

Lessons Learned From Making and Implementing Vaccine Recommendations in the U.S.

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After publication of certain vaccine recommendations made by the Advisory Committee on Immunization Practices, several unexpected events have occurred during implementation of these recommendations. These have included changes in recommendations following adverse events involved with a particular vaccine and the conferral of community protection as an offshoot of vaccination of a specific population. Vaccine shortages and hesitancy have also been proven impediments to full implementation, and vaccine recommendations have not gone unaffected by either public perception of a vaccine or by cost considerations.

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Introduction

Though the primary function of CDC's Advisory Committee on Immunization Practices (ACIP) is development rather than implementation of vaccine recommendations, over the years a number of lessons can be gleaned from implementation of vaccine recommendations that have been included in its childhood¹ and adult² immunization schedules (Table 1). Concurrently, many improvements have been made to the ACIP process.^{3,4} The objective of this paper is to highlight lessons learned when ACIP-recommended vaccines were added to these schedules and were implemented.

Following publication of certain ACIP vaccine recommendations in the *Morbidity and Mortality Weekly Report*, several unexpected events have occurred during implementation. Many of these events have impacted vaccine uptake and provided lessons that may be useful in considering recommendations for future vaccines. Table 1 lists select lessons learned following the addition of vaccines to the recommended immunization schedules.

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Vaccine Safety and Changing Recommendations

Despite extensive evaluation of new vaccines prior to U.S. Food and Drug Administration (FDA) licensure and ACIP recommendations for use, unexpected safety concerns may arise following implementation of ACIP recommendations. In these cases, ACIP must be flexible enough to consider modifying or withdrawing recommendations even in the absence of complete data.

For instance, in August of 1998, Wyeth's RotaShield (RRV-TV), a vaccine to protect against rotavirus illness, was licensed for use in infants. In 1999 ACIP, along with the American Academy of Pediatrics' (AAP's) Committee on Infectious Diseases, recommended use of the vaccine in healthy infants.^{5,6} However, vaccine clinical trials are often unable to detect rare events, and are typically conducted in healthy populations. Between September 1998 and July 1999, 15 cases of intussusception associated with RRV-TV vaccine were reported to the Vaccine Adverse Event Reporting System (VAERS).⁷ Of the infants who developed intussusception following vaccination with RRV-TV, 80% developed intussusception after the first dose and 80% showed symptoms within 1 week of receiving any dose of the vaccine.⁸ In response to the notable increase in cases, but in absence of a comprehensive study, ACIP evaluated results from RRV-TV's pre-licensure studies and from the VAERS reports. In November 1999, ACIP withdrew its recommendation for use of the vaccine, and Wyeth removed the product from the market.⁹

Despite indications that physician resistance to administering a new rotavirus vaccine—should one be made

Table 1. Implementation of Vaccines – Lessons Learned

Lessons Learned	Examples
Withdrawal of vaccine recommendations may occur because of unforeseen safety issues. Both safety and effectiveness monitoring are important, though recommendations may be based on incomplete data.	<ul style="list-style-type: none"> ● RotaShield and intussusceptions
A vaccine choice or recommendation based on minimizing adverse events may adversely impact duration of protection and herd effects as well as result in a need for earlier booster doses and repeat boosting strategies.	<ul style="list-style-type: none"> ● Switch from whole-cell pertussis vaccine to acellular pertussis vaccine
Unanticipated positive effects of vaccines both in the populations for which the vaccine is recommended and in the community	<ul style="list-style-type: none"> ● Community protection: PCV7 and PCV13 in the unvaccinated ● Community protection: Rotavirus vaccine in the unvaccinated
Vaccine shortages impact ability to implement recommendations	<ul style="list-style-type: none"> ● <i>Haemophilus influenzae</i> type b, PCV, and varicella vaccine shortages resulted in changes to recommendations. Even with vaccines that have multiple manufacturers, when one manufacturer is unable to produce others may not be able to rapidly make up for the reduced production of that manufacturer.
Differences in vaccine recommendations coming from different authorities can lead to confusion and delayed vaccine uptake.	<ul style="list-style-type: none"> ● New York State's decision to implement a second dose of MMR vaccine led to a revised ACIP recommendation to stem a measles outbreak ● Differences between ACIP and AAP in preferred age of administration for the second dose of MMR led to confusion, which was resolved by development of a harmonized immunization schedule in 1995
Public perception of a vaccine or the infection prevented can hinder vaccine uptake.	<ul style="list-style-type: none"> ● HPV vaccine recommendations for adolescents (associated with sexual practices, making parents reluctant)
Cost considerations in making vaccine recommendations are complex and changing.	<ul style="list-style-type: none"> ● Cost concerns overridden in the case of OPV and IPV vaccine use (i.e., perceived societal values of preventing vaccine injury outweighed pure economic analysis)

