Update on H5N1 Vaccines

Kanta Subbarao, MBBS, MPH
Laboratory of Infectious Diseases
NIAID, NIH

Evolution of H5N1 Viruses

- In 2011: 12 clades were identified.
- In the last 3 years, 8 new clades including 5th order subclades have emerged.
- Some clades e.g., 0, 1, 3, 4, 5, 6 and 9 have not been detected since 2010 or earlier.

WHO: H5N1 Candidate Vaccine Viruses

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<th>Clade</th>
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In preparation:

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Types of H5N1 Vaccines

- Inactivated
  - Whole virus ± alum
  - Split or subvirion ± adjuvant: alum or oil-in-water
- Live attenuated
- Recombinant
- Expressed HA (DNA or Vectored)
- VLPs

Outcomes of H5N1 Vaccine Studies

- Safety
- Immunogenicity HAI or Neutralizing Ab
  - Magnitude
  - Frequency
  - Quality: cross reactivity, affinity
  - Longevity
- Response to booster immunization

Clade 1 H5N1 Subunit Vaccines

- Unadjuvanted: 2 doses of 90 μg resulted in ‘protective titers’ in 58%; titers decreased by 6 mo but boosted and were more sustained with a 3rd dose.
- Alum adjuvant: A robust and consistent benefit of alum was not seen in adults; appeared beneficial in children; Ab titers may be sustained for longer.
- Oil-in-water adjuvants: Doses as low as 3.8 μg in adults and 1.9 μg in children induced neutralizing Ab against homologous virus and viruses from Clade 2.

Clade 1 H5N1 Whole Virion Vaccines

- Egg derived: 6 μg with Al phosphate or 10 μg X2 with alum induced antibodies in 90 and 78% respectively.
- Vero cell derived: 7.5 μg without alum was optimal.
- Safe and immunogenic in children, adults and the elderly; higher doses were reactogenic in young children.
- Cross clade antibodies against clade 2 viruses.
- Titers decreased by 12-17 months but were boosted with additional doses of WV or Split virion vaccine.
Clade 1 H5 Live Attenuated Vaccines

- Vaccine backbones are temperature sensitive, attenuated and cold adapted (ca) viruses.
- US (NIH/MedImmune): A/Ann Arbor/6/60 ca 6:2
- Russia (Microgen): A/Leningrad/134/17/57 ca 7:1
- With primary immunization (2 doses), Leningrad ca based H5N2 vaccine induced Ab in 47-55% of vaccinees
- AA ca based H5N1 vaccines were highly restricted in replication and were poorly immunogenic but subsequent administration of H5N1 subunit vaccine resulted in a rapid, robust and high quality Ab response in 73-80% of vaccinees.


Clade 1 H5 Vaccines: expressed HA and VLPs

- Baculovirus expressed HA:
  - 90 μg X 2 induced ‘protective’ titers in 52% of vaccinees.
  - 8 years later, a boost with 90 μg of split virion vaccine elicited Ab response in 70-76%.
- VLPs
  - Baculo VLPs 90 μg X 2 induced Ab in 61% of vaccinees; Ab cross-reacted across clades
  - 20 μg X 2 of plant VLPs + alum induced Ab in 75% of vaccinees.
- DNA and Adenovirus vectored: prime for robust response to inactivated subunit vaccine


Key Observations

- Options
  - Large dose of split virion vaccine or combined with an oil-in-water adjuvant
  - Whole virion vaccine
  - Prime-boost or sequential use of LAIV/DNA/Vectored vaccine followed by split virion vaccine
  - Magnitude and quality including cross reactivity of Ab can be influenced by adjuvant or sequence of prime/boost vaccines
  - Titers decrease over ~6-12 months but are boosted with additional doses of vaccine


Scientific Progress from H5N1 Vaccine Studies

- Use of larger doses of antigen
- Absence of a reproducible effect of alum
- Oil-in-water adjuvants for split virion vaccines
- Re-consideration of whole virion vaccines
- Awareness of the shortcomings of the conventional assays for HAI antibodies
- Use of novel platforms discussion
- Utility of prime-boost or sequential use of different vaccine platforms
- ‘Pre-pandemic’ vaccine usage

Licensure Criteria for Pandemic Influenza Vaccines

- Current licensure criteria for the assessment of pandemic vaccines were originally designed for the assessment of seasonal influenza vaccines.
- Are they entirely relevant or appropriate for assessment of H5 vaccines?

Knowledge Gaps-1

- Why is the H5 HA a poor immunogen?
- Will prior exposure to non-H5 influenza A viruses prime for responses to H5 vaccines?
- The WHO Global Influenza Programme recommends the development of vaccine seed viruses for distinct H5N1 clades. What is the extent of cross-reactive immunity and cross-protection conferred by vaccines based on heterologous clades of H5N1 viruses?

Knowledge Gaps-2

- We can generate H5N1 vaccines that elicit H5 Ab but titers decline in 6 months.
- Is this a problem?
  - In absence of exposure to the antigen, antibody titers will decrease
  - If there is on-going re-exposure to antigen, antibody titers may be maintained.
  - In the event of a significant re-exposure, memory responses may be protective
- Does the nature of the exposure matter?

Knowledge Gaps-3

- Is the demonstration from prime boost studies of a rapid high quality antibody response within 7 days of parenteral administration of purified antigen sufficient to assume that natural airborne exposure to the virus will also elicit a robust antibody response?
- What is the role of cross reactive (e.g. stem) antibodies in vaccine induced immunity?
Scenarios for Use of H5N1 Vaccines

• Vaccinate selected groups ahead of time and boost when a threat is recognized
  OR
• Wait till a threat is recognized and then vaccinate
  • With available vaccine?
  • Vaccine that matches the emerging virus?
  • 1st dose of available vaccine followed by a dose of the matched vaccine?