addition to age, include inherited deficiency of properdin or complement (C5–C9 or C3), anatomic or functional asple-

nia, household crowding, cigarette smoking (active or passive), recent viral respiratory infection, and close contact with a person with meningococcal disease.^{37,39} Also, blacks and people of low socioeconomic status have a higher incidence of invasive meningococcal disease than white and Asian ethnic groups.

Outbreaks of invasive meningococcal disease have occurred among those living in close quarters, such as military recruits and college freshmen in dormitories.⁴⁰ The incidence of invasive meningococcal disease in freshmen living in dormitories is nearly 3.6 times higher than in all people age 18 to 23 years (5.1 vs 1.4 per 100,000 person-years, respectively) and 8.5 times higher than the incidence among all college and university students (0.6 per 100,000 person-years).⁴⁰

More than 98% of cases in the United States are sporadic, but the frequency of localized outbreaks has increased since 1991.⁴¹

Almost all deaths from invasive meningococcal disease occur within 48 hours of onset

Invasive meningococcal disease by age and serogroup

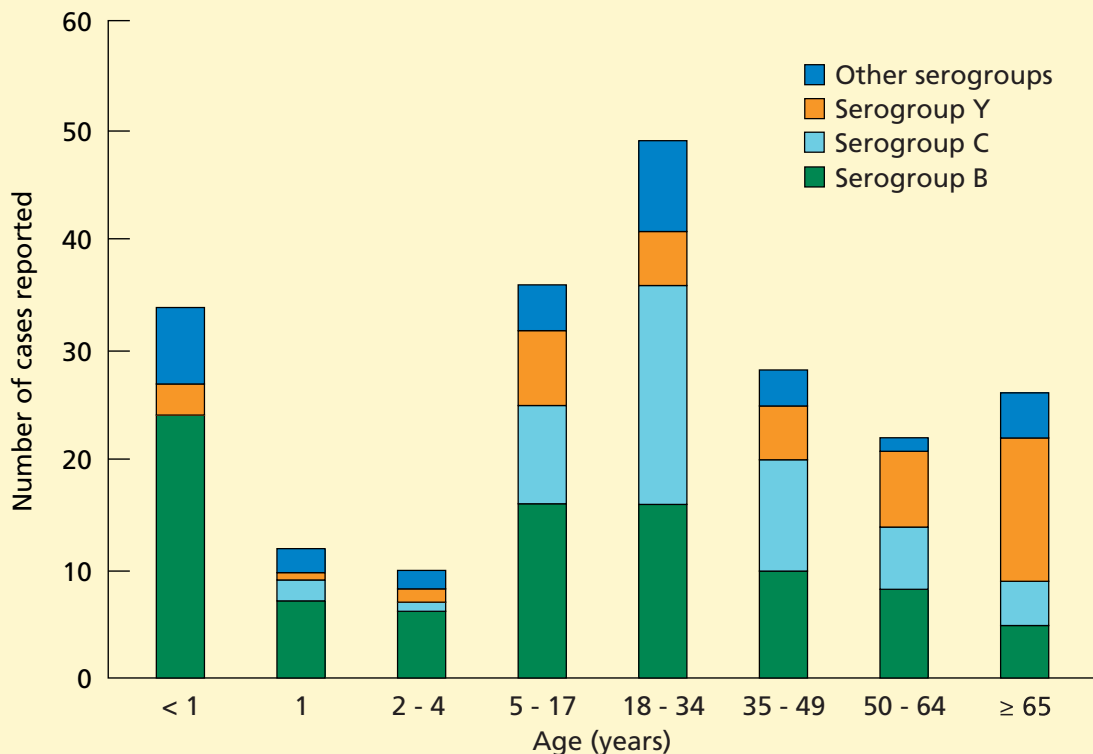


FIGURE 3. Age distribution of invasive meningococcal disease by serogroups. Active Bacterial Core Surveillance, 2003.

US CENTERS FOR DISEASE CONTROL AND PREVENTION. ACTIVE BACTERIAL CORE SURVEILLANCE (ABCS) REPORT EMERGING INFECTIONS PROGRAM NETWORK NEISSERIA MENINGITIDIS, 2003—PRELIMINARY. WWW.CDC.GOV/NCIDOD/DBMD/ABCS/SURVREPORTS/MENING03PRELIM.PDF.

