Licensure, Approval, and Uptake of Vaccines in the United States

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Immunization is one of the most effective public and private preventive health interventions, resulting in significant reductions in vaccine-preventable diseases and in substantial cost savings to the US healthcare system. Vaccine licensure, development of recommendations for use, and implementation of those recommendations leading to uptake, community protection, and effect on disease burden represent a complex system that requires collaboration in the areas of basic science, public health, vaccine delivery, outcome monitoring, and public perception. The Advisory Committee on Immunization Practices (ACIP) sets standards for immunization delivery for both public and private vaccine providers, and state immunization programs can use these ACIP recommendations to develop school immunization requirements.

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LICENSURE AND APPROVAL OF VACCINES

The Food and Drug Administration (FDA) licenses vaccines for the civilian and military populations in the United States [1]. It regulates vaccines and approves product labeling, including indications, contraindications, and precautions, but how FDA-licensed vaccines are actually used by healthcare providers usually is considered the practice of medicine and is not in the purview of the FDA. For example, indications in the package insert might allow vaccine providers to administer a vaccine to people covered by those indications. However, providers can decide not to use the vaccine in some of those circumstances. The Advisory Committee on Immunization Practices (ACIP) is chartered as a federal advisory committee that makes recommendations for the use of FDA-licensed vaccines to the director of the Centers for Disease Control and Prevention (CDC) [2]. Once accepted by the CDC’s director and published in the Morbidity and Mortality Weekly Report, a publication of the CDC, those recommendations become CDC policy [3]. ACIP recommendations (or recommendations of professional societies, such as the American Academy of Pediatrics) are what providers generally use to decide which vaccines should be administered to which individuals. The ACIP, in collaboration with professional societies, issues recommended immunization schedules for all children, all adults, and selected members of both groups with a specific underlying health or other condition. These schedules are updated annually and also include recommendations for catch-up immunization for people who are behind in the recommended schedule.

The FDA and the ACIP function under different mandates. The FDA is a regulatory agency; the ACIP has no regulatory authority. A vaccine is licensed by the FDA on the basis of review of a biological license application (BLA) submitted to the FDA by the manufacturer of that vaccine. A BLA contains extensive evidence of the demonstrated safety, effectiveness, and manufacturing consistency of a vaccine. The FDA licensure process includes approval of prescribing information, which is included in the package insert. Package inserts do not include recommendations made by the ACIP. Data in package inserts are the only data that vaccine manufacturers can use to promote or advertise their vaccines.

ACIP recommendations can be made after review of data that were not considered by the FDA, including disease burden, public health impact, cost-effectiveness, and other data not contained in the BLA submitted to the FDA by the vaccine manufacturer. States and professional organizations assist with implementing ACIP vaccine recommendations. The knowledge and attitudes among physicians regarding the vaccine licensure and recommendation process vary [4].

PROGRAMS THAT RELY ON ACIP VACCINE RECOMMENDATIONS

Programs and agencies that rely on vaccine recommendations from the ACIP are listed below. These programs deal with compensation for injury, health insurance, policy implementation, and immunization laws.
National Vaccine Injury Compensation Program
In rare cases, a vaccine can be associated with a serious adverse event, such as a severe allergic reaction. In these instances, the Vaccine Injury Compensation Program (VICP) can provide financial compensation to people who file a petition and are found to have been injured by a VICP-covered vaccine. Even in cases when such a finding is not made, petitioners might receive compensation through a settlement. The VICP is a no-fault alternative to the traditional legal system for resolving vaccine injury petitions. Any person of any age who received a covered vaccine and believes he or she was injured as a result can file a petition. Parents, legal guardians, and legal representatives can file on behalf of their child, a disabled adult, or a person who is deceased. The VICP uses a vaccine injury table that leads to automatic compensation for people who experience an adverse event after immunization that fits within the criteria listed in this table. Compensation for other adverse events also can be given if the plaintiff makes the case for a vaccine having played a role in that event. For vaccines covered by the VICP, plaintiffs must first go through the VICP before they can proceed to the tort system [5].

