An Accelerated Pathway Towards a Universal Influenza Vaccine

Anthony S. Fauci, M.D.
Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health
June 8, 2017
Seasonal vs. Pandemic Influenza

Influenza Virus

Neuraminidase (N)
Hemagglutinin (H)

Drift
Shift

Seasonal Influenza
- Annual occurrence
- Residual immunity in population

Pandemic Influenza
- Unpredictable rare occurrence
- “Naïve” population
Annual Disease Burden of Seasonal Influenza in the United States

- Deaths: 12,000 - 56,000
- Hospitalizations: 140,000 - 710,000
- Cases: 9,200,000 - 60,800,000

Source: CDC. Annual estimates since 2010
### Influenza Pandemics in the 20\(^{th}\)–21\(^{st}\) Centuries

<table>
<thead>
<tr>
<th>Year</th>
<th>Hype</th>
<th>Type</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1918</td>
<td>H1N1</td>
<td>“Spanish Flu”</td>
<td>~ 50 million</td>
</tr>
<tr>
<td>1957</td>
<td>H2N2</td>
<td>“Asian Flu”</td>
<td>1-2 million</td>
</tr>
<tr>
<td>1968</td>
<td>H3N2</td>
<td>“Hong Kong Flu”</td>
<td>700,000</td>
</tr>
<tr>
<td>2009</td>
<td>H1N1</td>
<td>“Swine Flu”</td>
<td>284,500</td>
</tr>
</tbody>
</table>
Current seasonal influenza vaccines are not consistently effective

Pandemics do occur and response after the fact is not effective

“Chasing after” potential pandemic outbreaks (pre-pandemic viruses) is costly and ineffective
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<table>
<thead>
<tr>
<th>Year</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004-05</td>
<td>10%</td>
</tr>
<tr>
<td>2005-06</td>
<td>21%</td>
</tr>
<tr>
<td>2006-07</td>
<td>52%</td>
</tr>
<tr>
<td>2007-08</td>
<td>37%</td>
</tr>
<tr>
<td>2008-09</td>
<td>41%</td>
</tr>
<tr>
<td>2009-10</td>
<td>56%</td>
</tr>
<tr>
<td>2010-11</td>
<td>60%</td>
</tr>
<tr>
<td>2011-12</td>
<td>47%</td>
</tr>
<tr>
<td>2012-13</td>
<td>49%</td>
</tr>
<tr>
<td>2013-14</td>
<td>52%</td>
</tr>
<tr>
<td>2014-15</td>
<td>19%</td>
</tr>
<tr>
<td>2015-16*</td>
<td>47%</td>
</tr>
</tbody>
</table>

*Estimate from Nov 2, 2015–April 15, 2016.

Source: CDC.gov
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Vaccine Lags Behind 2009 H1N1 Influenza Pandemic

Percent of ILI Visits Reported by Sentinel Providers, Weeks 30-50 2009

H1N1 Vaccine Doses Available

Children Return to School

6 months after virus isolation (April 2009), first vaccine doses become available

Number of Doses (millions)
Current seasonal influenza vaccines are not consistently effective

Pandemics do occur and response after the fact is not effective

“Chasing after” potential pandemic outbreaks (pre-pandemic viruses) is costly and ineffective
Pre-Pandemic vaccines: against circulating strains that *threaten* to cause a pandemic (e.g., H5N1, H7N9)

Pandemic vaccines: against strain causing an *existing* pandemic (e.g., 2009 H1N1)
Avian Influenza A (H5N1) Infection in Humans

The Writing Committee of the World Health Organization (WHO) Consultation on Human Influenza A/H5
President Bush today unveiled a strategy to combat the threat of an avian flu pandemic, calling for $7.1 billion in emergency spending to stockpile reserves of medicines and to press ahead with the development of a new vaccine.
Pandemic Influenza Preparedness
Strategy and Implementation