Polysaccharide vaccines are not immunogenic in children younger than 2 years and do not provide long-term protection

Meningococcal disease is seasonal, with the number of cases peaking in December and January.³⁰

13 Meningococcal serogroups

N meningitidis strains are serotyped by their capsular polysaccharides, and 13 different serogroups have been identified. Most cases of invasive meningococcal disease in the United States are caused by serogroups B, C, and Y, with each causing approximately one third of cases.

The proportion of cases caused by each serogroup varies by age (FIGURE 3).^{32,40,42} In infants younger than 1 year, more than half of the cases of invasive meningococcal disease in 2002 were due to serogroup B.^{32,37} However, a vaccine against serogroup B has been hard to develop, owing to difficulties inducing an adequate immune responses to its capsular poly-

saccharide antigen, which shares antigenic properties with a human neural adhesion molecule.³⁰ In people 11 to 18 years of age, 75% of cases of invasive meningococcal disease are caused by serogroups A, C, Y or W-135.^{30,43}

A new conjugate meningococcal vaccine

A polysaccharide meningococcal vaccine against serogroups A, C, Y, and W-135 (MPV4, Menomune-A, C, Y, W-135, sanofi pasteur) was recommended for use in people 2 years of age and older at high risk of invasive meningococcal disease.⁴³ However, polysaccharide vaccines are not immunogenic in children younger than 2 years and do not provide long-term protection because they are T-cell-independent antigens. In addition, polysaccharide vaccines do not reduce nasopharyngeal carriage or elicit herd immunity.⁴⁴

Conjugate vaccines covalently link the

polysaccharide antigen to an immunogenic protein carrier that is recognized by T cells and stimulates T-cell-dependent immunity to the covalently linked (conjugated) polysaccharide.⁴⁵ The advantages of conjugated vaccines have been proven by the successful implementation of polysaccharide-protein conjugate vaccines against *Haemophilus influenzae* type b and *Streptococcus pneumoniae*, which proved highly effective in infants and also reduced nasopharyngeal carriage, leading to herd immunity.⁴⁴

Use of a conjugate monovalent meningococcal C vaccine in the United Kingdom resulted in an 86.7% reduction in laboratory-confirmed meningococcal C disease in vaccine recipients. This vaccination program also demonstrated reductions in nasopharyngeal carriage and meningococcal C disease incidence in people who did not receive the vaccine.^{46–50}

Menactra (sanofi pasteur; also known as MCV4) is a conjugate meningococcal vaccine against serogroups A, C, Y, and W-135. It was licensed in 2005 in the United States for use in people 11 to 55 years of age⁵¹ on the basis of immunologic correlates of protection, similar to the conjugate meningococcal C vaccine used in the United Kingdom. Recommendations for meningococcal vaccination are shown in TABLE 2. The vaccine, if 100% effective, could reduce the burden of meningococcal disease by two thirds among people 18 to 23 years old.⁴³

Adverse reactions. In randomized controlled trials, MCV4 had rates of systemic adverse reactions similar to those of MPV4. However, the rates of fever (temperature $\geq 100.0^{\circ}\text{F}$, 38.8°C) were higher in MCV4 recipients than in MPV4 recipients (5.1% with MCV4 vs 3.0% with MPV4 in those 11 to 18; 1.5% with MCV4 vs 0.5% with MPV4 in those 18 to 55), although rates of high fever ($\geq 103.1^{\circ}\text{F}$ [39.5°C]) were similar with either vaccine in those 11 to 18 years old. In addition, in those 11 to 18, local adverse reactions were more frequent with MCV4 than with MPV4 (redness 10.9% vs 5.7%, swelling 10.85% vs 3.68%, induration 15.7% vs 5.2%, pain 59.2% vs 28.7%).^{38,51–53}

The difference in the frequency of local reactions is most likely due to the diphtheria toxoid contained in the conjugate vaccine,

as the rate of local reactions with MCV4 is similar to that reported after Td vaccination.^{51,52}

