S. Michael Marcy Memorial Lecture

Lessons Learned from Making Vaccine Recommendations

Larry K. Pickering, MD, FAAP
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FINANCIAL DISCLOSURE:
Larry K. Pickering, M.D., F.A.A.P.

I have no financial interest or other relationship with manufacturer(s) of product(s) or provider(s) of service(s) that will be discussed in this presentation.
Objectives

• Discuss the impact of vaccine preventable diseases on clinical practice and public health
• Review how vaccine recommendations are made
• Summarize the impact of these recommendations
• Highlight lessons learned from making and implementing vaccine recommendations
Composition of ACIP

- **15 voting members including chair**
  - US citizens; external to federal government
  - 4 year term
  - ACIP steering committee nominates, HHS selects
  - One consumer representative
  - Members screened for conflicts of interest upon appointment, annually through term, and at every ACIP meeting

- **8 ex officio members** – represent other government agencies involved in immunization (non-voting)
  (CMS, DoD, DVA, FDA, HRSA, IHS, NIH, NVPO)

- **30 liaison organizations** –
  - representatives of professional societies and organizations involved with immunization programs (non-voting)

- **Behind the scenes: ACIP Work Groups**
* This chart takes into account General Recommendations on Immunization, recommendations for health care professionals, the annual recommended routine childhood immunization schedule (1995-present), the annual recommended routine adult immunization schedule, and recommendations pertaining to vaccines such as those for rabies, yellow fever, smallpox, and Japanese encephalitis that are not part of any routine immunization schedule in the United States.
Lessons Learned From Making and Implementing Vaccine Recommendations in the U.S. 

L. Reed Walton, MA, 1 Walter A. Orenstein, MD, 2 Larry K. Pickering, MD 1, 3

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.

Lessons Learned from Vaccine Recommendations

- Unanticipated positive effects (herd effect)
- Withdrawal of vaccine recommendations made due to unforeseen safety issues
- Consequences of vaccine recommendations that are changed to minimize adverse events
- Vaccine shortages
- Adverse public perception of vaccines
- Impact of differences in recommendations from different advisory committees
- Role of cost considerations

Unanticipated positive effects of a vaccine both in the population for which the vaccine was recommended and in the community

Pneumococcal Vaccine Use in Children
Pneumococcal Vaccines

- Pneumococcal Polysaccharide (PPSV23)
  - 23-valent introduced in 1983: good efficacy for IPD; question of efficacy for non-bacteremic pneumonia

- Pneumococcal Conjugate (PCV7, PCV13)
  - PCV 7 introduced in children 2000-2001
  - Remarkable impact on invasive disease in all age groups and non-invasive disease in children
  - PCV13 introduced in children – 2010
  - PCV13 immunocompromised adults – 2012
  - PCV13 adults ≥65 years -- 2014
## Characteristics of polysaccharide and conjugate vaccines

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PS</th>
<th>Conj</th>
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<tbody>
<tr>
<td>T-lymphocyte dependent immune response</td>
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<tr>
<td>Immune memory</td>
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<td>Yes</td>
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<tr>
<td>Persistence of protection</td>
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<td>Yes</td>
</tr>
<tr>
<td>Booster effect</td>
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<td>Yes</td>
</tr>
<tr>
<td>Reduction of carriage</td>
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<td>Yes</td>
</tr>
<tr>
<td>Herd protection</td>
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<tr>
<td>Lack of hyporesponsiveness</td>
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<td>Yes</td>
</tr>
<tr>
<td>Immunogenic in young children</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Summary Impact of PCV7 and PCV13 Introduction,

Following PCV7 introduction, 280,000 cases & 19,000 deaths prevented.
PCV13 replaced PCV7 in 2010.
An additional 20,000 cases and 2,000 deaths prevented after introduction of PCV13.

