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Immunizations in the United States: A Rite of Passage

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We must plan for the future, because people who stay in the present will remain
in the past.

—Abraham Lincoln

In 1796, when Jenner showed successful inoculation of humans with cowpox to protect them from the devastation of smallpox, a revolution in science and medicine began [1]. More than 2 centuries later, immunizations were hailed as one of “ten great public health achievements” of the twentieth century [2,3]. Today, vaccination is a cornerstone of pediatric preventive health care and a rite of passage for nearly all of the approximately 11,000 infants born daily in the United States.

Immunizations have had a profound impact on the health of children, adolescents, and adults in the United States (Table 1). The most extraordinary success of immunizations was the worldwide eradication of smallpox. Declared in 1980, smallpox eradication was achieved through an unprecedented collaborative international initiative, led by the World Health Organization, establishing an example for other vaccine-preventable diseases [1]. Vaccination since has led to elimination of wild-type poliomyelitis and indigenous measles in the United States, both major causes of pediatric morbidity and mortality in the prevaccine era [4,5].

An integral part of achieving these successes was establishment of a federal immunization infrastructure, which followed the introduction of polio vaccination in the 1950s [3]. Immunization programs, legislation, and funding mecha-

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Table 1
Reported morbidity of selected vaccine-preventable diseases and vaccine coverage levels—US twentieth century and 2003

Disease	US, 20th century annual morbidity [3]	US, 2003 morbidity*	Vaccine coverage levels, 2003 [†]	Healthy People 2010 Coverage level goals
Diphtheria	175,885	1	85% [‡] (≥4 doses)	90%
Tetanus	1314	20	85% [‡] (≥4 doses)	90%
Pertussis	147,271	11,647	85% [‡] (≥4 doses)	90%
Poliomyelitis (paralytic)	16,316	0	92% [§] (≥3 doses)	90%
Measles	503,282	56	93% (≥1 dose)	90%
Mumps	152,209	231	93% (≥1 dose)	90%
Congenital rubella	823	1	93% (≥1 dose)	90%
Varicella		20,948	85% (≥1 dose)	90%

* MMWR Morb Mortal Wkly Rep 2004;53:687–96, number of reported cases.

[†] MMWR Morb Mortal Wkly Rep 2004;53:658–61, number of reported cases.

[‡] Administered as diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine.

[§] Inactivated polio vaccine.

^{||} Administered as measles, mumps, and rubella (MMR) vaccine.

nisms are now in place to ensure that immunizations are accessible to all children. As a result, coverage levels for most routinely recommended childhood vaccines in the United States are approaching or have surpassed the US Department of Health and Human Services Healthy People 2010 goal of 90% coverage [6].

Immunizations have changed the scope of pediatric practice in the United States. Pediatric residents now infrequently encounter varicella, which in the 1990s was commonplace. Likewise, although *Haemophilus influenzae* type b (Hib) was the leading cause of meningitis in young children before availability of Hib vaccines in 1985, most newly trained pediatricians will never see a case of invasive Hib [7]. This article reviews the US immunization program with an emphasis on its role in ensuring that vaccines are effective, safe, and available and highlights several new vaccines and recommendations that will affect the health of children and adolescents and the practice of pediatric medicine in future decades.

United States immunization program

Childhood and adolescent immunization schedule

The Centers for Disease Control and Prevention (CDC), American Academy of Family Physicians, and American Academy of Pediatrics (AAP) annually publish a childhood and adolescent immunization schedule. The Advisory Committee on Immunization Practices (ACIP), with input from many liaison organizations, periodically reviews the schedule to ensure consistency with new vaccine developments and policies [8]. The first combined immunization schedule was

published in 1995 and recommended six vaccines containing antigens against nine infectious diseases [9]: diphtheria and tetanus toxoids and whole-cell pertussis vaccine (DTP); tetanus and diphtheria toxoids (Td); measles, mumps, and rubella vaccine (MMR); Hib; oral polio vaccine (OPV); and hepatitis B virus vaccine. Ten years later in February 2005, there were ten vaccines against 13 infections in this schedule: diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP), Td, MMR, Hib, inactivated polio vaccine (IPV), hepatitis B virus vaccine, varicella vaccine, pneumococcal conjugate vaccine (PCV7), inactivated influenza vaccine, and meningococcal conjugate vaccine (MCV4). The 2005 schedule includes the conjugated meningococcal vaccine, which was licensed by the US Food and Drug Administration (FDA) on January 14, 2005 [8].

Immunization policy

Before a vaccination becomes part of routine clinical pediatric practice, three steps need to be taken: (1) the FDA must license the vaccine, (2) the ACIP and the Committee on Infectious Diseases of the AAP and AAFP must recommend the vaccine for use, and (3) the vaccine must be subsidized to cover children without private health insurance. Numerous government and partner organizations participate in bringing a vaccine from the bench into the clinic. Table 2 provides links where information about these organizations can be obtained.

Table 2
Websites for vaccine-related programs and organizations

	Website
Government programs	
National Immunization Program	www.cdc.gov/nip
National Vaccine Program Office	www.hhs.gov/nvpo/
Vaccines for Children	www.cdc.gov/nip/vfc/default.htm
Vaccine Injury Compensation Program	www.hrsa.gov/osp/vicp/INDEX.HTM
Advisory Committee on Immunization Practices	www.cdc.gov/nip/ACIP/default.htm
Nongovernment organizations	
National Network for Immunization Information	www.immunizationinfo.org/
Immunization Action Coalition	www.immunize.org
National Partnership for Immunization	www.partnersforimmunization.org
AAP: Immunization Initiatives	www.cispimmunize.org/
Vaccine schedule information	
CDC Recommended Childhood and Adolescent Immunization Schedule	www.cdc.gov/nip/recs/child-schedule.htm#mmwr
AAP Recommended Childhood and Adolescent Immunization Schedule	www.cispimmunize.org/
Vaccine safety information	
Vaccine Adverse Event Reporting System	www.vaers.org
Institute of Medicine Immunization Safety Review	www.iom.edu/project.asp?id=4705
Clinical Immunization Safety Assessment Network	www.vaccinesafety.net/CISA/index.htm

Abbreviations: AAP, American Academy of Pediatrics; CDC, Center for Disease Control and Prevention.

