The Use of Evidence in Making Vaccine Policy: The ACIP and SAGE

Arthur Reingold, MD
Professor and Division Head
Epidemiology/Biostatistics
School of Public Health
University of California, Berkeley
Conflicts of Interest

- None
Policy Making as Art, not Science

“Laws, like sausages, cease to inspire respect in proportion as we know how they are made.”

? Otto von Bismarck
John Godfrey Saxe
University of Michigan: March, 1869
Examples of Groups Promulgating Recommendations

**Vaccines**
- Advisory Committee on Immunization Practices (ACIP)
- Strategic Advisory Group of Experts (SAGE)
- Red Book Committee of the American Academy of Pediatrics

**Clinical Practice**
- U.S. Preventive Services Task Force
- American Cancer Society
Common Features of Advisory Groups

- Independence of Members
- Absent or Clearly Declared Conflicts of Interest
- Objectivity and Transparency of Process
- Evidence-Based
### Number of Diseases Prevented by Vaccines Included in the Routine Child/Adolescent Immunization Schedule

<table>
<thead>
<tr>
<th>Year</th>
<th>Diseases Prevented</th>
</tr>
</thead>
<tbody>
<tr>
<td>1964</td>
<td>Smallpox, Polio, Diphtheria, Pertussis, Tetanus, Measles, Rubella, Mumps</td>
</tr>
<tr>
<td>1985</td>
<td>Polio, Diphtheria, Pertussis, Tetanus, Measles, Rubella, Mumps, Hib (infant), HepB, Varicella</td>
</tr>
<tr>
<td>1995</td>
<td>Polio, Diphtheria, Pertussis, Tetanus, Measles, Rubella, Mumps, Hib (infant), HepB, Varicella, Pneumococcal, Influenza, Meningococcal, Rotavirus</td>
</tr>
<tr>
<td>2016</td>
<td>Polio, Diphtheria, Pertussis, Tetanus, Measles, Rubella, Mumps, Hib (infant), HepB, HepA, Varicella, Pneumococcal, Influenza, Meningococcal, Rotavirus, HPV</td>
</tr>
</tbody>
</table>
Figure 1. Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger—United States, 2018.

For those who fall behind or start late, see the catch-up schedule (Figure 2).

These recommendations must be read with the footnotes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars in Figure 1. To determine minimum intervals between doses, see the catch-up schedule (Figure 2). School entry and adolescent vaccine age groups are shaded in gray.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Birth</th>
<th>1 mo</th>
<th>2 mos</th>
<th>4 mos</th>
<th>6 mos</th>
<th>9 mos</th>
<th>12 mos</th>
<th>15 mos</th>
<th>18 mos</th>
<th>19-23 mos</th>
<th>2-3 yrs</th>
<th>4-6 yrs</th>
<th>7-10 yrs</th>
<th>11-12 yrs</th>
<th>13-15 yrs</th>
<th>16 yrs</th>
<th>17-18 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B (HepB)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st dose</td>
<td>2nd dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3rd dose</td>
<td></td>
<td></td>
<td></td>
<td>4th dose</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Rotavirus (RV1) (2-dose series); RV5 (3-dose series) |       |      |       |       |       |       |        |        |        |           |         |         |         |           |           |        |         |
| 1st dose                                     | 2nd dose |     |       |       |       |       |        |        |        |           |         |         |         |           |           |        |         |
|                                              | See footnote 2 |     |       |       |       |       |        |        |        |           |         |         |         |           |           |        |         |

| Diphtheria, tetanus, & acellular pertussis (DTaP; <7 yrs) |       |      |       |       |       |       |        |        |        |           |         |         |         |           |           |        |         |
| 1st dose                                     | 2nd dose |     |       |       |       |       |        |        |        |           |         |         |         |           |           |        |         |
|                                              | 3rd dose |     |       |       |       |       |        |        |        |           |         |         |         |           |           |        |         |
|                                              | 4th dose |     |       |       |       |       |        |        |        |           |         |         |         |           |           |        |         |

| Haemophilus influenza type b (Hib)            |       |      |       |       |       |       |        |        |        |           |         |         |         |           |           |        |         |
| 1st dose                                     | 2nd dose |     |       |       |       |       |        |        |        | 3rd dose or 4th dose |           |         |         |           |           |        |         |
|                                              | See footnote 4 |     |       |       |       |       |        |        |        |           |         |         |         |           |           |        |         |

| Pneumococcal conjugate (PCV13)               |       |      |       |       |       |       |        |        |        |           |         |         |         |           |           |        |         |
| 1st dose                                     | 2nd dose |     |       |       |       |       |        |        |        |           |         |         |         |           |           |        |         |
|                                              | 3rd dose |     |       |       |       |       |        |        |        |           |         |         |         |           |           |        |         |

| Inactivated poliovirus (IPV; <16 yrs)        |       |      |       |       |       |       |        |        |        |           |         |         |         |           |           |        |         |
| 1st dose                                     | 2nd dose |     |       |       |       |       |        |        |        | 3rd dose  |         |         |         |           |           |        |         |
|                                              | 4th dose |     |       |       |       |       |        |        |        |           |         |         |         |           |           |        |         |

| Influenza (IIV)                              |       |      |       |       |       |       |        | Annual vaccination (IIV) 1 or 2 doses |       |         |         | Annual vaccination (IIV) 1 dose only |       |        |         |

| Measles, mumps, rubella (MMR)                |       |      |       |       |       |       | 1st dose | 2nd dose |           |         |         |         |           |           |        |         |
|                                              | See footnote 8 |     |       |       |       |       |         |         |           |         |         |         |           |           |        |         |

| Varicella (VAR)                              |       |      |       |       |       |       |        | 1st dose | 2nd dose |           |         |         |         |           |           |        |         |
|                                              |       |      |       |       |       |       |        |         |         |           |         |         |         |           |           |        |         |