Ten months after Menactra was licensed, the CDC and the US Food and Drug Administration reported a possible association with Guillain-Barré syndrome.⁵⁴ Through September 2006, a total of 17 cases among Menactra recipients were reported to the Vaccine Adverse Events Reporting System (VAERS). The available data suggest the risk is small (relative risk 1.78, 95% confidence interval 1.02–2.85). However, the data for both the background incidence of Guillain-Barré syndrome and the VAERS reporting are quite limited.⁵⁵ Preliminary data from the Vaccine Safety Datalink, a collaborative project of the CDC and eight managed care organizations, have not identified any cases of Guillain-Barré syndrome among 126,506 doses of Menactra. Therefore, because of the increased risk and associated morbidity and mortality of meningococcal disease in adolescents, the recommendations for use of MCV4 remain unchanged.⁵⁵

■ HUMAN PAPILLOMAVIRUS

The most common sexually transmitted disease in the United States

HPV infects the squamous epithelium of the skin and mucosa, and different genotypes preferentially infect specific epithelial sites and body locations.

More than 30 of the approximately 100 HPV genotypes infect the genital tract. Genital HPV infection is the most common sexually transmitted infection in the United States (TABLE 3).^{56,57} The virus is primarily transmitted by sexual contact (genital-genital, manual-genital, oral-genital), and consistent use of condoms may reduce the risk of genital HPV infection.⁵⁸ HPV can also be vertically transmitted from mother to newborn via the genital tract.

Risk factors for HPV infection include young age, lifetime number of sexual partners, early age at first sexual intercourse, smoking, and oral contraceptive use. For men, being uncircumcised is a risk factor.^{59–62} In a study of 603 female college students, approximately

HPV types 16, 18, 31, 33, and 45 are detected in up to 97% of invasive cervical cancer cases

TABLE 3

Sexually transmitted infections in the United States, 2000

DISEASE	OVERALL US INCIDENCE	OVERALL US PREVALENCE	INCIDENCE IN AGES 15 TO 24	PREVALENCE IN AGES 15 TO 24
Chlamydia	2,800,000	1,900,000	1,500,000	1,000,000
Gonorrhea	718,000	NA	431,000	NA
Syphilis	40,000	NA	8,200	NA
Herpes simplex virus-2	1,600,000	45,000,000	640,000	4,200,000
Human papillomavirus	6,200,000	2,000,000	4,600,000	9,200,000
Hepatitis B (sexually transmitted)	48,600	750,000	7,500	NA
Human immunodeficiency virus	40,000	850,000	15,000	NA

DATA FROM CATES W. ESTIMATES OF THE INCIDENCE AND PREVALENCE OF SEXUALLY TRANSMITTED DISEASE IN THE UNITED STATES. SEX TRANS DIS 1999; 26(SUPPL):S2-S7. AND WEINSTOCK H, BERMAN S, CATES W. SEXUALLY TRANSMITTED DISEASE AMONG AMERICAN YOUTH: INCIDENCE AND PREVALENCE ESTIMATES 2000. PERSPECTIVE ON SEXUAL AND REPRODUCTIVE HEALTH 2004; 36:6-10.

10,000 US women contract cervical cancer each year, and 10 women die of it every day

40% of HPV infections occurred within 2 years of the first sexual experience,⁶¹ which emphasizes that any preventive strategy must be implemented before adolescents become sexually active.

HPV causes cervical cancer, genital warts

More than 90% of new HPV infections in college women spontaneously clear from the genital tract within 2 years.⁶³ However, persistent infection with so-called high-risk genotypes is associated with the development of cervical dysplasia, which may progress to cervical intraepithelial neoplasia (CIN) and ultimately to cervical cancer.⁶⁴

Over the past 20 years, we have learned that HPV infection is necessary for the development of cervical cancer, meaning that this type of cancer can be prevented through vaccination. Infection with a high-risk (oncogenic) HPV type is the most significant risk factor in the development of cervical cancer, with HPV types 16, 18, 31, 33, and 45 being detected in 63% to 97% of invasive cervical cancer cases worldwide.^{65,66} Together, HPV 16 and HPV 18 account for most cases of cervical cancer worldwide (54% and 13%, respectively).⁶⁶

An estimated 6.2 million people in the United States are infected with HPV each

year, and 9.2 million people 15 to 24 years of age are currently infected.⁶⁷ Worldwide, 9% to 13% of people are thought to be infected—approximately 630 million. In the United States, approximately 10,000 women contract cervical cancer each year; 10 women die of it every day. Worldwide, the World Health Organization estimates that 510,000 new cases of cervical cancer occur each year, making it the second leading cause of female cancer-related deaths worldwide after breast cancer.⁶⁸

HPV vaccines

One HPV vaccine is currently available, and another is in development.