Table 3
Clinical trials by phase in development of a vaccine

Clinical trials	Approximate duration in years	Study population	Criteria evaluated
Phase I	1.5	20–100	Assess safety
Phase II	2	100–1000	Expand safety data and determine optimal dose or schedule
Phase III	3.5	1000 – ≥10,000	Establish efficacy and determine safety
FDA consideration	1.5	Review process, license granted	All clinical trial data
Phase IV	Many	100,000 – millions	Monitor safety and effectiveness

Before FDA licensure, a new vaccine goes through 10 to 15 years of pre-clinical testing and clinical trials, costing pharmaceutical companies millions of dollars in new development costs. Before testing the vaccine in humans, a company files an Investigational New Drug application with the FDA followed by three phases of clinical trials that are performed to study vaccine safety, immunogenicity, and efficacy (Table 3) [10]. After completion of the prelicensure clinical trials, the manufacturer files a Biologics Licensure Application (BLA), and the FDA, with input from its advisory committee, determines if data support vaccine safety, immunogenicity, and efficacy (Fig. 1) [11]. After licensure, monitoring for rare adverse events continues for some vaccines through formal phase IV trials conducted by the FDA and manufacturer.

After FDA licensure of a new vaccine, information about the vaccine is reviewed by the ACIP. The ACIP comprises 15 voting members appointed by the Secretary of the Department of Health and Human Services. In addition, several professional medical and public health groups and industry representatives participate in ACIP discussions. To formulate recommendations, the ACIP establishes subject-specific working groups to review and synthesize data months to

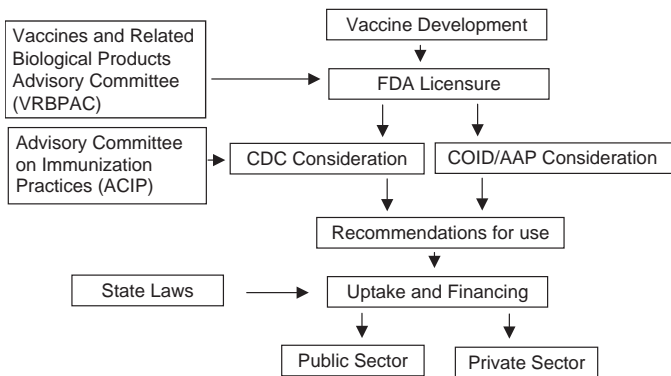


Fig. 1. Development of pediatric vaccine recommendations and policies. (From Pickering LK, Orenstein WA. Development of pediatric vaccine recommendations and policies. *Semin Pediatr Infect Dis* 2002;13:148–54; with permission.)

years before a recommendation is released. ACIP recommendations are subject to the approval of the CDC director (www.cdc.gov/nip/ACIP/charter). The American Academy of Family Physicians and the Committee on Infectious Diseases of the AAP also develop recommendations for vaccine use, which usually are the same as ACIP recommendations.

Ensuring that all US children and adolescents, regardless of health insurance status or income level, have access to recommended immunizations requires a complex system of financing comprised of private and public funding mechanisms (Table 4). In 2002, 57% of US children received vaccines purchased through the public sector, and 43% received vaccines purchased through the private sector. Most of the public-purchase vaccines are financed through the Vaccines for Children (VFC) program, an entitlement program established in 1994 as part of the Social Security Act [11,12]. Other government funding mechanisms include Section 317 of the Public Health Service Act of 1962, a federal grant program, and state and local government funding. These programs provide support for states to provide immunizations to children who do not qualify for the VFC program but who are not covered by private insurance. Fourteen states, referred to as “universal” purchase states, use a combination of federal and state funding to purchase and distribute vaccines recommended for children to all immunization providers in private and public sectors. The remaining 36 states purchase vaccines for uninsured and underinsured chil-

Table 4
Major government financing programs for childhood immunization

Variable	Vaccines for Children program	Section 317	State/local government
Type of program	Entitlement funded through Medicaid trust fund	Annual discretionary appropriation by Congress	Appropriations through state or local legislatures
Eligibility	Age <19 y and membership in ≥ 1 of the following categories: Medicaid-eligible; uninsured; Alaska Native or Native American; or underinsured at a federally qualified health center	No federal eligibility restrictions	Varies by state or local area
Financing of new vaccines and recommendations	Vote of ACIP and establishment of a federal contract; funds must be approved by the Office of Management and Budget and the Department of Health and Human Services	Funding must be sought from Congress	Funding must be sought from state legislatures
Proportion of childhood vaccine market purchased	41%	11%	5%

Abbreviation: ACIP, Advisory Committee on Immunization Practices.

Data from Hinman AR, Orenstein WA, Rodewald L. Financing immunizations in the United States. *Clin Infect Dis* 2004;38:1440–6.

dren who are not eligible for VFC. In addition, insurance provides vaccines for children in the private sector.

Immunization program challenges

As the number of vaccines has increased and the scope of the immunization program has expanded, new challenges have emerged. The increasing cost of vaccines, vaccine shortages, and immunization safety are important concerns the immunization program will continue to address in coming years.

The rising cost of fully immunizing a child in the United States is due to the increasing number of vaccines and the increasing price of existing vaccines. The estimated cost of completing the childhood immunization series through 6 years of age in 1987 was \$33.70 per child at the government-purchasing rate. The cost of immunizing a child through 6 years of age in 2003 was \$436 per child for all vaccines, not including influenza vaccine [12]. Increasingly, state and local health departments are required to make difficult choices about which vaccines to purchase using public funds, including Section 317 grant funds. The recommendation in 2000 to vaccinate routinely with PCV7 doubled the cost of immunizing a child. Section 317 and state funding have not been adequate to cover PCV7 for underinsured children in many states, including 7 of the 14 universal purchase states. The addition of new, effective childhood and adolescent vaccines to the schedule has the potential to create serious funding challenges in the future.

