CME

EARN CATEGORY I CME CREDIT by reading this article and the article beginning on page 24 and successfully completing the posttest on page 48. Successful completion is defined as a cumulative score of at least 70% correct. This material has been reviewed and is approved for 1 hour of clinical Category I (Preapproved) CME credit by the AAPA. The term of approval is for 1 year from the publication date of January 2010.

LEARNING OBJECTIVES

- Discuss the safety of the recommended childhood vaccinations
- Describe the barriers to adherence associated with vaccinations
- Explain methods clinicians can use to ease parental concerns and increase adherence to childhood vaccination schedules

Safety and adherence: Issues that hinder childhood vaccinations

Scrutiny of recommended childhood vaccines continues to support their effectiveness. However, misinformation still prevails, and many parents may need reassurance.

Jamie Michelle Womack, PA-C

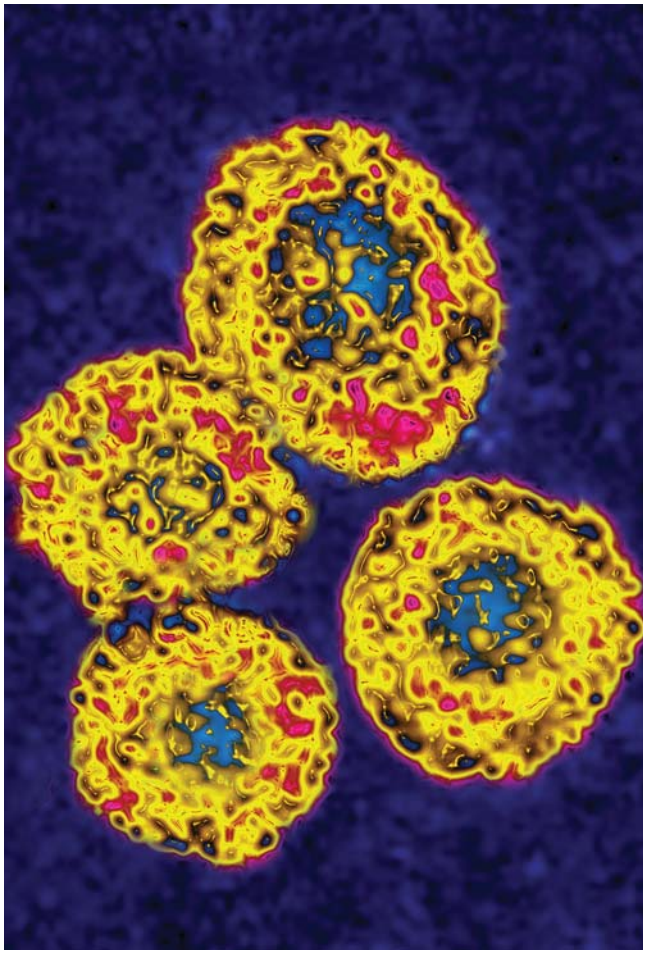
Immunization is a cornerstone of health care policy and a key component in infectious disease prevention. The savings in lives and money are almost incalculable. Vaccines have reduced mortality from diseases such as smallpox, polio, diphtheria, and measles by 99.9%.[1] The seven recommended routine childhood vaccines save an estimated $10 billion in direct costs and $43 billion in societal costs in the United States alone.[2]

Although the benefits of vaccines are overwhelmingly positive from economic and medical science perspectives, complex issues—such as safety, adherence, cost, and scheduling—hinder the implementation of immunization programs. Health care providers who care for children should have a thorough grasp of these potential complications and be prepared to educate parents appropriately so that barriers to adherence can be minimized. This paper reviews evidence on the safety of the recommended childhood vaccines and discusses methods that can improve adherence to immunization programs.

IMMUNIZATION RECOMMENDATIONS

The CDC recommends that children in the United States be immunized against 13 diseases—hepatitis B infection, rotavirus infection, diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b (Hib) infection, pneumococcal disease, polio, measles, mumps, rubella, chickenpox, and hepatitis A infection—by age 18 months.[3] Separate vaccinations are not required for all 13 diseases and some are administered in a series; therefore, completion of the recommended regimen requires 25 injections.