Gardasil (Merck & Co.), a quadrivalent vaccine against HPV types 6, 11, 16, and 18, was licensed in June 2006.⁶⁹ HPV 6 and HPV 11 are responsible for over 90% of anogenital warts.⁶⁸

Gardasil was evaluated in 20,541 women 16 to 26 years of age in four studies. In women who were seronegative for any of the serotypes contained in the vaccine by serologic and polymerase chain reaction testing, the vaccine was 100% efficacious in preventing HPV 16- or 18-related CIN grade 2 or 3 or adenocarcinoma in situ, which are precancerous or

dysplastic lesions. Efficacy against genital warts related to HPV types 6, 11, 16, or 18 in women who had never been exposed to these serotypes at enrollment ranged from 98.9% to 100%.⁷⁰⁻⁷²

Overall, the vaccine was well tolerated; the most common vaccine-related reactions were pain (in 84% of subjects), swelling (25%), erythema (25%), and pruritus (3%) at the injection site, and these were felt to be mild or moderate.⁷⁰

The vaccine was also studied for immunogenicity and safety in girls 9 to 15 years of age. The immunogenicity of Gardasil in this age group was greater than the immune responses seen in women 18 to 26 years of age. Based on these bridging immunogenicity data, Gardasil is indicated for girls and women 9 to 26 years of age.

Vaccines against sexually transmitted infections are most effective when given before the onset of sexual activity. The HPV vaccine is recommended to be routinely given as a three-dose series (ie, with booster doses at 2 and 6 months after the first dose) to girls 11 to 12 years of age. The recommendations also allow for the vaccine to be given to girls as young as 9 years of age as well as to girls and women 13 to 26 years of age. Ideally, they should be vaccinated before the onset of sexual activity, although sexually active females should also be vaccinated.⁷²

Cervarix, an HPV vaccine that is being developed by GlaxoSmithKline, targets HPV types 16 and 18 and is also given in three doses (with booster doses 1 and 6 months after the first dose). This vaccine was 91.6% protective against infection with HPV 16 and 18 and 100% protective against persistent infection in one study. The vaccine was also 93% effective against atypical squamous cells of undetermined significance or higher-grade pathology.⁷³

■ HERPES SIMPLEX

Herpes simplex virus (HSV) is another common sexually transmitted infection in the United States. More than one in five Americans over 12 years of age is infected with genital herpes.^{74,75} At least 50 million people in the United States are estimated to

have genital HSV infection, with an estimated 500,000 to 700,000 cases of symptomatic first-episode genital HSV infection occurring annually.

Most genital herpes infections are due to HSV type 2, but the incidence of HSV-1 as a cause of genital herpes is increasing.

Fewer than 10% of people who test positive for HSV know they are infected, implying that most infected persons have unrecognized symptomatic or asymptomatic infections.⁷⁴ However, in its classic form, primary infection begins with macules and papules that progress to vesicles, pustules, and ulcers, which then crust over. Localized symptoms include pain at the site of the lesions and tender regional adenopathy. Urethritis and cervicitis may occur with genital acquisition. During a clinically apparent first episode, approximately two thirds of women and 40% of men experience constitutional symptoms such as fever, headache, malaise, and myalgias.⁷⁶ Because HSV is a herpesvirus, it travels retrograde to sensory nerve ganglia, where it establishes latency and can reactivate intermittently.

