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Immunization Update 2010

Ever since 1796, when Edward Jenner introduced the world's first vaccine against smallpox, the role of vaccination has arguably become one of the most important advances in medicine. Jenner's contemporary, Benjamin Franklin, is often associated with the proverb, "An ounce of prevention is worth a pound of cure." Much has happened in the past 200 years in the field of immunization, and this issue of Primary Care Reports *summarizes current recommendations of practical import to the primary care physician. Even though large chain pharmacies now compete with physician offices in offering the influenza vaccine, the primary care physician still serves a critical role for patient advocacy, access, and information.*

—The Editor

The past decade has provided remarkable achievements in the development and use of vaccines against a wide variety of infectious diseases. Practitioners who care for children and adolescents understand that prevention of disease is greatly preferred over treatment. Vaccines are the ultimate tools in the prevention of infectious diseases in this population. Children may now be protected against infections that were common in children in both the distant and recent past. This increase in the number of such vaccines, combined with modifications in the use of existing products, creates a challenge for the practicing physician to remain current and implement vaccination recommendations. This article will review current recommendations for vaccination of infants, children, and adolescents.

Introduction

New vaccine products and new vaccine recommendations have appeared with increasing frequency in the recent past. During the past 25 years, the development of immunizations against a greater number of pathogens has greatly expanded the vaccine schedule for children. The vaccine schedule has also "grown up," recognizing that vaccines are not solely indicated for young children, but are part of an integrated continuum across other age groups. During the past decade, vaccine recommendations have also targeted the adolescent population. (*See Table 1.*) Additionally, some existing vaccines have been expanded to include new groups of vaccinees. The rapid growth in both the number of vaccines and in new and modified recommendations for their use can make it a challenge for the practicing physician to stay current in vaccine utilization. This article will review recent vaccine developments pertinent to the practicing pediatrician and primary care physician.

Meningococcal-conjugate Vaccine (MCV)

Meningococcal infection is known for its rapidity of onset and progressive, often fatal, disease in healthy individuals. While infection can extend across all age groups and vary seasonally and within differing geographic areas, the

Executive Summary

- The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention performs regular updates of immunization recommendations.
- Since 1976, there has been a 20-fold increase in the number of reported pertussis cases in the United States, with more than 5,200 cases reported during the first nine months of 2010 in California.
- The current recommendation is that all persons aged 6 months and older without contraindications should receive the annual influenza vaccination.
- HPV is the cause of virtually all cervical cancers and precancers, with types 16 and 18 accounting for up to 70% or more of cervical malignancies.
- All children should receive HAV vaccine at age 1 year.

epidemiology of the disease suggests certain groups are at higher risk for both acquisition and poor outcome. Young children, particularly infants, in the first few months of life, have a much greater incidence of infection than other age groups. However, individuals between 11 and 19 years of age are at increased risk for meningococcal infection as well, accounting for 17% of all invasive meningococcal disease.[1] A quadrivalent (serogroups A, C, Y, and W135) polysaccharide vaccine has been licensed for almost 20 years (Menomune®, Sanofi Pasteur) with its use limited to high-risk groups such as those in the military, asplenic individuals, persons with complement deficiencies, entering college freshmen, persons travelling to high-risk geographic areas, and those working in microbiology laboratories. Since 2005, a conjugate polysaccharide-protein vaccine (serogroups A, C, Y, and W135 — Menactra®, Sanofi Pasteur) has been recommended for all adolescents aged 11-18 years (ideally at the 11-12 year preadolescent visit or for those entering high school). College entrants and other high-risk groups should receive MCV4. As compared to polysaccharide vaccines, conjugate vaccines provide a more protective immune response by inducing robust T-cell lymphocyte involvement, rather than relying primarily on B-cell lymphocyte memory.

A second quadrivalent meningococcal-conjugate vaccine was licensed in early 2010 — Menveo® (Novartis). Either vaccine can be used to vaccinate individuals aged 11 to 55 years. Only Menactra®, however, is licensed for vaccinating children ages 2 through 10 years.

The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) updated its recommendations in 2009.[2] While restating the above recommendations, immunization is recommended for all persons ages 11-18 years and for those individuals ages 2-55 years at high risk for meningococcal infections. Recommendations were also made for subsequent vaccine doses in previously immunized individuals who remain at increased risk. (*See Table 2.*) For such persons older than 7 years of age vaccinated previously with any meningococcal vaccine, an additional dose should be administered 5 years later. For persons aged 2 to 6 years, revaccination is recommended 3 years after the previous dose. Persons with ongoing increased risk (e.g., asplenia) should be revaccinated every 5 years. Repeat immunization of students entering college who will be living in dormitories was not recommended, unless the previous vaccination was meningococcal polysaccharide vaccine (MPSV4).

A greater percentage of infections in infancy is caused by serogroup B meningococci. Currently, there is no available immunogenic vaccine against this serotype, which hinders full protection of this very young age group.

Varicella Vaccine

Before the introduction of live-attenuated varicella vaccine in 1995, varicella was a universal childhood disease in the United States. On the basis of data from the National Health Interview Survey for 1980-1990, approximately 4 million cases — equal to the entire annual birth cohort — were estimated to have occurred annually (annual incidence rate: 15 cases per 1000 population).[3] After introduction of vaccine in 1995, the number and rate of varicella-related hospitalizations, outpatient visits for chickenpox, and varicella-related deaths have all declined.[4] Despite vaccine coverage rates of greater than 90%, however, the proportion of cases occurring in vaccine recipients has increased. Protection afforded by a single dose of varicella vaccine in children does wane with time.[5] The incidence of breakthrough chickenpox in previously immunized children was demonstrated to increase more than 12 times from the first year of vaccination to year 8 after vaccination.

