“State-of-the-Art Clinical Lecture”

Advances in the Development of Universal Influenza Virus Vaccines

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AAMI Canada-CACMID Annual Conference
Ottawa, ON
April 5, 2019
Disclosure/Conflict-of-interest

Research Contract: Medicago (Influenza virus vaccine responses)

Speaking Honorariums: All from universities (Under $500)
Objectives

- List various strategies being used to develop universal influenza virus vaccines
- Describe the ways in which various vaccine platforms achieve protective immunity
- Identify current gaps in knowledge related to the successful development of a universal influenza virus vaccine
IAV pandemics

- 1918: H1N1 (Spanish flu)
- 1957: H2N2 (Asian flu)
- 1968: H3N2 (Hong Kong flu)
- 1977: H1N1 (Russian flu)
- 2009: H1N1

20XX?

Direct adaptation: mutation (bird)
Reassortment (bird–human)
Reassortment (bird–human)
Re-emergence of H1N1 strain
Reassortment (bird–pig–human)
Direct adaptation or reassortment?

TRENDS in Microbiology

Wantanabe et al., 2012
Widely considered to be the greatest “natural disaster” in human history

3-5% of the global population died during the pandemic (this would now amount to the population of North America)

4 pandemics since 1918 – none as severe

**VERY LIMITED improvements in pandemic preparedness over past 100 years!**
Seasonal influenza

Canada: 12,200 hospitalizations; 3,500 deaths

International: 3-5 million severe cases; 290,000 – 650,000 deaths

Influenza A virus (IAV)

- Negative-sense ssRNA genome
- 8 segments
- Enveloped
- Hemagglutinin (HA) and neuraminidase (NA) are the major antigenic determinants
- Nomenclature H\textsubscript{x}N\textsubscript{x}
IAV host range

Influenza A Virus
H1-H16
H17-H18

Modified from: Manz et al., 2013
IAV diversity

Different subtypes of Influenza A

Antigenic shift (Genetic shuffling)

New Influenza A subtype

Antigenic drift (Random mutation)

Different Influenza A strains

~1 nucleotide/genome
HA phylogeny

Yang and Seong, Viruses, 2014
Mallajosyula, Front. Immunol., 2015
HA phylogeny

Influenza A Group 1
- H1
- H2
- H5
- H3
- H7
- H10

Influenza A Group 2
- H1
- H2
- H5
- H3
- H7
- H10

Influenza B
- B/Tamagawa
- B/Victoria

Group 1

Group 2

Yang and Seong, Viruses, 2014
## Seasonal influenza vaccines: Canada

### Table 2: Choice of influenza vaccine for selected age and risk groups (for persons without a contraindication to the vaccine)

<table>
<thead>
<tr>
<th>Recipient group</th>
<th>Vaccine types available for use</th>
<th>Comments</th>
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</table>
| Children 6–23 months of age | TIV  
QIV  
Adjuvanted TIV | As TIV, QIV and adjuvanted TIV are authorized for this age group, NACI recommends that, given the burden of influenza B disease, QIV should be used. If QIV is not available, either unadjuvanted or adjuvanted TIV should be used. |
| Children 2–17 years of age | TIV  
QIV  
Quadrivalent LAV | In children without contraindications to the vaccine, any of the following vaccines can be used: LAV, QIV, or TIV. The current evidence does not support a recommendation for the preferential use of LAV in children and adolescents 2–17 years of age. Given the burden of influenza B disease in children and the potential for lineage mismatch between the predominant circulating strain of influenza B and the strain in a trivalent vaccine, NACI continues to recommend that a quadrivalent formulation of influenza vaccine be used in children and adolescents 2–17 years of age. If a quadrivalent vaccine is not available, TIV should be used. LAV is contraindicated for children with immune compromising conditions. LAV, TIV or QIV can be used in children with chronic health conditions and without contraindications (see the Contraindications and Precautions (Section IV) and Choice of vaccine product for children 2 to 17 years of age (Section V) sections below for more details). |
| Adults 18–55 years of age | TIV  
QIV  
Quadrivalent LAV | TIV and QIV are the recommended products for adults with chronic health conditions. TIV and QIV, instead of LAV, are recommended for health-care workers. LAV is contraindicated for adults with immune compromising conditions. |
| Adults 65–64 years of age | TIV  
QIV | TIV and QIV are authorized for use in this age group. |
| Adults 65 years of age and older | TIV  
QIV  
Adjuvanted TIV  
High-dose TIV | At the programmatic level, NACI recommends that any of the four influenza vaccines available for use in adults 65 years of age and older should be used: standard-dose TIV, high-dose TIV, MF59-adjuvanted TIV and QIV. High-dose TIV is expected to provide superior protection compared to standard-dose TIV; however, with cost-effectiveness assessments having been outside the scope of the evidence review and without data on the relative efficacy of these vaccines in low-risk and high-risk populations, NACI does not support the use of high-dose TIV for individuals with moderate or high risk. At the individual level, NACI concludes that high-dose TIV should be offered over standard-dose TIV to persons 65 years of age or older. NACI accepts that, given the burden of disease associated with influenza A(H1N1)2009, and the very low efficacy of standard-dose TIV in this age group, high-dose TIV should be offered over standard-dose TIV to persons 65 years of age and older. NACI also recognizes that high-dose TIV is not recommended for use in individuals with moderate or high risk. |
| Pregnant women | TIV  
QIV | LAV is not recommended because of the theoretical risk to the fetus from administering a live-virus vaccine. |

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National Influenza Immunization Coverage Suvery, Canada, 2016-2017

Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2017–2018
Limitations of current seasonal influenza vaccines

Limited breadth of protection
- strain-specific responses
- require annual reformulation (prediction-based)
- low vaccine uptake
- no protection against novel, pandemic strains

Suboptimal efficacy
- especially in high-risk groups (e.g. very young, very old)

Production timeline
- 6+ months between seed strain recommendations and vaccine administration
- worst for egg-based platforms

Egg-based adaptations
- Can have a profound and unexpected effect on efficacy
Why not just make pandemic vaccines when the need arises?

