US Immunization Policy

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DURING THE PAST CENTURY, THE AVERAGE LIFE EXpectancy of US citizens increased by 30 years, primarily due to improvements in sanitation and development and use of vaccines and antimicrobial agents.[1] Immunizations are one of the most cost-effective health intervention strategies available, saving society more than $5 for each dollar spent on most of the vaccines that are recommended routinely for children in the United States.[2] At the end of the 20th century, the percentage of children younger than 2 years who received all vaccines in the recommended childhood immunization schedule was at a record high of about 90%.[3] Immunization is one of the major public health achievements of the 20th century.[1] Despite this remarkable success, the National Immunization Program has been subjected to increasing attacks by a number of individuals and groups. We highlight the benefits of the vaccines in the recommended childhood immunization schedule, discuss the known risks of vaccinations, explore some of the current impediments to a maximally effective national immunization program, and discuss challenges that lie ahead.

Successes

The widespread use of vaccines, particularly in children, has resulted in the elimination of 2 devastating diseases, smallpox and polio, from the United States. The incidence of certain other serious diseases, including diphtheria, tetanus, whooping cough, invasive *Haemophilus influenzae* type b (Hib) disease, measles, mumps, and rubella, has been reduced by at least 95% from representative 20th-century annual morbidity.[1] During the past decade, 4 other vaccines have been introduced into the immunization program and offer the potential for substantial reduction against these diseases. The hepatitis B vaccine provides protection against a common cause of chronic liver disease and liver cancer, making it the first vaccine that is effective in preventing cancer. Varicella vaccine prevents serious complications associated with chickenpox, including secondary invasive group A streptococcal disease. A conjugated 7-serotype pneumococcal vaccine helps protect children from the most common bacterial cause of several types of serious infection, eg, meningitis, bacteremia, and pneumonia. Hepatitis A vaccine, recommended for select populations, protects individuals from illness due to this virus and also decreases spread of the organism responsible for this disease. Additional vaccines are likely to be added to the childhood immunization program in this decade, including vaccines that protect against respiratory syncytial virus and influenza virus infections, the 2 most common respiratory tract diseases that result in hospitalization of children, and meningococcal disease.

The importance of high immunization rates cannot be overemphasized since the consequences of lower immunization rates include substantial increases in hospitalizations and deaths due to vaccine-preventable diseases. For example, measles (rubeola) and Hib disease continue to be major causes of mortality and long-term morbidity in countries where these vaccines are unavailable or underused, while these 2 diseases have been virtually eliminated from the United States. An estimate of the impact of discontinuing measles vaccination in the United States is that 3 million to 4 million measles cases would occur annually and result in more than 1800 deaths, 1000 cases of encephalitis, and 80 000 cases of pneumonia.[4] Similarly, discontinuing Hib immunization in the United States would result in approximately 20 000 cases per year of invasive disease due to this organism, with 600 associated deaths.[1]

Adverse Effects

All preventive and therapeutic modalities used in medicine have adverse effects, and vaccines are no exception. Fortunately, serious adverse effects caused by commonly used vaccines are rare. Some examples of established adverse effects due to vaccines include thrombocytopenia due to measles-mumps-rubella (MMR) vaccine, paralysis due to oral polio vaccine (OPV), intussusception due to rotavirus vaccine, and febrile seizures following receipt of diphtheria-tetanus-pertussis (DTP) and MMR vaccines.[5-8] Recommen-

See also pp 464 and Patient Page.

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dations for use of a particular vaccine must be based on whether benefits outweigh potential risks. Factors that are considered in the decision should be clearly defined and openly discussed. These factors include assessment of benefits and risks for the individual person, benefits and risks for the individual compared with those for society, and alternative interventions. For example, the risk of thrombocytopenia, which occurs in 1 per 20 000 to 40 000 individuals receiving the MMR vaccine, is far outweighed by the risks of thrombocytopenia, hospitalization, and death due to natural measles.[5] In addition, the risk of febrile seizures after receipt of DTP or MMR vaccine is not associated with any long-term adverse consequences.[8]

While no vaccine can be considered to be completely without adverse effects, much has and continues to be done to maximize vaccine safety. The recent change to recommending use of inactivated polio vaccine (IPV) instead of live attenuated OPV in the United States was based on the changing risk-benefit ratios for the 2 vaccines. Oral polio vaccine provides excellent intestinal immunity and allows for secondary spread of the vaccine virus, which can result in protection of unimmunized individuals. Many countries where polio remains indigenous continue to use OPV because a substantial portion of their citizens are unimmunized and remain at risk for the disease. When polio was endemic in this country the additional protection afforded nonimmunized individuals by OPV outweighed the rare risk of vaccine-induced paralysis. However, as endemic polio was eliminated from the United States and the risk of importation of polio viruses into the United States decreased as global eradication of this disease neared, the risk-benefit ratio changed in favor of using IPV in the United States.

