

# Immunizations In The United States: Success, Structure, And Stress

A complex collaboration involving government, industry, providers, academe, professional societies, and third-party payers.

**by Walter A. Orenstein, R. Gordon Douglas, Lance E. Rodewald, and Alan R. Hinman**

**ABSTRACT:** Immunization is a great success of preventive medicine. In the United States, most vaccine-preventable diseases of childhood are at or near record lows while the number of diseases preventable by vaccination has increased. These successes result from a comprehensive system that includes basic research; developing and testing vaccine candidates; a manufacturing base; a regulatory authority; development of immunization policies; implementation of immunization recommendations; and a compensation system for the few people unavoidably injured by vaccines. Despite the successes, the system faces numerous challenges, including vaccine supply, cost, and safety; adult immunization; vaccine research and development; and biopreparedness.

**F**EW MEASURES IN PREVENTIVE MEDICINE can compare with the impact of vaccines.<sup>1</sup> Smallpox has been eradicated; polio is on the verge of eradication; and measles has been controlled or eliminated in numerous countries around the world. The impact of vaccination has been dramatic in the United States.<sup>2</sup> Exhibit 1 shows representative annual morbidity during the twentieth century for many of the vaccine-preventable diseases of childhood, most often in the years prior to vaccine availability, compared with reports of these diseases in 2004. All have been reduced by at least 87 percent, and most, by 99 percent or more. Sizable reductions in disease incidence also have been seen for three diseases that have become vaccine-preventable among young children in the past ten years: varicella (chickenpox), hepatitis A, and pneumococcal disease. Mortality from varicella among children ages 1–4 years declined 92 percent.<sup>3</sup> Invasive

.....  
*Walter Orenstein (worenst@emory.edu) is director of the Emory Program for Vaccine Policy and Development and associate director of the Emory Vaccine Center at Emory University in Atlanta, Georgia. Gordon Douglas is a consultant in vaccines, infectious diseases, and global health, based in Niantic, Connecticut. Lance Rodewald is director of the Immunization Services Division in the National Immunization Program at the U.S. Centers for Disease Control and Prevention in Atlanta. Alan Hinman is senior public health scientist, Public Health Informatics Institute, Task Force for Child Survival and Development, in Decatur, Georgia.*

**EXHIBIT 1**  
**Comparison Of Representative Twentieth-Century Annual Morbidity And Current Morbidity From Vaccine-Preventable Diseases, United States**

| Disease  | Twentieth-century annual cases | 2004 cases <sup>a</sup> | Percent decrease    |
|--|--------------------------------|-------------------------|---------------------|
| Smallpox   | 48,164                         | 0                       | 100.00 <sup>b</sup> |
| Diphtheria   | 175,885                        | 0                       | 100.00 <sup>b</sup> |
| Measles  | 503,282                        | 37                      | 99.99 <sup>b</sup>  |
| Mumps  | 152,209                        | 236                     | 99.85               |
| Pertussis  | 147,271                        | 18,957                  | 87.13               |
| Polio (paralytic)                                    | 16,316                         | 0                       | 100.00 <sup>b</sup> |
| Rubella  | 47,745                         | 12                      | 99.97               |
| Congenital rubella syndrome                          | 823                            | 0                       | 100.00 <sup>b</sup> |
| Tetanus  | 1,314                          | 26                      | 98.02               |
| <i>H. influenzae</i> , type b and unknown (<5 years) | 20,000                         | 172                     | 99.14               |

**SOURCE:** Adapted from U.S. Centers for Disease Control and Prevention, "Achievements in Public Health, 1990–1999: Impact of Vaccines Universally Recommended for Children—United States, 1990–1998," *Morbidity and Mortality Weekly Report* 48, no. 12 (1999): 243–248; and information provided by Barry Sirotkin, statistician, National Immunization Program, CDC, personal communication, 14 February 2005.

<sup>a</sup> Provisional data from CDC, "Notifiable Diseases/Deaths in Selected Cities Weekly Information," *Morbidity and Mortality Weekly Report* 53, no. 52 (2005): 1218.