Recurrent genital HSV-2 infections may be symptomatic or asymptomatic.^{77,78} Within 12 months after the diagnosis of genital HSV-2 infection, 90% of patients have at least one recurrence, 38% have six or more recurrences, and 20% have 10 or more recurrences.⁷⁹ Genital HSV-1 infections recur less frequently than HSV-2 infections.^{76,77}

An HSV-2 vaccine is under study

A candidate vaccine against HSV-2 (HSV-2 gD subunit vaccine) is currently undergoing clinical trials. In two large phase III studies in women and men, the vaccine was demonstrated to be safe.⁸⁰ However, it had no apparent efficacy against genital herpes disease among either women and men.

In a subset analysis among women who were seronegative to both HSV-1 and HSV-2, the vaccine's efficacy against genital herpes disease (HSV-1 or HSV-2) was 74%. However, the study was not designed to assess efficacy of the vaccine in women seronegative to HSV-1 and HSV-2. A phase III study of the vaccine in this population is ongoing. ■

Fewer than 10% of people who test positive for HSV know they are infected

REFERENCES

- Centers for Disease Control and Prevention. Summary of notifiable diseases—United States 2005. *MMWR* 2006; 54(53):2–92.
- Centers for Disease Control and Prevention. Certification of poliomyelitis eradication—the Americas, 1994. *MMWR* 1994; 43:720–722.
- American Academy of Pediatrics Committee on Infectious Diseases. Recommended childhood and adolescent immunization schedule—United States 2006. *Pediatrics* 2006; 117:239–240.
- Luman ET, Karker LE, Shaw KM, McCauley MM, Buehler JW, Pickering LK. Timeliness of childhood vaccination in the United States: days undervaccinated and number of vaccines delayed. *JAMA* 2005; 293:1204–1211.
- Middleman AB, Rosenthal SL, Rickert VI, Neinstein L, Fishbein DB, D'Angelo L; Society for Adolescent Medicine. Adolescent immunization: a position paper of the Society for Adolescent Medicine. *J Adolesc Health* 2006; 38:321–327.
- American Academy of Pediatrics. Recommendations for preventive pediatric healthcare, Committee on Practice and Ambulatory Medicine. *Pediatrics* 2000; 105:645–646.
- American Academy of Pediatrics. In: Pickering LK, Baker CJ, Long SS, McMillan JA, editors. Red Book. 2006 Report of the Committee on Infectious Disease. 27th ed. Elk Grove, IL: American Academy of Pediatrics; 2006.
- Yih WK, Lett SM, de Vignes FN, Garrison KM, Sipe PL, Marchant CD. The increasing incidence of pertussis in Massachusetts adolescents and adults 1989–1998. *J Infect Dis* 2000; 182:1409–1416.
- Senzilet LD, Halperin SA, Spika JS, Alagaratanum M, Morris A, Smith B; Sentinel Health Unit Surveillance Systems Pertussis Working Group. Pertussis is a frequent cause of prolonged cough illness in adults and adolescents. *Clin Infect Dis* 2001; 32:1691–1697.
- MacLean DW. Adults with pertussis. *J R Coll Gen Pract* 1982; 32:298–300.
- Aoyama T, Takeuchi Y, Goto A, Iwai H, Murase Y, Iwata T. Pertussis in adults. *Am J Dis Child* 1992; 146:163–166.
- Rothstein E, Edwards K. Health burden of pertussis in adolescents and adults. *Pediatr Infect Dis J* 2005; 24(suppl 5):S44–S47.
- Tan T, Trindade E, Skowronski D. Epidemiology of pertussis. *Pediatr Infect Dis J* 2005; 24(suppl 5):S10–S18.
- Cherry JD. The epidemiology of pertussis and pertussis immunization in the United Kingdom and the United States: a comparative study. *Curr Probl Pediatr* 1984; 14(2):1–78.
- Centers for Diseases Control and Prevention. Pertussis—United States, 1997–2002. *MMWR* 2002; 51(04):76.
- Mattoo S, Cherry JD. Molecular pathogenesis, epidemiology, and clinical manifestations of respiratory infections due to *Bordetella pertussis* and other *Bordetella* subspecies. *Clin Microbiol Rev* 2005; 18:326–382.
- Ward JI, Cherry JD, Chang SJ, et al; APERT Study Group. Efficacy of an acellular pertussis vaccine among adolescents and adults. *N Engl J Med* 2005; 353:1555–1563.
- Centers for Disease Control and Prevention National Immunization Program. Record of the meeting of the Advisory Committee on Immunization Practices, February 10–11, 2005. www.cdc.gov/nip/ACIP/minutes/acip-min-feb05.pdf. Accessed May 4, 2007.
