Immune responses to non-replicating avian influenza vaccines in clinical trials conducted in the USA

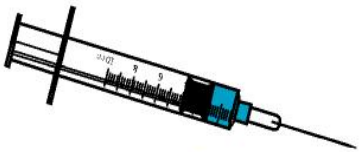
Immune Correlates of Protection Against Influenza A viruses in Support of Pandemic Vaccine Development

December 10, 2007

David S. Cho, PhD, MPH
Program Officer, Respiratory Diseases Branch
National Institute of Allergy and Infectious Diseases
National Institutes of Health
DHHS

Outline

- **Summary of a series of clinical trials evaluating *inactivated* pandemic influenza vaccines**
  - **H5N1 (NIH: 12 trials completed or in progress)**
  - **H9N2 (1), H7N7 (planned)**
- **“New” influenza vaccine technologies under development**

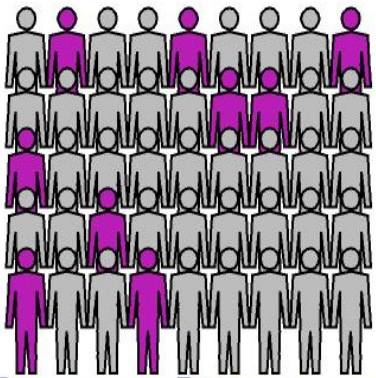


Vaccines

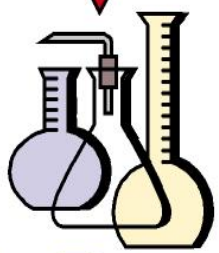
Therapeutics

Diagnostics

NIH Influenza Research



Surveillance and Epidemiology



Basic Research

Expansion of Research Capacity

The New York Times

January 20, 2004

Spread of Bird Flu in Asia Worries Officials

By LAWRENCE K. ALTMAN, M.D.

For a small number of bird watchers, the question is not how many species they can spot but what viruses infect the birds. In recent weeks, these bird-watching virologists have become worried about what they and the World Health Organization say is the "unprecedented" simultaneous appearance of an avian influenza virus in a number of countries.

NIH Influenza H5N1 Vaccine Development: Work with Partners

- **Gain experience with technical and logistical issues**
  - Generate vaccine reference viruses with reverse genetics
  - Support companies to produce vaccines
  - Standardize/qualify assays, provide reagents
- ***Rapidly* implement controlled clinical trials in various populations**
  - Safety, immunogenicity
  - Adults, elderly, children
- ***Rapidly* provide trial results to the global community;** transmit lessons learned

NIH Pandemic Preparedness Response

- **Awarded Pandemic Preparedness in Asia Contract**
  - **PI: Robert Webster, St. Jude Children's Research Hospital**
  - **Activities include:**
  - **animal influenza surveillance in Asia/US**
  - **use reverse genetics to generate avian influenza reference viruses suitable for vaccine production**
    - **Influenza A/Vietnam/1203/2004 (clade 1)**
  - **supporting animal surveillance training**

NIH NEWS RELEASE

National Institutes of Health

National Institute of Allergy and Infectious Diseases

FOR IMMEDIATE RELEASE
Thursday, May 27, 2004

NIAID Announces Contracts to Develop Vaccine Against H5N1 Avian Influenza

NIAID H5N1 Influenza Vaccine Development: Objectives and Obstacles

- **Gain experience with technical and logistical issues**
  - **Generate a reference virus using reverse genetics**
  - **Request Select Agent exemption**
  - **Produce reagents for standardization**
- **Obtain vaccine from a manufactures with licensed products**
- **Evaluate safety and immunogenicity of the H5N1 vaccine in well controlled clinical trials in various populations**

NIAID H5N1 Influenza Vaccine Development: Objectives and Obstacles (cont)

- **No internationally recognized standard for use in HAI or microneut assay validation studies**
- **Avian RBC's (turkey or chicken) have limited sensitivity for H5N1 viruses in HAI**
- **Horse RBC's improve assay sensitivity for H5N1 viruses in HAI**
- **Caveats:**
  - **No defined correlation of any H5 antibody assay with protective clinical outcomes**
  - **Lab to lab variability in assays limits comparisons between studies**

HAI & MN Assay Development

- Southern Research Institute (SRI) serves as the central laboratory for performing serological testing for H5N1 clinical trials
- SRI HAI assay from the WHO Manual on Animal Influenza Diagnosis and Surveillance, 2002.5, Rev. 1, modified to use horse RBCs for H5N1
- Serological assay SOPs HAI development report filed to IND
- Good correlation between HAI & MN assays