<sup>b</sup> Record low.

pneumococcal disease declined by 69 percent among young children.<sup>4</sup> Racial disparities in the burden of invasive pneumococcal disease were reduced markedly after the introduction of pneumococcal conjugate vaccine (PCV7).<sup>5</sup>

These disease reductions are associated with record or near-record highs in immunization levels among young children. The 2003 National Immunization Survey (NIS) reported that immunization rates of children ages 19–35 months were 90 percent or higher for most universally recommended vaccines.<sup>6</sup> School and day care laws in each state requiring vaccination have been associated with elimination of many vaccine-preventable diseases in those settings.<sup>7</sup>

In 2001, Ashley Coffield and colleagues ranked thirty clinical preventive services based on clinically preventable burden and cost-effectiveness.<sup>8</sup> Childhood immunization was the only service that received the maximum score. Most vaccines in use today are cost-saving to society. Fangjun Zhou and colleagues recently estimated that for every dollar invested in childhood vaccination against nine vaccine-preventable diseases, \$5.80 was saved in direct medical care costs. Further, when indirect benefits were taken into account, such as time off from work to care for ill children, the amount saved rose to \$17.70.<sup>9</sup>

The number of infectious diseases preventable by universal vaccination has risen since 1984, when children were routinely vaccinated against seven diseases (diphtheria, measles, mumps, pertussis, poliomyelitis, rubella, and tetanus). In 2005, U.S. children are routinely vaccinated against twelve diseases (all of the above, plus *Haemophilus influenzae* type b [Hib], hepatitis B, influenza, pneumo-

coccal disease, and varicella). Children also are protected against hepatitis A through immunization in areas that have high rates of hepatitis A.

To maintain the present successes, meet the challenges to the current system, and develop more vaccines, it is important to understand the current vaccine system and its strengths and vulnerabilities.

## Vaccination In The United States

The components of the U.S. vaccine system include vaccine discovery, development, manufacture, and distribution; regulation of vaccine development, production, and distribution; and development and implementation of vaccine use policies. Participants include federal, state, and local governments; vaccine companies; academe; medical societies; health care professionals; and insurers (Exhibit 2).

■ **Health burden determination.** New vaccines start with the recognition of an infectious disease burden worth preventing.<sup>10</sup> Estimation of disease burden often comes from disease surveillance and studies supported by the U.S. Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH).

■ **Vaccine research and development.** Basic research regarding pathogens and immune responses is supported primarily by the NIH and performed at universities,

### EXHIBIT 2

#### Major Components Of And Participating Groups In The U.S. Vaccine System

| Component                                 | Major participating groups  |
|---|---|
| Health burden determination               | Federal government  |
| Vaccine discovery                         | Federal government, academe, vaccine industry                                     |
| Vaccine development                       | Vaccine industry, academe, federal government                                     |
| Vaccine production and distribution       | Vaccine industry, commercial distributors, state and local governments            |
| Regulation                                | Federal government  |
| Vaccine policy                            | Federal government, professional medical societies                                |
| Vaccine financing                         | Federal government, state and local governments, insurance companies, individuals |
| Vaccine administration                    | Private health care providers, state and local governments                        |
| Monitoring vaccine use                    | Federal government, vaccine industry, state and local governments                 |
| Monitoring vaccine effectiveness          | Federal government, state and local governments, vaccine industry                 |
| Monitoring vaccine safety                 | Federal government, vaccine industry  |
| Vaccine injury compensation and liability | Federal government  |

**SOURCE:** Authors' analysis.

the NIH, other government agencies, and biotech companies.<sup>11</sup> Research ranges from fundamental new knowledge in laboratories not seeking vaccine discoveries to targeted research concerning a pathogen, its pathogenesis and mode of acquisition, and cellular and humoral immune responses to its antigens in animal infections. Understanding the correlates and mechanisms of immune protection greatly increases the ability to develop a vaccine. Animal studies help in evaluating dosing and schedules. Out of a vaccine discovery program come potential vaccine strategies to test.

Prelicensure human studies are divided into three phases. Phase I studies, which are generally considered part of vaccine discovery, typically involve twenty to eighty vaccinees.<sup>12</sup> Such trials usually start with adults and then move to groups likely to be the target populations for vaccines, such as young children. A decision to begin vaccine development is made when a candidate achieves promising results in preclinical and Phase I studies. Development continues until such a candidate vaccine is licensed for use by the appropriate regulatory body.<sup>13</sup>

Phase II trials involve up to several hundred vaccinees and can be divided into two types. Once preliminary safety and immunogenicity are demonstrated in Phase I, a Phase IIa study can be undertaken to gain further information by evaluating greater numbers of individuals. At this time the product must be defined, the process for manufacture determined, assays for release of a satisfactory product established, and the most appropriate immunological assays for clinical specimens agreed on. Larger Phase IIb trials can be used to obtain more information on dose and dose interval and on safety and immunogenicity among subjects for whom the vaccine might be recommended. Some Phase IIb trials are large enough to determine whether a vaccine is effective. However, the estimate of efficacy is usually imprecise, requiring more definitive trials.