AAP, American Academy of Pediatrics; ACIP, Advisory Committee on Immunization Practices; HPV, human papillomavirus; IPV, inactivated polio vaccine; MMR, measles, mumps, and rubella; OPV, oral polio vaccine; PCV, pneumococcal conjugate vaccine.

available—was elevated following withdrawal of RRV-TV,^{10,11} vaccine manufacturers persisted with vaccine development. Merck debuted its pentavalent RotaTeq (RV5) in 2006, and GlaxoSmithKline's monovalent Rotarix (RV1) was licensed in 2008. ACIP recommended RV5 for use in infants in 2006, and in February 2009 revised its guidelines to recommend that infants receive either RV5 or RV1, with no preference given.¹² For both vaccines, ACIP recommended administration of the first dose to be no later than when an infant is aged 15 weeks and stated no doses should be administered after age 8 months. This was to minimize use of vaccine during the period when the background risk of intussusception was greatest. Although post-licensure studies demonstrate that there is a slightly elevated risk for intussusception following the first dose of the new generation of rotavirus vaccines, benefits of rotavirus vaccine far outweigh this minimal risk.¹³

Unexpected Consequences

A vaccine recommendation based on minimizing short-term or perceived vaccine reactions may adversely

impact considerations such as duration of protection or community protection. In the 1990s, heightened instances of certain local and systemic adverse events such as erythema, seizures, febrile reactions, and—rarely—encephalopathy were reported in infants following administration of the whole cell-containing combination diphtheria/tetanus/pertussis vaccine (DTP).¹⁴ A group of concerned parents began to speak out against DTP as causing encephalopathy. However, the allegations that some children developed brain damage as a result of DTP had relied on case series rather than carefully controlled scientific studies.¹⁵ In 2011, many cases of this “vaccine encephalopathy” were re-diagnosed as Dravet syndrome, a severe myoclonic epilepsy in infancy, which is genetically triggered and often has its onset around the same time that an infant would receive a pertussis-containing vaccine.¹⁶

In 1991, acellular pertussis vaccines (DTaP) were licensed as the fourth and fifth doses in the childhood DTP series, with the whole-cell vaccines comprising the first three in the series.¹⁷ ACIP voted to adopt an all-DTaP dosing series in 1997, based on efficacy studies that

showed similar levels of protection and fewer adverse events compared with DTP.¹⁷

There was at the time, however, insufficient information on the duration of protection of the acellular pertussis component of the vaccine. As a result, in the early 2000s, there was an increase in pertussis among vaccinated adolescents, and later in the decade an emergence of disease among school-aged children. Older adolescents who had received three doses of DTP in childhood had durable protection, whereas protection waned for younger adolescents who had been vaccinated as children with DTaP only—and among schoolchildren who had completed their fifth dose of DTaP between ages 4 and 6 years.^{18,19}

This waning protection was projected to affect community (herd) protection in a vaccination cohort, endangering unvaccinated people.²⁰ This prompted the recommendation of a booster dose between age 11 and 12 years with tetanus toxoid/reduced diphtheria toxoid/acellular pertussis (Tdap) in 2006,²¹ and a 2013 recommendation that all expectant mothers be vaccinated with Tdap during each pregnancy to provide high enough levels of maternal antibody to their infants to protect them from pertussis until the infants were old enough to have active immunity induced through infant DTaP vaccination.²²

