Current Controversies in Vaccination Vaccine Safety

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Vaccination is ranked as one of the 10 greatest public health achievements of the last century and is the number one contributor to decreased global morbidity and mortality.1,2 Pediatric vaccinations have had the most profound impact of any intervention on increasing global child survival, accounting for 3 million pediatric lives saved annually.3 However, even in the 21st century, vaccine-preventable infectious diseases remain important causes of morbidity and mortality in many areas of the world. Globally, tetanus, measles, and pertussis are the main vaccine-preventable causes of death in children; sepsis and influenza-related pneumonia are among the top 10 causes of death in adults and children worldwide, including the United States.4,5

Although US pediatric vaccination rates remain high, there is a small but vocal antivaccine movement concerned about vaccine safety that may affect vaccination efforts in the United States and elsewhere.6 In adults, vaccine-preventable diseases result in $10 billion in health care costs and more than 30,000 preventable deaths annually; however, vaccination rates among adults remain poor and recommended vaccine schedules for US adults are markedly underutilized.7 Extending the success of childhood immunization programs to adult populations is therefore a major public health challenge, and recent misconceptions regarding vaccine safety may affect adult immunization initiatives as well. The challenges of developing vaccines against agents of bioterrorism add an important and complex dimension to monitoring safety in vaccine development.

Recommended Pediatric and Adult Vaccination Schedules

The US organization that determines pediatric and adult immunization policy and guidelines is the Advisory Committee on Immunization Practices (ACIP), an advisory group to the US Public Health Service and the Centers for Disease Control and Prevention (CDC). The ACIP includes representation from pediatric and general medical organizations and community advocates. The American Academy of Pediatrics and the American Academy of Family Physicians also develop separate ongoing pediatric and adult immunization guidelines that harmonize with the ACIP recommendations.

Current vaccines recommended for routine use by the ACIP for pediatric and adult use are outlined in Box 1,8,9 although there are a number of other vaccines available for pediatric and adult use in special circumstances. The US Public Health Service and CDC are assisted in review of new vaccines and new indications for current vaccines by the National Vaccine Advisory Committee, which is composed of academic physicians, public health agencies, and community advocates. Another organization that is critical to development of vaccine policy is the US Food and Drug Administration (FDA), which provides oversight of safety and efficacy claims for new vaccines. Although the FDA is not primarily responsible for vaccine policy, it is the sole US agency responsible for licensure and specific indications for vaccines proposed for use in the United States. Whenever there has been probable or even possible evidence of unacceptable vaccine-related adverse events, these committees and agencies have acted in collaboration to minimize harm and to preserve the public health.

Risks and Benefits

Rates of vaccine-preventable illnesses in children have reached record low numbers (Table).1,10 The success of vaccination programs has led to proportionally more concerns regarding vaccine safety than concerns about vaccine-preventable diseases, which would likely become reestablished in the absence of continued vaccination programs. A small number of highly publicized claims, unsubstantiated by valid data, regarding vaccine adverse events has further heightened the suspicion that some or all vaccines may cause unacceptable adverse events.4 These suspicions have been bolstered by the lack of experience or exposure to most vaccine-preventable illnesses, such as diphtheria, measles, tetanus, poliomyelitis, or Haemophilus influenzae-related invasive diseases, which were major causes of death and disability only a few decades ago.

All vaccines carry some risk of adverse reactions. The majority of adverse reactions to the routinely recommended vaccines are minor and are related to pain, erythema, or inflammation at the injection site. These local reactions are common and may occur in up to 50% of vaccinees. Systemic symptoms such as fever, headache, irritability, or diminished activity are less common; the frequency of systemic symptoms is vaccine-specific. Rarely, moderate to severe reactions to vaccines, such as febrile seizures and allergic reactions, occur at a frequency of 1

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reaction per thousands or millions of doses administered. The risks of moderate-to-severe vaccine reactions are carefully weighed against the benefits that vaccines produce in preventing serious and life-threatening illnesses in the vast majority of the general population. A summary of the risks and benefits for 6 recommended pediatric vaccine antigens is outlined in Box 2.11 A full listing of vaccine-associated adverse events is available online (http://www.cdc.gov/nip/publications/surv-manual/vaers.pdf).

**Box 1. Pediatric and Adult Vaccines Recommended by the Advisory Committee on Immunization Practices for Routine Use**

**Recommended Adult Immunizations**
- Hepatitis B vaccine (adults at risk)
- Measles-mumps-rubella vaccine
- Tetanus-diphtheria vaccine
- Varicella vaccine
- Influenza vaccine (adults aged ≥50 years and all health care workers)
- Pneumococcal polysaccharide vaccine (adults aged ≥65 years)

**Recommended Pediatric Immunizations**
- Conjugate Haemophilus influenzae type b vaccine
- Conjugate pneumococcal vaccine
- Diphtheria-tetanus-acellular pertussis (DTaP) vaccine (alternatives: DTP, DT, Td)
- Hepatitis B vaccine
- Inactivated polio vaccine
- Measles-mumps-rubella vaccine
- Varicella vaccine
- Hepatitis A vaccine (selected populations)
- Influenza vaccine (selected populations)
- Pneumococcal polysaccharide vaccine (selected populations)