Candidate vaccines that have been shown to be safe and immunogenic in Phase II studies can advance to the pivotal studies required for licensure. These large randomized, double-blind, placebo-controlled Phase III trials, which may enroll up to tens of thousands, usually measure the reduction in incidence of clinical disease among vaccine recipients compared with placebo recipients (vaccine efficacy). Many Phase III trials also attempt to determine an immunologic response, such as a serum antibody level, that correlates with protection from disease. This allows subsequent studies to measure an immune response, not protection from disease, which facilitates testing of the vaccine in various population subgroups. Phase III trials also allow the most methodologically rigorous evaluations of vaccine safety for common events, by comparing vaccine and placebo recipients.

Before Phase III studies can start, technology must be transferred from a research laboratory making small lots of doses to the final site of vaccine manufacture of full-scale lots (10,000–20,000 doses or more) in a facility complying with current Good Manufacturing Practices (cGMP).<sup>14</sup> This transfer includes both process and analytical procedures. Vaccine development requires extensive teamwork with shared goals, excellent project management so that all are aware of

goals and timelines, and a champion to push the project along.

Although vaccine development is primarily a responsibility of industry, much of the clinical testing is performed at academic medical centers (AMCs) and supported by industry funds. Government, particularly the NIH, plays a major role in vaccine evaluation by supporting vaccine trial networks of research centers around the world.

■ **Vaccine production and distribution.** Vaccine production is a costly, rigidly controlled series of processes performed in facilities that meet cGMP standards. Licensure of both the manufacturing plant and the product is required to sell a vaccine in the United States. The cGMP regulations involve the plant, equipment, and procedures and are designed to assure that vaccine is as safe as possible. Compliance requires substantial investments over time. The plant is built for a particular vaccine; its design is determined by the production processes involved. Since the end product of vaccine production cannot be measured with chemical precision, the processes by which the vaccine is made are required to meet certain specifications. These are designed and validated by the manufacturer and approved by the U.S. Food and Drug Administration (FDA). They measure progress at each step of the manufacturing process: protein content, viral infectivity, bacterial contamination, and endotoxin content. Samples of each manufactured lot must be submitted to the FDA for approval before they can be sold.

Vaccine production and distribution are almost exclusively the responsibility of vaccine companies and private distributors. As of 2004 there were only five major commercial manufacturers of vaccines that are widely used in the United States: Sanofi Pasteur, Chiron, GlaxoSmithKline, Merck Vaccine Division, and Wyeth Vaccines. Although the number of recommended vaccines has increased in the past two decades, the number of commercial manufacturers in 2004 was the same as in 1983. The actual producers have changed since 1983 as a result of acquisitions, mergers, some companies dropping out of the market, and some new companies entering. Vaccine companies distribute vaccines directly to end users, through private commercial distributors, or through state distributors.

■ **Regulation.** The FDA has responsibility for assuring that licensed vaccines are safe and effective. The agency reviews the safety and effectiveness of the vaccine, as well as information on the production facility and processes. It approves the labeling for a vaccine, including indications, contraindications, and precautions. It monitors vaccine production and distribution for licensed products with inspections of plants; evaluation of production processes; manufacturers' compliance with cGMP; and testing for purity, potency, and absence of contaminants. The FDA establishes criteria for release of vaccine and has the authority to recall vaccines because of problems with safety or effectiveness.

■ **Vaccine policy.** Recommendations for vaccine use are primarily determined by the CDC through its Advisory Committee on Immunization Practices (ACIP) and by professional societies. The recommended schedule of vaccines for children

and adolescents represents a collaboration of the ACIP, the American Academy of Family Physicians (AAFP), and the American Academy of Pediatrics (AAP).<sup>15</sup> The ACIP issues an adult immunization schedule, endorsed by many provider organizations.<sup>16</sup>

Vaccine recommendations can vary widely. Some vaccines (such as the measles vaccine) are recommended universally for all in certain age groups who do not have contraindications. Other vaccines have limited indications, such as for travelers. Vaccine recommendations have important implications for vaccine production since they largely determine the size of the potential market.

