Novel Approaches to Seasonal Influenza Vaccines

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The conclusions, findings, and opinions expressed in this presentation do not necessarily reflect the official position of the U.S. Centers for Disease Control and Prevention
Outline

- Global influenza epidemiology and the need for a better vaccine
- Novel approaches to seasonal influenza vaccines
  - Improved production platforms
    - Cell culture production
    - Recombinant vaccines
    - Virus-like particles
  - Improved immunogenicity and/or dose sparing strategies
    - Adjuvanted vaccines
    - Intradermal vaccines
    - High-dose vaccines
- Considerations for evaluation of novel seasonal influenza vaccines for use in LMICs
Global Influenza Epidemiology

- 1 billion episodes and 3-5 million severe episodes annually
- 300,000-500,000 deaths\(^1\)

- 870,000 (95% CI 610,000 to 1,237,000) hospitalizations in children <5 years; hospitalization rates >3 times higher in developing countries\(^2\)

- High risk groups targeted for vaccination:
  - Pregnant women (highest priority)
  - Healthcare workers
  - Children aged <5 years
  - Elderly
  - Persons with underlying conditions (cardiopulmonary, immunocompromising conditions)

\(^1\) [http://www.who.int/immunization/topics/influenza/en](http://www.who.int/immunization/topics/influenza/en)

Revised Estimates of Global Influenza Mortality

- Updated estimates using mortality data from 46 countries expected this year.
- 85% of deaths estimated to occur in LMICs.

Conventional Seasonal Inactivated Influenza Vaccines (IIV)

- Provide immunity primarily by inducing antibodies to HA protein
  - HAI titer $\geq 1:40$ correlates with 50% protection in younger, healthy adults
- Due to antigenic drift of viruses, vaccine strains are updated annually
  - Strains selected in February (Northern Hemisphere) and September (Southern Hemisphere)
  - 6-8 month production timeline
- Trivalent preparation includes an A/H1N1, A/H3N2, and B/Yamagata or B/Victoria strain
  - 15µg of HA per strain
  - given intramuscularly
- Shift to quadrivalent vaccine with additional B lineage strain
- Vaccine viruses grown in embryonated chicken eggs
- Three formulations: whole virus, split-virus, and subunit
## Variable Influenza Vaccine Effectiveness by Subtype

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Pooled VE (%)</th>
<th>Pooled Standard Error</th>
<th>VE Estimates (n)</th>
<th>p Value for Heterogeneity</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type B, Seasonal</td>
<td>54% (46–61)</td>
<td>0.083</td>
<td>36</td>
<td>&lt;0.0001</td>
<td>61.3</td>
</tr>
<tr>
<td>H3N2, Seasonal</td>
<td>33% (26–39)</td>
<td>0.050</td>
<td>34</td>
<td>&lt;0.0001</td>
<td>44.4</td>
</tr>
<tr>
<td>H1N1pdm09, Seasonal</td>
<td>61% (57–65)</td>
<td>0.048</td>
<td>29</td>
<td>0.005</td>
<td>44.4</td>
</tr>
<tr>
<td>H1N1pdm09, Monovalent</td>
<td>73% (61–81)</td>
<td>0.188</td>
<td>10</td>
<td>0.005</td>
<td>44.4</td>
</tr>
<tr>
<td>H1N1 (pre-2009), Seasonal</td>
<td>67% (29–85)</td>
<td>0.397</td>
<td>5</td>
<td>0.093</td>
<td>57.6</td>
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Data in parentheses are 95% CIs. VE = vaccine effectiveness.

**Table 2: Pooled VE by type and subtype in studies without age restriction**

Limitations of Conventional Seasonal IIVs

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<td>Recombinant antigens</td>
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- Limited global vaccine availability

- Limited efficacy in selected populations

- Lack of cross-protection against drifted strains and limited duration of protection

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Limited efficacy in selected populations

Lack of cross-protection against drifted strains and limited duration of protection

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<td>Increase vaccine immunogenicity and/or breadth of immune response with higher dose, adjuvants, or alternative routes of administration</td>
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<td>Lack of cross-protection against drifted strains and limited duration of protection</td>
<td>Increase breadth of immune response through novel antigenic targets</td>
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“There is a public health need to develop improved performance of currently available seasonal vaccines to offer protection over multiple seasons, and against drifted strains...Efforts to develop ‘universal’ vaccines that target conserved antigens, or conserved components of antigens, should continue in parallel.”

WHO PPC for Improved Influenza Vaccines

- “By 2022, influenza vaccines in advanced clinical development that can feasibly provide greater protection against drifted influenza A strains than currently available unadjuvanted, inactivated influenza vaccines, that protect against severe influenza A virus illness through at least one year after a primary series, and that are suitable for high-risk groups in low- and middle-income countries.”

