Immune Responses to Non-replicating Avian Influenza Vaccines in Clinical Trials Conducted in Other Countries

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Scope of Presentation

- History
- Whole virion vaccine concept
- Adjuvation concept with special reference to alum
- Prospects

Trials with Pandemic Prototype Vaccines: Undulation through Epidemiology

- The 1976 pandemics which did not occur: "swine flu" and the 1977 reappearance of H1N1: "pseudo-pandemic"
- The 1976 – 1977 trial experience
- The 1997 H5N1 shock in Hong Kong
- Increased trial activities: H2N2 and exploratory H5 work
- Phase 3 pandemic alert: ongoing since 2004
- Plethora of clinical trials with emphasis on H5N1 strains

Immunogenicity in H1N1 Whole Virion Vaccine Trials in 1977

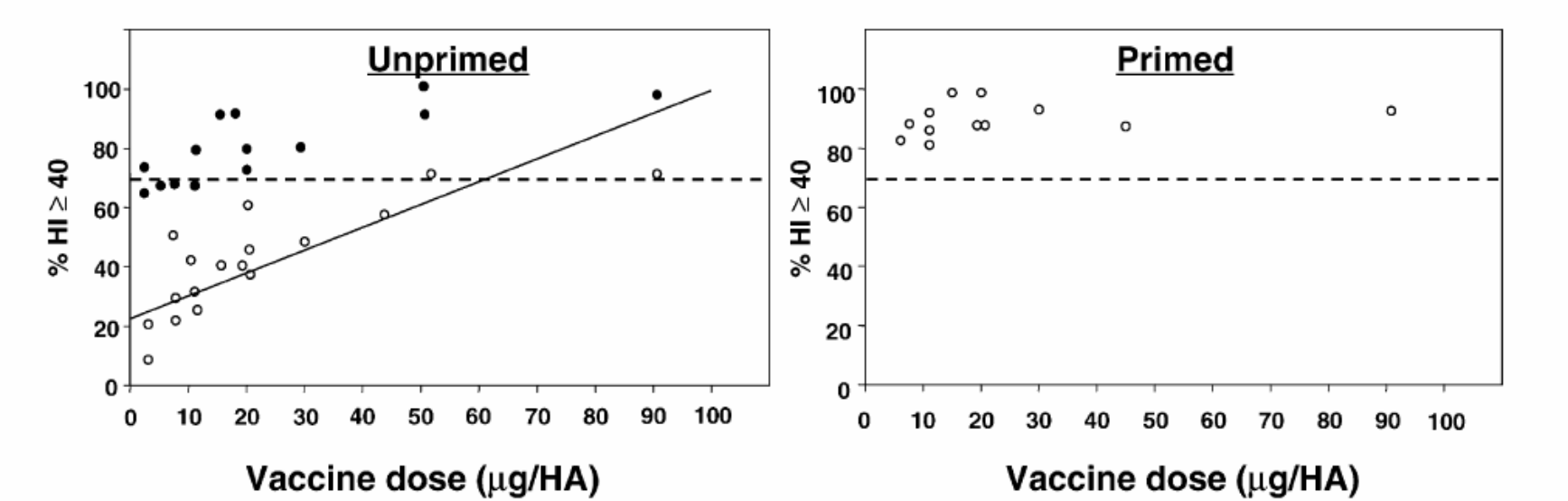


Fig. 1. Immunogenicity of A/USSR/92/77 (H1N1) whole virus vaccines in 1977 clinical trials. The incidence (%) of post-vaccination HI antibody ≥40 stimulated by vaccines of different potencies (μg HA) in primed and unprimed populations is shown for eight trials performed in the USA and the UK. Open circles, one dose; filled circles, two doses; dashed line, CPMP criteria [10]. Data from La Montagne et al. [7], Nicholson et al. [8], Potter et al. [9].