■ **Vaccine financing.** U.S. vaccine financing is a joint responsibility of the private and public sectors. The system for childhood vaccination is different from the system for adults. Approximately 43 percent of childhood vaccines are purchased in the private sector. Most of these are purchased by individual providers who are then reimbursed by third-party payers.

Based on 2002 data, approximately 57 percent of vaccines recommended for children were purchased through a federal contract.<sup>17</sup> Most of the funds come from a federal entitlement, the Vaccines for Children (VFC) program. VFC covers vaccines for children on Medicaid or without health insurance, and American Indians/Alaska Natives.<sup>18</sup> Children who have insurance that does not cover immunizations can also receive VFC vaccines but only at a federally qualified health center (FQHC). Vaccines purchased through VFC are supplied to state and local health departments, which distribute the vaccine to participating providers. The remainder of public-purchase funds comes from federal discretionary funds in the Section 317 grant program (approximately 11 percent of childhood vaccines purchased in 2002) and from state and local funds (5 percent of vaccines purchased in 2002).<sup>19</sup>

The mechanisms for obtaining public funds differ greatly between VFC and other funding sources. The law establishing VFC authorizes the ACIP to decide which vaccines should be included and hence funded for eligible children without going through the traditional annual discretionary appropriations process by Congress. Vaccines can be incorporated into VFC if a federal contract with the manufacturer is negotiated and funds for the contract are approved by the Office of Management and Budget (OMB). In contrast with the VFC program, the Section 317 grant program requires an annual appropriation by Congress. While VFC-eligible children can automatically receive recommended vaccines, there is no guarantee for children who rely on discretionary funds. For example, when the PCV7 vaccine was licensed in 2000, a contract was negotiated and VFC-eligible children began receiving that vaccine. However, because there was no increase in the 317 appropriation, nineteen states did not allow public-program access for children who were ineligible for VFC. Funds obtained through state appropriations also finance vaccines for some children but are subject to state discretionary appropriations. As of 2002, eight states purchased and provided all

vaccines for all children.<sup>20</sup> States are allowed to use the federal contract to purchase vaccines with their own public funds. In the past, the federal contract usually secured discounts of about 50 percent below catalog prices. More recent contract prices have had smaller discounts.

There are no programs comparable to VFC for adults. Vaccines for adults are largely purchased in the private sector using a reimbursement model, in which the immunization provider purchases vaccine up front and bills the patient or a third-party payer, such as Medicare or an insurance plan. A replacement model (such as VFC) provides government-purchased vaccine to the provider, who administers it to eligible people. The public health sector has had only a minimal role in purchasing adult vaccines. Only about 5 percent of influenza vaccines for adults are purchased through the CDC's federal contract.<sup>21</sup> Although most vaccines are purchased by the private sector, substantial amounts of federal funds are used to reimburse those purchasers. For example, Medicare covers both influenza and pneumococcal polysaccharide vaccines for its beneficiaries.

■ **Vaccine administration.** Vaccines are administered by private providers and public health clinics. According to the 2003 National Immunization Survey, 61 percent of vaccines administered to young children were administered exclusively in the private sector, 16 percent in the public sector, and 23 percent in a combination of the two or another type of provider, such as the military.<sup>22</sup> Data from the 2002 Behavioral Risk Factor Surveillance System (BRFSS) estimate that 32–58 percent of adults received their influenza vaccine in doctors' offices, 2–35 percent in the workplace, and 5–14 percent in alternative locations such as stores and pharmacies, depending on their age.<sup>23</sup>

Vaccine administration costs are financed by third-party payers, including Medicaid, Medicare, and private insurance. Reimbursement for vaccine administration is typically less than it costs to administer the vaccine. During the 1990s, payment for administration of children's vaccines was higher than that for adults, but beginning in 2005, Medicare providers will be reimbursed more than \$18 per vaccine—more than any state pays for giving childhood vaccines.<sup>24</sup>

■ **Monitoring vaccine use.** Monitoring vaccine use includes a biologics surveillance system and various immunization coverage surveys. The CDC's biologics surveillance system collects voluntary reports from manufacturers of the number of doses they distribute. Data give an estimate of the number of doses that have been used, although some vaccine may have been wasted or discarded.