- Davis JP. Clinical and economic effects of pertussis outbreaks. *Pediatr Infect Dis J* 2005; 24(suppl 6):S109–S116.
- Deen JL, Mink CA, Cherry JD, et al. A household contact study of *Bordetella pertussis* infections. *Clin Infect Dis* 1995; 21:1211–1219.
- Bigard KM, Pascual FB, Ehresmann KR, et al. Infant pertussis: who was the source? *Pediatr Infect Dis J* 2004; 23:985–989.
- Crowcroft NS, Booy R, Harrison T, et al. Severe and unrecognized: pertussis in UK infants. *Arch Dis Child* 2003; 88:802–806. (Erratum in: *Arch Dis Child* 2006; 91:453.)
- Grimpel E, Baron S, Levy-Bruhl D, et al. Influence of vaccination coverage on pertussis transmission in France. *Lancet* 1999; 345:1699–1700.
- Schmitt-Grohe S, Cherry JD, Heinger U, Uberall MA, Pineda E, Stehr K. Pertussis in German adults. *Clin Infect Dis* 1995; 21:860–866.
- Edwards KM, Decker MD, Mortimer EA. Pertussis vaccines. In: Plotkin SA, Orenstein WA, editors. *Vaccines*, 3rd ed. Philadelphia; WB Saunders Company, 1999:293–344.
- Kimura M, Kuno-Sakai H. Current epidemiology of pertussis in Japan. *Pediatr Infect Dis J* 1990; 9:705–709.
- Food and Drug Administration. Product approval information—Boostrix licensing action. www.fda.gov/cber/products/tdappla050305.htm. Accessed June 28, 2007.
- Food and Drug Administration. Product approval information—Adacel licensing action. www.fda.gov/cber/products/tda-pave061005.htm. Accessed June 28, 2007.
- Broder KR, Cortese MM, Iskander JK, et al; Advisory Committee on Immunization Practices (ACIP). Preventing tetanus, diphtheria, and pertussis among adolescents: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2006; 55(RR-3):1–34.
- Gold R. *Neisseria meningitidis*. In: Long SS, Pickering LK, Prober CG, editors. *Principles and Practice of Pediatric Infectious Disease*. Philadelphia; Churchill Livingstone, 2003:748–756.
- Rosenstein NE, Perkins BA, Stephens DS, et al. The changing epidemiology of meningococcal disease in the United States, 1992–1996. *J Infect Dis* 1999; 180:1894–1901.
- Active Bacterial Core surveillance (ABCs) 1997–2002 meningococcal surveillance reports. www.cdc.gov/ncidod/dbmd/abcs. Accessed June 28, 2007.
- Kirsch EA, Barton RP, Kitchen L, Giroir BP. Pathophysiology, treatment and outcome of meningococemia: a review and recent experience. *Pediatr Infect Dis J* 1996; 15:967–978.
- Edwards MS, Baker CJ. Complications and sequelae of meningococcal infections in children. *J Pediatr* 1981; 99:540–545.
- National Foundation for Infectious Diseases (NFID). The changing epidemiology of meningococcal disease among U.S. children, adolescents, and young adults, November 2004. www.nfid.org/pdf/meningitis/FINALChanging_Epidemiology_of_Meningococcal_Disease.pdf. Accessed June 28, 2007.
- Harrison LH, Pass MA, Mendelsohn AB, et al. Invasive meningococcal disease in adolescents and young adults. *JAMA* 2001; 286:694–699.
- American Academy of Pediatrics Committee on Infectious Diseases. Prevention and control of meningococcal disease: recommendations for use of meningococcal vaccines in pediatric patients. *Pediatrics* 2005; 116:496–505.
- Centers for Disease Control and Prevention. Summary of notifiable diseases—United States, 2003. *MMWR* 2003; 52:28.
- Densen P. Complement deficiencies and meningococcal disease. *Clin Exp Immunol* 1991; 86(suppl 1):57–62.
- Centers for Disease Control and Prevention. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2005; 54(RR-7):1–21.
- Jackson LA, Schuchat A, Reeves MW, Wenger JD. Serogroup C meningococcal outbreaks in the United States. An emerging threat. *JAMA* 1995; 273:383–389.
- Centers for Disease Control and Prevention. Active Bacterial Core Surveillance (ABCs) Report Emerging Infections Program Network. *Neisseria meningitidis*, 2003—preliminary. www.cdc.gov/ncidod/dbmd/abcs/survreports/mening03prelim.pdf.
- Centers for Disease Control and Prevention. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2000; 49(RR07):1–10.
- Granoff DM, Feavers IM, Borrow R. Meningococcal vaccines. In: Plotkin SA, Orenstein WA, editors. *Vaccines*, 4th ed. Philadelphia, WB Saunders Company, 2004.
- Wenger JD, Ward JI. *Haemophilus influenzae* vaccines. In: Plotkin SA, Orenstein WA, editors. *Vaccines*, 4th ed. Philadelphia, WB Saunders