Children must routinely receive two doses of varicella vaccine to confer optimal immunity.[6] Preschool-aged children should receive the first dose of varicella vaccine at age 12-15 months, with the second dose administered at age 4-6 years. The second dose of vaccine may be given earlier, provided more than 3 months have elapsed after the first dose. Individuals aged older than 13 years should receive 2 doses of vaccine, administered 4-8 weeks apart. All adolescents and adults without evidence of immunity should be vaccinated. Vaccination is especially recommended for susceptible persons who have close contact with persons

Table 1: Recommended Childhood and Adolescent Immunizations

Children Aged 0 to 6 Years
• Hepatitis B virus vaccine
• Rotavirus vaccine (RV1, RV4)
• Diphtheria, tetanus, and acellular pertussis vaccine (DTap)
• *Haemophilus influenzae* type b vaccine
• Pneumococcal conjugate vaccine (PCV7, PCV13)
• Inactivated poliovirus vaccine
• Influenza vaccine (given annually)
• Measles, mumps, rubella (MMR) vaccine
• Varicella vaccine
• Hepatitis A virus vaccine
• Meningococcal vaccine (certain high-risk children)
Adolescent
• Tetanus toxoid, reduced-dose diphtheria toxoid, and acellular pertussis (Tdap)
• Human papillomavirus vaccine (HPV4, HPV2)
• Meningococcal vaccine
• Influenza vaccine (given annually)
• Measles, mumps, rubella (catch-up if necessary)
• Varicella vaccine (second dose for those with only a single dose previously)
• Hepatitis B virus vaccine (catch-up if necessary)
• Inactivated poliovirus vaccine (catch-up if necessary)
• Hepatitis A vaccine (catch-up if necessary)
• Pneumococcal polysaccharide vaccine (certain high-risk adolescents)

at high risk for serious complications (e.g., health care personnel and household contacts of immunocompromised persons), as well as persons who live or work in environments in which transmission of varicella zoster virus is more likely (e.g., school teachers). Varicella vaccine is effective in preventing illness or modifying varicella severity in exposed unvaccinated children if administered within 3 to 5 days of exposure to the rash.[7]

Measles-Mumps-Rubella-Varicella Vaccine (MMRV)

MMRV vaccine was licensed in the United States in September 2005 and may be used instead of measles, mumps, rubella vaccine and varicella vaccine to implement the recommended 2-dose vaccine schedule for prevention of measles, mumps, rubella, and varicella among children aged 12 months to 12 years. At the time of its licensure, the use of MMRV vaccine was preferred for both the first and second doses over separate injections of equivalent component vaccines. Postlicensure studies and other evidence, however, have revealed that among children aged 12-23 months, one additional febrile seizure occurred 5-12 days after vaccination per 2,300-2,600 children who had received the first dose of MMRV vaccine compared with children who had received the first dose of MMR vaccine and varicella vaccine administered as separate injections at the same visit.[8]

In 2009, the ACIP adopted new recommendations regarding use of MMRV vaccine for the first and second doses and identified a personal or family (i.e., sibling or parent) history of seizure as a precaution for use of MMRV vaccine. For the first dose of measles, mumps, rubella, and varicella vaccines at age 12-47 months, either MMR vaccine and varicella vaccine or MMRV vaccine may be used. The benefits and risks of both vaccination options should be discussed with the parents or caregivers. Unless the parent or caregiver expresses a preference for MMRV vaccine, MMR vaccine and varicella vaccine should be administered for the first dose in this age group. For the second dose of measles, mumps, rubella, and varicella vaccines at any age (15 months to 12 years) and for the first dose at age 48 months or older, use of MMRV vaccine generally is preferred over separate injections of the equivalent component vaccines (i.e., MMR vaccine and varicella vaccine).

Tetanus Toxoid-Reduced-Dose Diphtheria Toxoid — Acellular Pertussis Vaccine (Tdap)

Since the introduction of pertussis vaccine almost six decades ago, there has been a dramatic decline in the incidence of pertussis in the United States, with only 1010 cases reported nationwide in 1976.[9] Since then, however, there has been a 20-fold increase in the number of reported pertussis cases in the United States. The increase in reported numbers may be due to a variety of factors, including greater awareness of the disease by practitioners, particularly among adolescents and adults, as well as improved diagnostic testing. Outbreaks secondary to waning immunity in the adolescent and young adult age groups have been noted. Others are a consequence of likely underimmunization of children. Pertussis in vaccinated middle-school populations might reflect that present-day childhood diphtheria-tetanus-acellular pertussis (DTaP) vaccines may be less antigenically potent when compared to previous diphtheria-tetanus-pertussis (DTP) vaccines.[10]

In California, more than 5,200 cases of pertussis during the first nine months of 2010 — the most reported in 60 years — have been reported.[11] Adolescents 10-19 years

Table 2: Meningococcal Vaccine Revaccination Guidelines

- **Persons previously vaccinated with either MCV4 or meningococcal polysaccharide vaccine and who are at prolonged increased risk for meningococcal disease should be revaccinated with MCV4.**
  - **Persons aged ≥7 years should be revaccinated 5 years after their previous meningococcal vaccine**
  - **Persons aged 2-6 years should be revaccinated 3 years after their previous meningococcal vaccine**

Persons at prolonged increased risk for meningococcal disease include:

- **Individuals with increased susceptibility such as persistent complement component deficiencies (e.g., C3, properdin, Factor D, and late complement component deficiencies)**
- **Children and adults with anatomic or functional asplenia**
- **Persons who have prolonged exposure (e.g., microbiologists routinely working with *Neisseria meningitidis*, or travelers to or residents of countries where meningococcal disease is hyperendemic or epidemic)**

Revaccination of college freshmen living in dormitories who were previously vaccinated with MCV4 is not recommended (unless initial vaccine was meningococcal polysaccharide vaccine)

of age and adults 20 years of age or older account for the preponderance of cases. These older individuals may transmit infection to young infants who are at greater risk of severe pertussis. Children too young to have completed their primary vaccine series account for the majority of pertussis-related complications, hospitalizations, and death. In the California outbreak, through October 2010, 59% of hospitalized cases were infants younger than 3 months of age and 74% were infants younger than 6 months of age. Of the nine reported deaths, 8 fatalities were infants younger than 2 months of age. Commonly, the index case for the transmission of the organism is a family member, frequently a parent.[12]

Tdap is recommended as a routine booster dose in adolescents, preferentially given at the 11-12 year visit. Tdap is preferred over the use of tetanus and diphtheria toxoid (Td) for wound management. The optimal interval between receipt of Tdap and a previous Td booster is 2 years or greater, but shorter intervals are acceptable. Practitioners should adopt a "cocoon" strategy that either vaccinates a mother immediately post-partum or the mother-to-be in the second or third trimester if she has not been immunized previously. Other family members who will have contact with the infant after birth should also receive Tdap. A routine booster dose every 10 years is recommended for all adults aged younger than 65 years. Health care workers should be immunized. Boostrix® (GlaxoSmithKline) is licensed for individuals aged 10-18 years and Adacel® (Sanofi Pasteur) for those aged 11-64 years.

