

**BIOMEDICAL ADVANCED RESEARCH and DEVELOPMENT AUTHORITY
INFLUENZA and EMERGING DISEASES DIVISION (IEDD):**

**Advanced Development,
Stockpiling, & Infrastructure/Capacity
Building---Countermeasures to Prevent
Pandemic Influenza**

Michael Perdue, PhD - Acting Director

HHS/ASPR/BARDA Pan Flu Program

**Progress Towards a Unified Nomenclature
System for the Highly Pathogenic H5N1 Avian
Influenza Viruses**

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WHO/OIE/FAO H5N1 Evolution Working Group

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Introduction

It was proposed to develop a clade nomenclature system based upon the evolution of the HA for several reasons:

1. To unify the system so that interpretation of sequence/surveillance data from different labs becomes easier.
2. To remove stigmatizing labelling of clades by geographical reference
3. To provide for easy future expansion of the phylogenetic tree
4. To provide a starting point for a more extensive system to follow based upon antigenic variation and reassortment into multiple genotypes.

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Introduction (cont.)

Phylogenetic analysis was performed by a variety of approaches on all of the publicly available H5 HA sequences that have evolved from the A/Goose/Guangdong/96 H5N1 HA lineage.

The initial results supported the idea that the currently circulating HPAI H5N1 viruses could be effectively grouped into numerous clades designated by a hierarchical numbering system.

For example the so-called 'Fujian-like lineage' within the antigenically distinct Clade 2 of H5N1 would be designated Clade 2.3, with distinct branches called 2.3.1 and 2.3.2 etc., while the 'Qinghai lineage' would be designated Clade 2.2

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Methodology

Sequence alignments

Nucleotide sequences of the highly pathogenic H5N1 hemagglutinin (HA) gene (only nearly complete sequences) were collected from publicly available databases:

- GenBank (NCBI)
- Influenza Sequence Database of Los Alamos National Laboratories (LANL)

Large alignments consisted of 1,300 HA sequences each approximately 1659 nucleotides
- after removing duplicate and redundant sequences to avoid biasing results
884 sequences were used for final analysis

Small alignments consisted of 109 HA sequences each approximately 1659 nucleotides
- isolates chosen include vaccine strains, reference strains, many human strains, pathogenesis study strains, geographically diverse strains

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Methodology

Phylogenetic trees

Neighbor-joining, maximum parsimony, maximum likelihood, and Bayesian trees were generated using PAUP (Version 4.0), MEGA (Version 3.1), and MrBayes with the DNA substitution model and rate heterogeneity determined by ModelTest (GTR+I+G).

Large tree rooted to ancestral H5 isolates (turkey/England/91 and chicken/Scotland/59).

Small tree rooted at the clade 0 node (gs/Guangdong/1/96 lineage).

1000 bootstrap replicates were performed to support tree topology.

Trees were compared to confirm clade topology, isolate placement, and to interpret clade designation criteria.

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Clade designation criteria

- 1) Maintain previously designated clade numbers where possible (i.e., Clade 2.2 remains 2.2 and Clade 1 remains 1)
 - exception was made for clade 3 (now called clade 0)
- 2) New clade designations based on phylogenetic tree topology derived from all available nearly complete HA sequences (the large tree)
 - H5N1 progenitors (closest to Gs/Guangdong/1/96) re-designated as Clade 0 (formerly called clade 3)
 - Subsequent clades numbered starting with Clade 3 (i.e., Clades 3-9)
 - Clades designated by presence of a distinct common node shared by at least 4 isolates (in a monophyletic group)
 - Additional branches in a clade were given a second or third-order clade designation as that clade diverged into more than one distinct lineage (i.e., Clade 2.2 or Clade 2.3.1; based on sharing of a common node and monophyletic grouping)

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Clade designation criteria

3) Average percentage pairwise distances between and within clades (using Kimura 2-parameter)

- Distinct clades should have > 1.5% average distances between other clades
- Distinct clades should have < 1.5% average distances within the clade

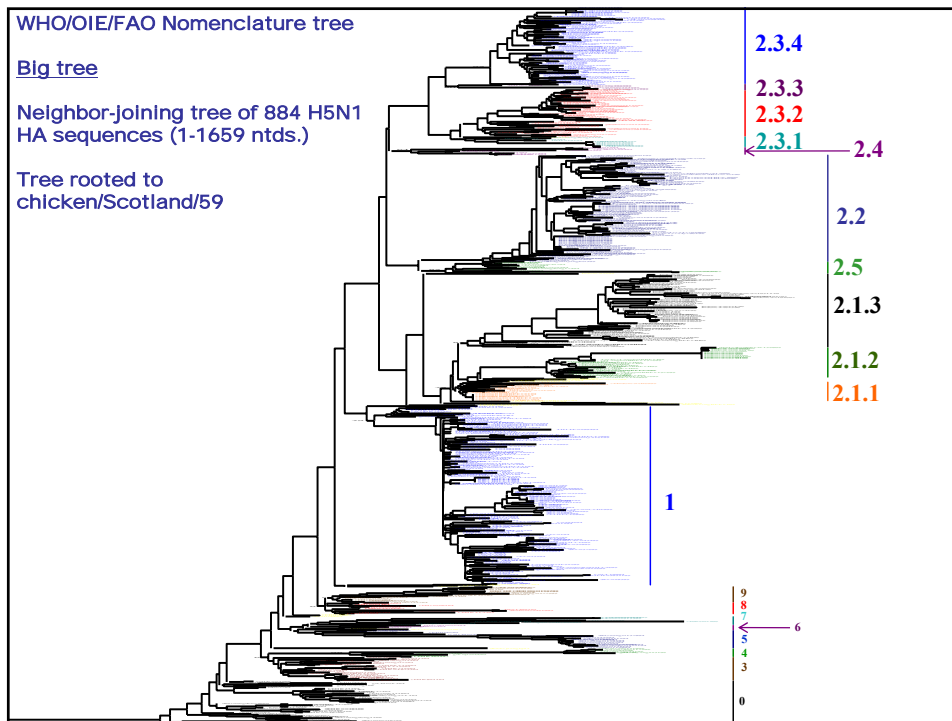
4) Bootstrap (based on 1000 neighbor-joining bootstrap replicates)