- Company, 2004.
46. **Salisbury D.** Introduction of a conjugate meningococcal type C vaccine programme in the UK. *J Paediatr Child Health* 2001; 37:S34-S36.
 47. **Miller E, Salisbury D, Ramsay M.** Planning, registration, and implementation of an immunization campaign against meningococcal serogroup C disease in the UK: a success story. *Vaccine* 2001; 20(suppl 1):S58-S67.
 48. **Balmer P, Borrow R, Miller E.** Impact of meningococcal C conjugate vaccine in the UK. *J Med Microbiol* 2002; 51:717-722.
 49. **Maiden MC, Stuart JM; UK Meningococcal Carriage Group.** Carriage of serogroup C meningococci 1 year after meningococcal C conjugate polysaccharide vaccination. *Lancet* 2002; 359:1829-1831.
 50. **Ramsay ME, Andrews NJ, Trotter CL, Kaczmarski EB, Miller E.** Herd immunity from meningococcal serogroup C conjugate vaccination in England: database analysis. *BMJ* 2003; 326:365-366.
 51. **FDA Center for Biologics Evaluation and Research.** Product approval information—licensing action. Meningococcal polysaccharide (serogroups A, C, Y and W-135) diphtheria toxoid conjugate vaccine. www.fda.gov/cber/products/mpdtave011405.htm. Accessed June 28, 2007.
 52. **FDA Vaccines and Related Biological Products Advisory Committee.** Briefing information. Tetravalent meningococcal conjugate vaccine. www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4072b1.htm. Accessed June 28, 2007.
 53. **Ruben FL, Froeschle JE, Meschievitz C, et al.** Choosing a route of administration for quadrivalent meningococcal polysaccharide vaccine: intramuscular versus subcutaneous. *Clin Infect Dis* 2001; 32:170-172.
 54. **Centers for Disease Control and Prevention.** Guillain-Barré syndrome among recipients of Menactra meningococcal conjugate vaccine—United States, June–July 2005. *MMWR* 2005; 54:1023-1025.
 55. **Centers for Disease Control and Prevention.** Update: Guillain-Barré syndrome among recipients of Menactra meningococcal conjugate vaccine—United States, June 2005–September 2006. *MMWR* 2006; 55:1120-1124.
 56. **Cates W Jr.** Estimates of the incidence and prevalence of sexually transmitted disease in the United States. *Sex Transm Dis* 1999; 26(suppl 4):S2-S7.
 57. **Weinstock H, Berman S, Cates W Jr.** Sexually transmitted disease among American youth: incidence and prevalence estimates, 2000. *Perspect Sex Reprod Health* 2004; 36:6-10.
 58. **Winer RL, Hughes JP, Feng Q, et al.** Condom use and the risk of genital human papillomavirus infection in young women. *N Engl J Med* 2006; 354:2645-2654.
 59. **Insinga RP, Dasbach EJ, Myers ER.** The health and economic burden of genital warts in a set of private health plans in the United States. *Clin Infect Dis* 2003; 36:1397-1403.
 60. **Burk RD, Ho GY, Beardsley L, Lempa M, Peters M, Bierman R.** Sexual behavior and partner characteristics are predominant risk factors for genital human papillomavirus infection in young women. *J Infect Dis* 1996; 174:679-689.
 61. **Winer RL, Lee SK, Hughes JP, Adam DE, Kiviat NB, Koutsky LA.** Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. *Am J Epidemiol* 2003; 157:218-226.
 62. **Schiffman M, Castle PE.** Human papillomavirus: epidemiology and public health. *Arch Pathol Lab Med* 2003; 127:930-934.