CDC, unpublished
Indirect Effects

- PCV7 introduction with near elimination of PCV7-type IPD among adults of all age groups
- Evidence of continued declines in PCV7-type IPD in adults due to herd effects
- Indirect effects of pediatric PCV13 program have further reduced the proportion of adult IPD and pneumonia caused by PCV13 types
- Studies report reduction in non-bacteremic pneumonia in adults following PCV7 and PCV13 introduction in children
Summary - Children

• Children <2 years of age – Direct effects
  – Since PCV13 introduction, vaccine-type IPD has decreased
  – Reductions appear to be driven by serotypes 19A and 7F
  – Findings are consistent with early impact of PCV13 on IPD

• Children 2-4 years of age – Direct/Indirect effects
  – Decrease in overall and serotype 19A IPD rates
  – May be due to direct effects, indirect effects or both
• Vaccine recommendations made based on minimizing adverse events associated with a vaccine

• Switch from whole cell to acellular pertussis vaccine
Pertussis

- Severe, debilitating cough illness ("100 day cough") in people of all ages
- Highest morbidity and mortality in infants
- Estimated worldwide deaths > 300,000/year
- Poorly controlled, despite high vaccine coverage in the U.S.
- First U.S. pertussis vaccines for adolescents and adults, Tdap, licensed in 2005
PERTUSSIS. Incidence,* by year — United States, 1982–2012

* Per 100,000 population.

Pertussis remains endemic in the United States with cyclic peaks occurring every 2–5 years. Incidence increased more than 150% during 2011–2012; cases reported in 2012 represent the largest number of reported cases in the United States since 1955.
Pertussis deaths by age group, 2000-2012*

*2012 data are provisional and reflect deaths reported to NNDSS as of October 19, 2012.
Contraindications for Administration of DTaP to Children

• Immediate anaphylactic reaction after receipt of DTaP
• Encephalopathy within 7 days after receipt of DTaP not attributable to another cause
• Children in the first year of life with an evolving neurologic disorder

Red Book 2012
DTP and Encephalopathy

Children with unexplained encephalopathy with seizures in the first year of life were identified

96 cases

14 with onset of symptoms within 72 hours of receipt of DTP vaccine

11 who met criteria for post vaccine encephalopathy, corresponded to phenotype for severe/myoclonic epilepsy of infancy (SMEI or Dravet syndrome)
Severe Myoclonic Epilepsy of infancy (SMEI) or Dravet Syndrome

- SMEI is often caused by severe and often spontaneous mutations in SCN1A gene

- 11 of the 14 children with presumed vaccine-related encephalopathy and 10 of 11 with the SMEI phenotype had mutations in this gene

- No family history of severe epilepsy was shown and the mutation was not found in parents from whom parental DNA was available

- 95% of mutations in SMEI occur de novo

- Provides compelling explanation of the cause of the encephalopathy
Dravet Syndrome

- Rare epileptic encephalopathy link to mutation in SCN1A (neuronal sodium channel α1 subunit)

- Characterized by an onset in infancy with polymorphous seizure types and developmental decline

- Previous study showed a proportion of patients previously diagnosed with alleged vaccine encephalopathy possess SCN1A mutations and clinical histories that enabled a diagnosis of Dravet syndrome
Methods

• 5 children who presented for epilepsy care with parental diagnosis of alleged vaccine encephalopathy caused by pertussis vaccinations in infancy were reported.

• Genetic testing showed that all children had Dravet syndrome.
Results of Five Children Evaluated

Initial development: All normal
Seizure onset: 2-7 months
Time between vaccination and seizures: <12 hours: 3, <24 hours: 2
Initial Seizure:
  - Febrile, generalized: 3
  - Afebrile, unilateral, clonic: 2
<table>
<thead>
<tr>
<th>Results (continued)</th>
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<tbody>
<tr>
<td>Subsequent seizures</td>
</tr>
<tr>
<td>Development/behavioral issues</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Brain MRI</td>
</tr>
<tr>
<td>SCN1A testing</td>
</tr>
<tr>
<td>Age at diagnosis</td>
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</tbody>
</table>
Summary