Vaccine use levels are measured by surveys. The NIS is a telephone survey that estimates the vaccination rates of children ages 19–35 months.<sup>25</sup> The NIS comprises seventy-eight independent surveys covering all fifty states and twenty-eight major urban areas. More than one million telephone calls are made annually to yield responses from approximately 30,000 households with children in the appropriate age group. Responsible adults in the households are asked to identify health caregivers, who are then queried about each child's record. Responses are

weighted on a number of factors, and attempts are made to correct for households without telephones. The NIS also collects information on sources of vaccination, vaccine safety beliefs, and other important topics.

States collect information on immunization coverage for licensed day care, school enterer, and school populations.<sup>26</sup> Coverage among school enterers is usually a census of all students in the schools.

During the past decade, extensive efforts have been made to develop a nationwide system of population-based immunization registries. When fully functional, these record every child immunization administered by any provider, determine immunization needs of individuals, remind parents and providers when immunizations are due, and measure immunization coverage. A Healthy People 2010 objective is to assure that 95 percent of children ages 0–6 years are enrolled in a population-based registry. Based on self-reported data from states, in 2002, registries contained immunization information on 43 percent of children.<sup>27</sup>

Two surveys are used to estimate immunization coverage among adults. The National Health Interview Survey (NHIS), a national probability sample of households that are visited to collect data, is considered the “gold standard” but is too small to provide state-specific data. The BRFSS is a telephone survey conducted by states, which provides national and state-specific estimates of influenza and pneumococcal vaccine coverage.

■ **Monitoring effectiveness.** The CDC is responsible for disease surveillance and evaluates whether vaccination is having the desired impact on disease occurrence. Most vaccine-preventable diseases are nationally notifiable. The Council of State and Territorial Epidemiologists reports to the CDC on the occurrence of specified diseases, usually including some demographic information and often including information on vaccination status, clinical signs and symptoms, and complications. The CDC analyzes the data to assess whether additional studies of vaccine effectiveness are warranted. The CDC also has sentinel surveillance systems that measure vaccine effectiveness for certain diseases such as varicella (or chickenpox) and diseases caused by encapsulated bacteria.<sup>28</sup> State health departments and the CDC also measure vaccine effectiveness during investigations of outbreaks of vaccine-preventable diseases and in special prospectively designed effectiveness studies.

■ **Monitoring safety.** Postlicensure vaccine safety is evaluated through multiple means. (1) Manufacturers may conduct active surveillance of adverse events as part of Phase IV studies. (2) Passive reports of adverse events are collected by the FDA and the CDC in the Vaccine Adverse Event Reporting System.<sup>29</sup> This system is usually helpful in providing signals about whether a vaccine may be causing an adverse event but usually cannot determine whether vaccine caused the event. For that, special studies are frequently needed. (3) The CDC supports the Vaccine Safety Data-link (VSD), which contains the complete medical records of members of seven large health maintenance organizations (HMOs) around the country.<sup>30</sup> The VSD can be used to conduct epidemiologic studies to determine if the incidence rate of a given

adverse event is higher among vaccinees than among nonvaccinees. (4) The CDC and the FDA may conduct special studies. For example, the CDC performed a large case-control study of intussusception, a form of intestinal blockage, to determine whether rotavirus vaccine was causing the problem.<sup>31</sup> (5) The CDC has formed the Clinical Immunization Safety Assessment Network, which reviews clinical patterns of syndromes after vaccination to determine unusual occurrences, sets the stage for special studies, and provides clinical guidelines for managing patients with suspected adverse events.<sup>32</sup>

■ **Vaccine injury compensation and liability.** Because most vaccine-preventable diseases are transmitted from person to person, when people are vaccinated they protect themselves as well as others. People who are indirectly protected include children too young for vaccination, people with contraindications to vaccination, those who fail to make an adequate immune response to vaccines, and those who are not vaccinated.

The National Vaccine Injury Compensation Program (VICP) was established in 1986 as recognition that society had an obligation to those injured by vaccines.<sup>33</sup> The VICP is a no-fault system funded by a seventy-five-cent excise tax on each dose of vaccine. People alleging vaccine injury must first file with the program. A vaccine injury table specifies conditions that are automatically eligible for compensation, with no need to prove causation. People alleging injuries that are not in the table must prove that vaccines actually were the cause. After going through the VICP, plaintiffs may accept the decisions and awards or reject them and enter the tort system. If an award is accepted, the plaintiff cannot sue the manufacturer or the vaccine provider.