*Adapted from the National Immunization Program, Centers for Disease Control and Prevention.*

**Misconceptions**

The rare occurrence of vaccine-preventable illnesses in the United States and other developed areas of the world has left the public with a number of misconceptions regarding the continued need for vaccinations. In these areas, there exists a poor perception of the real and continued risk of exposure and illness due to vaccine-preventable infections. It is therefore difficult for public health officials and health care practitioners to convey to the public a sense of urgency regarding vaccination. However, there is still a persistent risk of contracting vaccine-preventable illnesses among susceptible individuals. In addition, importation of vaccine-preventable illnesses is a constant concern in this era of global travel. For example, reported US measles cases have dropped by more than 99% since the inception of measles vaccination programs to an all-time low of 81 cases in 2000 (Table). However, more than half of the 108 US cases reported in 2001 occurred either among individuals who contracted measles in another country or secondary cases related to an imported case.12

In addition, no vaccine achieves 100% efficacy, so even among vaccinated individuals, a few will remain susceptible to infection in the event of exposure. In this situation, cohorts of vaccinated and unvaccinated susceptibles may serve as foci for disease outbreaks after exposure. Recent examples of outbreaks of vaccine-preventable illnesses among populations with poor or no immunization coverage underscore the need for continuous immunization programs in the absence of disease elimination or eradication.

An important misconception regarding vaccination is the perceived association of a variety of systemic adverse events linked to specific vaccines or to vaccine administration in general. In most cases, these associations are based on anecdotal reports or data not sufficiently stringent to support the association. For instance, a claim has been made that increased rates of diabetes mellitus in the general pediatric population are due to increased exposure to vaccine antigens in childhood.19 Scientifically rigorous studies have refuted this hypothesis.17,18 Another hypothesis linking measles immunization to development of autism has been the subject of intense international controversy.19 However, rigorous analysis of the incidence of autism relative to the timing of introduction of measles vaccine into populations has failed to demonstrate any temporal association between the 2 events, and no biologically plausible hypothesis has yet been developed to support an association.20-23

Recent efforts to improve vaccine safety by highly publicized changes in vaccine policy have led to a heightened awareness of the possible adverse effects of routine vaccine administration, especially to infants and young children. These changes include recent recommendations regarding the elimination of the mercury-based preservative thimerosal from vaccines,24 and the withdrawal of a rotavirus vaccine from the US market because of early postlicensure surveillance demonstrating an increased risk of intussusception associated with the first dose of this vaccine to young infants.25 Although these were rational and necessary policy changes, they have spurred some anxiety among those concerned about vaccine safety.

**Review of Perceived Vaccine Risks**

In an effort to gain an objective understanding of the risks and benefits of commonly recommended vaccines, the Institute of Medicine of the National Academy of Sciences was recently commissioned to produce reports on vaccine-related adverse events. In the last year, 4 such reports have been issued.30-33 The conclusions of the Insti-
tute of Medicine reports failed to support hypotheses that vaccines were associated with multiple sclerosis, neurodevelopmental disorders, or immune dysfunction and did not produce additional concerns regarding vaccine safety. Full summaries of the reports can be viewed at the CDC National Immunization Program Web site (http://www.cdc.gov/nip).

Tracking Vaccine-Associated Adverse Events

Proper and timely surveillance for identifying vaccine adverse events is a priority to ensure continued vaccine safety. The federal government provides vaccine safety surveillance through a network of active and passive surveillance systems. In 1990, the Vaccine Adverse Event Reporting System (VAERS) was established to provide postlicensure passive surveillance of vaccines. This surveillance system, managed jointly by the CDC and the FDA, was responsible for the identification of an association between administration of a rhesus rotavirus vaccine and an increased risk of intussusception among infants within 30 days of immunization.25 The VAERS identified this association, which led to cessation of rotavirus vaccination, less than 6 months after the vaccine was recommended for use in infants in the United States.

While VAERS has been a useful tool in monitoring vaccine safety, it is a passive system and therefore relies on reporting from individual health care providers. An active surveillance system providing ongoing evaluation of vaccine safety in large populations of vaccinated individuals has also been established by the CDC. The Vaccine Safety Datalink (VSD) project is a population-based network initiated by CDC with 4 large health maintenance organization partners.30 The VSD project maintains ongoing monitoring of automated immunization records linked to the medical records of more than 600,000 children younger than 7 years; a similar system is in place for immunized adults enrolled in the 4 health maintenance organizations. The VSD project has been used to define the safety of a number of vaccines in a variety of populations, such as the risk of febrile seizures after receipt of whole-cell pertussis and measles, mumps and rubella vaccines, the safety of recombinant hepatitis B vaccines in children, and the risk of chronic arthropathy in adults following rubella immunization. With active and passive surveillance systems, such as VAERS and VSD, potential vaccine adverse effects can be identified and further investigated by local, state, and federal public health agencies.