- SCN1A genetic testing has become more available recently.
- Patients of any age with an unexplained chronic encephalopathy and suggestive clinical history should be considered for genetic testing.
- The authors hope to raise awareness of this condition by publication of these 5 patients.
Immunizations are a cornerstone of the nation’s efforts to protect people from a host of infectious diseases. As required by the Food and Drug Administration, vaccines are tested for safety before they enter the market, and their performance is continually evaluated to identify any risks that might appear.
Conclusions of the 2011 IOM Report on DTP and Encephalopathy

Conclusion 10.1: The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and encephalitis.

Conclusion 10.2: The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and encephalopathy.

Switch from whole cell to acellular pertussis vaccine

- Safer vaccine with fewer adverse events
- Less immunogenic vaccine
Waning Tdap Effectiveness in Adolescents

- On basis of 1207 pertussis cases
- Tdap vaccine effectiveness (VE) was calculated
- VE in years following vaccination
  - Year one VE was 69%
  - Year four VE was 9%
- Conclusions:
  - Adolescents who were more remote from Tdap were more likely to test positive for pertussis than those vaccinated more recently
  - Routine Tdap did not prevent pertussis outbreaks

Investigation of Contacts of a Health Care Worker Who Worked While Ill with Pertussis — Maryland, August–September 2014

Kasi M. Chu, MD¹, Lucas A. Johnson, MD¹

(Author affiliations at end of text)

On September 5, 2014, the public health department of a Maryland hospital was notified of a case of Bordetella pertussis infection confirmed by polymerase chain reaction (PCR) in a staff health care worker (HCW). The HCW experienced onset of diarrhea and malaise (nonrespiratory symptoms atypical of the cattarhal phase of pertussis) on August 26. By September 2, paroxysms of coughing led the HCW to consult a colleague, who ordered the PCR test, prescribed a 5-day course of azithromycin, and advised avoidance of patient care until treatment completion. Contrary to the hospital’s infection control policy, neither the HCW nor the colleague reported the presumptive diagnosis of pertussis to the hospital’s public health department. The HCW continued to work in the outpatient department until the positive PCR result was received on September 5, at which time the hospital’s public health department was first notified. The hospital barred the HCW from further work at the hospital while ill, and, in collaboration with local and state public health counterparts, began a contact investigation and stratified patient and HCW contacts by level of exposure.

The HCW had received tetanus, diphtheria, and acellular pertussis vaccine (Tdap) in 2010 and reported an ill family member who had been exposed at school during a widespread <12 months, or contacts who themselves have close contact with infants under 12 months, pregnant women, or persons with preexisting health conditions at risk for severe illness or complications from pertussis. All 22 high-risk contacts were assessed for symptoms and received postexposure prophylaxis according to established guidelines (2). Additionally, six HCW high-risk contacts (three staff physicians, two residents, and one nurse) reported symptoms suggestive of pertussis and were excluded from work until completion of a course of antibiotics. No patient contacts reported symptoms. Nasopharyngeal swabs obtained from all symptomatic high-risk contacts were negative for pertussis by PCR. The remaining low-risk contacts, or their identified parents or guardians, were screened for symptoms, informed of the low-risk nature of the exposure, and provided education on the signs and symptoms of pertussis. All 47 persons identified as exposed were contacted by public health investigators.

HCW presenteeism (i.e., working while sick) can jeopardize the well-being of patients and coworkers (3). Because of the need to investigate and limit exposures, clinical activities in a facility can be disrupted when staff members are potentially exposed to transmissible disease. HCWs should not work while ill with a potentially contagious condition.