| Hepatitis A (HepA)                           |       |      |       |       |       |       |        | 2 doses | 2 doses |           |         |         |         |           |           |        |         |
|                                              | See footnote 10 |     |       |       |       |       |         |         |         |           |         |         |         |           |           |        |         |

| Meningococcal (MenACWY-D ≥9 mos; MenACWY-CRM ≥2 mos) |       |      |       |       |       |       |        |        |        |           |         |         |         |           |           |        |         |
|                                              | See footnote 11 |     |       |       |       |       |         |         |         |           |         |         |         |           |           |        |         |

| Tetanus, diphtheria, & acellular pertussis (TdAP; ≥7 yrs) |       |      |       |       |       |       |        |        |        |           |         |         |         |           |           |        |         |
|                                              | Tdap |     |       |       |       |       |         |         |         |           |         |         |         |           |           |        |         |

| Human papillomavirus (HPV)                    |       |      |       |       |       |       |        |        |        |           |         |         |         |           |           |        |         |
|                                              | See footnote 13 |     |       |       |       |       |         |         |         |           |         |         |         |           |           |        |         |

| Meningococcal polysaccharide (PPSV23)         |       |      |       |       |       |       |        |        |        |           |         |         |         |           |           |        |         |
|                                              | See footnote 11 |     |       |       |       |       |         |         |         |           |         |         |         |           |           |        |         |

| Pneumococcal polysaccharide (PPSV23)          |       |      |       |       |       |       |        |        |        |           |         |         |         |           |           |        |         |
|                                              | See footnote 5 |     |       |       |       |       |         |         |         |           |         |         |         |           |           |        |         |

**Range of recommended ages for all children** | **Range of recommended ages for catch-up immunization** | **Range of recommended ages for certain high-risk groups** | **Range of recommended ages for non-high-risk groups that may receive vaccine, subject to individual clinical decision making** | **No recommendation**

**NOTE:** The above recommendations must be read along with the footnotes of this schedule.
Figure 1-6: A timeline of vaccine development illustrating the growing cumulative number of vaccines produced in the 20th and 21st centuries. Source: Seth Berkley’s Presentation, 2011 IOM Annual Meeting.
Development of Vaccine Recommendations and Policies U.S.

Vaccines and Related Biological Products Advisory Committee (VRBPAC)

Vaccine development and testing

Submission to FDA for Biologics License Application (BLA)

FDA Licensure

CDC consideration

AAP Board of Directors Consideration

Recommendations for use published in MMWR

Recommendations for use published in Pediatrics

Uptake and financing

Public sector

Private sector

Example: BLA* Approval Letter from FDA (9vHPV)

December 10, 2014 Approval Letter - GARDASIL 9

Our STN: BL 125508/0
Merck Sharp & Dohme Corp.
Attention: Alison Fisher, Ph.D.
P.O. Box 1000
UG2D-68
North Wales, PA 19454-1099

Dear Dr. Fisher:

We have approved your biologics license application for Human Papillomavirus 9-valent Vaccine, Recombinant effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Human Papillomavirus 9-valent Vaccine, Recombinant under your existing Department of Health and Human Services U.S. License No. 0002. Human Papillomavirus 9-valent Vaccine, Recombinant is indicated in girls and women 9 through 26 years of age for prevention of the following diseases:

*Biologics License Agreement
Immunization Time-Line in the United States: Key Milestones

- 1955: Salk vaccine (IPV) introduced. Poliomyelitis Vaccination Assistance Act (Eisenhower) – start of Federal funding for vaccine purchase
- 1962: Sabin vaccine (OPV) introduced. Vaccination Assistance Act (Kennedy) – Federal funds for purchase of polio, diphtheria, pertussis, tetanus vaccines (measles added in 1965)
- 1963: Measles vaccine introduced. Creation of CDC Immunization Branch (precursor of National Immunization Program)
- **1964: establishment of ACIP**
- 1972: Federal Advisory Committee Act (Nixon) – ACIP designated as a Federal Advisory Committee
- 1993: Childhood Immunization Initiative (Clinton) – Vaccines for Children (VFC) Program adopted
Origins of the ACIP

- ACIP was established in **1964** by the Surgeon General of US Public Health Service
- Role: to provide advice and guidance to Director, CDC and Office of the Secretary of the Department of Health and Human Services on most effective means to prevent vaccine-preventable diseases in the civilian population
  - Vaccines and related agents (e.g., antisera, immune globulins, antiviral agents)
  - FDA-licensed vaccines (and unlicensed vaccines if warranted)
- ACIP votes on recommendations for vaccines covered by all 3 Office of Infectious Diseases Centers (OID: NCIRD, NCHHSTP, NCEZID*) and reports directly to the Director of CDC

*NCIRD: National Center for Immunization and Respiratory Diseases
NCHHSTP: National Center for HIV/AIDS, Hepatitis, STD, and TB Prevention
NCEZID: National Center for Emerging and Zoonotic Infectious Diseases
Legal Authority: the Charter

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

Centers for Disease Control and Prevention (CDC)
Atlanta GA 30333

CHARTER
of the
ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

Authority

The Advisory Committee on Immunization Practices was established under Section 222 of the Public Health Service Act (42 U.S.C. §237a), as amended. The committee is governed by the provisions of the Federal Advisory Committee Act, as amended, 5 U.S.C. App., which sets forth standards for the formation and use of advisory committees.

The Advisory Committee on Immunization Practices has been given statutory roles under subsections 1928(c) (2)(B)(i) and 1928(c) of the Social Security Act (42 U.S.C. §1396(c)(2)(B)(i) and 1396(c)(e)) and subsection 2713(a)(2) of the Public Health Service Act (42 U.S.C. §300gg-13(a)(2)).