At age 11 to 12 years, children should receive the adolescent/adult formulation of the diphtheria, tetanus, and per-



Rubivirus, the virus that causes rubella

tussis (DTP) vaccine and meningococcal vaccine; females should also receive the three-dose series against human papillomavirus (HPV).[4] An annual influenza vaccination is recommended for all children from age 6 months until their 19th birthday,[5] and certain high-risk children may need immunization against additional diseases.

Safety monitoring All vaccines in the United States must undergo extensive computer trials, animal trials, and clinical trials before they are licensed by the FDA. Manufacturers also must submit samples of each vaccine lot to the FDA before the vaccines are released for administration to the general public.

The National Childhood Vaccine Injury Act requires health care providers to report adverse events that occur subsequent to vaccination. The Vaccine Adverse Event Reporting System (VAERS) was established by the CDC and FDA to manage this information. VAERS reports can be made by anyone, but most reports are made by vaccine manufacturers (42%) or health care providers (30%). Reportable events are those deemed by the manufacturer to be a contraindication for subsequent doses or an event listed in the vaccine injury table (eg, the reportable events for the tetanus vaccine are anaphylaxis, brachial neuritis, and any acute complications or sequelae of these events).[6] The complete table is available at www.hrsa.gov/vaccinecompensation/table.htm.

VAERS is a passive surveillance system; therefore, its limitations include underreporting, variability in report quality, and uncertainty of causality.[7] The Vaccine Safety Datalink (VSD) addresses some of these weaknesses. The VSD project is a collaborative effort between the CDC and eight large managed-care organizations in which comprehensive medical and immunization histories of 5.5 million people are compiled. This large quantity of data allows for both planned vaccine safety studies and timely analysis of developing hypotheses.[6]

VACCINE SAFETY

Literature searches on MEDLINE, PubMed, and CINAHL were used to find research on vaccine efficacy and safety. The terms used were the names of each individual vaccine; *safety*, *childhood vaccines*; *safety*; and *immunization*. Additional articles were found through the "Related Links" feature in PubMed. Additional information was obtained from the CDC Web site. No reports of adverse events were found for the **Hib**, **pneumococcal conjugate**, **polio**, and **varicella** (**chickenpox**) vaccines.

Hepatitis B Allegations were made in the late 1990s that the hepatitis B vaccine caused neurologic disorders and demyelinating diseases. The vaccine's safety was reviewed by the Viral Hepatitis Prevention Board, which determined that there was no causal relation between the vaccine and these diseases. Observed temporal correlations were found to be coincidental, and any plausible biologic basis for the assertions was lacking.[8] Numerous studies since then also found no link between the vaccine and demyelinating disease.[9]

Rotavirus The first multivalent live oral reassortment vaccine, RotaShield, was withdrawn from the market 14 months after its introduction because a higher incidence of intussusception was seen in vaccinated infants. Currently, two rotavirus vaccines are licensed by the FDA: a mixed human and bovine rotavirus strain with five reassortments and a human rotavirus strain. Neither is associated with intussusception.[10] Five reports of Kawasaki disease in children receiving the mixed vaccine have been reported; however, this incidence is not higher than expected in this population.[11] No other adverse affects have been reported.

Diphtheria, tetanus, and pertussis A combination vaccine has been used for these diseases for many years with little or no controversy surrounding the diphtheria and tetanus components. However, concerns about the whole-cell pertussis component led to the development of an acellular pertussis form (DTaP). Studies have shown that systemic reactions were up to one-third fewer and milder after administration of DTaP than after administration of the vaccine with whole-cell pertussis (DTwP). Some studies reported extensive swelling after administration of booster doses in 2% to 6% of children, but this event can be reduced by using an intramuscular rather than subcutaneous route.[12] In the mid 1970s, a British study reported an increase risk of serious neuropathy after vaccination against pertussis. However, the study was found to have serious

