Influenza vaccines that induce broadly protective and long-lasting immune responses

Barriers to the development of next generation vaccines

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WHO's recent reviews

- Second WHO integrated meeting on development and clinical trials of influenza vaccines that induce broadly protective and long-lasting immune responses; Geneva, Switzerland, 5–7 May 2014 (http://www.who.int/immunization/research/meetings_workshops/2nd_influenzamtg_geneva_may14/en/)

- WHO Product development for vaccines advisory committee (PDVAC); meeting 8-10 September 2014 (http://www.who.int/immunization/research/meetings_workshops/pdvac/en/)

- 1st Global Vaccine & Immunization Research Forum (GVIRF); 4-6 March 2014, Bethesda MD (http://www.who.int/immunization/research/forums_and_initiatives/gvirf/en/)
GVAP R&D indicator

- Monitor progress towards a universal influenza vaccine (protecting against drift and shift variants)
- Target: at least one vaccine providing broad spectrum protection against influenza A virus licensed by 2020
WHO meeting on influenza vaccines that induce broadly protective and long-lasting immune responses
Geneva, 6-7 May 2014

Scope of consultation

- General considerations
- Mechanisms of protection in natural influenza-virus infection and vaccine-induced immunity
- Antigens for humoral and cellular responses
- New approaches to influenza - vaccine design
- Vaccine production aspects
- Novel routes of vaccine administration

Publication in preparation
What do we mean by "Universal influenza vaccine"?

- No single definition, most commonly quoted features are:
  - Induction of heterosubtypic immunity between influenza A types (protect against shift)
  - Possibly more limited to the two or more subtypes most commonly found in humans
  - Possibly protection against influenza B type through separate antigen component
  - Multi-year immunity

- Reasonable to assume incremental development of more broadly protective vaccines that protect over several years against subtype variants (protects against drift)
### Viral targets for broadly reactive influenza vaccines*

<table>
<thead>
<tr>
<th>Protein antigen</th>
<th>Targeted function</th>
<th>Proposed mechanism of protection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemagglutinin (HA), including stalk region</td>
<td>Receptor binding and membrane fusion</td>
<td>Inhibition of fusion, maturation of HA, ADCC</td>
</tr>
<tr>
<td>Ectodomain of M2 (M2e)</td>
<td>Ion channel</td>
<td>Complement-mediated lysis, ADCC, antibody-dependent NK cell activity</td>
</tr>
<tr>
<td>Neuraminidase (NA)</td>
<td>Cleaves sialic acid releasing virus from the surface of infected cells</td>
<td>Inhibition of viral spread</td>
</tr>
<tr>
<td>Matrix 1 (M1); Nucleoprotein (NP) and other NS antigens (PB1)</td>
<td>T cell stimulation</td>
<td>Cell lysis by CD8+ CTLs, CD4+ T cell mediated cytolysis and B cell stimulation</td>
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</tbody>
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(*adapted from status report prepared for PDVAC September 2014)
## New antigens, effector mechanisms and assays*

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<th>Protein antigen</th>
<th>Proposed mechanism of protection</th>
<th>Assays developed</th>
</tr>
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<tr>
<td>Hemagglutinin (HA), including stalk region</td>
<td>Inhibition of fusion, maturation of HA, ADCC</td>
<td>Improve HAI in relation to quality, affinity, mucosa; assess ADCC</td>
</tr>
<tr>
<td>Ectodomain of M2 (M2e)</td>
<td>Complement-mediated lysis, ADCC, antibody-dependent NK cell activity</td>
<td>Conformation-dependent anti-M2 antibodies – validation needed</td>
</tr>
<tr>
<td>Neuraminidase (NA)</td>
<td>Inhibition of viral spread</td>
<td>Assay for NA inhibition established – validation needed</td>
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<tr>
<td>Matrix 1 (M1); Nucleoprotein (NP) and other NS antigens (PB1)</td>
<td>Cell lysis by CD8+ CTLs, CD4+ T cell mediated cytolysis and B cell stimulation</td>
<td>Harmonization of various CMI assays needed</td>
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</table>
Vaccine platforms and delivery technologies

- Enhancement of humoral immune responses: HA, stalk, NA, M2e
  - Adjuvant (TLR5 ligand; alum; oil-in-water)
  - Particle (various VLP's, nanoparticle)
  - Peptide fusion to carrier
  - DNA, synthetic mRNA

- Induction of cellular immunity: M1, NP, PB1
  - Viral vectors (Ad4; AdHu5; ChAdOx1, MVA)
  - Live, replication-incompetent influenza vaccines (M2, PB2 knockout viruses)
  - Coupled peptides
  - DNA/electroporation; synthetic mRNA
General considerations on assessment of heterosubtypic immunity (1)

- No consensus on *primary clinical benefit* of a universal flu vaccine.
- Prevention of lab confirmed illness or prevention of severe disease? (no current influenza vaccine licensed on basis of severe disease).
- Possible disadvantage: residual infection and transmission
- Developing the ability to compare efficacy of one vaccine to another, avoiding the need in each case of large efficacy studies (as for LAIV)
  - Correlates of protection – how acceptable are they and can new ones be standardized for novel vaccines? Different for every type?
- Demonstration of cross-strain protection – need for large and multi-year studies?
- How to assess prior history of influenza infection?
General considerations on assessment of heterosubtypic immunity (2)

- Assessing applicability of animal study results to humans:
  - Can animal models of influenza prevention or treatment be improved?

- Determining the effect on efficacy of different virus specific components
  - Efficacy trials will have to be carried out for any novel vaccine
  - Will traditional outcomes be sufficient?

- Examining regulatory pathways to facilitate licensure of successful candidate vaccines
  - Traditional vaccines as comparator? – Which endpoint? – Safety?
  - New standards will have to be developed

- Will different vaccines be used for different population groups?
Vaccine development & evaluation: some conclusions (1)

- Need for assays beyond HAI: quality, affinity, mucosal titres...
- Validation of NA inhibition and M2e conformational antibodies needed, assessment of ADCC
- Concerted effort to develop CMI markers (build on CONSISE effort),
- Further develop animal models, also for pre-existing immunity
- Consider human challenge model for candidate down-selection
- Assess prime-boost strategies
- Need for a "roadmap" for new flu vaccines, with better definition of study endpoints and terminology
Vaccine development & evaluation: some conclusions (2)

- Costs for full development of universal flu vaccine estimated to be very high

- Uncertainties in terms of acceptable performance in relation to existing flu vaccines, which have moderate efficacy against matched strains and excellent safety profile

- Clinical development pathways/comparator vaccines not clear

- Both incremental changes and “game-changer” strategies approaches to developing universal or universal-type influenza vaccines should be pursued

- Call for increased collaboration
What could WHO do?

Working through the Product Development Vaccine Advisory Committee and other groups*:

- Initiating consensus building of roadmap development;
- Improving comparability of vaccine trials endpoints;
- Considering development of WHO preferred product characteristics to guide target product profiles for use by vaccine developers and funding bodies;
- Standardizing endpoints of public health value, including severity indices;
- Initiating regulatory discussions and consensus-building.

*At the 2014 PDVAC committee meeting the role of WHO in this process was acknowledged and given high priority.
Tables on clinical evaluation of influenza vaccines:
http://www.who.int/immunization/diseases/influenza/clinical_evaluation_tables/en/

Other resources:
http://www.who.int/immunization/research/development/influenza/en/