Pneumococcal Vaccine

In 2000, a 7-valent pneumococcal conjugate vaccine (PCV7) for routine use in infants and children was licensed in the United States. Routine childhood immunization with PCV7 has had a major impact on the epidemiology of infections caused by *Streptococcus pneumoniae* including: demonstration of reduced rates of nasopharyngeal colonization by pneumococcal vaccine serotypes in vaccinated children,[13] significant reductions in invasive pneumococcal disease (IPD — lower respiratory tract infection, bacteremia, meningitis) caused by vaccine serotypes in vaccinated children,[14] and modest reductions in noninvasive disease, such as acute otitis media, attributed to pneumococcal infection.[15] PCV7 administration has an indirect protection against vaccine-type pneumococcal carriage among family members living with PCV7-vaccinated children and a reduction in the rate of vaccine-type IPD in unvaccinated individuals.[16]

While widespread PCV7 use has remarkably reduced infections caused by vaccine strains 4, 6B, 9V, 14, 18C, 19F, and 23F, shifts among pneumococcal serotypes causing both noninvasive and invasive pneumococcal disease have occurred. Children who have received PCV7 have fewer infections caused by vaccine-type strains, but are at increased risk for infections caused by nonvaccine types. After early significant declines in IPD in young children following vaccine introduction, infections caused by nonvaccine serotypes have resulted in a leveling off of IPD rates since 2002.[17] Pneumococcal serotypes not represented in PCV7 accounted for only 20% of IPD cases in 1998-1999, but represented greater than 90% of cases in 2005. Infections caused by "replacement" strains (serotypes 11, 15, and 19A, among others) have been reported. Serotype 19A, which is structurally similar to the vaccine type 19F but for which the vaccine provides no cross protection, can be resistant to multiple antibiotics and has increasingly been identified in both IPD and local infections. Serotype 19A was the most common pneumococcal isolate causing IPD among children in 2005. The magnitude of the rise in disease caused by nonvaccine serotypes, however, has been small compared to the marked drop in the disease caused by vaccine serotypes.[18]

A recently-licensed 13-valent pneumococcal conjugate vaccine (PCV13) has incorporated these emerging serotypes into its composition. The vaccine contains the pneumococcal polysaccharide capsular serotypes 1, 3, 4, 5,6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. When administered to

Table 3: Recommended Transition Schedule from 7-valent Pneumococcal Conjugate Vaccine (PCV7) to 13-valent Vaccine (PCV13) Vaccination Among Infants and Children, According to Number of Previous PCV7 Doses Received — Advisory Committee on Immunization Practices (ACIP), United States, 2010

Infant Series			Booster dose	Supplemental PCV13 dose
2 mos	4 mos	6 mos	≥ 12 mos*	14-59 mos**
PCV7	PCV13	PCV13	PCV13	—
PCV7	PCV7	PCV13	PCV13	—
PCV7	PCV7	PCV7	PCV13	—
PCV7	PCV7	PCV7	PCV7	PCV13

* No additional PCV13 doses are indicated for children aged 12-23 months who have received 2 or 3 doses of PCV before age 12 months and at least 1 dose of PCV13 at age ≥ 12 months.

** For children with underlying medical conditions, a single supplemental PCV13 dose is recommended through age 71 months.

Adapted from: Centers for Disease Control and Prevention. Licensure of a 13-valent pneumococcal conjugate vaccine (PCV13) and recommendations for use among children — Advisory Committee on Immunization Practices, 2010. MMWR Morb Mortal Wkly Rep 2010;59:258-261.

infants concomitantly with other recommended vaccines at 2, 4, and 6 months, PCV13 was well tolerated and immunogenic, with most children developing protective antibody responses to each of the 13 serotypes.[19] The safety profiles of PCV7 and PCV13 are comparable. Children aged 2-59 months should routinely be vaccinated with PCV13.[18] Specific recommendations have been formulated for childhood vaccination during the transition period from PCV7 to PCV13 use. (*See Table 3.*) A supplemental dose of PCV13 is recommended for all children aged 14-59 months who have previously received 4 doses of PCV7. Children aged 24-71 months with chronic medical conditions that increase their risk for pneumococcal disease (functional or anatomic asplenia, immunocompromising conditions, and immunocompetent children with high-risk conditions including cardiopulmonary disease, diabetes mellitus, cerebrospinal fluid leaks, and those with cochlear implants) should receive 2 doses of PCV13 given at least 8 weeks apart.

Influenza Vaccine

Circulating influenza A and B types vary during annual epidemics due to the capacity of the virus to undergo frequent antigenic change (i.e., antigenic drift) and by point mutations and recombinant events that occur during replication of the virus. Influenza A viruses are further subtyped based on surface antigens: hemagglutinin and neuraminidase. Influenza infection among individuals who have little or no existing immunity to the viral type or subtype has the ability to cause a worldwide pandemic. In April 2009, infections in humans with a novel influenza A (H1N1) virus resulted in a worldwide pandemic.[20]

In the United States, annual influenza epidemics result in infections among persons in all age groups. Rates of infection, however, are highest among children, with rates of complications, hospitalizations, and death highest in persons aged older than 65 years, children younger than 5 years, and persons of any age who have underlying medical conditions that increase the risk of complications from influenza.[21] Influenza-related hospitalizations are substantially higher among children younger than 2 years of age compared with older children and similar to rates for other groups considered at higher risk for influenza-related complications (persons aged 2-64 years with underlying chronic medical conditions such as cardiopulmonary disorders, renal or hepatic dysfunction, diabetes mellitus; immunocompromised persons; pregnant women during the influenza season; those with conditions that compromise respiratory function or the handling of respiratory secretions; and individuals older than 65 years of age). In the HIN1 pandemic, however, serious infection predominated among children, younger adults, and resulted in serious illness among pregnant women. Importantly, children serve as effective disseminators of influenza virus throughout the community.

Two types of seasonal influenza vaccines are licensed in the United States: the trivalent inactivated vaccine (TIV) and trivalent live attenuated influenza vaccine (LAIV). Both have demonstrated efficacy and safety in adults and children. These vaccines given annually each contain influenza virus strains predicted to be prevalent in the upcoming influenza season, including influenza B types and influenza A subtypes. TIV contains inactivated virus, is administered by intramuscular injection, and is approved for use in all children 6 months of age and older and in all adults. There are a number of licensed TIV formulations available with differing recommendations dependent on the age groups vaccinated. Practitioners should refer to vaccine-specific recommendations for age-appropropriate administration. LAIV is given as a spray intranasally and is approved for persons aged 2-49 years. Persons at higher risk for complications of influenza infection because of underlying medical conditions should not receive LAIV.

Table 4: Summary of Influenza Vaccination Recommendations, 2010

- All persons aged ≥ 6 months
- Protection of persons at higher risk for influenza-related complications should continue to be targeted for vaccination as providers and programs transition to universal, routine vaccination of all persons aged ≥ 6 months.