Despite the increasing costs of immunization programs, numerous studies have shown that vaccination continues to be a cost-effective public health intervention. These studies show the need to continue to identify adequate funding sources to support immunization recommendations [13–16]. An Institute of Medicine (IOM) report on vaccine financing released in 2004 concluded, “alternatives to current vaccine pricing and purchasing programs are required to sustain stable investment in development of new vaccine products and attain their social benefits for all” [17].

In addition to the increasing cost of vaccines, an unparalleled number of vaccine shortages in the United States has had a substantial impact on vaccine delivery. From 2000 through 2005, vaccine shortages and changes in routine recommendations occurred for 9 of the 12 diseases for which childhood and adolescent vaccination is recommended (Fig. 2) [18–23]. The shortages affected millions of children and health care providers, even triggering suspension of vaccine school entry requirements [24,25]. Two vaccine shortages (PCV7 and tetanus and diphtheria toxoids [Td]) lasted nearly 2 years, one (PCV7) occurred twice [26], and one (inactivated influenza vaccine, 2004–05 season) halved the US influenza vaccine supply virtually overnight [17,22].

The causes of these widespread vaccine shortages are multifactorial. One important long-term factor is the decrease in number of vaccine manufacturers of childhood vaccines routinely recommended in the United States. In 1977, a federal immunization working group expressed concern about the stability of the US vaccine supply in the setting of “a steady attrition of specific

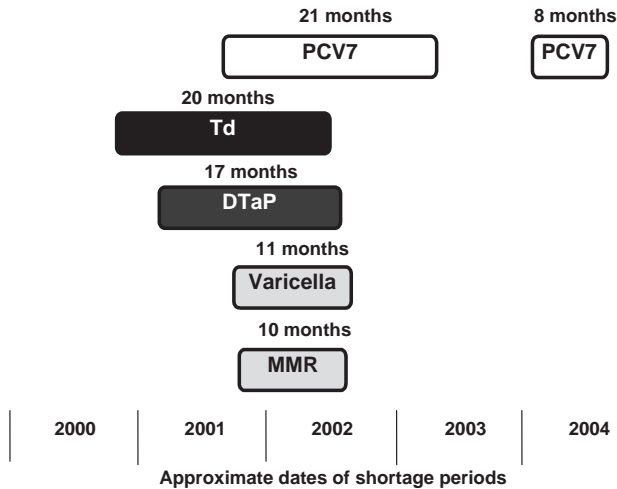


Fig. 2. Shortages of vaccines in the US childhood and adolescent immunization schedule, 2000–2004, not including influenzae vaccine shortage.

pharmaceutical manufacturers from the entire field of biologics” [17]. In 1993, six manufactures produced the six vaccines. In 2005, although four vaccines (PCV7, varicella, influenza, and MCV4) have been added to the recommended schedule, the number of manufacturers decreased to five. In addition, there are single manufacturers for four of the childhood and adolescent vaccines (MMR, varicella, PCV7, and MCV4). In response to concerns over fragility of the US vaccine supply, the General Accounting Office and National Vaccine Advisory Committee conducted in-depth reviews of the vaccine shortages and concluded that future disruptions in vaccine supply are likely to continue, and proposed solutions [17,27].

Vaccines are administered routinely to healthy children and must uphold a scrupulously high safety standard; however, no vaccine is completely safe. In 1986, the National Childhood Vaccine Injury Act was passed creating a compensation program for families affected by childhood vaccine-associated adverse events. Several other government programs and committees to ensure the safety of the vaccine supply also were created by this Act (Table 5).

As many vaccine-preventable diseases approach or reach elimination in the United States, continuing to balance the risks and benefits of each vaccine becomes increasingly important [28]. OPV, formerly recommended for routine use in the United States, was associated with vaccine-associated paralytic poliomyelitis (1 case among 2.4 million vaccine doses distributed). This rare adverse event was no longer considered acceptable after elimination of polio in the United States [29]. In 2000, the ACIP recommended using IPV for all doses of polio vaccine. Public perceptions of vaccine safety are a challenge to the continued success of the vaccination program. New parents and younger physicians grew up without appreciation of the morbidity and mortality of

Table 5
National Childhood Vaccine Injury Act, 1986

National Vaccine Injury Compensation Program	Limits manufacturer liability Provides payments to families of children who sustain documented injuries after routine immunization
National Vaccine Program	Develops and coordinates a comprehensive national vaccine plan
Advisory Commission on Childhood Vaccines	Advises Secretary of Health and Human Services on injury compensation program
National Vaccine Advisory Committee	Advises Secretary of Health and Human Services on national vaccine policy
Federal Excise Tax on Childhood Vaccines	1987 amendment to Compensation Act Proceeds used to finance payments to families of children affected by a vaccine-associated adverse event

Data from Schwartz B, Orenstein WA. Vaccination policies and programs: the federal government's role in making the system work. *Prim Care* 2001;28:697-711.

several vaccine-preventable diseases. Risk or perception of risk for adverse events becomes an important concern. Two current prominent public vaccine safety concerns are the perceived causal association between MMR and autism and thimerosal-containing vaccines and autism. As a result of heightened concerns about safety, in 2000 the CDC and National Institutes of Health commissioned the IOM of the National Academy of Science to convene an

Box 1. Institute of Medicine Immunization Safety Review Committee reports and dates of release, 2001-2004*

1. Measles-mumps-rubella vaccine and autism—April 2001
2. Thimerosal-containing vaccines and neurodevelopmental disorders—October 2001
3. Multiple immunizations and immune dysfunction—February 2002
4. Hepatitis B vaccine and demyelinating neurologic disorders—May 2002
5. SV40 contamination of polio vaccine and cancer—October 2002
6. Vaccinations and sudden unexpected death in infancy—March 2003
7. Influenza vaccines and neurologic complications—October 2003
8. Vaccines and autism—May 2004

* *Data from* http://www.iom.edu/search_results.asp?qs=immunization%20safety%20review%20committee%20reports.