The recommendation to discontinue use of rotavirus vaccine was based on data demonstrating that this vaccine was associated with intussusception at a rate of 1 case per 4670 to 9474 infants immunized.[7] This adverse event was detected rapidly through the surveillance systems established by the Centers for Disease Control and Prevention and the US Food and Drug Administration (FDA) to monitor rare adverse events. While the adverse event of intussusception due to rotavirus vaccine was clearly a setback to the ability to eliminate a major cause of hospitalization of infants due to diarrhea-induced dehydration, that this adverse event was detected and corrective action was taken immediately demonstrates the effectiveness of the current monitoring system to ensure vaccine safety.

Impediments

Despite unparalleled success in improving the health of children, the immunization program faces challenges that may be unprecedented and that potentially could threaten the continued successful control of vaccine-preventable diseases. These include (1) accusations about harmful vaccine effects that are not supported by available scientific data; (2) the coincidental but not causally related occurrence of an adverse event with receipt of an immunization; (3) the increasing number of vaccines being recommended for use; (4) the increasing cost of vaccines; and (5) the fragility of the vaccine supply.

The rarity of vaccine-preventable diseases in the United States shifts the focus of the public away from fear of the diseases and disease prevention to trepidation about vaccines because of the purported adverse events associated with immunizations. Loss of public confidence in vaccines leading to declining immunization rates in other countries has resulted in major outbreaks of vaccine-preventable diseases in these countries. In the past, public concern about possible adverse events due to whole-cell pertussis vaccine caused declining rates of immunization with DTP vaccine in Sweden, Japan, the United Kingdom, the Russian Federation, Ireland, Italy, the former West Germany, and Australia and resulted in a marked increase in infants contracting and dying of complications of whooping cough.[9]

Current concern about the alleged association of MMR vaccine and autism has caused declining immunization rates in Ireland that have led to a nationwide outbreak of measles.[10] The hypothesis that MMR vaccine causes autism was based on an uncontrolled case-report study.[11] Subsequently, a detailed review from the Institute of Medicine (IOM) Immunization Safety Review Committee (ISRC) concluded that multiple studies indicate that there is no scientific basis to support this hypothesis.[12] Despite the IOM refutation of this hypothesis, use of MMR vaccine continues to be less than previous levels in some countries. The events surrounding this hypothesis highlight the difficulty of overcoming public fears, even when the fear is based on a biologically implausible hypothesis and sound studies exist that refute the concern.

Economic and other nonscientific problems also can result in decreased immunization rates. For example, in the newly independent states of the former Soviet Union, a breakdown in the immunization program infrastructure due to economic problems resulted in more than 150 000 cases of diphtheria and more than 5000 deaths.[13] Persons in the United States are only a plane ride away from many of these vaccine-preventable infectious diseases that currently are rare in the United States, necessitating continued high immunization rates even when the disease incidence is low.

A number of important diseases or conditions, eg, sudden infant death syndrome (SIDS), seizure disorders, and autism, manifest themselves during the first 2 years of life, when as many as 20 doses of vaccines are given to children. Receipt of a particular vaccine may be associated temporally with one of these diseases. The crucial issue is whether the occurrence of 2 such events, receipt of a vaccine and occurrence of a subsequent illness, are related causally or represent a temporal but unrelated coincidence. Scientifically, the question hinges on biological plausibility and, if such plausibility exists, the need for careful and appropriate studies to ascertain whether the vaccine is causing the adverse event.

In addition to scientific plausibility, quality of preliminary scientific evidence, and potential population health burden, priority for research resources also should be determined by the level of public concern. For example, in 1992, a recommendation was made to give hepatitis B vaccine to all infants in the United States. Infancy is also the time when SIDS occurs. A number of individuals and groups became convinced that this vaccine caused SIDS. Despite the lack of a biologically plausible reason to believe that the vaccine caused SIDS, studies were performed to investigate this issue and no evidence of causality was found.[14] In subsequent years, the incidence of SIDS has decreased while the use of the hepatitis B vaccine has increased. The decrease in SIDS that occurred during this time was in fact related to the "Back to Sleep" campaign initiated by the American Academy of Pediatrics (AAP).[15] Other examples of a temporal association being cited as evidence of causality but subsequently proven false are hepatitis B vaccine with multiple sclerosis[16] and MMR with autism.[12,17] Even when studies do not support causality, a parent or other individual who witnesses a temporal association may remain convinced that the vaccine caused the illness or condition.