When vaccine supply is limited, vaccination efforts should focus on delivering vaccination to persons who are:

- Children aged 6–59 months
- Individuals aged ≥ 50 years
- Residents of nursing homes and other chronic care facilities
- Women who are pregnant during the influenza season (TIV may be administered at any time during the pregnancy, regardless of the stage of pregnancy)
- American Indians/Alaskan Natives
- Morbidly obese individuals (body-mass index ≥ 40)
- Individuals aged 6 months to 18 years who are receiving aspirin therapy and who might be at risk for developing Reye syndrome after influenza virus infection
- Household contacts and caregivers of children aged < 5 years (with emphasis on those caring for children < 6 months) and adults > 50 years
- Household contacts and caregivers of persons with medical conditions that place them at higher risk for severe influenza complications
- Health care personnel

Children with a history of asthma should not receive LAIV.

It is now recommended that all persons aged 6 months and older receive annual influenza vaccination. Since infants younger than 6 months of age cannot receive influenza vaccine, it is critical to immunize caregivers and household contacts of children in this very young age group. Protection of persons at higher risk of complications should continue to be a focus of efforts until routine universal vaccination of all persons aged 6 months and older is achieved. (*See Table 4.*)

To attain optimal protection in young children, 2 doses of either TIV or LAIV vaccine separated by 4 weeks or more have been recommended for the first vaccination in those aged 6 months to 9 years who were previously unvaccinated with seasonal influenza vaccine. If a previously unvaccinated child in this age range received only a single seasonal vaccine in one year, then two doses are necessary for the following year. Only a single annual dose is recommended for children aged 9-18 years and adults.

The emergence of a novel influenza virus in the H1N1 pandemic, however, has resulted in modified recommendations for childhood vaccination for the 2101-2011 influenza season.[21] The 2010-2011 vaccine contains the virus strains A/California/7/2009 (H1N1)-like (the same strain as was used for 2009 H1N1 monovalent vaccines), A/Perth/16/2009 (H3N2)-like, and B/Brisbane/60/2008-like. For those 6 months to less than 9 years, two doses of the current vaccine are necessary for children who:

- never received seasonal influenza vaccine before;
- were vaccinated for the first time in 2009-2010, but only received one dose;
- were previously vaccinated with seasonal influenza vaccine, but did not receive 2009 monovalent H1N1 vaccine.

One dose may be administered to all others aged 6 months through 8 years.

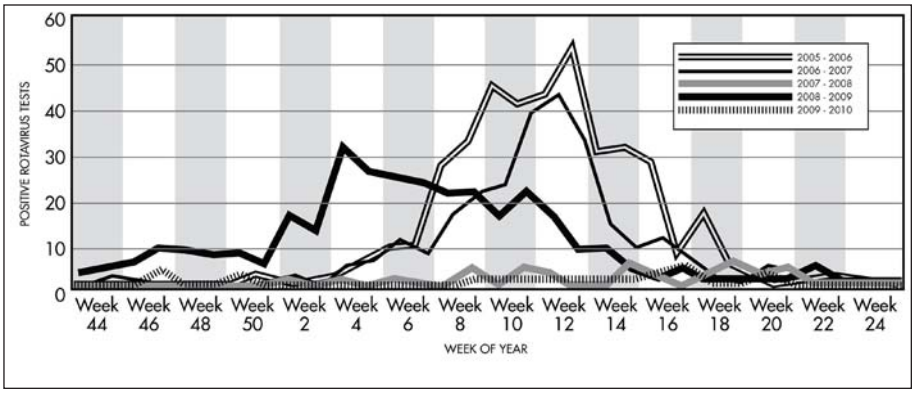
Rotavirus Vaccine

Rotavirus is the leading cause of infectious diarrhea in children. Most children in the world are infected with rotavirus by age 2 years. Rotavirus infection in infants and young children causes significant morbidity, resulting in hospitalizations and increased outpatient visits. In this country, the number of deaths attributed to rotavirus is low. The annual rotavirus season in the United States begins during late autumn in the Southwest, spreading across the country and ending in the Northeast by spring.[22]

A rotavirus vaccine was first approved for use in this country in 1998 but was withdrawn from the market due to an increased risk of intussusception in those vaccinated (1 per 10,000 vaccinated infants). Two rotavirus vaccines are currently available. A pentavalent vaccine RV5 (RotaTeq®, Merck), licensed in 2006, is a live, oral vaccine that contains five reassortant rotaviruses developed from human and bovine parent rotavirus strains. A monovalent vaccine RV1 (Rotarix®, GlaxoSmithKline), approved in 2008, is a live, oral vaccine derived from a human rotavirus strain.[23] Safety and efficacy were demonstrated for both vaccines in prelicensure clinical trials. Both have demonstrated efficacy in preventing rotavirus diarrhea in the year after vaccination, especially in the prevention of serious, dehydrating gastroenteritis. Use of the vaccine has demonstrated a fairly dramatic decrease in infections and hospitalizations and altered the rotavirus season in many areas. We have seen such changes in our own institution due to routine utilization of the vaccine in the community. (*See Figure 1.*)

The administration schedules for RV1 and RV5 differ. RV5 is given

Figure 1: Rotavirus Gastroenteritis, The Children's Medical Center of Dayton



as a 3-dose schedule at 2, 4, and 6 months of age. RV1 is administered in a 2-dose schedule at 2 and 4 months of age. The first dose of either vaccine should be given after 6 weeks of age but before 15 weeks of age. The final dose should be given before 8 months of age, with a minimum interval between doses of 4 weeks. The rotavirus vaccine series generally should be completed with the same product whenever possible. Vaccination should not be deferred, however, because the product used for a previous dose(s) is not available or is unknown. In these situations, vaccination should be continued or completed with the available vaccine. If any dose in the series was RV5 or the vaccine product is unknown for any dose in the series, a total of 3 doses of rotavirus vaccine should be administered.

Some children may experience loose stools or vomiting in the 42-day period after vaccination. Postlicensure monitoring of vaccinated children has not shown an increased risk of intussusception with either product. A serious allergic reaction to either the vaccine or vaccine components is a contraindication for vaccination. No safety or efficacy data exist for use in patients who are immunocompromised, those with acute gastroenteritis or preexisting gastrointestinal disease, or those with previous intussusception. Vaccination should be used with caution in such patients. Preterm infants (less than 37 weeks gestation) may be vaccinated according to the same schedule and precautions as full-term infants as long as the infant's chronological age meets the age requirements for rotavirus vaccine and the infant is clinically stable. The vaccine should be administered at the time of discharge from the neonatal intensive care unit or nursery, or after discharge.