Immunization Safety Review Committee [30]. Between 2001 and 2004, this independent expert committee published eight reports related to immunization safety concerns. The committee has made recommendations in the areas of public health response, policy review, research, and communications (Box 1). With respect to autism, the IOM concluded that the body of epidemiologic evidence favors rejection of a causal relationship between the MMR vaccine and autism. The committee also concluded that there is no relationship between thimerosal-containing vaccines and autism [30]. None of the eight IOM reports recommended a policy review of the current vaccine recommendations or change in the immunization schedule.

To help ensure safety of vaccines, a robust infrastructure consisting of several systems has been established to monitor vaccine safety after vaccine licensure. The Vaccine Adverse Event Reporting System, operated jointly by CDC and FDA, is a national passive surveillance system used to detect early warning signals and generate hypotheses about possible new vaccine adverse events or changes in frequency of recognized events [31]. Intussusception associated with receipt of rotavirus vaccine, leading to the withdrawal of the vaccine from the market in 1999, was an adverse event detected by the Vaccine Adverse Event Reporting System [31,32]. A third system is the Vaccine Safety Datalink, which consists of large linked databases from health maintenance organizations. Associations between serious medical events and immunizations can be evaluated through the Vaccine Safety Datalink. The newest system is the Clinical Immunization Safety Assessment Centers network, which consists of selected clinical academic medical centers in partnership with CDC to study the pathophysiology of vaccine reactions and develop clinical management protocols for affected patients [34]. These systems are crucial to the vitality and strength of the US immunization program.

Adolescent vaccination considerations

Since its inception, the major focus of the US immunization program has been on vaccinating infants and young children. Of the 10 vaccines routinely recommended for children and adolescents, only two, Td vaccine and the MCV4, are recommended for all adolescents [8]. In 1996, as a result of growing concern about morbidity associated with vaccine-preventable diseases in the hard-to-reach adolescent population, the ACIP recommended expanding efforts to immunize adolescents (11–21 years old) by establishing a routine vaccination visit at 11 to 12 years old [35]. In addition to providing Td and previously missed vaccinations, the report emphasized that this visit should be used to provide other important preventive health services. The anticipated addition of several new adolescent vaccines to the recommended schedule has stimulated a reappraisal of the approaches that most effectively and efficiently would increase the proportion of adolescents who receive newly recommended vaccines and develop ways to integrate these approaches with other adolescent health, education, and development programs.

Vaccines in the spotlight

Similar to all aspects of clinical medicine, immunization recommendations continuously change as new vaccines are licensed and new information becomes available. Since 1990, several new vaccination recommendations were implemented for existing and new vaccines. Notable examples are PCV7 and the hepatitis B vaccine; new recommendations for both have affected children and health care providers. Several vaccines with expected FDA licensure in the near future likely will alter the US immunization program and preventive health care practices (Table 6). Vaccines with a pediatric or adolescent focus under review by the ACIP are relevant to the prevention of pertussis, human papillomavirus (HPV), influenza, varicella, and rotavirus. This section presents a summary of these vaccines in addition to information on PCV7, hepatitis B vaccine, and MCV4. The potential impact of vaccines on the distant horizon also will be highlighted. Emphasis is on how recent and upcoming policy decisions might affect children and adolescents, health care providers, and society during the next decade.

Table 6
Selected pediatric vaccines in phase II and phase III clinical trials, 2004

Vaccine	Type	Age group	Development phase	Potential impact
Diphtheria, tetanus, pertussis	Diphtheria and tetanus toxoids and pertussis vaccine	Adolescents	Submitted to FDA	Decrease burden of disease in adolescents Might reduce overall burden of pertussis disease and protect unvaccinated infants from disease
Rotavirus	Live, attenuated, oral	Infants	Phase III	Reduce morbidity and mortality due to diarrhea and dehydration associated with rotavirus
Human papillomavirus	Virus-like particle vaccine	Adolescents	Phase III	Reduce rates of cervical cancer Reduce number of colposcopy and cervical biopsy procedures
MMR, varicella (MMRV)	Live, attenuated, combination	Anytime MMR given	Phase III	Decrease number of injections
DTaP, Hib, IPV, Hep B	Hexavalent combination	Infants	Phase II	Decrease number of injections
DTaP, Hib, polio	Combination	Infants	Phase III	Decrease number of injections

Data from <http://www.phrma.org/newmedicines/resources/2004-06-13.131.pdf>.

Pneumococcal conjugate vaccine

PCV7 was recommended for routine use in infants in the United States beginning in 2000. Before introduction of PCV7, *Streptococcus pneumoniae* (pneumococcus) was a leading cause of infectious morbidity in young children in the United States, annually causing approximately 17,000 cases of invasive disease in children younger than 5 years old, including 700 cases of meningitis and 200 deaths. In addition, the burden of pneumonia without bacteremia, otitis media, and sinusitis was substantial [36].

After introduction of routine PCV7 vaccination, the incidence of invasive pneumococcal disease declined dramatically, especially in children younger than 2 years old [37–39]. Active US population-based surveillance data show that within 2 years of PCV7 licensure, the rate of invasive pneumococcal disease in children younger than 2 years old declined by 69% [39]. In tandem with the decrease in invasive disease, data suggest the incidence of pneumococcal non-invasive disease, including otitis media, also decreased [40,41]. In addition to decreasing the burden of pediatric pneumococcal disease, PCV7 may have an impact on reducing pediatric antibiotic prescriptions and procedures such as blood cultures in young, febrile children [42].