H5N1 Vaccine Development: Sanofi Pasteur's Vaccine (US)

- **NIH completed series of clinical trials to evaluate the vaccine's safety and immunogenicity**
  - Adults (18-64 years), elderly (65+)
    - 7.5, 15, 45, and 90ug HA per vaccine dose or placebo
  - Children (2-9 years)
    - 45ug HA dose or placebo
- **2 or 3 doses of H5N1 vaccine or placebo by IM injection, ~ 1 month apart**
- **Endpoints:**
  - Safety – vaccine reactions
  - Antibody responses
    - Hemagglutinin inhibition (HI)
    - Microneutralization assays (MN)

The New England Journal of Medicine

Established in 1812 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY

VOLUME 354 MARCH 30, 2006 NUMBER 13

Safety and Immunogenicity of an Inactivated Subvirion Influenza A (H5N1) Vaccine

Treanor et al.

H5 Vaccine (Sanofi U.S.): Summary

- **Vaccine was safe/well tolerated**
  - At all dose levels
  - In all age groups
- **Antibody responses were dose-dependent**
  - Higher the dose, the higher the titers
  - Titers were similar across age groups
  - 3rd dose – boosted titers back to post dose 2 levels
- **Assays similar in trend/results**
  - Hemagglutination Inhibition (HI); qualified
  - Microneutralization (MN) assay
  - Long-term consistency

Comparison of HAI results in children, adults, and elderly subjects: Sanofi vaccine - post 2 doses

Dose group	Age Group	GMT (95% CI)	Percent responding (95%CI)*	Percent achieving a titer of ≥ 1:40 (95% CI)
45 ug	Children	17.3 (12.7, 23.5)	38 (28, 49)	38 (28, 49)
	Adults	17.0 (12.4, 23.3)	33 (24, 44)	33 (24 44)
	Elderly	16.7 (12.8, 22.0)	23 (15, 32)	35 (26, 45)
90 ug	Children	NT	NT	NT
	Adults	27.7 (20.3 38.0)	43 (33, 54)	44 (34 55)
	Elderly	26.2 (19.5, 35.2)	38 (28, 48)	46 (36, 56)

* Response requires both a 4-fold or greater increase over baseline, and achievement of a 1:40 titer or greater by HAI
- elderly/pediatric data: presented/not yet published

U.S. Food and Drug Administration

Department of Health and Human Services

For Immediate Release
April 17, 2007

FDA News

FDA Approves First U.S. Vaccine for Humans Against the Avian Influenza Virus H5N1

The U.S. Food and Drug Administration (FDA) today announced the first approval in the United States of a vaccine for humans against the H5N1 influenza virus, commonly known as avian or bird flu.

The vaccine could be used in the event the current H5N1 avian virus were to develop the capability to efficiently spread from human to human, resulting in the rapid spread of the disease across the globe. Should such an influenza pandemic emerge, the vaccine may provide early limited protection in the months before a vaccine tailored to the pandemic strain of the virus could be developed and produced.

National Institutes of Health

Can intradermal administration of H5N1 vaccine improve immunogenicity?

- **Compare ID vs. IM routes**
  - Healthy adults; received 2 doses, ~ 1 month apart
    - 3ug or 9ug intradermally or
    - 15ug or 45ug intramuscularly
  - **Results**:
    - Well tolerated
    - No clear advantage of ID route at dosages evaluated (3 and 9ug)
    - 3rd dose @ at 7 months: antibody titers declined, but boost back to least as high as 1 month post dose 2 levels
  - **Higher ID dose trial completed**
    - 30ug H5 vaccine given IM vs. ID; results pending

Patel, IDSA 2006

Can a clade 3 vaccine prime for a clade 1 vaccine response?

- **"Revaccination Study" - 37 subjects who received 2 doses of a rec H5HA vaccine (clade 3) in 1998-9 were given a single 90ug dose of the sanofi H5 vaccine in 2005**

- **Results (n = 37)**: Antibody responses in "primed" subjects (compared against H5 vaccine naïve subjects):
  - **Exceeded those who were unprimed**
  - **Exceeded those in the original 1998-9 study**
  - **Exceeded those who received 2 x 90ug doses**

  - **Responses could be due to the generation of long-lived memory CD4 cells and/or memory B cells**

  - **New clade 2 H5N1 vaccines will provide more opportunities to assess immunological priming; in production now**