Clinical Evidence Accumulated Before the 2004 H5N1 Outbreak Regarding Pandemic Prototype Vaccines

- Whole virion vaccines were found more immunogenic in unprimed population (1976/77 experience)
- For a pandemic model vaccine two doses of at least 15ug HA are needed but in case of H5 vaccines > 30 ug HA would be needed (1997 to 2003 experience)
- Initial evidence from H2N2 and exploratory H5 trials suggested that dose sparing might be possible both for whole and split prototype vaccines, i.e. MF 59, alum

Important Issues for Developing Pandemic Vaccines (Pre-2004)

- Consensus on the type of vaccine (i.e. whole virion, subunit, split, adjuvanted, live attenuated), dosing and/or adjuvation requirements to stimulate protective immune response
- Gain wider experience on reverse genetics technology
- Legal issues relating equity of vaccine supply (i.e. IP)
- Develop accelerated approval procedures for licensing
- Manufacturers to develop their own pandemic plans
- Comprehensive resource needs to support operational and logistical demands to target the global world population

Modified after J Wood (Vaccine 20, 2002, B40-B44,)

Summary of 1st (Nov 2005) and 2nd (May 2006) Meetings on Clinical Trials with Pandemic Prototype Vaccines

- Limited information on clinical trials of pilot vaccines was presented
- Results obtained show that H2N2, H5N1, H9N2 and H5N3 candidate vaccines are safe and well tolerated
- Immunogenicity results were highly variable, depending on vaccine formulations, antigen content and schedule of immunization
- Participants requested WHO to organize a 3rd meeting to evaluate progress in clinical trials

*Lancet Infect Dis, Feb 2006, **6**, 71-72; Lancet Infect Dis, Aug 2006, **6** , 6458-6460*

Pandemic Challenges to Influenza Vaccines (December 31, 2006)

- Immunological naiveté

  anticipated two dose regimens versus plausible one dose scenarios such as LAIV or some adjuvanted whole virion vaccines (?)

- Immunogenicity concerns

- Decreased HA yields in egg-based rH5N1 production

  when virus yields remain similar to seasonal vaccine strains

With current technologies the antigen yield could be three-fold lower, six-fold more antigen is required for vaccination and a two dose schedule is required.

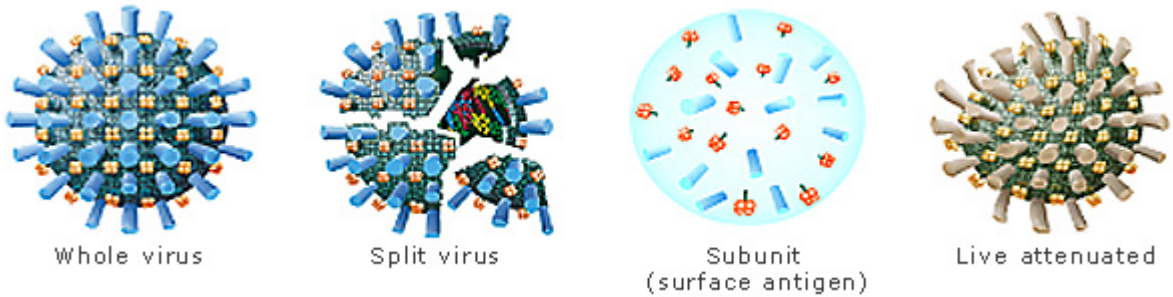
Summary of the 3rd WHO Meeting on Evaluation of Pandemic Influenza Prototype Vaccines in Clinical Trials 15-16 February 2007, WHO, Geneva

- Manufacturers from more than 10 countries are developing prototype pandemic influenza vaccines against H5N1 influenza virus.
- At least seven adjuvanted vaccines induced immune responses that meet international criteria for influenza vaccine licensing.
- Three of these vaccines contain purified viral antigens or split virus formulated with MF59 or AS03 or Alum as adjuvants. The others contain whole virus combined or not with Alum.
- Some of the adjuvanted vaccine formulations were shown to be immunogenic with low doses of antigen (3.75µg or 7.5 µg HA).
- It was demonstrated in some studies that vaccination with H5N1 vaccines was able to induce a potentially protective immune response against strains of H5N1 virus isolated at different times in a variety of geographical locations.

http://www.who.int/vaccine_research/diseases/influenza/meeting_150207/en/index.html

http://www.who.int/vaccine_research/diseases/influenza/flu_trials_tables/en/index.html

Structural Diagram of Licensed Seasonal Influenza Vaccines



(Source: IFPMA-IVS)