There are loopholes in the VICP. For example, nothing prohibits parents of injured children from seeking compensation in the tort system for their pain and suffering. Despite loopholes, liability against manufacturers has been markedly reduced.<sup>34</sup> The VICP paid approximately \$600 million for vaccines administered between 1988 and 2004; more than 98 percent of the awarded funds went to the claimant and approximately 2 percent for lawyers' fees.<sup>35</sup>

## Challenges To The Present Vaccine System

■ **Vaccine supply.** Since 2000 the United States has faced unprecedented supply disruptions. Vaccines against nine of the twelve vaccine-preventable diseases of childhood have been in short supply, requiring changes in the immunization schedule to reduce the number of doses children receive or prioritization of available vaccine to the groups at highest risk.<sup>36</sup> As of 2004 only four commercial companies produce vaccines for young children. Vaccines against seven vaccine-preventable diseases of childhood have only a single manufacturer. The fragility of the vaccine supply was illustrated in 2004 by the well-documented flu vaccine shortage.<sup>37</sup>

■ **Vaccine cost.** The cost of vaccines has increased greatly, as more are added to the schedule. The price of the recommended four doses of PCV is nearly equal to the

cost of the rest of the childhood schedule. As of February 2005 the price for the recommended vaccines that children should have before entry to elementary school was \$474 when purchased using the federal contract and \$782 when purchased privately.<sup>38</sup> Unless financing challenges are addressed, many children may not receive the full benefits of these vaccines.

■ **Vaccine safety.** Safety concerns, real and unsubstantiated, threaten the present system. After years of careful development, a rotavirus vaccine licensed in 1998 was withdrawn in 1999 when it was found to cause a rare but serious intestinal obstruction in 1 in 10,000 recipients. Also of concern are the numerous alleged vaccine safety concerns that are not supported by high-quality scientific evidence. Concerns about whole-cell pertussis vaccines, later shown to be unfounded, led to decreased pertussis vaccine coverage and to epidemics of whooping cough in the United Kingdom and Japan.<sup>39</sup> Allegations that vaccines cause autism, despite the great preponderance of scientific evidence against a causal relationship, threaten the industry base, because of substantial costs in defending against liability claims.<sup>40</sup>

■ **Adult immunization.** Although the system has been highly successful protecting children, it has not been as successful protecting adults. This stems in part from the fact that most vaccines for adults, such as influenza vaccine or pneumococcal polysaccharide vaccine (PPV), while effective, are not as effective as other vaccines used in children. But more important is the failure of the vaccine delivery system to reach adult target populations. For example, although at least 90 percent of children ages 19–35 months receive recommended childhood vaccines, only 66 percent of people age sixty-five and older received an influenza vaccine in 2002. Receipt of PPV was slightly lower—62 percent.<sup>41</sup>

■ **Vaccine research and development.** Recent estimates of the cost to bring a new drug to licensure range from \$110 million to \$802 million (2000 dollars).<sup>42</sup> Such information is primarily based on drugs, but vaccines have similar costs, and newer vaccines are more expensive to bring through the developmental steps. The National Vaccine Advisory Committee (NVAC) reviewed five vaccines that required from two to twenty-one years from Phase I to licensure.<sup>43</sup>

■ **Bioterrorism preparedness.** With the realization that a number of infectious agents could become weapons comes the need to develop vaccines against them. Vaccines as countermeasures for biological weapons are difficult to develop, however, because they cannot be tested in humans for actual protection against the organism but must rely on surrogate markers that imply immunity. Also, the government is nearly the sole source of support for their development, since there is little, if any, commercial use for these vaccines.

**T**HE U.S. VACCINE SYSTEM REPRESENTS a complex collaboration involving government, the vaccine industry, health care providers, academe, professional societies, and third-party payers. This partnership has resulted in record-low levels of vaccine-preventable diseases among children and record-high

levels of immunizations among children. While progress against vaccine-preventable diseases of adults is not nearly as great, substantial increases in rates of influenza and pneumococcal vaccines have occurred.

However, the system is fragile and needs improvement. The manufacturing base is limited, costs of developing vaccines have markedly increased, and regulatory compliance requires sizable ongoing investment. Short supplies of childhood vaccines highlight the fact that past successes cannot be taken for granted. Manufacturers must have adequate returns on their investments; providers must receive sufficient reimbursement for administering vaccines; resources must be available to effectively monitor vaccine use, effectiveness, and safety; loopholes in the liability protection afforded by the compensation program must be closed; and incentives need to be provided for developing new vaccines.