KEY POINTS

- Health care providers who care for children should have a thorough grasp of the complex issues—such as safety, adherence, cost, and scheduling—that may hinder successful implementation of immunization programs.
- The CDC recommends vaccination against 13 diseases—hepatitis B infection, rotavirus infection, diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b (Hib) infection, pneumococcal disease, polio, measles, mumps, rubella, chickenpox, and hepatitis A infection—by age 18 months.
- Additional recommended vaccines are the adolescent/adult formulation of the diphtheria, tetanus, and pertussis vaccine, the meningococcal vaccine, and the human papillomavirus vaccine (for females) at ages 11 to 12 years. All children should receive the seasonal flu vaccine annually from age 6 months until their 19th birthday.
- Recent evidence overwhelmingly rejects a causal relation between the measles-mumps-rubella vaccine and autism.

methodological errors, and multiple subsequent studies showed no correlation between the vaccine and adverse neurologic events.[13]

Influenza The CDC recommends annual vaccination against influenza for all children from age 6 months until their 19th birthday, as well as for adults older than 50 years, people with chronic diseases, health care workers, and certain additional populations.[5] No reports of morbidity associated with administration of the seasonal flu vaccine to children were found. Suspicions of mortality associated with vaccine administration to adults in Israel in October 2006 were deemed to be unfounded.[14] Meta-analyses found few adverse reactions other than pain and erythema at the injection site.[14]

Measles, mumps, and rubella (MMR) A causal association between vaccines, specifically MMR vaccine, and autism was suggested in a published report on 12 children with inflammatory bowel conditions and autism spectrum disorder (ASD).[15] Because the behavioral problems began after the MMR vaccine was given, the parents or doctors of eight of the children believed the vaccination might have contributed to the problems. The authors proposed a new syndrome of GI hyperplasia and inflammation linked to behavioral regression[15] and ignited a furor that continues today. As a result, the MMR vaccine is one of the most widely studied vaccines.

TABLE 1. Actions that improve adherence to vaccination schedules[31,39,40]

Educational
- Direct parents to reputable sources of information, such as the CDC
- Distribute vaccine information sheets or packets that parents can take home
- Educate clinical staff about immunization schedules
- Provide an immunization schedule at the child's 2-week checkup
- Provide vaccine information (videos, printed material) in the waiting room

Procedural
- Administer combination vaccines
- Check the child's immunization status at each visit
- Establish standing orders that allow nursing staff to administer overdue immunizations
- Give parents an updated immunization record after each vaccination
- Give parents the Web site address of an online state database (if applicable)
- Implement a reminder system (postcards, phone calls, or e-mail)
- Place the child's immunization record at the front of chart
- Provide a questions and concerns form for parents to bring to subsequent visits
- Survey parents to determine specific barriers
- Use a contraindications screening form

Autism is a neurodevelopmental disorder that manifests as behavioral and cognitive deficits. Genetic factors play a large role, and its neuropathology probably occurs early in fetal development.[15] The recent increase in the prevalence of autism (variously reported to be between 6- and 1,000-fold) is presumably caused in large part by an increased recognition of ASD and the widening of its diagnostic criteria. MMR vaccine is given between ages 12 and 15 months, and autism is usually diagnosed at age 15 to 18 months.[16] As a result, some people are more receptive to the theory that MMR vaccine could be an environmental factor.[16]

Recent evidence overwhelmingly rejects a causal relation between the vaccine and autism.[15,16] Particularly compelling evidence came from a Danish study of half a million children, including 100,000 who did not receive the MMR vaccine.[17] Study results indicated a relative risk associated with the MMR vaccine of 0.92 for autism (95% confidence interval [CI] 0.68-1.24) and 0.83 for ASD (CI 0.65-1.07).[17] A rare event can sometimes be defended despite a lack of epidemiologic evidence if there is compelling biologic evidence. However, no laboratory or clinical findings support the autism-GI theory, and no biologic mechanism explains the neurologic changes that express as autism.[17] Furthermore, 10 of the 13 authors of the original study later formally retracted the conclusions made in their article.[15]