Ali Gogi, N. IDSA 2006; manuscript submitted

Trials with Inactivated H5N1 Vaccines +/- Aluminum Adjuvants

- **Numerous trials completed, ongoing, planned**
  - **Published:**
    - Sanofi pasteur (France) 2 doses of vaccine (7.5, 15, 30ug) +/- AlOH
    - - Well-tolerated; adjuvant resulted in no significant increase in immunogenicity
    - Sinovac; 2 doses of whole virus vaccine (1.25, 2.5, 5, 10ug) + AlOH
    - - Well-tolerated; 2 x 10ug doses vaccine gave highest response
  - **Completed (preliminary results reported) or ongoing**
    - CSL - 2 doses + $AlPO_4$
    - 4 Japanese companies (whole virus vaccine; IM and SQ) + AlOH
    - Baxter (whole virus vaccine) +/- AlOH
    - Novartis (UK) (7.5, 15, 30ug) +/- AlOH (NIH)
    - Sanofi (US) +/- AlOH in adults and elderly (NIH)
- **Summary**
  - **Safety profile: well tolerated in adults, elderly**
  - **Aluminum adjuvants do not appear to significantly enhance immune response to H5N1 vaccines**

Lancet; www.clinicaltrials.gov; 2006 IFPMA

Trials with Inactivated H5N1 Vaccines +/- Other Adjuvants

- **Several trials completed or ongoing**
  - Preliminary results reported
  - Reporting low doses of vaccine with adjuvant of oil/water emulsion achieved high immune responses with low doses of antigen
    - Novartis (UK) +/- MF59 – as low as 7.5ug (NIH)
    - GSK (Belgium) +/- AS03 – as low as 3.75ug
- Safety profile reported to be well tolerated in adults
- Additional expanded studies ongoing or planned

www.clinicaltrials.gov; 2007 IFPMA

Inactivated Whole H5N1 Virus Vaccine Trial

- **Inactivated whole virus H5N1; produced by Baxter International**
- NIH Phase I/II trial to evaluate dose-related safety and immunogenicity in adults (18-64 years)
- 2 doses, approximately one month apart
- Dose levels: 3.75, 7.5, 15, 45, unadjuvanted or preadsorbed with AlOH
- Safety: Well tolerated
- Immunogenicity: Results expected by Feb'08 WHO meeting

Upcoming NIH Clade 2 H5N1 Vaccine Trials

- **Previous studies "clade 1" strain of H5N1**
- **Clade 2 H5 vaccine (DHHS)**
  - **Clade 2.1** reassortant: A/Indonesia/05 (CDC)
  - Clinical trial: safety/immunogenicity/prime-boost (NIH)
    - Planned start: late 2007

- **Other clade 2 vaccines**
  - **Clade 2.2** reassortant: A/BHG/Qinghai/1A/05 (St. Jude)
    - Vaccine production ongoing; sanofi pasteur
  - **Clade 2.3** reassortant: A/Anhui/1/05 (CDC)
    - Vaccine production ongoing; Novartis (UK); trial planned mid '08

Inactivated H9N2 Vaccine + Adjuvant Evaluation: Results

- **Novartis Inactivated H9N2 Subunit Vaccine with and without MF59 Adjuvant**
  - Evaluated in 96 healthy young adults
  - 2 doses of 3.75ug, 7.5ug, 15ug or 30ug
  - Safety profile: well-tolerated
  - Antibody titers and frequencies of responses higher at all doses with MF59 than any dose without adjuvant
  - Single 3.75 ug dose induced an antibody titer that reached a benchmark many consider to be “predictive of protection”
  - **Results published: Clin Infect Dis. 2006 Nov 1; 43(9): 1135**

H7N7 Vaccine: Phase I Trial

- **Planned for late 2007**
  - Subunit vaccine produced by Sanofi Pasteur/US (DHHS)
    - **H7N7 reference virus (CDC)**
  - Phase I trial to evaluate dose-related safety and immunogenicity in healthy adults
  - Planned dose levels: 7.5, 15, and 45ug
  - 2 doses, approximately one month apart