- International Surveillance
- Domestic Surveillance
- Vaccines
- Antivirals
- Communications
- State and Local Preparedness
FDA Approves First Adjuvanted H5N1 Influenza Vaccine for U.S. Stockpile

- Approved Nov. 22, 2013
- Made by ID Biomedical (GSK subsidiary)
- Includes AS03 adjuvant
Phase 2 Trials of 2013 H7N9 Vaccine in Healthy Adults

Serological Responses to an Avian Influenza A/H7N9 Vaccine Mixed at the Point-of-Use With MF59 Adjuvant
A Randomized Clinical Trial
MJ Mulligan, DI Bernstein, P Winokur et al

Effect of Varying Doses of a Monovalent H7N9 Influenza Vaccine With and Without AS03 and MF59 Adjuvants on Immune Response
A Randomized Clinical Trial
LA Jackson, AR Bellamy et al

Acceptable safety profile; two adjuvanted doses needed to induce adequate immune response
Five Waves of Human H7N9 Influenza Infections in China, February 2013-present

- 1,486 confirmed human cases, 559 deaths
- 5th wave: >40% of cumulative cases

Source: FAO, 5/10/2017
Improving seasonal influenza vaccines

Pandemic influenza vaccines

Universal influenza vaccines
Improving seasonal influenza vaccines

Pandemic influenza vaccines

Universal influenza vaccines
Evolution of Technologies for Influenza Vaccines

Egg-based → Cell-based → Recombinant DNA Technologies
New Platforms for Seasonal and Pandemic Influenza Vaccines

- Recombinant subunit
- Synthetic peptide
- Microbial vector
- Nanoparticle-based
- Virus-like particles (VLPs)
- DNA-based
- Novel delivery systems (e.g., microneedles)
Improving seasonal influenza vaccines

Pandemic influenza vaccines

Universal influenza vaccines
Vaccine Adjuvants

- Reduce amount of antigen needed
- Promote earlier, stronger, more durable immune responses
- May increase cross-protective immune response

![Graph showing antibody response over days for vaccines with and without adjuvants.](image)
Improving seasonal influenza vaccines

Pandemic influenza vaccines

Universal influenza vaccines
Induction of Unnatural Immunity: Prospects for a Broadly Protective Universal Influenza Vaccine

GJ Nabel and AS Fauci
Goals for Universal Influenza Vaccines

- **Breadth** to cover future drifted and pandemic strains

- **Durability** $\geq 5$ years
Key Workshop Topics/Gaps in Knowledge

- Goals of a universal vaccine program
- Epidemiology, transmission, natural history, and pathogenesis of influenza
- Protective immune mechanisms in influenza
- Pre-existing immunity to influenza; impact on infection and response to vaccination
Key Workshop Topics/Gaps in Knowledge (cont.)

- Universal vaccine platforms for influenza
- Diagnostics for assessing mechanisms of immune protection in influenza
- Animal models in influenza research
- Human influenza challenge model
Previous Examples of Catalyzing NIH Vaccine Initiatives

- NIAID Vaccine Research Center – Intramural

- NIAID Center for HIV/AIDS Vaccine Immunology (CHAVI)

- NIAID Centers for HIV/AIDS Vaccine Immunology and Immunogen Discovery (CHAVI-ID)
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NIAID Vaccine Research Center

Basic Research → Clinical Trials

VRC Senior Investigators
VRC Research: From HIV to Zika

- HIV
- West Nile virus
- Chikungunya
- Ebola/Marburg
- Influenza
- Malaria
- MERS-CoV
- RSV
- Tuberculosis
- Venezuelan, Eastern, and Western equine encephalitis viruses
- Zika
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Center for HIV/AIDS Vaccine Immunology (CHAVI)

- Consortium supported 2005-2012
- Multidisciplinary teams
- Multi-pronged approaches addressing key scientific challenges
- Frequent meetings
- Information sharing
- Collaborative projects
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Duke Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery

Scripps Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery
An NIH-led, bold initiative towards the development of a universal influenza vaccine