Another theory has proposed that **thimerosal** could be the cause of the increased prevalence of autism. Thimerosal is an organic mercury compound that breaks down into ethyl mercury, which is used in vaccines as an antibacterial and antifungal. Ethyl mercury has a half-life of less than 1 week and undergoes active intestinal excretion. Thimerosal has been used in medical applications for more than 60 years, and the only risk associated with it is rash and swelling at the injection site. The public may be confusing *ethyl* mercury with *methyl* mercury, which is commonly ingested by humans through fish consumption, accumulates in body tissues, and has a half-life of more than 1 month.[8] Existing evidence fails to support an association between thimerosal-containing vaccines and an increased prevalence of autism.[18] However, with the exception of some influenza vaccines, the use of thimerosal in the recommended childhood vaccines in the United States was discontinued in 2001.[19] In addition, subsequent studies in other countries have shown static or increased prevalence of autism among populations that were not exposed to thimerosal.[20]

Autism concerns continue to receive significant publicity in the United States. In February 2009, the Office of Special Masters of the US Court of Federal Claims decisively rejected claims that either the MMR vaccine or thimerosal caused autism in children. Lawyers selected three test cases from a group of 5,000 similar cases; after a thorough review of all the evidence, the claims in each case were separately rejected by three Special Masters.[21] Special Master Patricia Campbell-Smith concluded that "the combination of the thimerosal-containing vaccines and the MMR vaccine are not causal factors in the development of autism."[22] The rul-

ings in the other cases expressed similar confidence in this conclusion.[23,24]

Human papillomavirus The HPV vaccine (Gardasil) was studied in five clinical trials that included more than 21,000 participants before it was licensed in 2006, and more than 24 million doses have been distributed in the United States since licensure. Ninety-three percent of the almost 14,000 VAERS-reported events are considered nonserious (ie, fainting, pain and swelling at the injection site, headache, nausea, and fever), and expert review has not found a common medical pattern for the reported serious events (ie, involving hospitalization, permanent disability, life-threatening illness, or death) that would suggest vaccine causality. Some of the serious events that were reported include Guillain-Barré syndrome (GBS), blood clots, and death. However, investigators found that the incidence of GBS among vaccinated girls and women was no higher than it was in the general population, most people who developed blood clots had independent risk factors for clots, and no pattern was seen to suggest that any of the 26 confirmed deaths were caused by the vaccine.[25] A World Health Organization review of HPV vaccine safety covered both short-term events (fainting, pain at injection site, and other common acute reactions) and long-term events (pregnancy and events occurring up to 6 years after vaccination) and similarly found the only noteworthy complications to be muscle pain and injection site reaction.[26]

Meningococcus The CDC recommends vaccination against meningococcus for adolescents, college students living in dormitories, and other high-risk populations.[27] Since 2005, more than 12 million doses have been administered in the United States; as of April 30, 2007, 19 cases of GBS were reported as having occurred within 6 weeks of vaccine administration.[26] The background incidence of GBS in this population is not well-known; therefore, it cannot be determined if vaccination increases the risk for GBS. Further studies are planned, but the high morbidity (11%-19%) and mortality (10%-14%) of meningococcal disease warrant adherence to the CDC recommendation of routine vaccination.[27]

Acute neurologic events The most common adverse event from vaccination is fever, which is more likely to occur after administration of live attenuated vaccines (such as MMR) or vaccines that contain toxins or whole cell preparations (such as DTwP). Vaccine-related fevers may precipitate seizures in children, but the risk of recurrent seizures from vaccine-related fevers is not greater than the risk of recurrent seizures from non-vaccine-related fevers. Nor do vaccine-related fevers increase the likelihood of developing epilepsy or other neurologic disorders. Long-term outcomes for cognition and neurodevelopment are benign.[13] Hypotonic hyporesponsive events (defined as the acute onset of decreased muscle tone, reduced responsiveness, and pallor lasting from minutes to 24 hours) occur at a rate of 1 in 100,000 DTaP doses. Recurrence rates are low, and long-term consequences are benign.[13]

Minor sequelae Few children experience serious adverse events from vaccines, but minor events can be expected to occur in 19% of vaccinated children. The most common adverse reactions are swelling at the injection site (12.2 instances per 1,000 injections), pain at the injection site (10.3 per 1,000), nonmeasured temperature believed to be very high (4.6 per 1,000), and fever of 39°C to 40.5°C (4.4 per 1,000). The combination DTaP/Hib vaccine causes 43.4% of the reactions (mainly swelling at the injection site), and MMR vaccine causes 18.4% of the reactions (mainly fever of 39°C-40.5°C).[28]