Community Protection

Protection of unimmunized groups following widespread implementation has been an unexpected benefit of several vaccines. After ACIP recommended universal vaccination of children aged <2 years with 7-valent pneumococcal conjugate vaccine (PCV7) beginning in 2000, replaced by a 13-valent pneumococcal conjugate vaccine (PCV13) in 2010,²³ the U.S. and other countries experienced corresponding dramatic declines in invasive pneumococcal disease (IPD) caused by vaccine strains in vaccinated children.²⁴

However, the nationwide implementation of vaccine recommendations also significantly decreased the incidence of IPD among U.S. adults aged ≥65 years.²⁵ *Streptococcus pneumoniae* infections by serotypes in PCV13 in adults aged ≥65 years declined approximately 50% beginning in 2010 (when PCV13 replaced PCV7 in the routine childhood immunization schedule). Not taking the community protection into account when making recommendations can underestimate the benefits of vaccinating the group for whom vaccine is recommended, causing underestimation of the economic and health benefits. Nevertheless, in addition to the community benefits of childhood vaccination with PCV13, routine use of PCV13 in adults aged ≥65 years was recommended by ACIP in August 2014 because concerns

remained about health burden in that population at that time.²⁶

In 2008, when rotavirus vaccine coverage reached 57% of infants aged <1 year, hospital discharges that were coded as rotavirus and as cause-unspecified gastroenteritis decreased for groups aged 0–4, 5–14, and 15–24 years.²⁷ The estimated 15% of the total 66,000 averted hospitalizations and 20% of the \$204 million in averted direct medical costs attributed to the vaccine program were among unvaccinated people aged 5–24 years. In another study, pediatric rotavirus vaccination correlated with a relative decline of 50% in rotavirus identification from adult bacterial stool culture during the peak rotavirus season, suggesting that rotavirus vaccine protects both those vaccinated as well as those not vaccinated against rotavirus infection.²⁸ The unvaccinated are protected because of decreased transmission of the virus owing to immunity in vaccinees, which decreases exposure to the virus among the unvaccinated.

Vaccine Shortages

Beginning in 2000 in the U.S., occasional shortages of vaccines in the recommended immunization schedules have occurred and some have had unexpected consequences. ACIP actions taken in response to shortages have sometimes had deleterious effects on vaccine uptake and can alter perception of the recommendation. Shortages of several vaccines resulted in temporary changes in recommendations for their use.^{29–31}

One vaccine shortage occurred in December 2007 with the recall of certain lots of *Haemophilus influenzae* type b (Hib) conjugate vaccines—PedvaxHIB and Comvax—by Merck. The other manufacturer of a Hib-containing vaccine product was unable to meet demand for product following the recall. This Hib vaccine shortage resulted in a short-term change in recommendations: the booster dose to be administered at age 12–15 months was to be temporarily deferred until stock was replenished.³² In 2008 in Minnesota, five cases of invasive Hib disease were reported after Minnesota physicians reported lack of enough product to finish the full Hib series.³³ Physicians also reported that primary series coverage of the Hib series also suffered because of the shortage of the booster dose, suggesting the possibility that the series was perceived as less important by the public.³⁴

Vaccine Uptake

Differences in recommendations and other factors can influence the rate at which an ACIP recommendation is adopted by providers. Confusion can result among vaccine program implementers when public health

decisions on the state level and among those in medical professional societies are different from those of ACIP. Prior to 1989, ACIP recommended only one dose of measles vaccine routinely, to be given during a scheduled preschool visit.³⁵ A second dose had been discussed and rejected by ACIP owing to cost considerations. In 1989, there was a resurgence of measles, which initially included outbreaks among college students who had been vaccinated at preschool age.³⁶ When a group of public health officials in New York State vowed to implement a second dose regardless of national standards,³⁶ ACIP then agreed that a second dose would be advisable and released a corresponding statement.³⁷ The AAP also recommended a second dose, with age recommendations that diverged from ACIP's. ACIP proposed that the second dose be given at age 4–6 years, whereas the AAP recommended the second dose be administered to adolescents at age 11–12 years.³⁸ The ACIP recommendation took advantage of an existing immunization delivery infrastructure, which included a scheduled immunization visit at age 4–6 years. The AAP recommended age 11–12 years to achieve a two-dose cohort more rapidly in populations experiencing outbreaks (middle school students through college). Differences in the recommendations caused confusion for both public health personnel and healthcare providers. The recommendations were eventually reconciled in a harmonized schedule developed by ACIP in collaboration with the AAP to avoid confusion.