Outline

- Global influenza epidemiology and the need for a better vaccine
- **Novel approaches to seasonal influenza vaccines**
  - Improved production platforms
    - Cell culture production
    - Recombinant vaccines
    - Virus-like particles
  - Improved immunogenicity and/or dose sparing strategies
    - Adjuvanted vaccines
    - Intradermal vaccines
    - High-dose vaccines
- Product development and regulatory challenges
Cell Culture-Based Vaccines

- **Characteristics**
  - Mammalian-derived cell lines infected with influenza virus to produce vaccine antigen (Vero and MDCK cells)
  - *Potential* advantages: higher virus yield, ability to bank cells, avoids egg-induced mutations\(^1\)
  - Disadvantage: some virus strains may not grow well in cell culture\(^1\)

- **Licensure\(^2,3\)**
  - Optaflu™ (Novartis) in Europe for persons >18 years
  - Fluval AB™ (Omninvest) in Europe for persons >4 years; aluminium phosphate gel adjuvant
  - Flucelvax™ (Seqirus, Inc.) quadrivalent in US for persons >4 years

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\(^1\) [FDA’s Contributions to Advancing New Technologies for Developing Safe and Effective Influenza Vaccines](https://www.fda.gov)


\(^3\) [https://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm328629.htm](https://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm328629.htm)
Recombinant Vaccines

- Baculovirus expression systems
  - Recombinant baculovirus in which non-essential gene (polyhedron) is replaced with influenza HA and is used to infect cultured insect cells
  - *Potential* advantage: rapid production timeline, avoids egg-induced mutations

Flublok® (Protein Sciences Corporation)

- **Product characteristics and licensure**
  - contains 45µg of rHA per strain
  - trivalent licensed in US (2013) and Mexico (2016)\(^1\); quadrivalent licensed in US in 2016\(^2\)
  - currently indicated for persons \(\geq 18\) years; use in pregnant women under consideration (June meeting of US ACIP)

- **Phase III placebo-controlled trial in healthy adults 18-49 years\(^3\)**
  - 2007-2008 season with mismatch between vaccine and circulating strains
  - 45% (95% CI 19, 63%) efficacy against culture-confirmed ILI
  - suggests potential for better cross-protection than conventional IIV

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\(^2\) [https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM524732.pdf](https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM524732.pdf)
\(^3\) Treanor et al. Vaccine. 2011; 29: 7733-7739.
Flublok® (Protein Sciences Corporation)

Randomized trial in healthy children 6-59 months

- Children 6-35 months randomized to FluBlok 45µg vs. FluBlok 22.5µg vs. IIV 7.5µg
  - More local reactions with FluBlok 45µg but similar profiles for FluBlok 22.5µg vs. IIV
  - FluBlok immunogenicity generally lower than IIV
- Children 36-59 months randomized to FluBlok 45µg vs. IIV 15µg
  - Reactogenicity profile similar in both groups
  - FluBlok immunogenicity generally lower or similar to IIV

Phase III trial in healthy children 6-17 years (NCT01959945)

- FluBlok QIV 45µg per strain vs. IIV 15µg strain
- Results not published

Virus-Like Particle (VLP) Vaccines

- “Hollow-core” virus particles from expressed viral structural proteins without viral genome; “replication incompetent”¹
  - HA, NA, M1 (and sometimes M2)
  - Advantages: Rapid scale-up/production, dose-sparing and broader immune response
  - No licensed seasonal VLP influenza vaccines

- Phase I-II dose-ranging RCT in healthy adults aged 18-49 years²
  - Plant-based quad VLP vaccine (Medicago) 3µg vs. 9µg vs. 15µg vs. placebo, N=120
  - VLP vaccine 9µg and 15µg met CHMP* criteria for all strains, elicited HAI titers against drifted H3N2 and B strains
  - suggests potential for dose-sparing and better cross-protection than conventional IIV

* European Committee for Medicinal Products for Human Use
Adjuvanted Vaccines

- May improve antigen delivery, vaccine immunogenicity, and breadth of immune response\(^1\)
  - MF59 (squalene oil-in-water emulsion): induced higher ab titers in selected populations
  - Alum: no or limited improvement compared to non-adjuvanted influenza vaccines
  - Others (AS03, DNA sequences, bacterium-derived components)

- Potential disadvantage: may induce unwanted immune responses

- Licensed MF59 adjuvanted seasonal influenza vaccines\(^2,3\)
  - FluAd\(^\text{TM}\) (Seqirus, Inc.) standard dose licensed in >38 countries for elderly
  - FluAD Pediatric\(^\text{TM}\) (Seqirus, Inc.) (7.5µg per strain) licensed for children 6-23 months

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\(^2\) [Link to FDA approved products](https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM478669.pdf)
\(^3\) [Link to Novartis product information](https://www.novartis.ca/sites/www.novartis.ca/files/fluad_scrip_e%202016.pdf)
MF59 Adjuvanted IIV Safety and Performance in Selected Target Groups

- **Elderly**
  - Induced stronger immune response compared to IIV in phase III trial\(^1\)
  - Induced broader immune response against drifted strains compared to IIV\(^1,2\)