Established Influenza Vaccine Production Technologies

Egg-based virus propagation

i) Inactivated (whole virion, split and subunit) vaccines

ii) Inactivated vaccines with adjuvant

iii) Live attenuated virus vaccines

Cell culture substrate based virus propagation

i) Inactivated vaccines

ii) Inactivated vaccines with adjuvant

iii) (Live attenuated virus vaccines)

Available H5 Vaccine Platforms

- **Egg derived inactivated whole virion vaccines**
- Tissue culture derived inactivated whole virion vaccines
- **Egg derived inactivated split/subunit vaccines**
- Tissue culture derived inactivated split/subunit vaccines
- Egg derived live attenuated vaccines

Serological Criteria for Assessment of the Vaccine in the 18 to 60 Year Old Age Group

- Number of seroconversions or significant increase in anti-HA antibody titre > 40 %;
- Mean geometric titre increase > 2.5;
- Proportion of subjects achieving an anti-HA antibody titre of equal or > 40 should be > 70 %.

Important Reminder

- Due to inherent variability in the haemagglutination inhibition and neutralization antibody assay systems used to measure immunogenicity, and the lack of standardized methods for these assays, it is unwise to attempt to make direct comparisons of results from different clinical trials
- Trial-to-trial comparison of immunogenicity cannot be done as study designs and tests are not standardized
- Data presented to WHO were in some cases obtained in small groups of volunteers, and further trials will be carried out by the manufacturers

Inactivated Whole Virion H5 Vaccines

- Wild-type H5N1, cell-based vaccine, adjuvanted with Al-hydroxide and/or non-adjuvanted – Baxter (Austria)
- Egg-based rH5N1 vaccine, adjuvanted with Al-hydroxide – Japanese consortium: Biken, Denka Seiken, Kitasato, and Kaketsuken (Japan)
- Egg-based rH5N1 vaccine, adjuvanted with Al-phosphate – Omninvest (Hungary)
- Egg-based rH5N1 vaccine, adjuvanted with Al-hydroxide - Sinovac (People's Republic of China)
- Egg-based rH5N1 vaccine, adjuvanted with Al-hydroxide + Al-phosphate – GlaxoSmithKline Biologicals (Germany)
- ?Cell-based rH5N1 vaccine, adjuvanted with Al-hydroxide - Nobilon (The Netherlands)?

Cell Derived Inactivated Whole Virion Wilde Type H5N1 Vaccine (Baxter)

- H5N1 A/Vietnam/1203/2004 with and without alum (OH)
- Two dose schedule (0, 21),N=270, aged 18 to 45 years
- High immunogenicity (MN) at low doses, i.e. 7.5 ug HA
- The non-adjuvanted formulation is more immunogenic
- Cross-neutralization against clade 1, 2, and 3
- Cross-protection (mice)

Alum Adjuvanted Egg-based Whole Virion rH5N1 Vaccine (Sinovac)

- A rA/Vietnam/1194/2004 vaccine: NIBRG-14 (Al-hydrox)
- Two dose schedule (0, 28),N=120, aged 18 to 60 years
- Dose finding study with 1.25, 2.5, 5, and 10 ug HA content + placebo
- All three EMEA (CPMP) criteria were met with the vaccine containing 10 ug HA

EMEA Immunogenicity Scores for an Alum Adjuvanted Whole Virion Vaccine (10 ug HA)

- HI titre equal or above 40: 78%
- 4-fold or higher increase of HI titre: 78%
- GMT increase: 11.5-fold

(Sinovac: Lin et al., Lancet, 2006)

Alum Adjuvanted Egg-based Whole Virion rH5N1 Vaccine (Omninvest)

- A rA/Vietnam/1194/2004 vaccine: NIBRG-14 (Al-phos.)
- N= ~~650, three trials including elderly up to 83 years old
- One dose schedule with 6ug HA content
- All three EMEA (CPMP) criteria were met with one dose (both in the adults and the elderly group)
- Cross neutralization (HI, MN) with H5N1strains from different phylogenetic clades
- Higher cross neutralization in elderly versus adult group

Potential Cross-reactive Immunogenicity: Alum Adjuvanted Whole Virion Vaccine I

- rA/Vietnam/1194/2004 vaccine: NIBRG-14, AlPO4 adj.
- 1 dose schedule, N=44 (18-60y), N=44 (over 60 y)
- HI and MN tests against strains:

  rA/Barheaded goose/Quinghai/1A/05 (H5N1) (St Jude,clade2.2)