.....  
 Walter Orenstein was supported in part by National Institutes of Health (NIH) Grant no. 1 P20 RR020735-01.

#### NOTES

1. "Ten Great Public Health Achievements—United States, 1900–1999," *Morbidity and Mortality Weekly Report* 48, no. 12 (1999): 241–243.
2. "Impact of Vaccines Universally Recommended for Children—United States, 1990–1998," *Morbidity and Mortality Weekly Report* 48, no. 12 (1999): 243–248.
3. H.Q. Nguyen, A.O. Jumaan, and J.F. Seward, "Decline in Mortality due to Varicella after Implementation of Varicella Vaccination in the United States," *New England Journal of Medicine* 352, no. 5 (2005): 450–458.
4. C.G. Whitney et al., "Decline in Invasive Pneumococcal Disease after the Introduction of Protein-Polysaccharide Conjugate Vaccine," *New England Journal of Medicine* 348, no. 18 (2003): 1737–1746.
5. B. Flannery et al., "Impact of Childhood Vaccination on Racial Disparities in Invasive *Streptococcus pneumoniae* Infections," *Journal of the American Medical Association* 291, no. 18 (2004): 2197–2203.
6. U.S. Centers for Disease Control and Prevention, "National Immunization Survey, List of Tables, 2003," [www.cdc.gov/nip/coverage/NIS/03/toc-03.htm](http://www.cdc.gov/nip/coverage/NIS/03/toc-03.htm) (28 February 2005).
7. "Vaccination Coverage among Children Entering School—United States, 2002–03 School Year," *Morbidity and Mortality Weekly Report* 52, no. 33 (2003): 791–793.
8. A.B. Coffield et al., "Priorities among Recommended Clinical Preventive Services," *American Journal of Preventive Medicine* 21, no. 1 (2001): 1–9.
9. F. Zhou et al., "Economic Evaluation of Routine Childhood Immunization with Dtap, Td, Hib, IPV, MMR, and Hepb Vaccines in the United States, 2001" (Unpublished paper, CDC, 2005).
10. R.I. Glass et al., "The Epidemiology of Rotavirus Diarrhea in the United States: Surveillance and Estimates of Disease Burden," *Journal of Infectious Diseases* 174, Supp. 1 (1996): S5–S11.
11. G.K. Folkers and A.S. Fauci, "The Role of U.S. Government Agencies in Vaccine Research and Development," *Nature Medicine* 4, no. 5 Supp. (1998): 491–494.
12. N.W. Baylor and K. Midthun, "Regulation and Testing of Vaccines," in *Vaccines*, 4th ed., ed. S.A. Plotkin and W.A. Orenstein (Philadelphia: Elsevier, 2004), 1539–1556.
13. G.D. Douglas, "The Vaccine Industry," in *Vaccines*, ed. Plotkin and Orenstein, 47–51.
14. G.B. Ebbert and E.D. Mascolo, "Vaccine Manufacturing," in *Vaccines*, ed. Plotkin and Orenstein, 53–67.
15. L.K. Pickering and W.A. Orenstein, "Development of Pediatric Vaccine Recommendations and Policies," *Seminars in Pediatric Infectious Diseases* 13, no. 3 (2002): 148–154.
16. "Notice to Readers: Recommended Adult Immunization Schedule—United States, 2003–2004," *Morbidity and Mortality Weekly Report* 52, no. 40 (2003): 965–969.
17. Unpublished data, CDC.
18. W.A. Orenstein, L.E. Rodewald, and A.R. Hinman, "Immunization in the United States," in *Vaccines*, ed. Plotkin and Orenstein, 1357–1386.

