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# Lessons learned from making and implementing vaccine recommendations in the U.S.

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A B S T R A C T

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.



## 1. 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 childhood [1] and adult [2] 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.

## 2. 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 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

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**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. | • 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. | • 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 | • Community protection: PCV7 and PCV13 in the unvaccinated<br>• Community protection: Rotavirus vaccine in the unvaccinated |
| Vaccine shortages impact ability to implement recommendations | • *Haemophilus influenzae* 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. | • New York State's decision to implement a second dose of MMR vaccine led to a revised ACIP recommendation to stem a measles outbreak<br>• 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. | • HPV vaccine recommendations for adolescents (associated with sexual practices, making parents reluctant) |
| Cost considerations in making vaccine recommendations are complex and changing. | • 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.

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].

## 3. 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].

## 4. 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].