Development of Human Influenza H5N1 Vaccines in Japan: Research and Clinical Trials

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H5N1 HPAI viruses cannot be used for conventional vaccine production

1. Poor growth in eggs due to killing of embryos in early period
2. Possible infection to manufacturing workers

Modification of the cleavage site of

HPAI PVQRERRRRK /G
LPAI PQ - - - - RETR / G
Lessons from A/HK/156/97(H5N1) vaccine

To potentate the poor immunogenicity of H5N1 pandemic vaccines

• Need for adjuvants (Alum, MF59, ISCOM, ASO3, Ampligen, etc.)

  Optimum formulation, efficacy, safety

Need for clinical trials of adjuvanted vaccine

  International cooperation and licensure

• Whole virus vaccines are a little more immunogenic

  Adjuvanted, whole virus formulation may spare antigen contents, thereby making more vaccine supply possible
Concept of vaccine development in Japan

- Better immunogenicity
- Antigen sparing
- Based on seasonal vaccine production
- License for whole virus vaccine retained

Egg-grown, formalin-inactivated, alum-adjuvanted, whole virus vaccine
(Alum is the only adjuvant licensed in Japan)
Helper virus-independent, cloned cDNAs-based system  (*Twelve or seventeen plasmid system*)

From Neumann & Kawaoka (2001)
Immunogenicity in mice

**GMT**

- HI titer ($10^{2n}$)
- Dose (g HA)

**Sero-conversion**

- % HI • 40
- Dose (g HA)

- Plain whole virus vaccine
- Alum adjuvanted
Vaccine development (2)

2004~
Test vaccines to A/Vietnam/1194/2004(H5N1) NIBRG-14 (Clade1)
RG-modified HA + NA; 6 genes from A/PR/8 Whole virus vaccine
(15, 5 and 1.75 µg HA + Alum adjuvant)
Non-clinical studies in animals; Sept. 2005
Safety
Immunogenicity
Human trials (Phase 1); January 2006 ~
15, 5, and 1.75 µg HA + Alum adjuvant
Two-dose, i.m. or s.c.
Safety, Immunogenicity
Antigen yields of NIBRG-14 were 1/5-1/10 of those of interpandemic viruses.

Immunogenicity of NIBRG-14 in mice was enhanced by adding aluminum hydroxide gel.

Toxicity of the Alum-adjuvanted whole virus vaccine was comparable to that of DTaP vaccine.
Plan of Phase I Studies

- Alum-adjuvanted whole virus vaccine, NIBRG-14
- Healthy male adults (15-20 in each group)
- Each manufacture performs Phase I study
- 1.75 µg, 5 µg and 15 µg HA/dose to be evaluated, 15-20 volunteers/group
- Vaccination routes to be compared for i.m. and s.c.
- Saline as a control, 5 volunteers/group
- Serum HI and NT Abs to be assayed

1st dose, sc. or im.  3 weeks  2nd dose, sc. or im.  3 weeks
1. Blood samples  2.  3.
## Summary of Phase 1 Clinical study results (2006)

<table>
<thead>
<tr>
<th>NIBRG-14 vaccine (HA content, μg/dose)</th>
<th>Criterion 1 (mGMT increase &gt;2.5 folds)</th>
<th>Criterion 2 (Seroconversion rate &gt;40%)</th>
<th>Criterion 3 (Seropositive cases &gt;70%)</th>
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Effectiveness

- Egg-grown, formalin inactivated, Alum-adjuvanted, whole virus vaccine of H5N1 NIBRG-14 vaccines induced good serum antibody responses in healthy adults.
- Meeting the EMEA and the FDA criteria:
  - One shot with 5 µg HA or 15 µg HA
  - Two shots each with 1.75 µg HA
Safety

• No serious adverse events defined in ICH E2B guideline were observed in all 450 participants.
• Frequency of systemic and local side effects might be dose-dependent.
• All vaccinees were well tolerated.

Immunogenecity, safety and tolerability were verified.
Improvement of yields of NIBRG-14 in eggs

- Deletion in the stalk of the neuraminidase was corrected by adding the 20 amino acids.

- M gene form the H5N1 virus was used.

- Yields in eggs were improved 4 to 5 times.

- Antigenic stability and susceptibility to neuraminidase inhibitors are under investigation.
Issues in pandemic vaccine policy

1. Production of pandemic vaccines
   - Urgent development
     Technology, IPR, safety and efficacy, clinical trials, licenses, antigenic drift
   - Production capacity
     Infrastructure, facilities, supply of eggs, incentive

2. Access, supply and immunization
   - Short of vaccine supply
   - Priority of vaccination target groups
   - Equitable international supply of limited amount
   - Infrastructure and feasibility of immunization program