The decline in invasive pneumococcal disease is beyond what would be expected from childhood vaccination, given vaccine efficacy and PCV7 coverage data, suggesting that herd immunity may play a role in protecting unimmunized people from invasive disease [37]. Reduced nasopharyngeal carriage of vaccine-containing serotypes in vaccinated children is believed to contribute to development of herd immunity against pneumococcus. Rates of invasive pneumococcal disease seem to be declining among some unvaccinated groups after implementation of universal infant PCV7 vaccination. In addition, postlicensure surveillance data suggest a decrease in antibiotic-resistant strains of *S. pneumoniae* [37,39].

Because PCV7 includes only 7 of the more than 90 serotypes of pneumococcus, there is theoretical concern that serotype replacement might occur in highly vaccinated populations. One study noted an increase in the proportion of cases of invasive pneumococcal disease resulting from nonvaccine serotypes, but the total number of cases was not changed [38]. This study supports the need for continued pneumococcal surveillance in the post-PCV7 era [43].

Hepatitis B

Hepatitis B vaccine holds a unique place in the US immunization schedule because they are the only vaccines licensed for neonates and the only licensed vaccine that prevents cancer. The continued evolution of hepatitis B vaccine recommendations reflects many of the challenges associated with vaccines that will be licensed in the near future.

Before 1982, an estimated 200,000 to 300,000 people in the United States were infected annually with hepatitis B virus, including approximately 20,000

children [44]. Although most vaccine-preventable diseases are spread via contact or airborne droplets, hepatitis B infection is spread via exposure to infected blood or blood products, sexual contact, and injection devices. Much of the transmission of hepatitis B in adults is silent; there is no accompanying rash or symptoms. Although adults have a 10% chance of developing chronic hepatitis B virus infection, infants infected perinatally who do not receive hepatitis B immunoglobulin and vaccine at birth have a 90% chance of developing chronic infection. Twenty-five percent of these infections lead to hepatocellular carcinoma [45].

The complexity of hepatitis B transmission required a vaccination strategy to protect infants and high-risk adults from infection. The first ACIP hepatitis B recommendation in 1982 was to vaccinate groups known to be at high risk for hepatitis B virus infection, such as health care workers, men who have sex with men, and intravenous drug users [46]. In 1984, the ACIP expanded recommendations to include infants born to mothers who were hepatitis B surface antigen (HBsAg) positive. Recognition of the difficulty in identifying mothers infected with hepatitis B led to a recommendation in 1988 to test all women for HBsAg during the prenatal period. Vaccinating high-risk groups continued to be difficult because no foundation existed to vaccinate adolescents and adults who already were participating in high-risk activities. In 1991, a universal infant vaccination strategy was instituted to achieve the goal of reducing transmission of hepatitis B virus [46]. It is recommended that the first dose be given at or before 2 months of age with a preference for all infants to receive the first dose at birth. Neonatal vaccination works by protecting the infant from contracting hepatitis after vertical or horizontal exposure. Giving all infants the birth dose protects infants whose mothers were not tested for HBsAg during pregnancy. Infant vaccination eventually will provide protection against hepatitis B virus to adolescents who may engage in high-risk activities before exposure. From 1990 to 2002, rates of hepatitis B virus infection in children and adolescents younger than 20 years old declined more than 88% in the United States [47].

Meningococcal vaccines

From 2000 to 2002, approximately 2400 to 3000 cases of invasive meningococcal disease occurred annually in the United States [48]. The case-fatality ratio for meningococcal disease is approximately 10%, and severe sequelae (eg, neurologic disability, limb loss) occur in approximately 10% of survivors [49]. Nasopharyngeal carriage of *Neisseria meningitidis* occurs in approximately 5% to 10% of the US population [48]. Transmission is through direct contact with respiratory tract droplets of infected individuals. Infants younger than 1 year of age have the highest rates of meningococcal disease, with an annual incidence of 6.5 cases per 100,000 population during 2002 [50]. During the 1990s, incidence rates of meningococcal disease increased among adolescents and young adults [49]. Evidence also showed that college freshmen living in dormitories have a

modestly increased risk of meningococcal disease (4.6 cases per 100,000) compared with other persons the same age [49].

A meningococcal polysaccharide (MPS) vaccine containing the antigens of serogroups A, C, Y, and W135 has been used in the United States since licensure in 1981. This vaccine protects against the serogroups that cause approximately two thirds of meningococcal disease that occurs in persons 18 to 23 years old in the United States. More than half of cases in infants are due to serogroup B, however, for which a licensed vaccine does not exist in the United States [49]. Similar to other polysaccharide vaccines, MPS induces a T cell-independent immune response resulting in poor long-term immunity and inconsistent immunogenicity in children younger than 2 years old. An additional shortcoming is that MPS does not reduce nasopharyngeal carriage or induce herd immunity [48]. Before February 2005, MPS vaccine was recommended for groups at high risk for meningococcal disease and for outbreak control. Educating college freshmen about the potential for the MPS vaccine to prevent severe infection also was recommended. Some states required proof of vaccination or vaccine waiver for entry into colleges and universities [49].

Employing the same technology used to develop PCV7, a meningococcal serogroup C conjugate vaccine was licensed in the United Kingdom in 1999. The vaccine was introduced into the routine infant schedule, with catch-up vaccination for older children and adolescents. In the 2 years after introduction of infant meningococcal conjugate vaccine, the incidence of serogroup C meningococcal disease declined by 87% in vaccinated persons and at least 34% in unvaccinated persons, suggesting the vaccine produced herd immunity [48].

In the United States, a quadrivalent meningococcal conjugate vaccine (serogroups A, C, Y, and W-135) (MCV4) was licensed on January 14, 2005, for use in persons 11 to 55 years old. During prelicensure clinical trials, immune responses to MPS and MCV4 were similar in adolescents and adults. Because MCV4 induces T cell-mediated immunity, the duration of protection is thought to be longer than immunity produced by MPS. On February 10, 2005, the ACIP voted to recommend that MCV4 be administered universally to adolescents ages 11 to 12 and around 15 years of age, and college freshmen living in dormitories; a VFC resolution also was passed. With the addition of MCV4 to the immunization schedule, a new era of adolescent vaccination was launched. In the United States, meningococcal conjugate vaccines for use in children younger than 11 years of age are under study.