Current Challenges in Development

Vaccine safety is only one challenge to maintenance of effective US vaccination programs. New obstacles to development of vaccines and implementation of vaccination programs have arisen and must be addressed. These include the decreased number of manufacturers who produce current vaccines or are available to develop new vaccines, the lack of adequate vaccine production facilities leading to vaccine shortages, development of multiple antigen vaccines that are more difficult to bring to licensure than single antigen vaccines, and the recent challenges of developing vaccines against agents used for bioterrorism. The latter issue is particularly complex and beyond the scope of this review. Major challenges in development of vaccines for bioterrorist tools include the lack of previous experience by manufacturers and public health agencies with this venue for vaccine development and implementation on a large scale, issues regarding the appropriate study populations for these vaccines, the level

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Table. Baseline 20th Century Annual US Morbidity and 2000 Morbidity From 9 Diseases With Vaccines Recommended Before 1990 for Universal Use in Children

<table>
<thead>
<tr>
<th>Disease</th>
<th>Baseline Reporting Years</th>
<th>Baseline Prevaccine 20th Century Annual Morbidity</th>
<th>2000 Morbidity</th>
<th>Decrease, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallpox</td>
<td>Average annual number of cases during 1900-1904</td>
<td>48,164</td>
<td>0</td>
<td>100</td>
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<tr>
<td>Diphtheria</td>
<td>Average annual number of reported cases during 1920-1922</td>
<td>175,885</td>
<td>4</td>
<td>100</td>
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<tr>
<td>Pertussis</td>
<td>Average annual number of reported cases during 1922-1925</td>
<td>147,271</td>
<td>6,755</td>
<td>95.4</td>
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<tr>
<td>Tetanus</td>
<td>Estimated number of cases based on reported number of deaths during 1922-1926</td>
<td>1,314</td>
<td>26</td>
<td>98</td>
</tr>
<tr>
<td>Poliomyelitis (paralytic)</td>
<td>Average annual number of reported cases during 1951-1954</td>
<td>16,316</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Measles</td>
<td>Average annual number of reported cases during 1958-1962</td>
<td>503,282</td>
<td>81</td>
<td>100</td>
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<tr>
<td>Mumps</td>
<td>Number of reported cases in 1968</td>
<td>152,209</td>
<td>323</td>
<td>99.8</td>
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<tr>
<td>Rubella</td>
<td>Average annual number of reported cases during 1966-1968</td>
<td>47,745</td>
<td>152</td>
<td>99.7</td>
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<tr>
<td>Congenital rubella syndrome</td>
<td>†</td>
<td>823</td>
<td>7</td>
<td>99.2</td>
</tr>
<tr>
<td>Haemophilus influenzae type b</td>
<td>‡</td>
<td>20,000</td>
<td>167</td>
<td>99.2</td>
</tr>
</tbody>
</table>

*Adapted from Centers for Disease Control and Prevention.110†Estimated number of cases based on seroprevalence data in the population and on the risk that women infected during a childbearing year would have a fetus with congenital rubella syndrome.‡Estimated number of cases from population-based surveillance studies before vaccine licensure in 1985.
Box 2. Risk From Disease vs Risk From Vaccines

Measles-Mumps-Rubella

Risk From Disease

Measles
- Pneumonia: 1 in 20
- Encephalitis: 1 in 2000
- Death: 1 in 3000

Mumps
- Encephalitis: 1 in 300

Rubella
- Congenital Rubella Syndrome: 1 in 4 (if woman infected during first trimester [≤16 weeks])

Risk From MMR Vaccine

Encephalitis or severe allergic reaction: 1 in 100,000

Diphtheria-Tetanus-Pertussis

Risk From Disease

Diphtheria
- Death: 1 in 20

Tetanus
- Death: 3 in 100

Pertussis
- Pneumonia: 1 in 8
- Encephalitis: 1 in 20
- Death: 1 in 200

Risk From DTP Vaccine

Continuous crying, then full recovery: 1 in 100
Convulsions or shock, then full recovery (hypotonic/hyporesponsive episode): 1 in 1750
Acute encephalopathy: 0 to 10.5 in 1,000,000
Death: none proven

*Reproduced from National Immunization Program, Centers for Disease Control and Prevention. Risk expressed as number of adverse events per persons with disease or number of adverse events per vaccinated persons.

Sources of Information

Increasing public awareness of the controversies surrounding vaccine safety and the need to maintain the achievements of vaccination programs have resulted in creation of a variety of vaccine information sources. Specific vaccination schedules may be found at the CDC National Immunization Program Web site (http://www.cdc.gov/nip). In the private sector, the National Network for Immunization Information also has a Web site (http://www.immunizationinfo.org) with current information regarding vaccine safety as well as links to other sites with related information. These sites can serve as rapid, accurate, and objective sources of current information on vaccine recommendations, risks, benefits, and frequently asked questions regarding vaccines. Timely and accurate information regarding vaccine safety issues will facilitate continued implementation of safe and effective immunization programs.

REFERENCES