- **Children**
  - phase III trial in children 6-71 months; 2 doses aIIV vs. IIV plus booster given 1 year later\(^3\)
    - aIIV elicited stronger immune response against matched and drifted strains
    - aIIV recipients had higher HAI titers after 1 year suggesting more durable response
  - phase III trial in children 6-71 months; randomized to aIIV vs. IIV vs. non-influenza control\(^4\)
    - 75% (95% CI 55, 87) relative efficacy of aIIV vs. IIV

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\(^3\) Vesikari, T. et al. PIDJ. 2009; 28: 563-571.
MF59 Adjuvanted IIV Safety and Performance in Selected Target Groups

- Persons with HIV infection
  - Phase IV randomized trial in adults with HIV on HAART
  - aIIV vs. IIV
  - aIIV induced higher GMT for all 3 vaccine strains

Intradermal (ID) Vaccines

- Stimulates antigen presenting cells in dermis
- Advantages: dose-sparing (40% less antigen); improved immunogenicity; potential for broader protection
- Disadvantage: administration by Mantoux method prone to imprecision; improved microinjection system now available
- Licensed ID seasonal influenza vaccines
  - Intanza™ or Fluzone™ ID (Sanofi Pasteur) approved in >40 countries
    - 9µg per strain for persons 18-64 years
    - 15µg per strain for persons ≥60 years
  - Fluzone™ ID available as quadrivalent
  - BD Soluvia™ microinjection system single use syringe

Intradermal Vaccine Safety and Performance in Selected Target Groups

- Healthy younger adults:
  - ID 9µg as immunogenic as intramuscular (IM) IIV 15µg per strain\(^1\)
  - Demonstrated dose sparing
  - Higher rates of local reactions with ID (mild and transient)

- Elderly
  - ID 15µg as immunogenic as IM IIV 15µg per strain\(^1\)
  - Evidence for increased immunogenicity and cross-protection against drifted strains\(^1-3\)

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Intradermal Vaccine Safety and Performance in Selected Target Groups

- Persons with HIV
  - No difference in immunogenicity between ID 9µg vs. IM IIV 15µg per strain\(^1\)
  - No difference in immunogenicity between ID 15µg vs. IM IIV 15µg per strain\(^2\)

- Pregnant women
  - Prospective pregnancy registry on pregnancy and fetal outcomes among women exposed to Fluzone ID vaccine [NCT02554409]

\(^1\) Ansaldi, F. et al. Human Vaccines & Immunotherapeutics. 2012; 8: 1048-1052.
High-Dose Vaccines

- Potential advantages: improved immune response, more durable immune response
- Disadvantages: manufacturing burden
- Fluzone High-Dose™ (Sanofi Pasteur) trivalent licensed in the US and Canada for persons aged ≥65 years
  - 60µg per strain
High-Dose Vaccines

- Systematic review and meta-analysis of RCTs in elderly\(^1\)
  - 7 trials of FluZone™ High-Dose vs. standard dose IIV
  - 24% (95% CI 10, 35) relative efficacy based on 2 trials with lab-confirmed illness outcomes
  - FluZone™ High-dose elicited higher rates of seroprotection and GMTs
  - Severe outcomes (hospitalization and death) not assessed

- Observational cohort study in elderly\(^2\)
  - FluZone™ High-Dose vs. standard dose IIV
  - Primary outcome was death within 30 days of emergency visit/hospitalization for influenza
  - 24% (95% CI 0.6, 42) relative effectiveness

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2 Shay, DK et al. JID. 2017; 215.
High-Dose Vaccines

- Phase IV trial in adults with HIV infection\(^1\)
  - FluZone™ High-Dose 60µg per strain vs. IIV 15µg strain, N=195
  - Primary end-point: rate of seroprotection (HAI titer \(>1:40\))
  - 11% of participants had CD4 count <200
  - FluZone High-Dose™ induced higher rates of seroprotection and seroconversion and higher post-vaccination GMTs

Summary

- Multiple vaccines that are currently licensed in limited groups offer opportunities for dose-sparing and potential for improved production.

- Limited data suggest:
  - Multiple novel influenza vaccine approaches (e.g. recombinant, MF59 adjuvanted, ID, VLP) may induce improved cross-protection against drifted strains.
  - MF59 adjuvanted vaccines may induce more durable protection.
  - Multiple novel influenza vaccine approaches (e.g. MF59 adjuvanted, ID, and high-dose) may offer improved immunogenicity in certain populations with lower immune response to conventional unadjuvanted IIV.
Outline

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- Product development and regulatory challenges
Considerations for Evaluation of Second Generation Influenza Vaccines for Use in LMICs

- Defining correlates of protection for
  - different populations
  - vaccines that act via multiple immune protective mechanisms

- Defining clinically meaningful endpoints for efficacy against severe disease

- Need for multi-year trials to show durable and cross-protective efficacy

- Evaluating safety and benefit in target groups (e.g. pregnant women, elderly, children, persons with HIV)
Acknowledgements

- CDC Influenza Division
  - Lisa Grohskopf
  - Danielle Iuliano
  - Katherine Roguski
Questions?