Pertussis vaccine

Pertussis remains endemic in the United States despite high immunization coverage rates of infants and young children [51]. Immunity to pertussis wanes approximately 5 to 10 years after vaccination, and loss of immunity seems to play a major role in the continued circulation of pertussis [52]. In 2003 and 2004, 11,647 and more than 18,000 cases of pertussis were reported to the CDC,

respectively [53]. Much of the reported increase is thought to be due to increasing physician recognition of pertussis as a nonspecific, persistent cough illness in adolescents and adults, coupled with increasing use of polymerase chain reaction testing for diagnosis of all age groups. How much of the reported increase is due to enhanced surveillance or improved diagnostic methodology is unclear. One study suggested that a true increase in the incidence of pertussis disease occurred in young infants in the United States between 1980 and 1999 [54].

The burden of pertussis disease in adolescents is substantial. Of the reported cases of pertussis in the United States in 2003, 39% were in adolescents; the true number of cases is likely to be much higher (CDC, unpublished data). Although pertussis is rarely life-threatening in adolescents, the morbidity and societal costs associated with adolescent pertussis disease are important [55]. In a Canadian study, 47% of adolescents with pertussis reported a cough duration of at least 9 weeks [56]. Paroxysms, shortness of breath, posttussive vomiting, and difficulty sleeping occur commonly in adolescents with pertussis disease [55,56]. To reduce pertussis disease in adolescents, some countries have recommended an adolescent booster dose. In summer 2004, two manufacturers submitted BLAs to the FDA for use of adolescent and adult pertussis vaccines in the United States (tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed (Tdap). The BLA indication for one vaccine includes persons 10 to 18 years old, and the other includes persons 11 to 64 years old.

Policymakers are reviewing several strategies for pertussis vaccination in adolescents and adults. A cost-benefit analysis in the United States found universal vaccination for persons 10 to 19 years old to be the most economic strategy [57]. The expected impact of adolescent pertussis vaccination would be to reduce the risk of pertussis in vaccinated adolescents. Ideally, another public health goal of pertussis vaccination is to reduce transmission to infants younger than 6 months old who have not completed the primary vaccination series and are at highest risk of death from pertussis. The role of an adolescent vaccination program in reducing transmission to infants is unknown. Vaccinating mothers and other close family members of young infants, referred to as a “cocoon strategy,” is one method under consideration to decrease pertussis transmission to infants. One study suggested that adult family members are the most frequently identified source for pertussis transmission to infants [58]. Universal replacement of the Td booster given every 10 years with Tdap is another strategy being discussed. Finally, vaccinating women during pregnancy and vaccinating neonates against pertussis have been raised as potential strategies to improve control of pertussis, although pertussis vaccines for these indications are unlikely to be licensed in the United States in the near future [59,60].

Human papillomavirus vaccine

More than 200 types of papillomaviruses have been recognized on the basis of DNA sequence analyses [61]. Papillomaviruses are ubiquitous, have been

detected in a wide variety of animals and humans, and are specific to their respective hosts. HPV is associated with a variety of clinical conditions that range from benign skin and mucous membrane lesions to cancer. Most HPV infections are benign. Clinical manifestations with the most frequently associated HPV type are as follows: skin warts (types 1, 2, 3, and 10), recurrent respiratory papillomatosis (types 6 and 11), condyloma acuminata (types 6 and 11), and cervical cancer (types 16, 18, 31, 33, and 45). Based on the association of HPV with cervical cancer and precursor lesions, HPVs can be grouped into low-risk and high-risk HPV types [61]. In the United States and Europe, HPV 16 accounts for approximately 50% of the cases of cervical cancer, with types 18, 31, and 45 accounting for an additional 25% to 30% of cases [62].

HPV is one of the most common causes of sexually transmitted diseases in men and women worldwide, causing almost all of the morbidity and mortality associated with cervical cancer [61]. Epidemiologic studies have shown that the risk of contracting genital HPV infection and cervical cancer is related directly to sexual activity. Several specific factors increase the risk of becoming infected with HPV, including multiple sexual partners at any time, having sex with a person who has had multiple sexual partners, sexual activity at an early age, presence of other sexually transmitted diseases, and HPV type.

Vaccination against high-risk HPV types could reduce substantially the incidence of cervical cancer. Administration of HPV-16 vaccine has been shown to reduce the incidence of HPV-16 infection and HPV-related cervical intraepithelial neoplasia [63]. In addition, a bivalent HPV vaccine was efficacious in preventing persistent cervical infections with HPV-16 and HPV-18 and associated cytologic abnormalities and lesions [64]. Currently, two HPV vaccines are in the final stages of phase III testing. One vaccine contains HPV types 16, 18, 6, and 11, and the second HPV vaccine contains types 16 and 18. Applications for licensure are expected to be filed with the US FDA in late 2005 or 2006.

Rotavirus vaccine

Rotavirus is a common cause of gastrointestinal tract illness in young children. By 5 years of age, nearly all children test seropositive for rotavirus, indicating previous infection. In the United States, rotavirus disease leads to an estimated 600,000 clinic visits, 50,000 to 60,000 hospital admissions, and 20 to 40 deaths annually [33].

The first rotavirus vaccine was licensed in the United States in 1998 and was removed from the market and from the immunization schedule in 1999 because of an association with intussusception. This vaccine was a tetravalent rhesus human reassortant vaccine [65,66]. Currently, several other rotavirus vaccines are in different stages of development. Two late-stage vaccines have completed phase III clinical trials. One vaccine is derived from a monovalent human strain, and the other is a pentavalent bovine-human reassortant vaccine. Large-scale phase III trials did not show an association of these vaccines with intussusception, but postlicensure monitoring is planned. In January 2005, Mexico became

the first country to make a new rotavirus vaccine available. The company has filed license applications in more than 20 other countries outside the United States. The manufacturer of the second rotavirus vaccine plans to release it first in the United States after licensure by the US FDA. After licensure in the United States, educational efforts that address identifiable barriers to achieving practitioner advocacy and patient acceptance will be necessary to ensure implementation of rotavirus vaccine recommendations [67]. Ensuring physician acceptance of the vaccine is critical to achieving high coverage levels [67].