Objective and Scope of Activities

The Secretary, Department of Health and Human Services (HHS), and by delegation the Director, Centers for Disease Control and Prevention (CDC), are authorized under Section 311 and Section 317 of the Public Health Service Act, (42 U.S.C. §243 and 42 U.S.C. §247b), as amended, to assist states and their political subdivisions in the prevention and control of communicable diseases; to advise the states on matters relating to the preservation and improvement of the public’s health; and to make grants to states and, in consultation with the state health authorities, to agencies and political subdivisions of states to assist in meeting the costs of communicable disease control programs.

Description of Duties

The Advisory Committee on Immunization Practices shall provide advice and guidance to the Director of the CDC regarding the most appropriate selection of vaccines and related agents for effective control of vaccine-preventable diseases in the civilian population. Recommendations made by the ACIP are reviewed by the CDC Director, and if adopted, are published as official CDC/HHS recommendations in the Morbidity and Mortality Weekly Report (MMWR). The CDC Director informs the Secretary, HHS, and the Assistant Secretary for Health, of immunization recommendations.
Federal Advisory Committee Act

- Federal Advisory Committee Act (FACA) – enacted by Public Law 92-463 on October 6, 1972

- Mechanism to seek advice and recommendations of US citizens in Federal Government’s decision-making process
  - Committees provide relevant, objective advice
  - Meetings open to public; all committee documents available for public inspection

- ACIP designated as FACA committee in 1972

- Currently ~1000 Federal Advisory Committees in the US, advising 50 federal agencies
  - 21 federal advisory committees at CDC
Vaccines for Children Program

- Vaccines for Children (VFC) Program – established in August 1993, operational since October 1994
  - Unique statutory authority established by Omnibus Budget Reconciliation Act of 1993 (42 U.S.C. § 1396a) gives ACIP authority to determine vaccines included in the VFC Program
- VFC is a federal entitlement program - current cost is ~$4 billion annually
- Eligible children (0 through 18 years of age):
  - Medicaid eligible; uninsured; American Indian/Alaska native: underinsured
- Currently, approximately 48% of young children in the US are entitled to VFC
- During ACIP meetings members vote first on vaccine recommendation; then take a separate vote on whether to include the vaccine in VFC
- Not affected by Affordable Care Act
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
  - CMS, DoD, DVA, FDA, HRSA, IHS, NIH, NVPO (non-voting)

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

- Behind the scenes: ACIP Work Groups
Expertise & Perspective of ACIP Members

- Pediatrics
- Internal medicine
- Family medicine
- Infectious diseases
- State/local health department
- Public health, preventive medicine
- Nursing
- Immunology
- Vaccine research and policy
- Economics, cost-effectiveness
- Consumer concerns
**Ex Officio Members (8)**

- Centers for Medicaid & Medicare Services (CMS)
- Department of Defense (DOD)
- Department of Veterans Affairs (DVA)
- Food and Drug Administration (FDA)
- Health Resources and Services Administration (HRSA)
- Indian Health Service (IHS)
- National Institute of Health (NIH)
- National Vaccine Program Office (NVPO)
Liaison Organizations *

- Organizations with broad involvement in immunization; organization funds participation of representative
- Designated representative brings perspective of the organization; keeps organization & membership apprised of ACIP deliberations and recommendations
- Members serve on work groups
- Members attend and participate in every ACIP meeting
- Four organizations assist with development and publication of immunization schedules “harmonized” with ACIP (AAFP, AAP, ACOG, ACP)

*non-voting
Liaison Organizations (30)

1. American Academy of Family Physicians
2. American Academy of Pediatrics
3. American Academy of Physician Assistants
4. American Geriatric Society
5. America’s Health Insurance Plans
6. American College Health Association
7. American College of Nurse Midwives
8. American College of Obstetricians and Gynecologists
9. American College of Physicians
10. American Medical Association
11. American Nurses Association
12. American Osteopathic Association
13. American Pharmacists Association
14. Association of Immunization Managers
15. Association of State and Territorial Health Officials
16. Association of Teachers of Preventive Medicine
17. Biotechnology Industry Organization
18. Canadian National Advisory Committee on Immunization
19. Council of State and Territorial Epidemiologists
20. Infectious Diseases Society of America
21. National Association of County and City Health Official
22. National Association of Pediatric Nurse Practitioners
23. National Foundation for Infectious Diseases
24. National Immunization Council & Child Health Program (Mexico)
25. National Medical Association
26. National Vaccine Advisory Committee
27. Pediatric Infectious Diseases Society
28. Pharmaceutical Research & Manufacturers of America
29. Society for Adolescent Health & Medicine
30. Society for Healthcare Epidemiology of America
Process

- Three 2-day meetings annually – February, June, and October. Held in CDC Global Communications Center
- Follow FACA* rules and procedures: meetings must be open to the public with time for public comment
- Meeting slides, live webcast archive, minutes posted on ACIP website within 90 days of meeting
- Recommendations become final once approved by CDC Director, adopted by HHS/CDC and published in MMWR
- Vaccine recommendations are recommendations only – not mandates. States and professional organizations usually endorse or follow ACIP recommendations

* Federal Advisory Committee Act
ACIP Work Groups

- Gather, analyze and prepare information for presentation to ACIP
  - WG proceedings are confidential; not subject to FACA law, but are subject to FOIA requests
  - WGs do not vote or determine policy
  - WGs present draft policy options to ACIP for review and vote in open, public meetings

- Work by teleconference/webinar throughout the year

- WG must be chaired by an ACIP member and include at least 1 other ACIP member
  - Other members: lead CDC staff (SME), liaison representatives, ex officio members, invited consultants; other CDC staff including ISO provide technical input and support
  - Vaccine manufacturers may not serve on WGs, but may be invited to present data
ACIP Work Groups – March 2016

1. Adult immunization
2. Child/adolescent immunization
3. General recommendations
4. Influenza
5. Human papillomavirus vaccines
6. Meningococcal vaccines
7. Pneumococcal vaccines
8. Herpes zoster vaccine
9. Japanese encephalitis / yellow fever vaccines
10. Hexavalent vaccine
11. Cholera vaccine
12. RSV vaccines
13. Hepatitis vaccines
14. Evidence based recommendations