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References
Assessment of the U.S. 5-dose DTaP Schedule

• Children with pertussis compared with control had lower odds of having received the 5-dose DTaP series
• As time since last DTaP dose increased, the odds of pertussis increased (consistent with progressive decrease in estimated vaccine efficacy each year after the final dose of DTaP)
• Among cases and controls, 8% of cases and 1% of controls, respectively, had not received any pertussis-containing vaccines

JAMA 2012; 308:2126.
Implementable Changes in Practice

- Immunize all recommended children and adults with pertussis-containing vaccine
- People with vaccine encephalopathy should be tested for the sodium channel gene SCN1A
- Don’t believe everything you read or hear on television, and emphasize safety of vaccines to parents
Related Articles

Tdap vaccine effectiveness in adolescents during the 2012 Washington State pertussis epidemic.
Anna M Acosta et al., Pediatrics, 2015

Waning Tdap Effectiveness in Adolescents.
Nicola P Klein et al., Pediatrics, 2016

Comparative effectiveness of acellular versus whole-cell pertussis vaccines in teenagers.
Nicola P Klein et al., Pediatrics, 2013

Kristine M Bisgard et al., Pediatrics, 2005

Study: Tdap effectiveness declines steadily after first year
Melissa Jenco et al., AAP News, 2016

FDA Approves GlaxoSmithKline's New Combination Vaccine For Children
Catharine Paddock PhD, Medical News Today, 2008

Cost-effectiveness analysis of universal maternal immunization with tetanus-diphtheria-acellular pertussis (Tdap) vaccine in Brazil
MDLinx

Impact of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccinations on reported pertussis cases among those 11 to 18 years of age in an era of waning pertussis immunity: a follow-up analysis
MDLinx

Whooping Cough Epidemic In Washington State
Medical News Today, 2012
• Vaccine recommendations withdrawn because of unforeseen safety issues

Rotashield and intussusception
Rotavirus Vaccine (RotaShield®) and Intussusception

Historical information as RotaShield® was taken off U.S. market in 1999

The U.S. Advisory Committee on Immunization Practices (ACIP) voted on October 22, 1999 to no longer recommend use of the RotaShield® vaccine for infants because of an association between the vaccine and intussusception.

Questions about Rotashield® and Intussusception

Q: What was RotaShield®?
A: RotaShield® vaccine was the first vaccine to prevent rotavirus gastroenteritis approved for use in the United States in August 1998. For more information about rotavirus, see Question & Answers about Rotavirus.
• Vaccine shortages impact ability to implement recommendations

• *Haemophilus Influenzae* type b, pneumococcal, and varicella shortages resulted in changes to recommendations
Microbiology of *Haemophilus influenzae b*

- Gram negative pleomorphic bacillus
- Encapsulated (typeable) and unencapsulated (nontypeable)
- 6 antigenic types with distinct capsular polysaccharides (a, b, c, d, e, f)
Haemophilus influenzae b: History

- Before 1985, Hib was the leading cause of bacterial meningitis among children < 5 years of age
- Common cause of several other conditions
- Disease resulted in permanent neurologic sequelae, including deafness
### Haemophilus influenzae Invasive Disease: 2014

<table>
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<th>Count</th>
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<tr>
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<tr>
<td>Serotype b</td>
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<tr>
<td>Non-serotype b</td>
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<tr>
<td>Unknown serotype</td>
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MMWR 2014;63:702-715
Neurologic Complications

- n=126 (53 with neurologic complications; 67 without complications and normal EEGs and CT scans)
- Complications:
  - Seizures: 23%
  - Comatose: 13%
  - Hearing loss: 12%
  - Hemiparesis: 6%
  - Other cranial nerve deficits: 6%
Katherine Woglom

- 10-year-old child developed epiglottitis
- Followed by pneumonia and meningitis
- Transferred to Babies Hospital at Columbia University
- Episode lasted from May 16, 1935 until death on September 13, 1935 (120 days)
Prevention and Control of *Haemophilus influenzae* Type b Disease

Recommendations of the Advisory Committee on Immunization Practices (ACIP)
Interim Recommendations for the Use of *Haemophilus influenzae* Type b (Hib) Conjugate Vaccines Related to the Recall of Certain Lots of Hib-Containing Vaccines (PedvaxHIB® and Comvax®)