Varicella vaccine

Varicella vaccine, licensed for use in the United States in 1995, is a live, attenuated virus vaccine developed from the vesicles of a healthy infected child with chickenpox. This vaccine is recommended as a single dose for children 12 months to 12 years old. Susceptible persons 13 years old or older should receive two doses administered 4 weeks apart. Before varicella vaccine became widely used, varicella was one of the most recognizable rashes seen by pediatricians and was associated with 11,000 hospitalizations and 100 deaths in the United States each year [68]. In 2003, the vaccine had 85% coverage levels, resulting in a significant decrease in mortality, morbidity, and hospitalizations attributable to varicella [68].

Breakthrough varicella infections in vaccinated children occur in 15% of children exposed to varicella. Breakthrough infections usually are mild (<50 lesions), however, with few complications [69]. Vaccinated children with mild disease were only one third as contagious as children with moderate-to-severe disease, whether they were vaccinated or unvaccinated. Vaccine effectiveness for prevention of moderate disease (>50 lesions and complications requiring a visit to a clinician) was 92% [69]. A second dose of varicella vaccine has been approved by the FDA and is being considered for the routine childhood vaccination schedule.

The impact of varicella vaccine on the incidence of zoster infections in adults in the United States is unknown. Varicella vaccine may protect children receiving the vaccine from zoster when they become adults. Studies suggest, however, that continued exposure to varicella protects latently infected adults [70]. Vaccination in children could lead to an increase in zoster incidence in unvaccinated adults because exposure to varicella-infected children has declined, but zoster surveillance is limited. A vaccine to prevent herpes zoster in adults is under investigation.

Influenza vaccines

Since the worldwide influenza pandemic of 1918 that caused an estimated 25 to 50 million deaths, the control of influenza circulation has been a major challenge to clinicians and public health experts. The threat of an unpredictable

influenza pandemic and the concern about avian influenza heighten the importance of preventing morbidity and mortality caused by epidemics of influenza disease in the United States, which cause more than 250,000 hospitalizations and more than 36,000 deaths annually [71]. Implementing the expansion of influenza vaccine recommendations to 6- to 23-month-old children and prioritizing vaccine during influenza vaccine shortages are important issues the US immunization program faces regarding influenza prevention.

Influenza virus contains eight major proteins, including hemagglutinin (HA), which controls viral penetration and attachment, and neuraminidase (NA), which controls viral particle release and spread. Influenza strains are identified by type (A, B, and C) and by subtype categorized by HA and NA. There are 15 different HA and 9 different NA subtypes. Major changes in HA and NA, called *antigenic shifts*, are associated with emergence of novel influenza viruses to which little or no immunity exists in the exposed population. Antigenic shifts were the cause of the three influenza pandemics in the twentieth century (Table 7) [72]. Minor changes in HA and NA, called *antigenic drifts*, define the influenza viruses that circulate each year. Influenza vaccines are developed yearly based on antigenic drifts. Worldwide surveillance established by the World Health Organization allows predictions to be made regarding antigenic drifts, which enables vaccine to be updated before the start of an influenza season. Recommendations for which influenza strains should be included in the vaccine are made in early spring before influenza season. Three influenza types are formulated and combined to make a new trivalent vaccine each year.

Two types of influenza vaccines are licensed for use in the United States. One is an inactivated vaccine recommended for persons ≥ 6 months of age in high-risk groups and their close contacts. The second is a cold adapted, live, nasally administered vaccine licensed for healthy people 5 to 49 years of age, including close contacts of high-risk persons. The ACIP and AAP recommended in 2004 to expand influenza vaccine recommendations to include all children 6 to 23 months old and household contacts of children up to 23 months old as well as to continue immunization of all children in high-risk groups. This recommendation was made based on epidemiologic data showing that healthy children in this age group are at high risk of hospitalization from influenza, and that deaths in this age group occur [73–76]. More than 150 reports of pediatric influenza-associated deaths during the 2003–04 influenza season stimulated the addition

Table 7
Influenza pandemics in the twentieth century

Year	Pandemic name	Strain	Approximate deaths	
			US	Worldwide
1918	Spanish flu	H1N1	675,000	25–50 million
1957	Asian flu	H2N2	70,000	>1 million
1968	Hong Kong flu	H2N2	34,000	>1 million

of influenza-associated pediatric mortality to the Council of State and Territorial Epidemiologists list of nationally notifiable diseases [77].

The influenza vaccine is unique to the recommended childhood and adolescent immunization schedule because it is the only vaccine that requires a visit during a certain time of year and that requires annual immunization. Even if the circulating strains of virus are the same as the year before, an annual booster is necessary to retain immunity. In addition, children 6 months to 8 years old are recommended to have two doses of influenza vaccine administered 1 month apart if they previously have never been vaccinated for influenza [76]. Adding influenza into the childhood schedule is challenging for public health officials and primary care physicians developing programs to attain high coverage rates in children 6 to 23 months old.

Vaccines on the horizon

Vaccine development is expanding to include products against cancers, chronic diseases, and other infectious diseases. Vaccines against inflammatory diseases for which an infectious cause has not been identified, such as multiple sclerosis and rheumatoid arthritis, are being developed as therapeutic vaccines. Scientists effectively are using new biologic tools to improve existing vaccines. New technologies also are being used to improve vaccine delivery systems, producing better combination, oral, and intranasal vaccines.