First 4 Work Groups are permanent
World Health Organization’s Strategic Advisory Group of Experts on Vaccines (SAGE)

- Initiated in 1999
- Independent Advisory Committee
- 15 members, 4 year terms
- Began using GRADE, 2007
- Began using Evidence to Recommendation Tables, 2014
- Meets ≥ 2 times a year in Geneva
SAGE and ACIP: Similarities

- Provide advice to decision-makers and funders
- A broad range of perspectives and expertise represented
- Evidence-based
- Generally limited to licensed products
# SAGE & ACIP: Differences

<table>
<thead>
<tr>
<th></th>
<th>ACIP</th>
<th>SAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary target audience</td>
<td>U.S.</td>
<td>Low and Middle Income Countries</td>
</tr>
<tr>
<td>Decision-making process</td>
<td>Vote</td>
<td>Consensus</td>
</tr>
<tr>
<td>Committee Composition</td>
<td>Includes clinicians and diverse perspectives</td>
<td>Primarily Technical Experts</td>
</tr>
<tr>
<td>Audience present at meetings</td>
<td>Includes anti-vaccination and pro-vaccination groups</td>
<td>Limited presence of general public; no press</td>
</tr>
<tr>
<td>Cost considerations</td>
<td>Less important</td>
<td>More important</td>
</tr>
</tbody>
</table>
Evidence Based Recommendation (EBR)

- EBR approach approved by ACIP in October 2010

- System to be used: Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework

- GRADE tables linked to ACIP recommendations:
  
  http://www.cdc.gov/vaccines/acip/recs/GRADE/table-refs.html
Process for Grading Evidence

- Determine key outcomes (e.g. efficacy, effectiveness, safety)
- Assemble evidence base
- GRADE evidence
- Create GRADE tables
GRADE of Evidence is Categorized into Four Types

1. Randomized controlled trials (RCTs), or overwhelming evidence from observational studies.
2. RCTs with important limitations, or exceptionally strong evidence from observational studies (OS).
3. OS, or RCTs with notable limitations.
4. Clinical experience and observations, OS with important limitations, or RCTs with several major limitations.

Vaccine 2011; 29:9171-76
Evidence to Recommendation Framework

- Develop precise question(s) to be answered [i.e. Population, Intervention, Comparison, and Outcome(s)]

- Assess key criteria (e.g. scope of problem; potential benefits and harms; strength of the evidence; values and preferences; level of uncertainty; acceptability to key stakeholders; feasibility of implementation; etc.)
Challenging Issues - General

- Role of cost-effectiveness (economic) analyses
- Recommendations may differ from licensing indications
- Increasing number of vaccines in the routine child/adolescent immunization schedule
- Vaccine hesitancy among some members of the public
Examples of Challenging Issues – Specific

- PCV13 dose reduction in children (4 to 3 doses)
- HPV vaccine: transition from 4vHPV to 9vHPV
- Waning protection from Tdap vaccine
- Meningococcal B-containing vaccines
- Changing Live Attenuated Influenza Vaccine (LAIV) recommendations
LAIV Recommendations Summary, 2003-2016

- 2003: LAIV3 licensed for 5 through 49 years; in 2007, for 2 through 49 years
  - Recommended for healthy non-pregnant persons; no preference
- 2012: LAIV4 licensed; replaced LAIV3 for 2013-14 season
  - Recommended for healthy non-pregnant persons; no preference
- 2014: Preferential recommendation for healthy 2- through 8-year olds
  - Basis: pre-2009 pandemic data showing superiority of LAIV3 to IIV
- February 2015: Preferential recommendation removed following poor effectiveness of LAIV4 against H1N1pdm09 among 2- through 17-year-olds during 2013-14 season
  - No statistically significant effectiveness, whereas IIV was effective
LAIV Recommendations Summary, 2003-2016 (cont’d)

- June 2015: No better performance than IIV against H3N2 in 2014-15
  - Poor VE for LAIV4 and IIV during a drifted H3N2-predominant season
  - LAIV3 superior to IIV for drifted H3N2 viruses in pre-pandemic study
- 2015-16 season: LAIV4 H1N1pdm09-like virus changed to A/Bolivia/559/2013/H1N1pdm09 for 2015-16
  - Studies revealed poor fitness of previous LAIV4 H1N1pdm09-like vaccine virus, A/California/7/2009/H1N1pdm09
- June 2016: Poor effectiveness of LAIV4 against H1N1pdm09 for 2015-16
  - LAIV4 not recommended in the United States for 2016-17 and 2017-18
LAIIV and IIV vaccine effectiveness ages 2–17 years, by influenza type/subtype, 2015-16

U.S. Flu VE Network
2015-16 U.S. Season
Presented at ACIP, June 2016
MedImmune ICICLE Study

2015-16 U.S. Season

Presented at ACIP, June 2016

ICICLE: 2015-16 Adjusted Estimates of Effectiveness

- Results similar for 1) those fully vaccinated, 2) excluding those negative for any respiratory virus, and 3) excluding those with high-risk conditions.