The number of routine parenteral immunizations currently being administered to children, especially infants, has increased substantially during the past 2 decades. Currently, infants receive up to 5 immunization injections at each of their 2-, 4-, and 6- month well-child health care visits. Some parents and physicians are concerned about the discomfort associated with multiple injections.[18] Multiple simultaneous immunizations add to the difficulty in assessing whether a temporally associated event is causally related and, if so, to which antigen. A number of solutions to the multiple-injection problem have been proposed, including adding more routine office visits, but this has the drawback of adding cost and inconvenience for parents and may result in decreased numbers of children receiving immunizations on time. The best short-term answer is increasing the number of FDA-approved combination vaccines, eg, hepatitis B; IPV; diphtheria, tetanus, and acellular pertussis (DTaP); conjugated Hib; and conjugated pneumococcal vaccines.[19] An alternative long-term solution involves developing vaccines delivered via other routes, eg, oral, intranasal, or transdermal.

All states require that some or all routinely recommended vaccines be given to children prior to the time they attend child care or school. Some parents object to these requirements because they believe that mandates affect their right to make decisions for their children. Furthermore, given the marked decrease in the prevalence of many of these vaccine-preventable diseases, parents may believe that the risk of adverse effects from the vaccine outweighs the risk of the disease for their child. However, studies demonstrate that unimmunized individuals place both themselves and others at higher risk for these diseases. In Colorado, children aged 3 to 5 years who did not receive the pertussis or measles vaccines were, respectively, 17 and 66 times more likely to develop disease than vaccine recipients. Unimmunized children aged 6 to 10 years were 15 and 59 times more likely to acquire pertussis and measles, respectively, than immunized children.[20] Furthermore, because no vaccine is 100% effective in preventing disease, the risk of immunized children acquiring disease from contact with an unimmunized infected person also is increased, especially when immunization rates decline. A recent editorial provides a strong rationale for continuing a vaccine mandate program as a safety net in each state.[21] Optimally, it should be possible to be able to achieve high immunization rates in the United States without mandates. Committees that formulate vaccine recommendations need to work with experts in the area of health communication to maximize nonregulatory mechanisms for ensuring high immunization rates. Additionally, more effective educational tools for informing parents of the true risk-benefit ratio of current vaccines are required, as are additional mechanisms to provide parents with valid information about vaccines.[22]

Challenges

Educational and other activities need to be escalated to enhance public awareness and confidence in the US immunization program. The public needs to believe that their concerns about possible adverse events are shared by the medical community and investigated when appropriate. As a result, in 2000, the US Public Health Service asked the IOM, as an independent nongovernment group, to form the standing ISRC to examine purported vaccine adverse events. The goal of the committee is to review emerging information concerning adverse events associated with vaccines. Members were chosen for their expertise in the areas of immunology, pediatrics, infectious diseases, neurology, internal medicine, health communication, risk perception, biostatistics, epidemiology, and public health. Each member was selected carefully to avoid any real or perceived conflicts of interest.

For various vaccine safety concerns, the ISRC has been asked to assess both the scientific plausibility and the significance of each issue in broader societal context and to recommend actions for public health responses to the issue. The resulting action will be based on an assessment of the scientific evidence related to the adverse event and the level of societal concern. Assessment of scientific evidence will include the extent to which data support a causal relationship between vaccine administration and the adverse event. Assessment of the extent of societal concern will include perceived urgency, seriousness of the adverse event, likelihood that the hypothesis will be proven correct, cost and feasibility of conducting additional research, number of people potentially affected, and the benefits of the vaccine weighed against the possible risk of adverse effects. The continuing work of this committee on various issues related to vaccine safety should enhance the public's confi-

dence that the US immunization program takes safety of vaccines very seriously and is committed to making vaccine policy as safe as possible.

Inadequate financing of vaccines looms as a major impediment to delivery of vaccines recommended for all children. While the Vaccines for Children Program covers the poorest children as an entitlement, other children may not be immunized because their insurance does not include immunizations. At the same time that new vaccines are being added to the recommended childhood immunization schedule, the price of new vaccines is escalating and the discount on contracts that are negotiated between industry and the federal government for purchase of vaccines administered to children in the public sector are decreasing. For example, addition of a conjugated pneumococcal vaccine to the immunization schedule doubled the cost of vaccines in the 2000 recommended childhood immunization program compared with that of the previous year. If this trend continues, the cost of additional new vaccines eventually may not be able to be absorbed under the current system of paying for vaccines. The Advisory Committee on Immunization Practices, the AAP, and the American Academy of Family Practice may be forced to make recommendations about vaccine use based mainly on the cost-benefit ratio to society; even then the costs may outstrip available funds in the public and private sectors. The issue that our society needs to address is whether children, regardless of their socioeconomic status, should have access to all recommended childhood vaccines and, if so, how the cost of these vaccines will be supported. This issue is an important example of a broader question that relates to whether our society will continue to demand greater cost-effectiveness from preventive health care measures than for treatments of already-established diseases.