The science behind new vaccines continues to advance at a remarkable pace, driven by an evolving understanding of the cellular and molecular processes involved in different responses of the immune system [78]. Many infectious organisms have evolved over thousands of years to evade this immune response. Adjuvants to vaccines are now being used not only to create an immune response, but also to focus the immune response down a desired path [79]. DNA vaccines, plasmids of DNA encoding the desired antigen, also are being developed with the intention of simplifying vaccine production and eliminating the possible risk of organism reversion [78]. As was true during the time of Jenner, vaccines continue to push the frontiers of science and medicine.

In 2000, the IOM published a report prioritizing development of vaccines to be used in the United States. The IOM committee considered vaccines that could be licensed within 20 years directed against conditions of domestic health importance [80]. Health benefits of these vaccines were measured by a standard health outcome measure, quality-adjusted life years gained. These vaccines were placed into categories of most favorable to least favorable (Box 2). Since publication of this report, PCV7 has been licensed for infants beginning at 2 months of age (most favorable category), and HPV vaccine (more favorable category) and rotavirus vaccine administered to infants (favorable category) are on the near horizon as discussed in this article. Since release of this report, several organisms not included on the IOM list have emerged or became larger public health threats, including West Nile virus, metapneumovirus, methicillin-resistant *Staphylococcus aureus*, the coronavirus associated with severe acute respiratory syndrome

Box 2. Institute of Medicine report on vaccines for the twenty-first century

Most favorable: vaccination strategy would save money

- Cytomegalovirus vaccine administered to 12-year-olds
- Influenza virus vaccine administered to the general population (once per person every 5 years)
- Insulin-dependent diabetes mellitus therapeutic vaccine
- Multiple sclerosis therapeutic vaccine
- Rheumatoid arthritis therapeutic vaccine
- Group B streptococcus vaccine given to women during first pregnancy and to high-risk adults
- *Streptococcus pneumoniae* vaccine given to infants and 65-year-olds

*More favorable: vaccination strategy would incur small costs (<\$10,000) for each QALY**

- *Chlamydia* vaccine administered to 12-year-olds
- *Helicobacter pylori* vaccine administered to infants
- Hepatitis C vaccine administered to infants
- Herpes simplex virus vaccine administered to 12-year-olds
- HPV vaccine administered to 12-year-olds
- Melanoma therapeutic vaccine
- *Mycobacterium tuberculosis* vaccine administered to high-risk populations
- *Neisseria gonorrhoeae* vaccine administered to 12-year-olds
- Respiratory syncytial virus vaccine administered to infants and 12-year-olds

Favorable: vaccination strategy would incur moderate costs (>\$10,000 but <\$100,000) per QALY gained

- Parainfluenza virus vaccine administered to infants and women during their first pregnancy
- Rotavirus vaccine administered to infants
- Group A streptococcus vaccine administered to infants
- Group B streptococcus vaccine given to high-risk adults and low utilization in 12-year-olds or women during their first pregnancy

Less favorable: vaccination strategy would incur significant costs (>\$100,000→\$1 million per QALY gained)

- *Borrelia burgdorferi* vaccine given to resident infants born in and immigrants of any age to geographically defined high-risk areas
- *Coccidioides immitis* vaccine given to resident infants born in and immigrants of any age to geographically defined high-risk areas
- Enterotoxigenic *Escherichia coli* vaccine administered to infants and travelers
- Epstein-Barr virus vaccine administered to 12-year-olds
- *Histoplasma capsulatum* vaccine given to resident infants born in and immigrants of any age to geographically defined high-risk areas
- *Neisseria meningitidis* type b vaccine given to infants
- Shigella vaccine given to infants and travelers or travelers only

* Quality-adjusted life year (QALY) takes into account quantity and quality of life generated by health care interventions. QALY is calculated by placing a weight on time in different health states. The cost per QALY is the cost required to generate 1 year of perfect health.

Data from www.iom.edu/vaccinepriorities.

(SARS), and avian influenza virus (H5N1). The ongoing outbreak of H5N1 influenza in Asia, associated with high mortality rates, has stimulated research of a vaccine that has the potential to thwart a possible major influenza pandemic. Circulating H5N1 viruses may adapt to humans through genetic mutation or reassortment with human influenza strains, allowing for human-to-human transmission, facilitated by the fact that most humans lack preexisting immunity owing to lack of previous exposure [81]. These emerging infectious diseases and the need to prevent them add further complexity to immunization schedules of the future.

Summary

Until the twentieth century, approximately half of children in the United States died as a result of childhood illness. Until the 1920s, infectious diseases were the leading cause of death in the United States. In the first edition of the *Red Book* published by the AAP in January 1938, 18 chapters dealt with infectious diseases, ranging from the common cold to smallpox. Except for pertussis, diphtheria, and

tetanus, and smallpox, active immunization was not available for the other 14 conditions in this edition. Currently, active immunization exists for 12 of the 18 diseases contained in the eight pages of the 1938 *Red Book*, and one disease, smallpox, has been eradicated. Since then, many other infectious disease have emerged or reemerged, including SARS, HIV, West Nile virus, metapneumovirus, avian influenza, and methicillin-resistant *S. aureus*. Many of these conditions are expected to be controlled in the future by immunizations.

As the recommended childhood and adolescent immunization schedule continues to expand, the US immunization program will be challenged to integrate novel immunization strategies into the current immunization infrastructure. The impact of future vaccines in the United States will be more difficult to calculate because they will prevent fewer deaths than vaccines in the past. The cost of these vaccines will continue to increase, and funding support will be challenged. The risk of adverse vaccine events will have to be weighed against the risk of the disease if not vaccinated. Pediatric health care providers face a growing complexity of problems in children, including injury, obesity, asthma, and mental health and behavioral disorders. As the cost and complexity of the childhood and adolescent immunization schedule increase, considering the role of immunizations within the context of other preventive health interventions and overall societal values becomes increasingly important. Immunizations are one of the most effective clinical preventive services in pediatric practice [15]. Despite the challenges facing the US immunization program, immunizations will likely remain on the list of great public health accomplishments of the twenty-first century, and the legacy of Jenner will continue.

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