ADHERENCE ISSUES

Requirements and exemptions Although the United States does not require vaccinations, proof of immunization must be provided to attend school. This requirement is based on the danger posed by most vaccine-preventable diseases; their high contagion, especially in school settings; the remarkable safety of vaccines; and the overall health and financial benefits of immunization. All states allow exceptions based on medical reasons, and most (48 states) allow exemptions for religious reasons. Only 17 states allow exemptions based on philosophical reasons;[29] however,

From the AAPA Committee on Diversity

A late-breaking update on HPV vaccine eligibility

The CDC's Advisory Council on Immunization Practices (ACIP) Vaccines for Children Program adopted a resolution on October 21, 2009, that updates the groups eligible for the human papillomavirus (HPV) vaccine. The resolution identified males aged 9 to 26 years as eligible for the quadrivalent HPV vaccine.[1]

Among men, anal and oropharyngeal cancer incidence is increasing while penile cancer incidence is decreasing.[2] High-risk male populations for anal cancers include men who have sex with men, persons with HIV, and African-Americans.[2]

African-American males are also at higher risk for HPV-associated oropharyngeal cancers, whereas rates of HPV-related penile cancers are elevated among Hispanic males.[2]

Up-to-date information on the quadrivalent HPV vaccine and other vaccine-related issues is available on the CDC/ACIP Web site, www.cdc.gov/vaccines/recs/acip/slides.htm.

REFERENCES

1. Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices-Vaccines for Children Program: vaccines to prevent human papillomavirus. Resolution No 010/09-1. Adopted and effective October 21, 2009. http://www.cdc.gov/vaccines/programs/vfc/downloads/resolutions/1009hpv-508.pdf. Accessed December 2, 2009.
2. Centers for Disease Control and Prevention (CDC). Burden of male HPV-associated disease: an overview [slide presentation]. February 25, 2009. http://www.cdc.gov/vaccines/recs/acip/downloads/mtg-slides-feb09/10-2-hpv.pdf. Accessed December 2, 2009.

legal rulings in some states have effectively equated religious exemptions with philosophical reasons. Furthermore, requirements and enforcement of both religious and philosophical exemptions are highly variable from state to state.[30]

Children who remain unvaccinated can be a risk to the larger population, and officials must weigh a parent's right to choice against public health issues. Local regulations and possibly the geographic clustering of people with similar beliefs can result in uniquely low compliance rates that flirt with ineffective coverage in individual counties and sometimes individual schools. For example, infectious disease and epidemiologic theories suggest that 93% to 95% immunization coverage is required to prevent a measles outbreak.[30] Outbreaks caused by lack of herd immunity have not remained theoretical; in December 2005, a mumps outbreak began in Iowa and spread to 10 other states within 6 months (the MMR immunization rate in Iowa was 90.3%).[30]

Increased refusals to vaccinate are in large part a result of the very success of immunization programs. As people forget or have never witnessed the true devastations of these diseases, they may become complacent about vaccination requirements.[31] More recently, highly publicized misinformation about vaccine side effects—especially autism—has given rise to increasing antivaccination sentiment.

Barriers to adherence Although increasing in numbers, families who seek exemptions from vaccination are by far in the minority. Among families who are not opposed to vaccination, adherence rates are influenced by factors related to both characteristics of the parent and child and the health care system structure.[32]

Race, education, socioeconomic status, access to health care, family demographics, and attitudes towards health care all affect vaccination adherence rates.[32,33] Among parents with concern about the safety of vaccines, 72% nonetheless vaccinated their child primarily because of the risk of their child getting the disease and 17% cited state laws for enrollment into school or daycare.[34] In a large-scale study of parental health beliefs about the vaccination process, 74% of parents found nothing difficult about the process. Concern about side effects was the most commonly reported barrier (22.6%) followed by concern over the number of immunizations required at a single visit, but these concerns did not impact immunization rates. One study concluded that only 8% of underimmunization is related to parental perception of the immunization process.[35]

Poverty and its associated factors are an enormous barrier to health care in general, and both preventive services and vaccination are no exception. Vaccine costs have historically been underwritten by the Vaccination Assistance Act (Section 317 of the Public Health Service Act) and state health department funding. The introduction of new vaccines and increases in the recommended number of doses for existing vaccines dramatically increased the cost of immunizations and widened corresponding gaps in immunization coverage. In response, the Vaccines for Children Program, which provides free vaccines for children who are uninsured, underinsured, American Indian, or on Medicaid, was passed in 1993.