- Primary concern: effectiveness against H1N1pdm09 in 2013-14, 2015-16
- Point estimates of LAIV4 effectiveness against H1N1pdm09 varied in U.S.
- Higher point estimates in studies conducted outside the U.S.
  - e.g., Canada, United Kingdom, Germany, Finland (which have continued to use LAIV)
- Sources of variability not completely understood; possibilities include
  - Differences in use of trivalent as compared with quadrivalent LAIV
  - Small sample size and imprecision of estimates in most individual studies
    - Particularly when stratifying by vaccine types and influenza types/subtypes
  - Differences in prevalence of prior vaccination among children in different countries and populations
Feb, 2018 ACIP Meeting Influenza Session

10:30 Influenza Vaccines

Introduction
Fluarix Quadrivalent: efficacy in children 6-35 months of age
Surveillance update
VE update
Results of a randomized trial of a new H1N1 LAIV strain in US children
Review of LAIV for 2 through 17 year olds
Considerations and proposed recommendations
Public comment
Vote
VFC Vote

Dr. Chip Walter (ACIP, WG Chair)
Dr. Leonard Friedland (GSK)
Ms. Lynnette Brammer (CDC/NCIRD)
Dr. Brendan Flannery (CDC/NCIRD)
Dr. Raburn Mallory (MedImmune/AstraZeneca)
Dr. Lisa Grohskopf (CDC/NCIRD), Dr. Jill Ferdinands (CDC/NCIRD)
Dr. Lisa Grohskopf (CDC/NCIRD)
Dr. Lisa Grohskopf (CDC/NCIRD)
Dr. Jeanne Santoli

Vote
VFC Vote
Influenza Work Group

**ACIP Members**
Emmanuel (Chip) Walter (Chair)
Robert Atmar
Ed Belongia
Hank Bernstein
Peter Szilagyi

**Ex Officio Members**
Karin Bok (HHS)
David Cho (FDA)
Lucia Lee (FDA)
Cynthia Nolletti (FDA)
Roshan Ramanathan (FDA)
Chris Roberts (NIH)

**Consultants**
Jeff Duchin
Wendy Keitel
Ruth Karron
Jamie Loehr

**Liaison Representatives**
Kevin Ault (ACOG)
Sarah Coles (AAFP)
Sarah Despres (Consumer representative)
Jan Englund (PIDS)
Sandra Fryhofer (ACP; AMA)
Ian Gemmill (NACI)
Marie-Michèle Léger (AAPA)
Susan Lett (CSTE)
Flor Munoz (AAP)
Kathy Neuzil (IDSA)
William Schaffner (NFID)
Rob Schechter (AIM)
Ken Schmader (AGS)
Patsy Stinchfield (NAPNAP)
Rob Stirling (NACI)
Tamara Sheffield (AHIP)
Matthew Zahn (NACCHO)
Workgroup Activities Since October 2017 Meeting

- Discussion of LAIV
  - Combined US Individual patient-level data analysis of LAIV effectiveness
  - Systematic review of LAIV effectiveness
  - Update from MedImmune on U.S. Pediatric shedding/immunogenicity study
Agenda Overview

- Efficacy of Fluarix Quadrivalent in Children 6 through 35 Months of Age
  - Dr. Leonard Friedland (GlaxoSmithKline)

- Surveillance Update
  - Ms. Lynnette Brammer (CDC/NCIRD/Influenza Division)

- Vaccine Effectiveness Update
  - Dr. Brendan Flannery (CDC/NCIRD/Influenza Division)

- Results of a randomized trial of a new H1N1 LAIV strain in US Children
  - Dr. Raburn Mallory (MedImmune/AstraZeneca)

- Review of LAIV effectiveness for 2- through 17-year-olds
  - Dr. Lisa Grohskopf (CDC/NCIRD/Influenza Division)

- Considerations and Proposed Recommendations
  - Dr. Lisa Grohskopf (CDC/NCIRD/Influenza Division)
Results of Randomized Trial of a New H1N1 LAIV Strain in US Children

February 21, 2018

Raburn Mallory, MD
Senior Director Clinical Development
MedImmune/AstraZeneca
Improved LAIV strain selection identified a new H1N1 strain that is more immunogenic in children

- LAIV is not recommended in the US as H1N1 vaccine strains used in 2013-2014 and 2015-2016 had reduced effectiveness
- A broad-based scientific investigation determined that H1N1 LAIV strains used in those seasons replicate less well compared to older more effective LAIV strains
- Assays measuring replicative fitness were incorporated into strain selection for 2017-2018 and a new H1N1 strain (A/Slovenia) selected
- A clinical trial was conducted in US children to determine if new A/Slovenia strain was more immunogenic compared to previous A/Bolivia strain used in 2015-2016
- In the study, the new A/Slovenia H1N1 strain induced antibody responses that were significantly higher than those seen with the A/Bolivia strain
  - Immune responses were similar to those seen with a highly effective pre-pandemic LAIV H1N1 strain
- Clinical study results validate improved strain selection process
- New strain selection process applied to all future LAIV strains and data reviewed by FDA/EMA annually

LAIV = Live attenuated influenza vaccine
The A/Slovenia strain was shed by a higher proportion of children from Day 4 through Day 7, after Dose 1 of the vaccine.

The study met its primary endpoint: HAI seroconversion rates were significantly higher for the A/Slovenia strain than for the A/Bolivia strain.

Similar results seen for neutralizing antibodies and for nasal IgA.

A/Slovenia HAI seroconversion rates were similar to those seen in children the same age vaccinated with a highly efficacious pre-pandemic H1N1 strain.
Summary

- A broad-based scientific investigation determined that H1N1 LAIV strains used in 2013-2014 and 2015-2016 had reduced replicative fitness compared to older more effective vaccine strains.

- New assays measuring how well strains replicate were incorporated into strain selection for 2017-2018 and a new H1N1 strain (A/Slovenia) was selected.

- In a randomized trial in US children, the new A/Slovenia strain induced antibody responses that were significantly higher than those seen with the 2015-16 H1N1 strain.
  - Immune responses similar to those seen with a highly effective pre-pandemic LAIV H1N1 strain.

- Clinical study results validate improved strain selection process.

- New strain selection process applied to all future LAIV strains and data reviewed by FDA/EMA on an annual basis.

- LAIV is an important vaccine option for providers, patients, and parents in the US and other countries where it continues to be recommended.

LAIV = Live attenuated influenza vaccine
What is new since 2016? What is still not known?