On December 13, 2007, Merck & Co., Inc. (West Point, Pennsylvania) announced a voluntary recall of certain lots of two *Haemophilus influenzae* type b (Hib) conjugate vaccines, PedvaxHIB® (monovalent Hib vaccine) and Comvax® (Hib/hepatitis B vaccine). Providers should return unused vaccine from these recalled lots using procedures outlined on the Merck website at [http://www.merckvaccines.com/PCHRrecall.pdf](http://www.merckvaccines.com/PCHRrecall.pdf). Additional information regarding the affected lots is available online from the Food and Drug Administration (FDA) at [http://www.fda.gov/consumer/updates/hib121307.html](http://www.fda.gov/consumer/updates/hib121307.html). Merck has suspended production of its Hib conjugate vaccines and does not expect to resume distribution of these vaccines until the fourth quarter of 2008. The recall of PedvaxHIB and Comvax and suspension of production are expected to result in short-term disruption to the Hib vaccine supply in the United States.

Merck issued this voluntary recall as a precautionary measure because the company cannot assure the sterility of equipment used during manufacture of these lots. However, the potency of the vaccine in the recalled lots was not affected, and Merck reported that no contamination of vaccine has been detected. Therefore, children who received Hib conjugate vaccine from the recalled lots do not need revaccination or any special follow-up.

Two other Hib conjugate vaccines manufactured by Sanofi Pasteur (Swiftwater, Pennsylvania) and currently licensed and available for use in the United States, ActHIB® (monovalent Hib vaccine) and TriHIBit® (diphtheria and tetanus toxoids and acellular pertussis [DTaP] Hib vaccine), are unaffected by the recall. However, Sanofi Pasteur likely will not be able to immediately provide adequate Hib vaccine to vaccinate fully all children for whom the vaccine is recommended.

The recommended vaccination schedule for all available Hib-containing vaccines consists of a primary series (consisting of 2 or 3 doses, depending on the formulation) administered beginning at age 2 months and a booster dose at age 12--15 months. Because of the short-term reduction in available doses of Hib-containing vaccines, CDC, in consultation with the Advisory Committee on Immunization Practices (ACIP), the American Academy of Family Physicians, and the American Academy of Pediatrics, recommends that providers temporarily defer administering the routine Hib vaccine booster dose administered at age 12--15 months except to children in specific groups at high risk, which are described in this report. Providers should register and track children for whom the booster dose is deferred to facilitate recalling them for vaccination when supply improves.
Invasive *Haemophilus influenzae* Type B Disease in Five Young Children — Minnesota, 2008

On January 23, this report was posted as an MMWR Early Release on the MMWR website (http://www.cdc.gov/mmwr).

In 2008, five children aged <5 years were reported to the Minnesota Department of Health (MDH) with invasive *Haemophilus influenzae* type b (Hib) disease; one died. Only one of the children had completed the primary Hib immunization series; three had received no doses of Hib-containing vaccine (*I*). The five Hib cases are the largest number among children aged <5 years reported from Minnesota since 1992. The cases occurred during a Hib vaccine recall and continuing nationwide shortage that began in December 2007. The recall of certain lots of the two Hib-containing vaccines manufactured by Merck & Co., Inc. (West Point, Pennsylvania) and cessation of production of both vaccines left only one manufacturer of Hib vaccine in the United States (Sanofi Pasteur, Swiftwater, Pennsylvania) (*2,3*). In response, CDC recommended that health-care providers defer the routine 12–15 month booster dose for children not at increased risk for Hib disease (*2,3*). CDC also emphasized that all children should complete the primary series with available Hib-containing vaccines. However, Minnesota vaccination data indicate that primary Hib series coverage was lower during 2008 than coverage with other vaccines administered at the same ages and lower than Hib coverage in previous years. Increases in Hib coverage have occurred in subsequent years; however, the recommended number of doses administered remains less than the number of doses recommended.