Although vaccine subsidies improve immunization coverage, cost remains a barrier. Pediatricians' charges are not reimbursed by the government and must be borne by parents, insurance plans, or the provider. New vaccines have recently been added and changes in vaccine recommendations occur regularly; additional funding is never guaranteed. Furthermore, even the cost of transportation to the doctor's office can be prohibitive for families living at or below poverty level.[36]

A large part of underimmunization can be traced to simple factors, such as lack of parental knowledge and health care provider practices. Many parents do not know when immunizations are due or do not have accurate immunization histories for their children, which can lead to both over- and underimmunization.[37] Parents often receive information about vaccinations from non-evidence-based sources and have misperceptions of the risks and benefits.[31] Many medical practices do not have systems that can identify underimmunized patients or provide reminders for the parents.[37]

> "Vaccines are overwhelmingly safe, and the most current and accurate information should be provided to parents."

IMPROVING ADHERENCE

Individual health care providers and practices can take simple steps to greatly impact their patients' adherence to immunization schedules. Their efforts should focus on both parental education and office procedures (**Table 1**).

Parents are looking for a range of clearly-stated information when making decisions about immunizing their children. Evidence-based information written at appropriate reading levels should be provided to the whole community for maximum impact.[38] Practitioners can consider providing an immunization schedule for the child at the 2-week check-up[39] and additional information periodically throughout the child's care. Health care providers are required by law to distribute and discuss vaccine information statements (VISs) before administering each vaccine; however, this requirement is often not met. VISs can be obtained from the CDC and most local health departments, and are available in 30 languages.[31]

Proper education on the risks and benefits of vaccines must often be provided in a very short amount of time. In one study, 40% of providers cited a lack of time as the most common barrier to parental education on immunization.[31] Some effective methods of time-efficient parental education are vaccine information packets, question and concerns forms that parents can complete and bring to a subsequent

visit, a list of reputable sources of information, vaccine safety videos shown on monitors in the waiting room, and use of a contraindications screening form.[31]

Failure to incorporate the parental perspective into public health strategies is believed to be another significant reason for adherence failure.[30] Impediments to adherence can sometimes be easily resolved if a practitioner takes the time to elicit a parent's specific concerns. For example, watching their child receive up to five injections in a single office visit is troublesome for most parents. Combination vaccines offer a safe way to reduce this number without sacrificing immunologic coverage.[35] Combination vaccines may also reduce the risk of error and take less time than administering multiple injections.[40]

Adjusting office procedures to prevent coverage gaps can be simple. Practitioners should consider having support staff check a child's immunization status at each visit. Immunization records can be placed at the front of a child's chart to keep relevant information easily accessible. A reminder system can provide postcards, phone calls, or emails to parents when their children are due for vaccinations. Finally, consider implementing standing orders that allow nursing staff to administer overdue immunizations.[39]

CONCLUSION

Primary care providers should be able to competently answer questions and guide action in order to adequately treat patients and educate parents. Vaccines are overwhelmingly safe, and the most current and accurate information about vaccine safety should be provided to parents. Practitioners should also address parents' nonmedical concerns, such as scheduling and cost. If a parent is willing to adhere to an immunization schedule, further efforts can ensure on-schedule vaccination and high patient and parent satisfaction. Realistic and dedicated efforts by health care providers can improve their patients' adherence to vaccination schedules and help realize the enormous individual and societal benefits that immunization offers. **JAAPA**

Jamie Womack is a recent graduate of the PA program at Eastern Virginia Medical School, Norfolk, Virginia. She currently works at Blue Ridge Bone and Joint in Asheville, North Carolina. The author has indicated no relationships to disclose relating to the content of this article.