- LAIV4 contains new H1N1pdm09-like virus (A/Slovenia) since 2017-18 (used in UK, Finland, Canada)
  - H3N2-predominant season thus far; no H1N1pdm09 VE estimates

- Recent shedding/immunogenicity data for new H1N1pdm09-like virus encouraging
  - Effectiveness of this formulation against H1N1pdm9 not known
  - Likely to remain unknown until next H1N1-predominant season (assuming adequate uptake)
  - Cannot predict when this will occur
Evidence to Recommendation Framework

- Problem, Benefits/Harms, Values, Acceptability, and Implementation
Problem:

- Influenza is an important cause of morbidity and mortality in children.
  - Pediatric deaths ranging from 37 (2011-12) to 171 (2012-13) each non-pandemic season since 2004-05;
  - 358 deaths during 2009 pandemic period.
  - Also important cause of hospitalizations—data from FluView Interactive:

<table>
<thead>
<tr>
<th>Season</th>
<th>Hospitalizations/100,000 persons-years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-4 years</td>
</tr>
<tr>
<td>2013-14</td>
<td>47.3</td>
</tr>
<tr>
<td>2014-15</td>
<td>57.3</td>
</tr>
<tr>
<td>2015-16</td>
<td>42.5</td>
</tr>
<tr>
<td>2016-17</td>
<td>40.8</td>
</tr>
</tbody>
</table>
Benefits vs. Harms:

- Benefit of the current formulation of LAIV4 against H1N1pdm09-like viruses is currently not known (no effectiveness data yet)
- Data suggest good effectiveness of LAIV4 against influenza B viruses
- Data suggest LAIV4 is comparable to IIV against H3N2
- No new safety concerns raised for LAIV4 at the time that the recommendation for its use was removed
- Potential for harm if new formulation of LAIV4 is not effective
Values: How does the target population view the balance of the benefits and risks?

- Some communications (published/unpublished letters) have expressed concern that lack of recommendation for LAIV may be detrimental in some settings (e.g., school-based clinics)
- Maintaining consumer confidence in influenza vaccines is important in the setting of low VE estimates overall
Acceptability: Risk of recommending LAIV without effectiveness data against H1N1 with the new strain

*Work Group Perspectives: A plausible root cause of reduced effectiveness against H1N1pdm09 identified*

– Some expressed view other factors (interference) may have contributed
– Varying viewpoints regarding promise of the shedding study data
  • Some viewed it as encouraging.
  • Others expressed concern about the size of the study and problems with using immunogenicity/shedding to gauge effectiveness of LAIV
– If issue not resolved, potentially more influenza cases.
– Understanding that influenza VE varies by season for all vaccines, and that initial licensure of some newer vaccines (e.g., some recent quadrivalents) has been based upon immunogenicity data
  • Risk similar to introduction of new influenza vaccine product
Acceptability: Risk that if LAIV is not recommended in the US during 2018-2019, it may not return to market

**Work Group Perspectives: It is valued to have multiple types of influenza vaccine available**

- LAIV remains a licensed product.
- Challenge of holding all manufacturers to the same standards for effectiveness of influenza vaccines
  - Effectiveness of LAIV has been examined each season
  - For most other individual influenza vaccines, recommendation is not based upon annual assessment of product-specific VE
Implementation: Has influenza vaccine coverage been impacted by not recommending LAIV?

- National vaccination coverage remained stable during the 2016-2017 influenza season
  - Local variation likely, reports of reduced coverage in areas with strong school-based programs that relied on LAIV

- National coverage did not increase, and was 2% lower in the 5-12 year-old age group
Influenza Vaccination Coverage by Age Group, Children 6 months–17 years, NIS-Flu, United States, 2016–17 Season

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Unweighted Sample Size</th>
<th>%* ±95% CI†</th>
<th>Difference from the 2015–16 Season ±95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months–17 years</td>
<td>143,169</td>
<td>59.0 ± 0.7</td>
<td>-0.3 ± 1.1</td>
</tr>
<tr>
<td>6 months–4 years</td>
<td>44,094</td>
<td>70.0 ± 1.3</td>
<td>0.0 ± 1.9</td>
</tr>
<tr>
<td>6–23 months</td>
<td>16,374</td>
<td>76.3 ± 2.0</td>
<td>1.0 ± 2.6</td>
</tr>
<tr>
<td>2–4 years</td>
<td>27,720</td>
<td>66.2 ± 1.6</td>
<td>-0.6 ± 2.4</td>
</tr>
<tr>
<td>5–17 years</td>
<td>99,075</td>
<td>55.6 ± 0.8</td>
<td>-0.3 ± 1.2</td>
</tr>
<tr>
<td>5–12 years</td>
<td>63,130</td>
<td>59.9 ± 1.0</td>
<td>-1.9 ± 1.6†</td>
</tr>
<tr>
<td>13–17 years</td>
<td>35,945</td>
<td>48.8 ± 1.3</td>
<td>2.0 ± 1.9†</td>
</tr>
</tbody>
</table>

* Percentage vaccinated.
† Confidence interval half-widths.
‡ Statistically significant difference between the 2016–17 season and the 2015–16 season by t-test (P<0.05).
Policy Question: Should LAIV be recommended for the 2018-19 season?

<table>
<thead>
<tr>
<th>Factor</th>
<th>WG Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problem</td>
<td>• Influenza is an important source of morbidity and mortality among children.</td>
</tr>
<tr>
<td>Benefits and harms</td>
<td>• Benefit of LAIV for H3N2 comparable to IIV.</td>
</tr>
<tr>
<td></td>
<td>• Data suggest good effectiveness for influenza compared with no vaccine.</td>
</tr>
<tr>
<td></td>
<td>• Limited immunogenicity and shedding data suggest new H1N1pdm09 virus in LAIV4 may promote improved effectiveness (however, this is not yet known).</td>
</tr>
<tr>
<td></td>
<td>• No vaccine safety concerns at the time LAIV vaccine was not recommended by ACIP.</td>
</tr>
<tr>
<td></td>
<td>• Potential for harm if vaccine ineffective.</td>
</tr>
<tr>
<td>Values</td>
<td>• Several papers and unpublished and published letters, indicate support for availability of a non-injectable formulation of influenza vaccine.</td>
</tr>
<tr>
<td>Acceptability</td>
<td>• Varying levels of accepting risk of vaccine not being as effective against H1N1 and potential detriment to confidence in influenza vaccines.</td>
</tr>
<tr>
<td>Implementation</td>
<td>• While national coverage appears not to have been impacted by lack of LAIV recommendation, LAIV is an important option for school-based clinics and may contribute to efforts to increase vaccination coverage.</td>
</tr>
<tr>
<td>Summary</td>
<td>• There was not complete agreement on the WG.</td>
</tr>
<tr>
<td></td>
<td>• Most felt the issue should be discussed at ACIP.</td>
</tr>
<tr>
<td></td>
<td>• A recommendation would need to acknowledge lack of effectiveness data for current LAIV4 against H1N1pdm09 like viruses.</td>
</tr>
</tbody>
</table>
## ACIP Vote