Private Health Insurance
Immunization is financed through private health insurance, safety-net programs, and patient out-of-pocket spending. Most insurance companies are now required to cover the cost of immunizations and preventive healthcare. According to the Patient Protection and Affordable Care Act (ACA), insurers must cover ACIP-recommended vaccine costs (of both the vaccine and its administration) for persons served by an in-network provider. The source of coverage varies substantially according to age. Children who do not have public or private insurance are covered automatically by the Vaccines for Children program (VFC).

Vaccines for Children Program
The VFC helps provide vaccines to children whose parents or guardians cannot afford them. This program helps ensure that all children have a better chance of receiving recommended vaccinations on schedule. Vaccines available through the VFC are those recommended by the ACIP [6]. After ACIP approval of a vaccine recommendation for children and adolescents, the ACIP then votes to have that vaccine placed in the VFC. Funding for the VFC is approved by the Office of Management and Budget and allocated through the Centers for Medicare and Medicaid Services to the CDC. The CDC then purchases vaccines at a discount and distributes them to grantees (ie, state health departments and certain local and territorial public health agencies), which in turn distribute them at no charge to private physicians’ offices and public health clinics registered as VFC providers. Providers are allowed to charge an administration fee, but VFC-eligible children cannot be denied any vaccine if their parents or guardians cannot afford that fee.

State Health Departments
Unlike children, adults who are uninsured or underinsured are not covered by any public program until they become eligible for Medicare. State-funded county and city health departments are principally responsible for adult immunizations and are subject to funding uncertainties and capacity constraints; therefore, coverage varies considerably from state to state.

State School-Entry Immunization Laws
State laws establish vaccination requirements for school-aged children. These laws often apply to not only children who attend a public school but also those who attend a private school or child care facility. States also might require immunization of healthcare providers and of patients/residents of healthcare facilities.

Armed Forces (Military)
Department of Defense policy follows ACIP recommendations unless a military-relevant reason to do otherwise exists [7].

LESSONS LEARNED AFTER IMMUNIZATION LICENSURE
After the addition of certain vaccine recommendations made by the ACIP, several unexpected events have occurred after implementation [6]. Some of these events have influenced vaccine uptake and provided lessons learned that can be useful when considering recommendations for future vaccines. The following examples highlight some of these lessons.

- Withdrawal of vaccine recommendations can occur because of unforeseen safety issues, as occurred with RotaShield and intussusception, which was not expected to occur when it was licensed originally.
- Unanticipated positive effects of vaccines can occur in the population for which the vaccine is licensed and recommended and in the community. Such effects appeared when the 7-valent (PCV-7) and 13-valent (PCV-13) pneumococcal vaccines were used in the pediatric population; these vaccines benefitted not only the children who were immunized (by preventing invasive disease caused by Streptococcus pneumoniae serotypes contained in the vaccines) but also adults, who at that time had not been immunized [8].
- Negative public perception of a vaccine can hinder its uptake, as happened with introduction of the human papilloma virus (HPV) vaccine [9]. In the future, additional lessons can be learned as new ACIP vaccine recommendations are added to the vaccine schedules.
COMMUNITY PROTECTION

The direct impact of vaccines in preventing disease in children and adults is well known [10]. However, the major public health impact of community protection (also referred to as herd protection, herd immunity, community immunity, and indirect effect) provided by vaccines is not fully appreciated [11]. Community protection occurs when people who are immunized block organism transmission, thereby protecting indirectly people who are not vaccinated or are undervaccinated. This community protection limits the spread of pathogens throughout the community.

Community protection is particularly important for children and adults who cannot receive immunizations because of age, comorbidity, or receipt of chemotherapy, for people who cannot develop an appropriate immune response to an immunization (because of primary or secondary immunodeficiency), and for the limited number of people for whom a protective immune response is not achieved after vaccination according to recommendations (vaccine failure).

SUMMARY

Discrepancies between FDA licensure of and ACIP recommendations for the use of vaccines occur. However, the successes of the childhood and adult immunization programs in the United States are well documented, as evidenced by the eradication of smallpox, elimination of polio in the United States, and historically low levels of many vaccine-preventable diseases such as diphtheria, tetanus, pertussis, rubella, and measles. Valuable sources of vaccine information are shown in Table 1.

Note

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References