REFERENCES

1. McCullers JA. Evolution, benefits, and shortcomings of vaccine management. *J Manag Care Pharm.* 2007;13(7 suppl B):S2-S6.
2. Zhou F, Santoli J, Messonnier ML, et al. Economic evaluation of the 7-vaccine routine childhood immunization schedule in the United States, 2001. *Arch Pediatr Adolesc Med.* 2005;159(12):1136-1144.
3. Centers for Disease Control and Prevention (CDC). Recommended immunization schedule for persons aged 0 through 6 years—United States, 2009. CDC Web site. http://www.cdc.gov/vaccines/recs/schedules/downloads/child/2009/09_0-6yrs_schedule_pr.pdf. Accessed December 8, 2009.
4. Centers for Disease Control and Prevention (CDC). Recommended immunization schedule for persons aged 7 through 18 years—United States, 2009. CDC Web site. http://www.cdc.gov/ vaccines/recs/schedules/downloads/child/2009/09_7-18yrs_schedule_pr.pdf. Accessed December 8, 2009.
5. Centers for Disease Control and Prevention (CDC). Key facts about seasonal flu vaccine. CDC Web site. http://www.cdc.gov/flu/protect/keyfacts.htm. Last updated October 16, 2009. Accessed December 8, 2009.
6. Centers for Disease Control and Prevention (CDC). History of vaccine safety. CDC Web site. http://www.cdc.gov/vaccinesafety/basic/history.htm#ncvia. Last modified February 26, 2009. Accessed December 8, 2009.
7. Varricchio F, Iskander J, Destefano F, et al. Understanding vaccine safety information from the Vaccine Adverse Event Reporting System. *Pediatr Infect Dis J.* 2004;23(4):287-294.
8. François G, Duclos P, Margolis H, et al. Vaccine safety controversies and the future of vaccination programs. *Pediatr Infect Dis J.* 2005;24(11):953-961.
9. Centers for Disease Control and Prevention (CDC). FAQs about hepatitis B vaccine (Hep B) and multiple sclerosis. CDC Web site. http://www.cdc.gov/vaccinesafety/Vaccines/multiplesclerosis_and_hep_b.html. Last modified/reviewed October 9, 2009. Accessed December 8, 2009.
10. Dennehy PH. Rotavirus vaccines: an overview. *Clin Microbiol Rev.* 2008;21(1):198-208.
11. Centers for Disease Control and Prevention (CDC). Kawasaki syndrome and RotaTeq vaccine. CDC Web site. http://www.cdc.gov/vaccinesafety/Vaccines/Rotavirus.html. Last modified/reviewed October 9, 2009. Accessed December 8, 2009.
12. Rennels MB. Extensive swelling reactions occurring after booster doses of diphtheria-tetanus-acellular pertussis vaccines. *Semin Pediatr Infect Dis.* 2003;14(3):196-198.
13. Brown NJ, Berkovic SF, Scheffer IE. Vaccination, seizures and 'vaccine damage.' *Curr Opin Neurol.* 2007;20(2):181-187.
14. Kokia ES, Silverman BG, Green M, et al. Deaths following influenza vaccination—background mortality or causal connection? *Vaccine.* 2007;25(51):8557-8561.
15. DeStefano F. Vaccines and autism: evidence does not support a causal association. *Clin Pharmacol Ther.* 2007;82(6):756-759.
16. Doja A, Roberts W. Immunizations and autism: a review of the literature. *Can J Neurol Sci.* 2006;33(4):341-346.
17. DeStefano F, Thompson WW. MMR vaccine and autism: an update of the scientific evidence. *Expert Rev Vaccines.* 2004;3(1):19-22.
18. Stehr-Green P, Tull P, Stellfeld M, et al. Autism and thimerosal-containing vaccines: lack of consistent evidence for an association. *Am J Prev Med.* 2003;25(2):101-106.
19. Centers for Disease Control and Prevention (CDC). Mercury and thimerosal. CDC Web site. http://www.cdc.gov/vaccinesafety/concerns/thimerosal/index.html. Last modified/reviewed October 9, 2009. Accessed December 11, 2009.
20. Schechter R, Grether JK. Continuing increases in autism reported to California's developmental services system. *Arch Gen Psychiatry.* 2008;65(1):19-24.