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>12</td>
</tr>
<tr>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>Recused</td>
<td>1</td>
</tr>
</tbody>
</table>
Purpose of the Resolution

- The purpose of this resolution is to add live attenuated influenza vaccine (LAIV) to the VFC Program.
Should Committees That Write Guidelines and Recommendations Publish Dissenting Opinions?

Daniel M. Musher, MD

Departments of Medicine and Molecular Virology and Microbiology, Baylor College of Medicine; and Medical Care Line (Infectious Disease Section), Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX

Available online 6 April 2016

CrossMark

Show less

doi:10.1016/j.mayocp.2016.01.018

Get rights and content
AAP recommends influenza vaccination for all children > 6 months.

ACIP reintroduced LAIV4 as an option for the 2018-2019 season.

The effectiveness of the new LAIV4 formulation for 2018-2019 for A/H1N1 is unknown.

The AAP prefers IIV (trivalent or quadrivalent) for influenza vaccination in children because effectiveness of quadrivalent live attenuated influenza vaccine (LAIV4) against A/H1N1 was inferior in prior seasons.

LAIV4 may be used for children who would not otherwise receive influenza vaccine and for whom it is appropriate.
Summary

- Reviewing and GRADing Evidence is “Easy”
- Making Recommendations Based on the Evidence can be Hard
Backup Slides
Review of LAIV Effectiveness data, 2010-11 through 2016-17

- Combined individual patient-level analysis of U.S. studies (US-IPD)
  - 5 studies and three seasons with LAIV4 (2013-14 through 2015-16)
  - Greater power for age group analyses
  - More precise estimates through pooling of data across multiple studies
  - Evaluation of effect of prior vaccination

- Systematic review and meta-analysis (SR/MA)
  - U.S. and non-U.S. studies from 2010-11 season forward
  - Evaluation of quality of individual studies (risk of bias; problems related to small sample size)
  - Summary VE results and exploration of heterogeneity

Jessie Chung, MPH
Brendan Flannery PhD
**Included studies summary—Combined US-IPD analysis**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Study Inclusion</th>
<th>Testing</th>
<th>Current Season vaccination status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza Clinical Investigation in Children (ICICLE), MedImmune</td>
<td>3521</td>
<td>ARI with fever &lt;5 days duration</td>
<td>RT-PCR</td>
<td>EMR, immunization registries</td>
</tr>
<tr>
<td>Influenza Incidence Surveillance Project (IISP), CDC</td>
<td>1102</td>
<td>ARI with fever and cough/sore throat ≤7 days duration</td>
<td>RT-PCR</td>
<td>EMR, immunization registries</td>
</tr>
<tr>
<td>LSU Health Sciences Center (LSU)</td>
<td>3822</td>
<td>Clinical laboratory testing for influenza</td>
<td>Rapid test; RVP</td>
<td>Immunization registry</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>of negatives</td>
<td></td>
</tr>
<tr>
<td>US Air Force School of Aerospace Medicine dependents (USAFSAM), US DoD</td>
<td>1935</td>
<td>ARI with fever and cough/sore throat &lt;72 hours duration</td>
<td>Culture, RT-PCR</td>
<td>Immunization registry, parent report</td>
</tr>
<tr>
<td>Flu VE Network, CDC</td>
<td>6793</td>
<td>ARI with cough ≤7 days duration</td>
<td>RT-PCR</td>
<td>EMR, immunization registries</td>
</tr>
</tbody>
</table>
Adjusted VE of LAIV4 by influenza (sub)type and age group—Combined US-IPD analysis

![Adjusted vaccine effectiveness graph](chart.png)
Relative Effectiveness Slides—Example of Format

Odds Ratio

Favors LAIV  Favors IIV
Any influenza (all 3 seasons)