 63. **Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD.** Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med* 1998; 338:423-428.
 64. **Munoz N, Bosch FX, de Sanjose S, et al; International Agency for Research on Cancer Multicenter Cervical Cancer Study Group.** Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med* 2003; 348:518-527.
 65. **Walboomers JM, Jacobs MV, Manos MM, et al.** Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999; 189:12-19.
 66. **Clifford GM, Smith JS, Plummer M, Munoz N, Franceschi S.** Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis. *Br J Cancer* 2003; 88:63-73.
 67. **Weinstock H, Berman S, Cates W Jr.** Sexually transmitted diseases among American youth: incidence and prevalence estimates 2000. *Perspect Sex Reprod Health* 2004; 36:6-10.
 68. **Jansen KU, Shaw AR.** Human papillomavirus vaccines and prevention of cervical cancer. *Annu Rev Med* 2004; 55:319-331.
 69. **Food and Drug Administration.** Gardasil Product Insert. www.fda.gov/cber/label/hpvmer060806lb.pdf. Accessed June 28, 2007.
 70. **Villa LL, Costa RL, Petta CA, et al.** Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomized double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncol* 2005; 6:271-278.
 71. **Skjeldestad FE, FUTURE II Steering Committee.** Prophylactic quadrivalent human papillomavirus (HPV) (types 6, 11, 16, and 18) L1 virus-like particle (VLP) vaccine (Gardasil) reduces cervical intraepithelial neoplasia (CIN) 2/3 risk. Presented at the 43rd annual meeting of the Infectious Diseases Society of America, San Francisco, CA, October 7, 2005. Abstract LB-8a.
 72. **Centers for Disease Control and Prevention.** Press release: CDC's Advisory Committee recommends human papillomavirus virus vaccination. www.cdc.gov/od/oc/media/pressrel/r060629.htm. Accessed June 28, 2007.
 73. **Harper DM, Franco EL, Wheeler C, et al; GlaxoSmithKline HPV Vaccine Study Group.** Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomized controlled trial. *Lancet* 2004; 364:1757-1765.
 74. **Flemming DT, McQuillan GM, Johnson RE, et al.** Herpes simplex virus type 2 in the United States, 1976 to 1994. *N Engl J Med* 1997; 337:1105-1111.
 75. **Kimberlin DW.** Neonatal herpes simplex infection. *Clin Microbiol Rev* 2004; 17:1-3.
 76. **Kimberlin DW, Rouse DJ.** Genital herpes. *N Engl J Med* 2004; 350:1970-1977.
 77. **Corey L, Adams HG, Brown ZA, Holmes KK.** Genital herpes simplex virus infections: clinical manifestations, course, and complications. *Ann Intern Med* 1983; 98:958-972.
 78. **Ratray MC, Corey L, Reeves WC, Vontver LA, Holmes KK.** Recurrent genital herpes among women: symptomatic v. asymptomatic viral shedding. *Br J Vener Dis* 1978; 54:262-265.
 79. **Benedetti J, Corey L, Ashley R.** Recurrence rates in genital herpes after symptomatic first-episode infection. *Ann Intern Med* 1994; 121:847-854.
 80. **Stanberry LR, Spruance SL, Cunningham AL, et al; GlaxoSmithKline Herpes Vaccine Efficacy Study Group.** Glycoprotein-D-adjuvant vaccine to prevent genital herpes. *N Engl J Med* 2002; 347:1652-1661.

ADDRESS: Sylvia H. Yeh, MD, Harbor-UCLA Medical Center, UCLA Center for Vaccine Research, 1124 West Carson Street, Liu Research Building, Torrance, CA 90502; e-mail syeh@labiomed.org.

Visit our web site at <http://www.ccjm.org>

Contact us by e-mail at ccjm@ccf.org