A Vaccine’s Journey from Licensure to Recommendation & Beyond

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March 21, 2019
Massachusetts Chapter of AAP
Disclaimers/Disclosure

- I have no financial relationship with the manufacturer(s) of any commercial product(s) discussed in this presentation.

- I may discuss the use of vaccines in a manner not consistent with the Package Insert, but all recommendations are in accordance with recommendations from the ACIP & AAP.
Today’s Learning Objectives

• Why we vaccinate
  – Individual protection
  – Understanding community protection (herd immunity)

• How FDA evaluates a vaccine

• How the CDC makes recommendations
  – Why there may be differences between the package insert and recommendations for vaccine use

• How vaccine safety is monitored

• Vaccine administration: from needle to micropatch
Licensed Vaccines in United States, 2019

Routine childhood use (16 diseases)
- Diphtheria, tetanus, pertussis
- Haemophilus influenzae type b
- Hepatitis A
- Hepatitis B
- Human papillomavirus
- Influenza
- Measles, mumps, rubella
- Meningococcal (ACWY)
- Pneumococcal
- Poliomyelitis
- Rotavirus
- Varicella

Special settings (11 diseases)
- Adenovirus
- Anthrax
- Bacille de Calmette-Guérin (BCG)
- Cholera
- Japanese encephalitis virus
- Meningococcal B
- Rabies
- Typhoid
- Vaccinia (smallpox)
- Yellow fever
- Zoster (shingles)
Epidemics in the 21\textsuperscript{st} Century

1. MERS  
   coronavirus
2. SARS  
   coronavirus
3. A/2009(H1N1)pdm  
   influenza virus
4. Acute flaccid myelitis  
   EV-D68 (?)
5. Ebola virus  
   filovirus
6. Zika virus  
   flavivirus
Other Vaccines in Development

1. C. difficile
2. Cytomegalovirus
3. Dengue
4. Hexavalent vaccine (Vaxelis)
5. Lyme
6. Norovirus
7. RSV
8. S. aureus
9. Streptococcus, group A
10. Streptococcus, group B
11. West Nile virus
12. Zoonotic influenza viruses
Mortality Rates per 100,000 Population in United States, 1900-2015
### Vaccine Impact on Disease in U.S.

<table>
<thead>
<tr>
<th>Disease</th>
<th>20th Century Estimated Annual Cases</th>
<th>2016 Reported Cases</th>
<th>Percent Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallpox</td>
<td>29,005</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>21,053</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Polio (paralytic)</td>
<td>16,316</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Measles</td>
<td>530,217</td>
<td>69</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>Rubella</td>
<td>47,745</td>
<td>5</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>Congenital Rubella Syndrome</td>
<td>152</td>
<td>1</td>
<td>&gt;99%</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> b</td>
<td>20,000</td>
<td>22</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>Mumps</td>
<td>162,344</td>
<td>5,311</td>
<td>97%</td>
</tr>
<tr>
<td>Tetanus</td>
<td>580</td>
<td>33</td>
<td>94%</td>
</tr>
<tr>
<td>Pertussis</td>
<td>200,752</td>
<td>15,737</td>
<td>92%</td>
</tr>
</tbody>
</table>
Community Protection

Blue = not immunized but still healthy

Yellow = immunized but healthy

Red = not immunized, sick and contagious
Community Protection

Important for:

1. Children/infants too young to be vaccinated
2. Pregnant women
3. People in whom vaccinate induced immunity has waned
4. Immunosuppressed patients who cannot be vaccinated
5. Elderly who may not mount an adequate immune response to a vaccine
6. People with inadequate access to vaccinations
7. People who remain unvaccinated by choice
Development of Vaccine Recommendations

- CBER = Center for Biologics Evaluation and Research
- VRBPAC = Vaccines and Related Biological Products Advisory Committee
- ACIP = Advisory Committee for Immunization Practice

Vaccine Development & Testing

BLA Submitted to FDA/CBER

FDA Licensure

CDC Recommendations

VRBPAC

ACIP

(AAP, ACOG, AAFP)
The Vaccine Trials Paradigm

• Phase 1
  – Preliminary safety & immune response in small number of subjects

• Phase 2
  – Safety & immunogenicity in larger groups; target populations, selection of formulation, compatibility with concomitant vaccines

• Phase 3
  – Efficacy in large scale trials (randomized, controlled, double blind design when possible)
  – licensure

• Phase 4
  – Impact & safety post-licensure under real-life conditions, modifications in formulation and immunization schedule
Considerations Before a Vaccine is Licensed & Recommended

- Safety
- Efficacy
- Age when disease is most likely to occur
- Effect of age on the immune response
- Duration of the immune response
- Need for booster doses
- Equity
- Vaccine supply

- Compatibility with existing schedule
- Simplification of the immunization schedule
- Minimization of the number of doses
- Cost-effectiveness
- Impact on community (herd) immunity
- Vaccine acceptance by members of the public
Recommendations for IIV & LAIV, 2018-19

• ACIP (CDC)
  – For the 2018-19 season, providers may choose to administer any licensed, age-appropriate influenza vaccine (IIV, RIV4, or LAIV4).
  – LAIV4 is an option for those for whom it is otherwise appropriate, based on age and health.

• COID (AAP)
  – For the 2018-19 season, AAP recommends IIV3/4 as the primary choice for all children because LAIV4 was inferior against A/H1N1 in past seasons and efficacy is unknown for the upcoming season.
  – LAIV4 may be offered for children who would not otherwise receive an influenza vaccine.
Vaccine Safety

• Prelicensure
  – Clinical trials
    • Phases 1, 2, 3, 4

• Postlicensure
  – Vaccine Adverse Events Reporting System
  – Vaccine Safety Datalink (VSD)
  – Clinical Immunization Safety Assessment Network (CISA)
## CDC Immunization Safety Office Post-Licensure Vaccine Safety Monitoring Infrastructure

<table>
<thead>
<tr>
<th>System</th>
<th>Collaboration</th>
<th>Description</th>
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<tbody>
<tr>
<td>Vaccine Adverse Event Reporting System (VAERS)</td>
<td>CDC and FDA</td>
<td>US frontline spontaneous reporting system to detect potential vaccine safety problems</td>
</tr>
<tr>
<td>Vaccine Safety Datalink (VSD)</td>
<td>CDC and 9 Managed Healthcare Plans</td>
<td>Large linked database system used for active surveillance and research (~9.2 million members (~3% of US pop.) - Conducts monitoring &amp; evaluation - Rates &amp; risk estimates can be calculated</td>
</tr>
<tr>
<td>Clinical Immunization Safety Assessment (CISA) Project</td>
<td>CDC and 7 Academic Centers</td>
<td>Expert collaboration that conducts individual clinical vaccine safety assessments and clinical research</td>
</tr>
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</table>
The Primary Objectives of VAERS

• Detect new, unusual, or rare vaccine adverse events
• Monitor increases in known adverse events
• Identify potential patient risk factors for particular types of adverse events
• Identify vaccine lots with increased numbers or types of reported adverse events
• Assess the safety of newly licensed vaccines
# VAERS: Reporting System
Co-administered by CDC & FDA

## Strengths
- Rapid signal detection
- Can detect rare adverse events
- Generates hypothesis
- Encourages reports from providers and accepts reports from patients and others
- Data available to public

## Limitations
- Reporting bias (e.g. underreporting, stimulated reporting)
- Inconsistent data quality and completeness
- Not designed to assess if vaccine caused an adverse event
- Lack of unvaccinated comparison group
Microneedle Patch
Microneedle Patch
The End