A/H1N1pdm09 (2013-14 and 2015-16)
### Influenza (sub)type/Age group

<table>
<thead>
<tr>
<th>Influenza (sub)type/Age group</th>
<th>Total</th>
<th>Influenza Positive</th>
<th>Influenza Negative</th>
<th>aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Influenza A/H3N2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-17 y LATV</td>
<td>1009</td>
<td>234 (23)</td>
<td>775 (77)</td>
<td>1.3 (1.06, 1.58)</td>
</tr>
<tr>
<td>2-4 y LATV</td>
<td>320</td>
<td>56 (18)</td>
<td>264 (83)</td>
<td>1.99 (1.49, 2.64)</td>
</tr>
<tr>
<td>5-8 y LATV</td>
<td>353</td>
<td>86 (24)</td>
<td>267 (76)</td>
<td>1.16 (0.74, 1.82)</td>
</tr>
<tr>
<td>9-17 y LATV</td>
<td>336</td>
<td>92 (27)</td>
<td>244 (73)</td>
<td>1.15 (0.87, 1.51)</td>
</tr>
<tr>
<td>2-17 y IV</td>
<td>1922</td>
<td>311 (16)</td>
<td>1611 (84)</td>
<td></td>
</tr>
<tr>
<td>2-4 y IV</td>
<td>822</td>
<td>67 (8)</td>
<td>756 (92)</td>
<td></td>
</tr>
<tr>
<td>5-8 y IV</td>
<td>506</td>
<td>107 (21)</td>
<td>399 (79)</td>
<td></td>
</tr>
<tr>
<td>9-17 y IV</td>
<td>594</td>
<td>137 (23)</td>
<td>457 (77)</td>
<td></td>
</tr>
<tr>
<td><strong>Influenza B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-17 y LATV</td>
<td>1561</td>
<td>58 (4)</td>
<td>1503 (96)</td>
<td>0.72 (0.46, 1.13)</td>
</tr>
<tr>
<td>2-4 y LATV</td>
<td>4048</td>
<td>197 (5)</td>
<td>3852 (95)</td>
<td></td>
</tr>
<tr>
<td>5-8 y LATV</td>
<td>1796</td>
<td>47 (3)</td>
<td>1751 (97)</td>
<td></td>
</tr>
<tr>
<td>9-17 y LATV</td>
<td>1039</td>
<td>75 (7)</td>
<td>964 (93)</td>
<td></td>
</tr>
<tr>
<td>2-17 y IV</td>
<td>511</td>
<td>7 (1)</td>
<td>504 (99)</td>
<td>0.56 (0.21, 1.53)</td>
</tr>
<tr>
<td>2-4 y IV</td>
<td>1796</td>
<td>47 (3)</td>
<td>1751 (97)</td>
<td></td>
</tr>
<tr>
<td>5-8 y IV</td>
<td>556</td>
<td>25 (5)</td>
<td>531 (96)</td>
<td>0.68 (0.42, 1.11)</td>
</tr>
<tr>
<td>9-17 y IV</td>
<td>1212</td>
<td>75 (6)</td>
<td>1137 (94)</td>
<td>0.81 (0.38, 1.72)</td>
</tr>
</tbody>
</table>

---

A/H3N2 (2014-15)

Any Influenza B (all 3 seasons)
Included Paper Characteristics

- 15 test-negative case-control studies (TNCC)
  - United States (9), United Kingdom (3), Canada (2), Germany (1)
- 1 prospective cohort study
  - United States (1)
- 2 cluster randomized trials
  - Canada (2)
- No individually randomized trials
- One retrospective cohort study from Finland did not meet testing modality criteria
  - included in sensitivity analysis for pooled H1N1pdm09 estimate
Summary points—US-IPD and SR/MA

- LAIV vs. no vaccine for influenza A(H1N1)pdm09:
  - Significant effectiveness for 9-17 yrs in US-IPD
  - In SR/MA, significant effectiveness only in non-US studies
    • More imprecise estimates/higher risk of bias for 3/4 of these
  - No studies with effectiveness estimates for LAIV containing A/Slovenia

- LAIV vs. IIV for influenza A(H1N1)pdm09:
  - IIV better for all age groups in US-IPD
  - IIV better in SR/MA

- LAIV vs. IIV for influenza B: Point estimate favors LAIV for both analyses, but not significantly different

- LAIV vs. IIV for A(H3N2): IIV better for 2-4 yrs in US-IPD; no significant difference in other age groups or in SR/MA
Key changes made in the way LAIV strains are selected annually

- Human nasal epithelial cell culture now used to assess the replicative fitness of new LAIV strains
  - Previous strains were assessed for fitness in MDCK (dog kidney) cells and eggs
  - For post-pandemic H1N1 strains results were not predictive of human nasal cell replication
- TCID$_{50}$ assay added to quantify new LAIV strains
  - FFA measures infectivity of vaccine viruses through expression of antigen on the cell surface
  - TCID$_{50}$ measures spread of vaccine virus between cells following multiple rounds of replication
  - For post-pandemic H1N1 strains TCID$_{50}$ values were up to 3 logs lower than FFA results
  - As a result, post-pandemic H1N1 strains with reduced effectiveness may not have sustained intranasal replication to the level needed for optimal effectiveness
- All future strains now only selected if they have high levels of replication in human nasal epithelial cells and when the FFA and TCID$_{50}$ assays give similar results*

* TCID$_{50}$ and FFA results to be submitted and reviewed by FDA and EMA as part of annual strain change process
LAIV effectiveness investigation: Root Causes

• Likely root cause = Reduced replicative fitness of H1N1pdm09 LAIV strains

• No support for the following as likely root causes:
  - Pre-existing immunity from prior vaccination
  - Quadrivalent-specific vaccine virus interference
  - Vaccine virus temperature stability and heat exposure during shipping
  - Manufacturing
  - Stability at 2-8 °C
Unlikely Root Cause: Pre-existing immunity among vaccinated children

LAIV3 demonstrated low to no vaccine effectiveness against post-pandemic strains in 2010-2011 season 1,2

Given observations of reduced effectiveness with LAIV3, quadrivalent-specific interference considered an unlikely root cause of the reduced VE

Interference could be a contributing factor to the low effectiveness in context of reduced replicative fitness of post-pandemic LAIV strains

However, A/Slovenia strain in the quadrivalent formulation was more immunogenic than the A/Bolivia strain in the trivalent or quadrivalent formulations

Immunogenicity of A/Slovenia was similar to a highly effective pre-pandemic strain in the trivalent formulation

Unlikely Root Cause: Vaccine virus interference from quadrivalent formulation

- LAIV3 demonstrated low to no vaccine effectiveness against post-pandemic strains in 2010-2011 season\(^1,2\)
- Given observations of reduced effectiveness with LAIV3, quadrivalent-specific interference considered an unlikely root cause of the reduced VE
- Interference could be a contributing factor to the low effectiveness in context of reduced replicative fitness of post-pandemic LAIV strains
- However, A/Slovenia strain in the quadrivalent formulation was more immunogenic than the A/Bolivia strain in the trivalent or quadrivalent formulations
- Immunogenicity of A/Slovenia was similar to a highly effective pre-pandemic strain in the trivalent formulation