Human Papillomavirus (HPV) Vaccine

HPV is the most prevalent of all sexually transmitted infections. Approximately one-half of all adults acquire HPV during their lifetime. Most of these infections clear spontaneously, and only a minority will have disease. HPV is the cause of virtually all cervical cancers and precancers. Up to 15 oncogenic HPV types contribute to cervical cancer, but HPV types 16 and 18 account for 70% or more of cervical malignancies. Nononcogenic HPV types, most often HPV types 6 and 11, are associated with 90% of external genital warts. Other HPV-associated conditions include vulvar, vaginal, anal, head/neck carcinomas, and recurrent respiratory papillomatosis.[24]

Quadrivalent HPV vaccine HPV4 (Gardasil®, Merck & Co) composed of HPV-6, -11, -16, and -18 virus-like particles was licensed for use in females in 2006. A bivalent HPV vaccine HPV2 (Cervarix®, GlaxoSmithKline) containing HPV-16 and -18 virus-like particles was licensed for use in females in 2009. HPV4 is directed against two oncogenic viruses (HPV 16 and 18) and two nononcogenic types (HPV 6 and 11). HPV2 is directed against the oncogenic HPV types 16 and 18. In preclinical licensure trials, both vaccines were highly efficacious against HPV 16- and 18-related cervical precancerous lesions. HPV4 also demonstrated high efficacy against HPV 6- and 11-related genital warts and HPV 16- and 18-related vaginal and vulvar precancerous lesions.[25]

Routine vaccination with 3 doses of either HPV2 or HPV4 is recommended for females aged 11 or 12 years and can be started in females as early as age 9 years. Ideally, vaccine should be administered before potential exposure to HPV through sexual contact. Vaccination is recommended for females aged 13 through 26 years who have not been vaccinated previously or who have not completed the 3-dose series. If a female reaches age 26 years before the series of vaccinations is completed, remaining doses can be administered after age 26 years. Whenever feasible, the same HPV vaccine should be used for the entire vaccination series. No studies address interchangeability of HPV vaccines. If one does not know or have available the HPV vaccine previously administered, either HPV2 or HPV4 can be used to complete the series to provide protection against HPV 16 and 18. For protection against HPV 6- or 11-related genital warts, a vaccination series with less than 3 doses of HPV4 might provide less protection against genital warts than a complete 3-dose HPV4 series. It is important that vaccinated women continue with regular cervical cancer screening. HPV vaccines may be administered to immunocompromised individuals.

Syncope can occur after vaccination with HPV vaccines and has been observed among adolescents and young adults. To avoid serious injury related to a syncopal episode, patients should be observed for 15 minutes after they are vaccinated. In clinical trials, vaccine safety among recipients was similar to those receiving placebo vaccines. HPV vaccines are not recommended for use in pregnant women.

In 2010, HPV4 was licensed

Table 5: Summary of New and Updated Vaccination Recommendations, 2010

Children

- Routine annual influenza vaccination (ages >6 months)
- Hepatitis A vaccine at 12-23 months
- Rotavirus vaccination for infants
- Two-dose varicella vaccine administration (12-15 months and 4-6 years with catch-up for other age groups)
- MMRV vaccine guidelines to minimize risk of potential adverse event of febrile seizures

Adolescents

- Meningococcal conjugate vaccine (age 11-12 with catch-up vaccination through age 18 years)
- Human papillomavirus vaccine for girls (age 11-12 with catch-up vaccination through age 18 years)
- Tetanus toxoid, reduced-dose diphtheria toxoid, and acellular vaccine – Tdap (age 11-12 with catch-up vaccination through age 18 years)
- Human papillomavirus vaccine for boys
- Routine annual influenza vaccination

Other

- Preference for the use of Tdap over Td (tetanus toxoid-reduced-dose diphtheria toxoid) for wound management
- Hepatitis A vaccine for postexposure prophylaxis
- Reduced (4-dose) rabies vaccine schedule for postexposure prophylaxis

for administration to males aged 9 through 26 years to reduce their likelihood of acquiring genital warts caused by HPV types 6 and 11. Clinical trials documented efficacy in preventing genital warts and demonstrated a safety profile similar to that in placebo recipients. As with females, the vaccine would be most effective when given before exposure to HPV through sexual contact.[26]

Hepatitis A Virus (HAV) Vaccine

The hepatitis A childhood immunization strategy in the United States has been implemented incrementally, beginning with the recommendations in 1996 to vaccinate children living in communities with the highest disease rates and continuing in 1999 with CDC's recommendations for vaccination of children living in states, counties, and communities with consistently elevated hepatitis A rates. In 2006, routine vaccination of children nationwide with HAV vaccine was recommended.[27]

The likelihood of having symptoms with HAV infection is related to age. In children younger than 6 years, 70% of infections are asymptomatic; if illness does occur, it is typically not accompanied by jaundice.[28,29] Among older children and adults, infection typically is symptomatic, with jaundice occurring in more than 70% of patients. While the incidence of infection tends to be higher in younger age groups, morbidity and need for hospitalization is greater in older persons. The infection has a fecal-oral mode of transmission and the asymptomatically infected child can serve as the index case for transmission to others.

All children should receive HAV vaccine at age 1 year (i.e., 12-23 months). A second dose of the vaccine should be administered 6-18 months later. Catch-up vaccination of unvaccinated children aged 2-18 years is recommended. Two HAV vaccines (Vaqta®, Merck & Co., Havrix®, GlaxoSmithKline) are available, and both are highly immunogenic when administered to children and adolescents according to multiple schedules; 97-100% of persons aged 2-18 years had protective levels of antibody 1 month after receiving the first dose, and 100% had protective levels 1 month after the second dose. The vaccine is also recommended for unvaccinated older children who reside in areas of high HAV prevalence. Other groups to be vaccinated include those at higher risk of HAV infection, including persons traveling to countries that have high endemicity of HAV infection, users of illicit drugs, and men who have sex with men.[27]

For individuals acutely exposed to HAV, administration of immune globulin (IG) has been traditionally recommended to prevent infection. The current guideline for postexposure prophylaxis against HAV infection, however, is to administer either IG or HAV vaccine.[30] The vaccine offers additional benefit in affording long-term protection against HAV infection. In persons aged 12 months to 40 years, HAV vaccine is preferentially recommended. For individuals older than 40 years of age, use of the vaccine is permitted, but IG administration is preferred. IG should continue to be utilized in infants younger than 12 months, immunocompromised persons, and those with chronic liver dysfunction. Vaccine or IG should be administered as soon as possible after exposure. The efficacy of IG or HAV vaccine when administered more than 2 weeks after exposure has not been established.