Major Challenges to Pandemic Vaccine Development and Availability

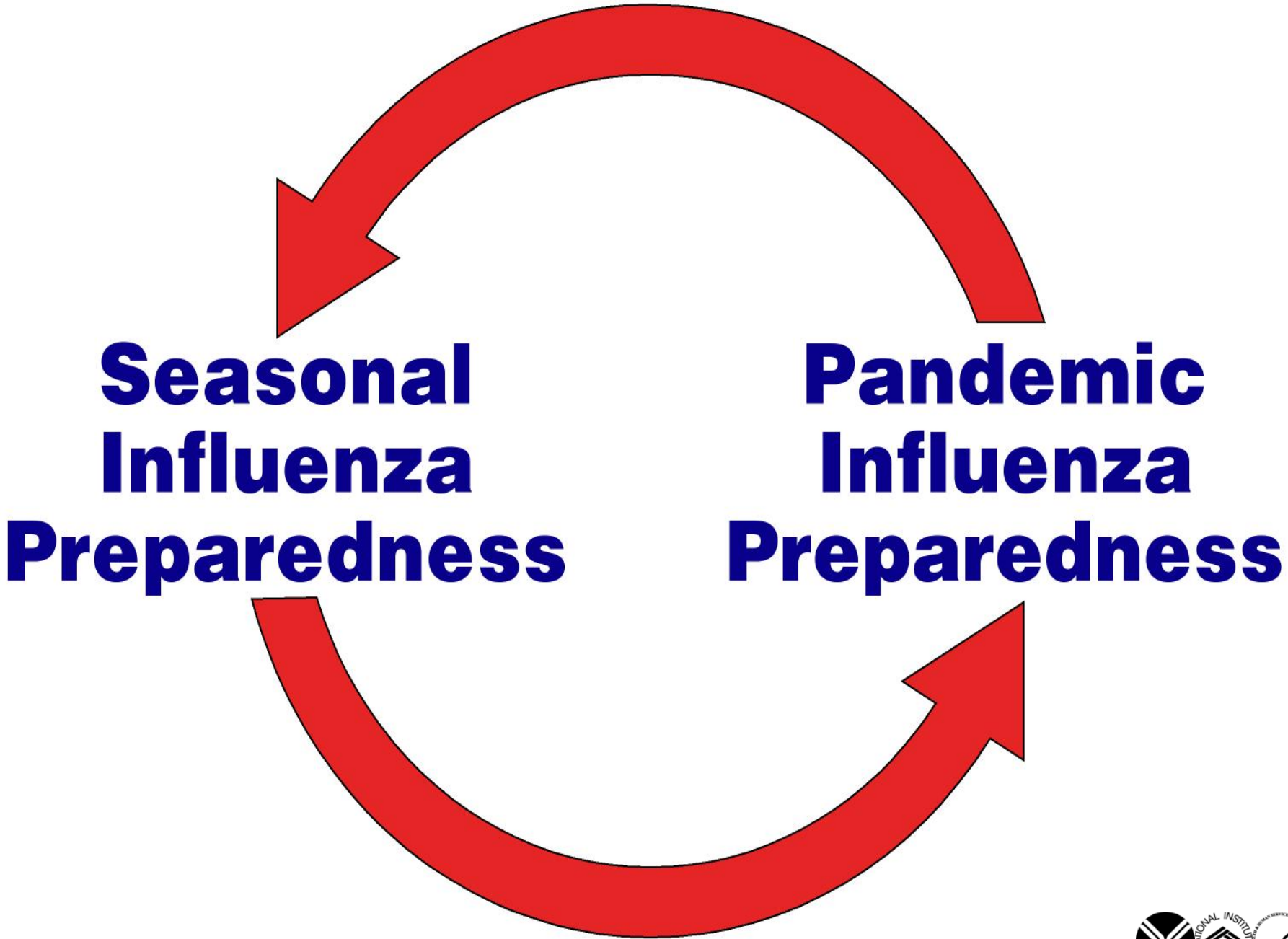
- **Expand production of current (egg-based) vaccine**
- **Accelerate development of modern (non-egg) vaccines**
- **Evaluate dose-sparing technology (adjuvants, intramuscular vs. intradermal route)**
- **Target new antigens**

Beyond Eggs and Cell Culture: NIH Research Efforts to Develop New Vaccine Platforms / Technologies

- **Goal: Develop "agile" vaccine platforms or common epitope or "universal" vaccines**
  - **DNA**
    - **Plasmid-based; single or multiple gene combinations**
  - **Vector**
    - **Adenovirus, alphavirus, attenuated salmonella strains**
  - **Recombinant subunit expression systems**
    - **Baculovirus, drosophila**
  - **Peptide vaccines**
    - **Synthesized multigenic peptides (e.g. CTL peptides)**

Progress in Influenza H5N1 Vaccine Development

- **Successful use of reverse genetics for vaccine reference virus production**
- **Development of assays, regents, strain libraries**
  - **Efforts underway to decrease lab to lab variability**
- **Expanding manufacturing capacity; more needed**
- **Development and evaluation of multiple approaches aimed at enhancing immunogenicity**
  - **Adjuvants**
  - **Substrates**
  - **Delivery devices, routes**


Seasonal
Influenza
Preparedness
Pandemic
Influenza
Preparedness