Another challenge is presented by the fragility of the vaccine supply illustrated recently by shortages of influenza, DT, tetanus toxoid, DTaP, MMR, varicella, and conjugated pneumococcal vaccines.[23-25] In addition, 2 less frequently used vaccines for prevention of cholera and typhoid fever in young children have been withdrawn from the US market. The reasons for these shortages are multiple and complex, including that (1) some of the manufacturing plants producing vaccines are old, and major upgrades or new plants are needed to meet FDA standards for good manufacturing practices; (2) the prices of the older vaccines (eg, dT and MMR) are relatively low and make it difficult for companies to justify spending the money needed to upgrade the facilities; and (3) some companies have withdrawn completely from the vaccine business or stopped making some vaccines for multiple reasons, including their belief that the profit potential is greater in other therapeutic areas. These shortages and withdrawals have the potential to seriously threaten the health of adults as well as children because they include vaccines used in both populations (eg, DT) and will decrease herd immunity afforded to adults by high immunization rates in children (eg, varicella).

The anthrax bioterrorism attack in the United States has raised additional immunization policy issues, including (1) prioritization of who should receive a vaccine that is available in limited supply (eg, prioritization of anthrax vaccine among armed forces personnel, public health workers involved in outbreak control, and postal workers at affected sites); (2) whether to administer a vaccine in anticipation of a possible attack or after an attack has occurred (eg, it is estimated that a recommendation to give smallpox vaccine to everyone in the United States would cause several hundred deaths due to complications from the vaccine but could prevent a much greater number of deaths if a widespread smallpox attack occurred); and (3) the possible diversion of immunization production facilities and resources from manufacturing of vaccines recommended in the childhood immunization schedule.

The US immunization program has been extremely successful in reducing sequelae due to vaccine-preventable diseases. However, substantial room for improvement exists to maximize protection against disease while minimizing perceived and real risks. The National Vaccine Advisory Committee will be addressing many of the issues discussed herein. Solving these vaccine-related issues is one important way to ensure that each child will have the best possible opportunity for a healthy and productive life.

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EDITORIAL

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Daytime Sleepiness, Agonist Therapy, and Driving in Parkinson Disease

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FRUCHT AND COLLEAGUES[1] PROPOSED THE UNIQUE association between treatment of Parkinson disease (PD) with 2 newer dopamine agonists and the occurrence of sudden onset of sleep, or sleep attacks. They described a series of 8 patients with PD treated with pramipexole or ropinirole who were involved in motor vehicle collisions because they fell asleep at the wheel. This small case series prompted grave concerns about the safety of prescribing the non-ergot dopamine agonists to patients with PD who drive. Recommended prescribing practices in many countries were altered.[2,3] Multiple anecdotal and retrospective reports followed, all linking agonist therapy with excessive daytime sleepiness and sudden onset of sleep in patients with PD.[4-7] Yet these reports did not systematically assess the frequency of daytime sleepiness in patients treated with other medications. This was a serious omission. Although levodopa initially was observed to cause transitory sleeplessness[8], within 5 years somnolence was also reported as an adverse effect.[9,10] For example, in one series of 131 patients with PD treated with levodopa monotherapy, treatment was limited in 14% due to somnolence.[11]

See also p 455.

The controversy engendered by the report by Frucht et al is ongoing. The pivotal questions include whether sleepiness in PD is specific to treatment with dopamine agonists, whether PD patients can be screened for the likelihood of developing excessive daytime sleepiness and sleepiness while driving, and what drugs to use in the treatment of PD.

In this issue of THE JOURNAL, Hobson and colleagues[12] from the Canadian Movement Disorders Group address several of these questions. The study by Hobson et al differs from the prior case reports and retrospective observations by conducting a prospective evaluation of a large number of patients included from multiple movement disorders centers. This study systematically applied the validated Epworth Sleepiness Scale (ESS) and the Inappropriate Sleep Composite Score (ISCS) questionnaire, and assessed the contribution of other factors in addition to drug use in the development of daytime sleepiness in PD. A total of 638 patients with PD (420 of whom were actively driving) were studied using the ESS with 3 modifications, and the newly developed ISCS.

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