For those traveling or working in countries with high or intermediate hepatitis A endemicity, either HAV vaccine or IG may be given. HAV vaccination at the age-appropriate dose, however, is preferred to IG. The first dose of HAV vaccine should be administered as soon as travel is considered. Based on limited data indicating equivalent postexposure efficacy of IG and vaccine among

Table 6: Useful Immunization-related Websites

Immunization Action Coalition http://www.immunize.org
CDC's immunization schedule for infants, children, adolescents, and adults http://www.cdc.gov/vaccines/recs/schedules
CDC's "Pink Book" — Epidemiology and Prevention of Vaccine-Preventable Diseases http://www.cdc.gov/vaccines/pubs/pinkbook
ACIP's "General Recommendations on Immunization" http://www.cdc.gov/mmwr/PDF/rr/rr5515.pdf
American Academy of Pediatrics Immunization Site http://www.aap.org/immunization
Vaccine information Center — The Children's Hospital of Philadelphia http://www.chop.edu/service/vaccine-education-center/home.html
Institute for Vaccine Safety — Johns Hopkins Bloomberg School of Public Health http://www.vaccinesafety.edu

healthy persons aged younger than 40 years, 1 dose of single-antigen HAV vaccine administered at any time before departure can provide adequate protection for most healthy persons. Older adults, immunocompromised persons, and individuals with chronic liver disease or other chronic medical conditions planning to depart to an endemic area in less than 2 weeks should receive the initial dose of vaccine and simultaneously receive IG (0.02 mL/kg) at separate anatomic injection sites. Completion of the vaccine series according to the licensed schedule is necessary for long-term protection.

Rabies Vaccine

For unvaccinated persons, the combination of human rabies immune globulin and vaccine is recommended for both bite and nonbite exposures, regardless of the time interval between exposure and initiation of postexposure prophylaxis (PEP). If PEP has been initiated and appropriate laboratory diagnostic testing (i.e., the direct fluorescent antibody test) indicates that the animal that caused the exposure was not rabid, PEP may be discontinued. A reduced 4-dose regimen of rabies vaccine administered intramuscularly is now recommended for previously unvaccinated persons. The first vaccine dose should be administered as soon as possible after exposure in combination with rabies immune globulin (RIG). The date of the first vaccine dose is considered to be day 0 of the PEP series. Additional doses then should be administered on days 3, 7, and 14. Intramuscular vaccine should be administered in the deltoid area for adults and the anterolateral aspect of the thigh for children. The gluteal area should not be used because administration of vaccine in this area might result in a diminished immunologic response. Children should receive the same vaccine dose (i.e., vaccine volume) as recommended for adults.

Conclusion

Current recommendations for vaccination of children and adults have dramatically evolved over the recent past. (*See Table 5.*) Over time, an increasing number of vaccines has been introduced. Undoubtedly, changes in the vaccination schedule and further introduction of new vaccines will occur with regular frequency in the years ahead. Modifications of the use of older and current vaccines will likely occur as we increase our experience with these agents. We have progressed quite a distance in diminishing or almost eliminating the scourge of many vaccine-preventable diseases. It is the role of the practitioner to be both cognizant of these changes and additions and to administer these effective tools in disease prevention. It is a further responsibility to educate the public on the importance of timely receipt of immunizations to prevent illness among both the pediatric population and other age groups.

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Physician CME Questions

26. Which group has the highest risk of meningococcal infection?
    A. young children, particularly infants, in the first few months of life
    B. adolescents
    C. college students
    D. elderly

27. Which one of the following statements is true regarding varicella vaccine?
    A. Preschool-aged children should receive the first dose of varicella vaccine at 12-15 months of age with second dose at age 4-6 years.
    B. Individuals older than 13 years need only one dose of vaccine.
    C. All adolescents and adults, regardless of immunity status, should be vaccinated.
    D. Varicella vaccine is ineffective in preventing illness if administered within 5 days of exposure to the rash.

28. Routine childhood immunization with PCV7 has been associated with which one of the following:
    A. decreased risk for infections caused by nonvaccine types
    B. significant reductions in invasive pneumococcal disease
    C. pneumococcal serotypes not represented in PCV7 represent only 20% of invasive pneumococcal serotypes in 2005
    D. serotype 6B being the most common pneumococcal isolate causing invasive pneumococcal infection among children in 2005

29. Which of the following statements regarding HPV is *false*?
    A. HPV is the most prevalent of all sexually transmitted infections.
    B. About one-half of all adults acquire HPV during their lifetime.
    C. Routine vaccination with either HPV2 or HPV4 should not be administered until after sexual activity has occurred.
    D. HPV4 is licensed for administration to males aged 9-26 to reduce likelihood of acquiring genital warts.

30. Which of the following statements regarding influenza is *false*?
    A. Rates of infection are highest among children.
    B. Two types of seasonal vaccines are licensed in the United States: trivalent inactive and trivalent live attenuated.
    C. All persons aged 6 months and older without contraindications should receive vaccination.
    D. Children with a history of asthma should receive live attenuated influenza vaccine.

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CME Answer Key

26. A; 27. A; 28. B; 29. C; 30. D

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Can vitamins stop photoaging of the skin?

Source: Zussman J, et al. Vitamins and photoaging: Do scientific data support their uses? *J Am Acad Derm* 2010;63: 507-525.

UV light is responsible for some of the skin changes associated with aging, which is known as photoaging (PHA). Expenditures in the United States for so-called "cosmeceuticals" is anticipated to reach more than $6 billion this year, although only a few components of commonly applied topical agents have any clearly demonstrated benefit.

Vitamin A derivatives, particularly the prescription retinoids such as tretinoin cream and tazarotene, are FDA-approved for aging-related fine line wrinkles, skin roughness, and mottled hyperpigmentation. OTC vitamin A derivatives have less convincing evidence, but of these, retinol should be the preferred agent according to Zussman et al.

Amelioration of PHA has been seen in several topical vitamin C trials using L-ascorbic acid; chemically related compounds (e.g., ascorbyl palmitate, ascorbyl tetraiopalmitate) provide greater vitamin C stability, but do not have sufficient clinical trial outcomes data to advocate for them.

Topical formulations of vitamin E, although widely touted for antioxidant potential, do not have data to support their use in management of PHA. Limited data on topical niacin suggest promise.

The best method to address photoaging is overall good nutrition and an appropriate combination of sunscreen and sun avoidance. ■

Once weekly exenatide vs sitagliptin or pioglitazone for type 2 diabetes

Source: Bergenstal RM, et al. Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): A randomised trial. *Lancet* 2010;376:431-439.