In 2008, five children aged <5 years were reported with invasive Hib disease; one died (Table). The patients resided in five different counties in Minnesota and had no known relationship to each other. Three patients had received no vaccinations because of parent or guardian deferral or refusal. One child was aged 5 months and had received 2 doses of Hib PRP-TT vaccine in accordance with the primary series schedule. Another child had received 2 doses of Hib PRP-OMP vaccine, but no booster dose, per CDC recommendations during the shortage. Subsequent to Hib infection, this child was diagnosed with hypogammaglobulinemia. None of the five were enrolled in group child care. The five cases in 2008 were the most reported for 1 year from Minnesota since 1992, when 10 cases were reported (Figure 1).

Although the recall and cessation of production of Merck Hib-containing vaccines in December 2007 resulted in a nationwide Hib vaccine shortage, supply of the remaining two products manufactured by Sanofi Pasteur is adequate for all infants to complete the 3-dose primary vaccine series. However, in February 2008 the Minnesota Vaccines for Children program began receiving reports from vaccine providers regarding shortages of vaccine in their offices. In response, MDH advised providers to ensure completion of the primary series as recommended whenever possible and to track and recall infants who had not completed the primary series so that they could be vaccinated as soon as doses were available. On January 13, MDH examined 2008 vaccination coverage data in the Minnesota Immunization Information Connection (MIIC), Minnesota’s immunization registry. Data were reviewed for 25,699 children born between November 1, 2007 and March 31, 2008 (Figure 2). Among children aged 7 months, 3-dose primary Hib series coverage was 46.5%, which is lower than the age-appropriate coverage for children who had received pneumococcal conjugate or diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccination. In contrast, data from
<table>
<thead>
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<th>Age</th>
<th>Clinical</th>
<th>Doses of Hib Vaccination</th>
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<tr>
<td>7 months**</td>
<td>Meningitis</td>
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<tr>
<td>20 months</td>
<td>Epiglottitis</td>
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<tr>
<td>3 years</td>
<td>Pneumonia</td>
<td>0</td>
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<tr>
<td>5 months</td>
<td>Meningitis</td>
<td>2 and 4 months</td>
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<tr>
<td>15 months*</td>
<td>Meningitis</td>
<td>2 and 5 months</td>
</tr>
</tbody>
</table>

*immune deficiency
**died

MMWR 2009;58:60
• Long-term sequelae of invasive Hib disease are major
• Reduction of invasive Hib disease is a major accomplishment
• Hib disease still occurs – high risk and unimmunized
Current Vaccine Shortages & Delays
Last Updated December 7, 2015

This web page contains the latest national information about vaccine supplies and provides guidance to healthcare providers who are facing vaccine shortages or delays.

⚠️ Note: Only those vaccines included on the recommended childhood and adolescent immunization schedule are included in this update.

Chart of Vaccines* in Delay or Shortage

Vaccines are listed in order used for the Childhood and Adolescent Immunization Schedule.

National Vaccine Supply Shortages

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Shortage</th>
<th>Temporary Change From Routine Recommendation</th>
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</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Rotavirus</td>
<td>No</td>
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</tbody>
</table>
CDC’s Vaccine Supply/Shortage Webpage can be found at:

http://www.cdc.gov/vaccines/vacgen/shortages/default.htm
Future Considerations

- Pertussis vaccines: duration of protection of Tdap
- Tdap repeat doses in pregnancy: safety
- Use of PCV13 in adults and integration with PPSV23
- Use of herpes zoster vaccines in adults at 50 years of age, duration of protection, and next generation vaccine
- Integration of 9vHPV, number of doses, and spacing
- Meningococcal B-containing vaccines in HIV infected
- Many influenza vaccine preparations
- RSV vaccines in the elderly
- Travel vaccines: cholera, Japanese encephalitis, yellow fever
- Vaccine hesitancy and pseudoscience
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