  A/Swan/Nagybaracska/01/2006 (H5N1)(classic reassortant, clade 2.2)

  rA/Anhui/01/2005 (H5N1)-PR8-IBCDC-R65 (CDC, clade 2.3)

(Fazekas et al. at the 3rd WHO meeting on influenza vaccines with broad spectrum and long lasting immune responses, 2007)

Potential Cross-reactive Immunogenicity: Alum Adjuvanted Whole Virion Vaccine II

Hemagglutination Inhibition Test (1% chicken blood cell):

Seroconversion

	NIBRG-14	rAnhui	Nagybaracska	rQuinghai
18-60 y:	91% +	57% +	41% +	32% -
Over 60 y:	68% +	50% +	61% +	46% +

(Passing score: 40 and 30%, adult and elderly, respectively)

(Omninvest presentation: Fazekas et al., ibid)

Alum Adjuvanted Whole Virion Vaccines

Some alum adjuvanted whole virion vaccines were highly immunogenic and showed significant cross neutralization with H5N1 strains of different phylogenetical clades.

Caveat: No alum-free control arms

Inactivated Subunit H5 Vaccines

- Egg-based rH5N1 vaccine, adjuvanted with MF 59 - Novartis (Italy)
- Egg-based rH5N1 vaccine, adjuvanted with Al-hydroxide Solvay (The Netherlands)
- Cell-based rH5N1 vaccine, adjuvanted with Al-hydroxide Solvay (The Netherlands)
- Egg-based rH5N1 vaccine, adjuvanted with polyoxidonium or Al-hydroxide – Microgen (Russia)

Inactivated Split H5 Vaccines

- Egg-based rH5N1 vaccine, adjuvanted with Al-phosphate – CSL (Australia)
- Egg-based rH5N1 vaccine, adjuvanted with AS-03 – GlaxoSmithKline Biologicals (Germany)
- Egg-based rH5N1 vaccine, adjuvanted with AF-03 - Sanofi Pasteur (France)
- Egg-based rH5N1 vaccine, adjuvanted with Al-hydroxide Sanofi Pasteur (France)

Alum Adjuvanted Split or Subunit Vaccines

Alum adjuvation up to now has provided only modest or no antigen sparing effect versus initial clinical data with split non-adjuvanted vaccines.

Conclusion: Safety and Immunogenicity

- Vaccines reported to WHO at four meetings held in 2005-2007 were described as safe and well tolerated in the age groups studied
- Vaccine immunogenicity was demonstrated to vary based on type of vaccine, dose, and the presence of adjuvants
- The next global clinical trial meeting will be held on 14-15 February 2008 in Geneva

A Purist's Conclusion:The Whole Virion Concept and the Novel Adjuvants

- Whole virion + MF59, AS, AF-03 etc.

  Not tested in clinic: -

- Split/subvirion without Alum

  Tested in clinic: +

- Split/subvirion + Alum

  Tested in clinic: +

- Split/subvirion + MF59, AS, AF-03 etc.

  Tested in clinic: +

- Whole virion without Alum

  Not tested in clinic: -* (exc.)

- Whole virion + Alum

  Tested in clinic: +

Selected Electronic Publications from the Initiative for Vaccine Research (WHO) Web Site

- **3rd WHO Meeting on Evaluation of Pandemic Influenza Prototype Vaccines in Clinical Trials, February 2007**
  http://www.who.int/vaccine_research/diseases/influenza/meeting_150207/en/index.html
- **Tables on the Clinical Trials of Pandemic Influenza Prototype Vaccines**
  www.who.int/vaccine_research/diseases/influenza/flu_trials_tables/en/index.html
- **Options for Live Attenuated Influenza Vaccine in the Control of Epidemic and Pandemic Influenza, June 2007**
  www.who.int/vaccine_research/diseases/influenza/meeting_120707/en/index.html
- **Mapping of Intellectual Property Related to the Production of Pandemic Influenza Vaccines**
  www.who.int/vaccine_research/diseases/influenza/Mapping_Intellectual_Property_Pandemic_Influenza_Vaccines.pdf