The incretin class of medications (exenatide, liraglutide, sitagliptin, saxagliptin) all share the favorable quality of not being associated with weight gain. Recently published data support the efficacy, tolerability, and simplicity of once-weekly exenatide. Bergenstal et al compared exenatide once weekly (EXEN-W) with sitagliptin (STG) or pioglitazone (PIO) as add-on therapy for persons with type 2 diabetes (n = 491) who had not attained goal with metformin.

At the end of 26 weeks, several outcomes favored EXEN-W. A1c on EXEN-W was 0.6% lower than STG, and 0.3% lower than PIO. Weight loss was also greatest in the EXEN-W group. Adverse effect profiles with each treatment arm were consistent with prior trials, and the discontinuation rate was similar for each group.

EXEN-W reduced systolic BP more than sitagliptin, but similarly to pioglitazone. Favorable lipid effects were seen with each treatment arm: The greatest increase in HDL was seen with pioglitazone.

As clinicians make their therapeutic choices for diabetes management, the relevance of medication impact upon CV risk factors such as BP, weight, and lipids merits our consideration. ■

Tai chi for fibromyalgia

Source: Wang C, et al. A randomized trial of tai chi for fibromyalgia. *N Engl J Med* 2010;363:743-754.

FDA-approved pharmacologic treatments for fibromyalgia (FIB) include duloxetine, milnacipran, and pregabalin. Although each of these agents has shown both statistically significant and clinically relevant impact, few patients are relieved of all problematic symptoms. Hence, additional treatment paths for FIB are sought.

Exercise has long been recognized as having a favorable impact on FIB, although it has been uncertain which type of exercise should be preferred. For a variety of reasons, some patients will not readily embrace strenuous or aerobic exercise programs, leaving a therapeutic gap in activity programs that can be relied upon to improve FIB symptoms and functionality.

Wang et al enrolled FIB patients (n = 66) into a 12-week program comparing tai chi to a stretching + wellness education component. For the physical activities, both groups participated in two 60-minute sessions per week for 12 weeks. Fibromyalgia patients were diagnosed using the American College of Rheumatology criteria.

At the conclusion of the study, Fibromyalgia Impact Questionnaire and SF-36 physical component scores were superior in the tai chi group as compared to the stretching group. Discontinuation of medications used to treat FIB was seen in both active treatment groups, with a trend favoring tai chi.

Tai chi instruction was provided by a single tai chi master to all of the subjects in that group. Generalizability — whether clinicians can anticipate similar efficacy when tai chi is taught by others — remains to be confirmed. ■

Prevalence of hearing loss in U.S. adolescents

Source: Shargorodsky J, et al. Change in prevalence of hearing loss in U.S. adolescent. *JAMA* 2010;304:772-778.

My grandmother always claimed that listening to loud rock and roll music would be the demise of my hearing … but I still don't know if she was right. In those days we used to listen to something called a record player (younger clinicians interested to see such an archaic device can readily locate one on Google), and I have always wondered whether those cars bouncing up and down at the traffic light next to me, loaded with rap music, would be determined to be similarly ototoxic, or worse. Well, if the NHANES data are correct, we still don't know.

According to this analysis of data from NHANES, the prevalence of hearing loss has increased when one compares the 1988-1994 interval with 2005-2006. Indeed, the relative risk of any hearing loss (induced by any factor) has increased by more than 30%.

Hearing loss was associated with poverty and a history of > 3 ear infections, but not exposure to persistent (> 5 hrs/week) loud noise or firearm use. In support of grandma's point of view, a recent study from Australia noted hearing loss 70% more often in teens who had used personal stereo devices.

Overall, the prevalence of any hearing loss increased from 11.1% to 14.0% over the decade studied; further elucidation of modifiable risk factors would be helpful. ■

When to initiate dialysis? Early vs late GFR threshold

Source: Cooper BA, et al. A randomized, controlled trial of early versus late initiation of dialysis. *N Engl J Med* 2010;363:609-619.

The number of individuals requiring renal replacement therapy (dialysis) continues to grow. Because dialysis is an expensive, time-intensive, and intrusive intervention, it is wise to try to refine an optimum threshold for initiation of dialysis. Intuition might suggest that earlier is better than later, but few data to support this notion are in evidence.

Cooper et al performed a study of adults (n = 828) who qualified for dialysis. Study subjects were randomized to either early (GFR = 10-15 mL/min/1.73 m^2) or late (GFR = 5-7 mL/min/1.73 m^2) dialysis. The primary outcome of the trial was all-cause mortality.

Over an 8-year interval, 828 diabetic subjects with Stage V CKD (GFR < 15 mL/min/1.73 m^2) were randomized to initiate dialysis at either the early or late GFR threshold. The mean time to dialysis initiation in the early group was 1.8 months vs 7.4 months in the late group, but this difference might be expanded further, since more than 75% of the late start group actually initiated dialysis because of symptoms before reaching a GFR of 7.

Overall mortality during 3.6 years of follow-up was not significantly different between the two groups. There does not appear to be any mortality detriment associated with delaying dialysis until GFR is 7 mL/min/1.73 m^2 or less, although many patients may require earlier dialysis due to symptoms. ■

Postoperative abdominal wall hernias: Best repair methodology

Source: Itani KM, et al. What to advise patients about hernias. *Arch Surg* 2010;145:322-328.

The literature indicates that almost one-fourth of persons who undergo abdominal surgery will subsequently incur an abdominal wall hernia. The optimum method for repairing such hernias has not been established. Itani et al performed a randomized trial of laparoscopic vs open repair of ventral incisional hernias at four Veterans Affairs hospitals (n = 162).

There was a substantial risk reduction for complications in the laparoscopic group vs the open repair group (absolute incidence = 31.5% vs 47.9%). In particular, surgical wound site infection was almost 4-fold less in the laparoscopic group. Pain scores at 1 year were less in the laparoscopic group, and return to work was quicker. The only major advantage of open surgical treatment was the incidence of major complications, primarily bowel injury (4.4% in the laparoscopic group vs 1.4% in the open surgery group). One additional advantage of open surgical repair was a trend toward lower recurrence in this group (8.2% vs 12.5%; *P* = NS).

In general, asymptomatic incisional ventral hernias do not require repair, but once they are symptomatic, laparoscopic surgery shows distinct advantages. The surgeons in this trial had not performed a high volume of laparoscopic procedures; hence, clinicians might anticipate even better outcomes as experience accrues. ■

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Dabigatran Leading Race to Replace Warfarin

In this issue: FDA Advisory Committee recommends approval of dabigatran, safety of proton pump inhibitors, effectiveness of glucosamine and chondroitin, FDA Actions.