Source: CIDRAP
Limitations of current seasonal influenza vaccines

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Qualities of a “universal” influenza virus vaccine

There is no universally accepted definition – means different things to different people/groups

<table>
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<tr>
<th>NIH</th>
<th>Bill and Melinda Gates Foundation</th>
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<tr>
<td>At least 75% effective</td>
<td>At least 70% protection against moderate/severe disease in all age groups</td>
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<tr>
<td>Protect against group 1 and group 2 influenza A viruses</td>
<td>All strains of influenza A and B viruses</td>
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<tr>
<td>At least 1 year of protection</td>
<td>3-5 years of protection</td>
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<td>Suitable for all age groups</td>
<td>6 weeks and older</td>
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Universal influenza virus vaccine strategies

All “universal” influenza virus vaccine strategies seek to generate immune responses against conserved viral epitopes

**T cell vaccines**

- Usually peptides, DNA, or viral-vectored
- Often target conserved, *internal* viral proteins
- Designed to generate high numbers of cytotoxic T lymphocytes to eliminate infected cells

**B cell/antibody vaccines**

- Usually inactivated virus, live-attenuated virus, recombinant protein, DNA, mRNA, VLPs
- Target viral surface proteins
- Designed to elicit high titers of broadly-neutralizing antibodies
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**BiondVax: M-001 ("Multimeric-001")**

- Peptide composed of 9 epitopes derived from HA, NP and M1 (produced in *E. coli*)
- Designed to elicit cell-mediated immunity (T cells)
- Potential to be used as a "primer" prior to seasonal influenza vaccination
- Currently in Phase III clinical trials (Europe)
  - Standalone
  - Adults aged 50+

Gottlieb and Ben-Yedidia. *J Autoimmun.*, 2014
Adar *et al.* Vaccine, 2009
• “MVA” = modified vaccinia Ankara

• Viral vector for expression of NP and M1

• Designed to elicit cell-mediated immunity (T cells)

• Currently in Phase IIb clinical trials
  - Administered in conjunction with seasonal IIV

Lillie et al., Clin Infect Dis, 2012
Universal influenza virus vaccine strategies

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Ted Ross/Sanofi Pasteur: Computationally optimized broadly-reactive antigen “COBRA”

- Similar to a recombinant “consensus HA”
- Designed to elicit broadly-reactive antibodies that bind to the HA head domain
- Effect at eliciting broad heterologous protection (i.e. pan-H1, pan-H3)
- Could be particularly useful as a “supra-seasonal” vaccine
Humoral immunity against IAV

A/New Caledonia/20/1999
SEASONAL

A/Brisbane/59/2007
DRIFTED SEASONAL
“Headless”/Mini-HA

Palese Laboratory (Icahn School of Medicine at Mount Sinai, New York, NY)

Steel et al., mBio, 2010


NIH

Entering Phase I Clinical Trials

1x 20 mcg

OR

2x 40 mcg

Crucell (Janssen)
• Can be produced as recombinant proteins, or incorporated into current inactivated and live-attenuated vaccine platforms

• Designed to elicit bnAbs that target the HA stalk

• Flexibility to strategically incorporate relevant head domains (e.g. H5, H7)

• Currently in Phase I clinical trials
  - I.M. prime-boost of IIV (GSK)
  - LAIV + IIV prime-boost (PATH)
HA stalk-binding bnAb-mediated protection: Defying convention
Mechanisms of stalk-binding bnAb-mediated neutralization

HA stalk-binding bnAbs are relatively weak neutralizers

KB2 & 6F12 = H1 stalk
29E3 & 7B2 = Cal/09 head
The immune response to IAV is POLYCLONAL

1. Specificity
2. Isotype

Adapted from Mouquet, 2015
Isotype matters...a LOT!

Isotype + specificity regulate Fc-FcR interactions

He et al., Proc Natl Acad Sci USA, 2016
Isotype + specificity regulate Fc-FcR interactions

He et al., Proc Natl Acad Sci USA, 2016
Isotype + specificity regulate Fc-FcR interactions

He et al., Proc Natl Acad Sci USA, 2016
Efficient FcR signaling by HA stalk-binding bnAbs requires two points of contact

Leon et al., Proc Natl Acad Sci USA, 2016
Alveolar macrophages are critical for protection mediated by IgG bnAb

He et al., Nat Communications, 2017
Remaining questions/barriers

• New “correlates of protection” need to be established
  - Interpretation of Phase I/II clinical trials will be difficult since it is unclear what levels of bnAbs/T cells are needed to confer protection

• How do we measure vaccine efficacy?
  - Prevention of PCR-confirmed infection?
  - Prevention of “moderate/severe disease?”

• Novel platforms/strategies needed for vaccinating children (and the elderly)?
  - bnAbs only need boosting in adults – but need to be established in children (ditto for T cells)

• Most efficient/effective strategy for performing Phase III (efficacy) trials?
  - Universal vaccine vs. placebo not possible in all jurisdictions
  - Universal vaccine + seasonal vaccine?
  - Human challenge model?
Acknowledgements

The Boris Family Fund for Excellence in Health Research