19. A.R. Hinman, W.A. Orenstein, and L. Rodewald, "Financing Immunizations in the United States," *Clinical Infectious Diseases* 38, no. 10 (2004): 1440–1446.
20. CDC, "Vaccines for Children: Vaccine Supply Policy Public," 15 April 2003, [www.cdc.gov/nip/vfc/st\\_immz\\_proj/data/vacc\\_supply\\_public\\_2002.htm](http://www.cdc.gov/nip/vfc/st_immz_proj/data/vacc_supply_public_2002.htm) (28 February 2005).
21. Unpublished data, CDC.
22. CDC, "National Immunization Survey, List of Tables, 2003."
23. Unpublished data, CDC.
24. Centers for Medicare and Medicaid Services, "Medicare Announces New Preventive Benefits and Physician Payment Increases in Final Physician Payment Rule for 2005," Press Release, 3 November 2004, [www.cms.hhs.gov/media/press/release.asp?Counter=1248](http://www.cms.hhs.gov/media/press/release.asp?Counter=1248) (28 February 2005).
25. P.J. Smith et al., "Overview of the Sampling Design and Statistical Methods Used in the National Immunization Survey," *American Journal of Preventive Medicine* 20, no. 4 Supp. (2001): 17–24.
26. "Vaccination Coverage among Children Enrolled in Head Start Programs, Licensed Child Care Facilities, and Entering School—United States, 2000–01 School Year," *Morbidity and Mortality Weekly Report* 52, no. 9 (2003): 175–180.
27. D.L. Bartlett, "Immunization Registry Progress—United States, January–December 2002," *Morbidity and Mortality Weekly Report* 53, no. 20 (2004): 431–433.
28. J.F. Seward et al., "Varicella Disease after Introduction of Varicella Vaccine in the United States, 1995–2000," *Journal of the American Medical Association* 287, no. 5 (2002): 606–611; and A. Schuchat et al., "Active Bacterial Core Surveillance of the Emerging Infections Program Network," *Emerging Infectious Diseases* 7, no. 1 (2001): 92–99.
29. F. Varricchio et al., "Understanding Vaccine Safety Information from the Vaccine Adverse Event Reporting System," *Pediatric Infectious Disease Journal* 23, no. 4 (2004): 287–294.
30. R.T. Chen et al., "Vaccine Safety Datalink Project: A New Tool for Improving Vaccine Safety Monitoring in the United States, the Vaccine Safety Datalink Team," *Pediatrics* 99, no. 6 (1997): 765–773.
31. T.V. Murphy et al., "Intussusception among Infants Given an Oral Rotavirus Vaccine," *New England Journal of Medicine* 344, no. 8 (2001): 564–572.
32. R.T. Chen, R.L. Davis, and K.M. Sheedy, "Safety of Immunizations," in *Vaccines*, ed. Plotkin and Orenstein, 1557–1581.
33. G. Evans, D. Harris, and E.M. Levine, "Legal Issues," in *Vaccines*, ed. Plotkin and Orenstein, 1591–1617.
34. *Ibid.*
35. HRSA, "National Vaccine Injury Compensation Program, Post-1988 Monthly Statistics Report," 28 January 2005, [www.hrsa.gov/osp/vicp/monthly\\_stats\\_post.htm](http://www.hrsa.gov/osp/vicp/monthly_stats_post.htm) (28 February 2005).
36. J.M. Santoli et al., "Strengthening the Supply of Routinely Recommended Vaccines in the United States: Recommendations from the National Vaccine Advisory Committee," *Journal of the American Medical Association* 290, no. 23 (2003): 3122–3128.
37. "Interim Influenza Vaccination Recommendations, 2004–05 Influenza Season," *Morbidity and Mortality Weekly Report* 53, no. 39 (2004): 923–924.
38. CDC, "CDC Vaccine Price List," 7 February 2005, [www.cdc.gov/nip/vfc/cdc\\_vac\\_price\\_list.htm](http://www.cdc.gov/nip/vfc/cdc_vac_price_list.htm) (28 February 2005).
39. E.J. Gangarosa et al., "Impact of Anti-Vaccine Movements on Pertussis Control: The Untold Story," *Lancet* 351, no. 9099 (1998): 356–361.
40. "The Politics of Autism; Lawsuits and Emotion vs. Science and Childhood Vaccines" (Editorial), *Wall Street Journal*, 29 December 2003.
41. "Public Health and Aging: Influenza Vaccination Coverage among Adults Aged  $\geq 50$  Years and Pneumococcal Vaccination Coverage among Adults Aged  $\geq 65$  Years—United States, 2002," *Morbidity and Mortality Weekly Report* 52, no. 41 (2003): 987–992.
42. J.A. DiMasi, R.W. Hansen, and H.G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics* 22, no. 2 (2003): 151–185.
43. G. Peter et al., "Lessons Learned from a Review of the Development of Selected Vaccines: National Vaccine Advisory Committee," *Pediatrics* 104, no. 4, Part 1 (1999): 942–950.