Advisory Committee recommends approval of dabigatran

In the race to find a drug to replace warfarin, Boehringer Ingelheim may have a leg up with the impending approval of dabigatran. The Cardiovascular and Renal Drugs Advisory Committee of the FDA unanimously recommended approval of the drug in September for the prevention of stroke and systemic clots in patients with atrial fibrillation. Dabigatran is a direct thrombin inhibitor that is given in a fixed dose twice a day and does not require monitoring. It is speculated that dabigatran will replace warfarin as the preferred anticoagulant in many settings, including many patients with atrial fibrillation. The approval was based on the Randomized Evaluation of Long-Term Anticoagulation Therapy trial, which was published last December. The study of more than 18,000 patients with atrial fibrillation showed that dabigatran given at a dose of 110 mg was similar in effectiveness to warfarin in prevention of strokes and systemic embolism, but had a significantly lower rate of major hemorrhage. A higher dose of 150 mg was associated with lower rates of stroke and systemic embolism compared to warfarin and similar rates of hemorrhage (*N Engl J Med* 2009;361:1139-1151). The FDA panel recommended approval of the higher dose, but was split on recommending the 110 mg dose. There was a slightly higher rate of heart attacks with dabigatran compared to warfarin, although the reviewers did not think this was serious enough to warrant holding the drug back. Dabigatran, once approved, will be marketed as Pradaxa®. Several companies are working on their own products to fill the same niche in what has been estimated to be a $10-20 billion market. Drugs in development include Bristol-Myers Squibb's apixaban and rivaroxaban, which is being jointly developed by Bayer Healthcare and Johnson & Johnson. Both drugs are direct inhibitors of Factor Xa. ■

Safety of proton pump inhibitors

Recent studies have suggested that proton pump inhibitors (PPIs) may negate some of the benefit of clopidogrel (Plavix®) in patients with cardiovascular (CV) disease. A new study refutes these findings, and at the same time raises more questions about the safety of PPIs. In a nationwide cohort study from Denmark, all patients discharged after first-time myocardial infarction (MI) were reviewed during 2000-2006. Of the more than 56,000 patients, 16% were rehospitalized for MI or stroke or experienced CV death. Nearly 25,000 patients were discharged on clopidogrel, of which nearly 30% received a concomitant PPI. Patients who were discharged on the combination of a PPI with clopidogrel or on a PPI alone had elevated but similar rates of death or rehospitalization for MI at 30 days (hazard ratio [HR], 1.29 for the combination [95% CI, 1.17-1.42]; HR, 1.29 for PPI alone [CI, 1.21-1.37]), indicating that

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the risk of a PPI with clopidogrel was no higher than a PPI alone. The authors conclude that there seems to be no significant interaction between PPIs and clopidogrel; however, PPIs may be associated with an increased risk for adverse CV outcomes after discharge. The authors postulate that the increased CV risk from PPIs is likely caused by unmeasured confounders (*Ann Intern Med* 2010;153:378-386). As pointed out in an accompanying editorial, this study may be very confusing for clinicians who have recently received warnings regarding the combination of clopidogrel with a PPI. It further highlights the potential risks of PPIs in patients with questionable or inappropriate indications for the drugs and the need for further studies into their risks and benefits (*Ann Intern Med* 2010;153:413-415). ■

Glucosamine and chondroitin

Millions of patients take glucosamine and chondroitin on a daily basis, hoping it is a safe alternative treatment for osteoarthritis. A new study suggests that the combination is ineffective but harmless. In a meta-analysis of 10 trials and more than 3800 patients, glucosamine, chondroitin, or the combination was compared to placebo with regard to pain scores and X-ray appearance of the hip and knee joint. None of the endpoints crossed the boundary of the minimal clinical important difference (95% credible intervals). The authors conclude that compared with placebo, glucosamine, chondroitin, and the combination do not reduce joint pain or have an impact on narrowing of joint space of the hip or knee. They further state that insurers should not cover the cost of these preparations, but since there is little harm, patients may wish to continue buying and taking it (*BMJ* 2010;341:c4675). ■

FDA Actions

The FDA has announced that it will significantly restrict the use of rosiglitazone (Avandia®) to patients with type 2 diabetes who cannot control the disease on other medications. The FDA had the option of removing the drug from the market, a move that was recently taken by the European Medicines Agency; however, the agency decided to limit access at least for now. Rosiglitazone has been associated with an elevated risk of cardiovascular events.

The FDA has approved fingolimod (Gilenya®), the first oral drug to reduce relapses and delay disability progression in patients with relapsing-remitting multiple sclerosis. The drug is the first of a new class called sphingosine 1 phosphate receptor modulators. Patients need to be closely monitored for symptomatic bradycardia. Fingolimod will be marketed by Novartis Pharmaceuticals.

The Endocrinologic and Metabolic Drugs Advisory Committee of the FDA has voted against recommending approval of lorcaserin hydrochloride for the treatment of obesity (see September *Pharmacology Watch*). Although the drug was shown to be effective, resulting in at least a 5% body weight loss for half of patients taking the drug over 1 year, there were concerns over valvular heart disease. Arena Pharmaceuticals argued that valvulopathy was not a significant issue and that they met the FDA's predefined goals for safety. The FDA is not required to follow subcommittee recommendations, however it usually does.

The same subcommittee also recently reviewed the weight-loss drug sibutramine (Meridia-Abbott Laboratories) and delivered a **split vote on whether sibutramine should stay on the market.** Sibutramine has been the subject of controversy since last November when initial data from the Sibutramine Cardiovascular Outcomes trial revealed a higher rate of cardiovascular disease associated with the drug. The full study was published in September and showed that cardiovascular events were observed significantly more frequently in the sibutramine group than in the placebo group (11.4% vs 10.0%; $P = 0.02$). The rate of cardiovascular death or death from any cause, however, was no different in the two groups (*N Engl J Med* 2010;363:905-917). The FDA subcommittee voted 8-8, with 8 members voting to remove the drug from the market and the other 8 voting to allow the drug to remain on the market with tougher warnings and a restricted distribution pattern. The FDA vote is expected later this fall.

The **FDA has approved pegloticase for the treatment of refractory gout in patients who have not responded to or can't tolerate conventional therapy.** The drug is administered intravenously every 2 weeks. It appears to work by metabolizing uric acid to allantoin, which is then cleared through the kidneys. The approval was based on two 6-month trials in more than 200 patients that showed the drug reduces uric acid levels and reduces uric acid deposits in joints and soft tissue. About one in four patients will experience severe allergic reactions to the infusion, so patients should be given an antihistamine and a corticosteroid prior to administration. The drug was not studied in patients with congestive heart failure and should not be used in this population. Savient Pharmaceuticals will market pegloticase as Krystexxa™. ■