Influenza Vaccines: Challenges and Data-Driven Solutions

Outline

- How are influenza vaccines produced?
- Overview of the 2017-2018 flu season
- Challenges to influenza virus vaccine production
  - egg-adaptations
- What can you do?

Anatomy of an influenza virus

H3N2 circulates in humans (since 1968)
H1N1 (<1957; >1977)
Neuraminidase (NA)

Hemagglutinin (HA)

Influenza A virus
- 18 HA
- 11 NA

Influenza B virus
- Two HA lineages
  - "Victoria"
  - "Yamagata"

How are influenza vaccines produced?

- WHO/FDA strain selection
- Manufacturers produce seed viruses in cells or eggs
- FDA tests vaccine candidates for safety, potency
- FDA licensing, vials filled & distributed
  ~ 6 months

How are vaccine strains selected?

- Which viruses are making people sick? (Clinical)
- How rapidly is a strain spreading? (Surveillance)
- How well does the previous vaccine protect against circulating strains? (Lab)

2017-2018 influenza vaccine strain recommendations

- A/Michigan/45/2015 (H1N1)pdm09-like virus
- A/Hong Kong/4801/2014 (H3N2)-like virus
- B/Brisbane/60/2008-like virus
Why is H3N2 such a problem child?

- Increased antigenic drift
- Red blood cells

H1N1  +  H3N2  →  H7N9
Vaccine efficacy

Vaccine efficacy for the H3N2 virus

2014-2015

2016-2017

Good match?

Vaccine efficacy ~18% ~43%

Circulating and vaccine strains of IAV H3N2 differ with respect to a glycosylation site in HA

Vaccine H3N2 viruses

Circulating H3N2 viruses

H3N2 HA (T160) is antigenically distinct from HA (K160)

Antibodies raised against H3N2 HA K160 do not neutralize H3N2 containing HA T160

Seth J. Zost et al., Proceedings of the National Academy of Sciences Nov 2017, 114 (37) 12578-12583; DOI:10.1073/pnas.1723773114
Influenza H3N2 vaccine antigens elicit different responses in humans

Other challenges

- **CHALLENGE:** lengthy timeline for vaccine production
  - vaccine not prepared in time for 2nd wave of 2009 H1N1 pandemic
- **SOLUTION:** stockpile vaccine stocks of viruses w/ pandemic potential
- **CHALLENGE:** requirement for annual vaccination
- **SOLUTION:** universal vaccine; increase response to conserved HA stalk?
- **CHALLENGE:** emerging, novel influenza viruses
- **SOLUTION:** universal vaccine, enhanced surveillance

What can YOU do?

- **Get your flu shot!**
- **Encourage other people to get their flu shot!**
  - 25% protection is better than 0%
  - Still 67% effective against H1N1
- **Prevent severe disease; risk of medically-attended illness reduced 60% in vaccinated individuals**
- **Know the science. Don’t shy away from talking about the challenges but communicate how science is winning the battle by working these things out**

Acknowledgements

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  - Armando Soto

Highly pathogenic H5N1 viruses replicate in macrophages
**H5 HA promotes virus replication in macs**

![Image of bar graph showing viral replication](image)

Cline et al. J. Virol. 87(3) 2013

**Replication in macrophages correlates with enhanced disease severity**

![Image of graph showing disease severity](image)

Cline et al. J. Virol. 87(3) 2013

**Phagocytosis is a pro-host macrophage response**

Phagocytosis
- Engulf dead/dying infected cells; increased in IAV-infected mice (Hashimoto et al. 2007)
- Reduces viral load
- Inhibitors of phagocytosis → increased mortality (Watanabe et al. 2005)

**Macrophage phagocytosis is impaired by H5 IAV infection in a replication-dependent manner**

![Image of graph showing phagocytosis impairment](image)

**Responsiveness to IFN-γ is impaired by H5 IAV in a replication-dependent manner**

![Image of graph showing IFN-γ responsiveness](image)

**H5 IAV infection inhibits IFN-γ-dependent gene expression**

![Image of gel showing gene expression](image)
Hemagglutination inhibition assay (HAI)

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<th>Components</th>
<th>Interaction</th>
<th>Inhibitory Result</th>
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<tr>
<td>A</td>
<td>RBCs</td>
<td>No Reaction</td>
</tr>
<tr>
<td>B</td>
<td>Virus + RBCs</td>
<td>Hemagglutination</td>
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<tr>
<td>C</td>
<td>Virus + Antbody</td>
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