21. Hitti M. Vaccine court rejects autism claims. WebMD Web site. http://www.webmd.com/brain/autism/news/20090212/vaccine-court-rejects-autism-claims. Accessed December 8, 2009.
22. *Hazlehurst v United States.* US Court of Federal Claims. No. 03-654V. http://www.uscfc.uscourts.gov/sites/default/files/Campbell-Smith%20Hazlehurst%20Decision.pdf. Accessed December 3, 2009.
23. *Cedillo v United States.* US Court of Federal Claims. No. 98-916V. http://www.uscfc.uscourts.gov/sites/default/files/Hastings-Cedillo.pdf. Accessed December 3, 2009.
24. *Snyder v United States.* US Court of Federal Claims. No. 01-162V. http://www.uscfc.uscourts.gov/sites/default/files/Vowell.Snyder.pdf. Accessed December 3, 2009.
25. Centers for Disease Control and Prevention (CDC). Reports of health concerns following HPV vaccination. CDC Web site. http://www.cdc.gov/vaccinesafety/Vaccines/HPV/gardasil.html. Last modified November 5, 2009. Accessed December 3, 2009.
26. Progress towards interrupting wild poliovirus transmission, January 2006-May 2007. *Wkly Epidemiol Rec.* 2007;82(28-29):245-251.
27. Centers for Disease Control and Prevention (CDC). Update: Guillain-Barré syndrome among recipients of Menactra meningococcal conjugate vaccine—United States, June 2005-September 2006. MMWR Morbid Mortal Wkly Rep. 2006;55(41):1120-1124. CDC Web site. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5541a2.htm. Reviewed October 19, 2006. Accessed December 8, 2009.
28. Carrasco-Garrido P, Gallardo-Pino C, Jiménez-Garcia R, et al. Incidence of adverse reactions to vaccines in a paediatric population. *Clin Drug Investig.* 2004;24(8):457-463.
29. Salmon DA, Siegel AW. Religious and philosophical exemptions from vaccination requirements and lessons learned from conscientious objectors from conscription. *Public Health Rep.* 2001;116(4):289-295.
30. Thompson JW, Tyson S, Card-Higginson P, et al. Impact of addition of philosophical exemptions on childhood immunization rates. *Am J Prev Med.* 2007;32(3):194-201.
31. Tenrreiro KN. Time-efficient strategies to ensure vaccine risk/benefit communication. *J Pediatr Nurs.* 2005;20(6):469-476.
32. Falagas ME, Zarkadoulia E. Factors associated with suboptimal compliance to vaccinations in children in developed countries: a systematic review. *Curr Med Res Opin.* 2008;24(6):1719-1741.
33. Alfredsson R, Svensson E, Trollfors B, Borres MP. Why do parents hesitate to vaccinate their children against measles, mumps and rubella? *Acta Paediatr.* 2004;93(9):1232-1237.
34. Shui IM, Weintraub ES, Gust DA. Parents concerned about vaccine safety: Differences in race/ethnicity and attitudes. *Am J Prev Med.* 2006;31(3): 244-251.
35. Taylor JA, Darden PM, Brooks DA, et al; Pediatric Research in Office Settings; National Medical Association. Association between parents' preferences and perceptions of barriers to vaccination and the immunization status of their children: a study from Pediatric Research in Office Settings and the National Medical Association. *Pediatrics.* 2008;110(6):1110-1116.
36. Hinman AR, Drenstein WA, Rodewald L. Financing immunizations in the United States. *Clin Infect Dis.* 2004;38(10):1440-1446.
37. Strategies to sustain success in childhood immunizations. The National Vaccine Advisory Committee. *JAMA.* 1999;282(4):363-370.
38. Yarwood J. Communicating vaccine benefit and risk—lessons from the medical field. *Vet Microbiol.* 2006;117(1):71-74.
39. Parve J. Remove vaccination barriers for children 12 to 24 months. *Nurse Pract.* 2004;29(4):35-38.
40. Koslap-Petraco MB, Parsons T. Communicating the benefits of combination vaccines to parents and health care providers. *J Pediatr Health Care.* 2003;17(2):53-57.