Public Perception

Uptake of human papillomavirus (HPV) vaccine has been slow following vaccine recommendations because of a number of factors. Physicians have cited multiple barriers to HPV vaccination of both male and female adolescents.^{39,40} Holman et al. found that parents consistently cited recommendations by healthcare providers as one of the most important factors in their decision to vaccinate their children.³⁹ However, a 2011 interview study found that clinicians were often reluctant to engage in conversation about HPV vaccine out of concern for the impact that it might have on relationships with patients because of discussions about a sexually transmitted infection at an age when this seemed to be irrelevant to the pre-teenager.⁴¹ The fact that the initial recommendations were gender-specific, focused on female adolescents, may have reinforced the issue of a sexually transmitted infection as key rather than the message that this was a highly effective anti-cancer vaccine. Older adolescents were more likely to be vaccinated because of a combination of self-election to have the vaccine and parental beliefs that only older

adolescents should be vaccinated. The proportion of healthcare providers recommending the vaccine at younger ages has increased, especially among physicians aged 45 years or younger and among pediatricians.⁴²

After the licensure of and recommendations for HPV4 and HPV2, a number of factors combined to cause a slower-than-optimal rate of adoption for those vaccines. The factors include concern about sexual disinhibition following HPV vaccination of pre-teenage girls, although studies have shown that neither being offered HPV vaccine nor receiving it affected sexual behavior.^{43–45} Availability of HPV9, which contains five additional strains, will protect against additional cancer-causing HPV strains, but initially may add confusion regarding HPV9 vaccination for adolescents who previously had received HPV2 or HPV4.

Cost Considerations and Vaccine Implementation

The cost effectiveness of implementation of a specific vaccine is among factors that ACIP considers prior to making recommendations.⁴⁶ However, ACIP has no cost-effectiveness threshold for decision making; thus, cost considerations may be less influential in crafting new recommendations than safety concerns or new information. For instance, 132 cases of vaccine-associated paralytic poliomyelitis (VAPP) occurred between 1980 and 1995 in recipients or close contacts of people receiving the live attenuated oral polio vaccine (OPV).⁴⁷ A 1996 study by Miller and colleagues⁴⁸ compared the relative costs of the then-current four-dose OPV schedule with both a four-dose inactivated polio vaccine (IPV) and a sequential schedule of two IPV doses and two OPV doses. Compared with the costs of treatment and compensation related to the estimated 9.5 occurrences of VAPP each year, a switch to either the all-IPV schedule or a sequential schedule would incur additional costs of \$40 million in the first case and \$20 million in the second, a cost of approximately \$3 million per case of VAPP prevented. However, influenced in part by the appeals made by victims of VAPP at ACIP meetings, the committee in 1997 voted to adopt the sequential (two-dose IPV, two-dose OPV) schedule.

Several policymaking challenges will need to be addressed by ACIP in the future, including clarification of the role and impact, if any, of cost effectiveness in making vaccine recommendations.

Conclusions

Since 1964, ACIP has played a major role in almost every significant development in U.S. immunization policy. As

the number of new vaccines grows and ACIP is called upon to make recommendations for these new vaccines, there will be more lessons learned following implementation. Some of these lessons may, as they have in the past, cause ACIP to revise recommendations, which may have additional implications for vaccine implementation. In addition, new vaccines in the pipeline are likely to be more expensive. Recent experience indicates they might have shorter duration of immunity, recommendations may be for more obscure indications or for narrower populations, and other classes of vaccines such as therapeutic vaccines may need to be considered.⁴⁹ There will be many new challenges because of the nature of vaccines on the horizon, not just because of the number. There will be more opportunities to use the lessons of the past and there will be future lessons to be learned in dealing with this increasingly complex playing field.

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