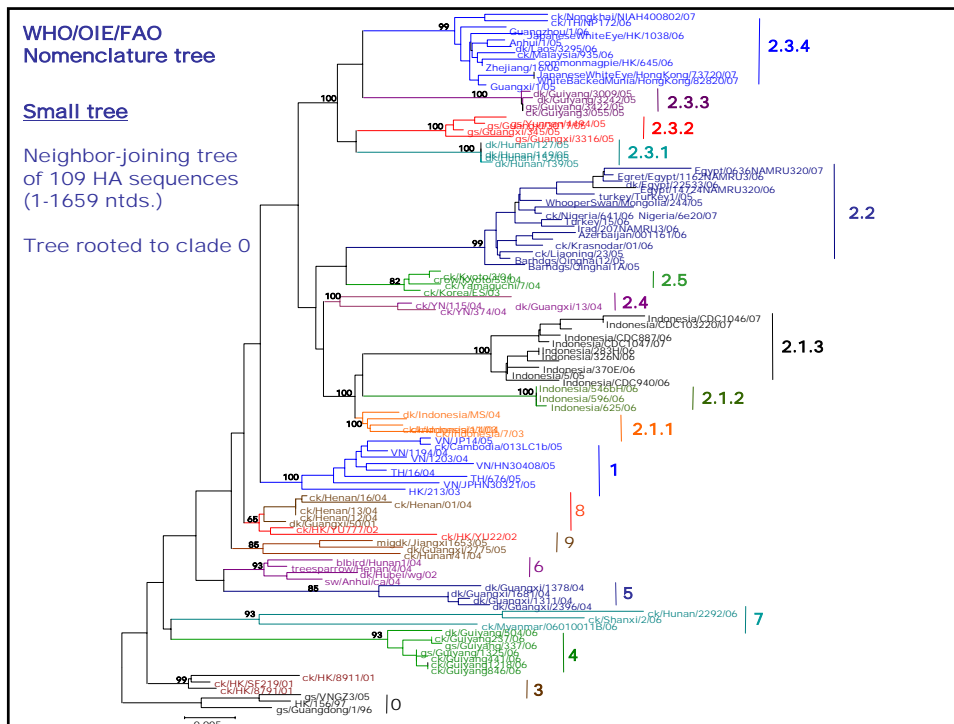
- ≥ 60 bootstrap value at clade defining node

For each clade identified, a representative prototype virus was named in order to facilitate interpretation of the proposed numbering system.

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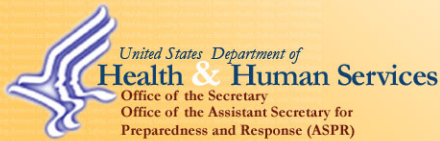
United States Department of Health & Human Services
Office of the Secretary
Office of the Assistant Secretary for Preparedness and Response (ASPR)

U.S. H5N1 Vaccine Stockpile Inventory: 2008

H5N1 Vaccine Strain	Clade	2004	2005	2006	2007	Totals
A/VTN/1203/04	1	0.23	4.31	0.78		5.32
A/Indo/05/05	2.1			6.44	2.25	8.69
A/BHG/QL/1A/05	2.2				6.42	6.42
A/Anhui/1/05	2.3				2.51	2.51
Totals (90 ug/dose)		0.23 M	4.31 M	7.22 M	11.18 M	22.94 M
Totals w/adjuvants 7.5 ug/dose		2.76 M	51.72 M	86.64 M	134.16 M	275.28 M

¹ Adjusted for usage and potency

- Stockpile manufacturing requirements:
 - Produce U.S.-licensed seasonal influenza vaccines
 - Store, test, formulate & fill in U.S.
 - Able to manufacture H5N1 bulk vaccine at commercial scale



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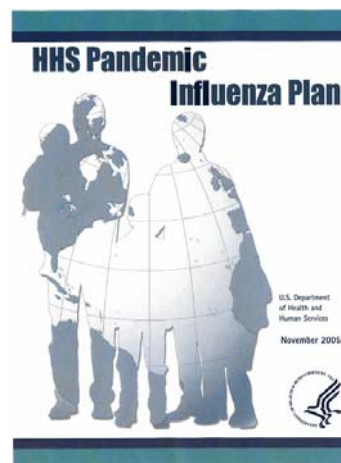
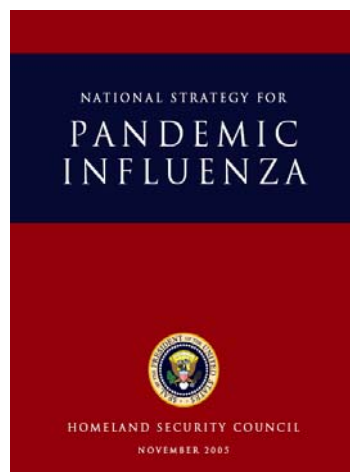
What's BARDA

- Biomedical Advanced Research & Development Authority established by PAHPA in Jun. 07 in HHS/ASPR
- Implements USG strategies & policies for MCMs from the Public Health Emergency Medical Countermeasure Enterprise (PHEMCE)
- Coordinates integrated product portfolio approach to planning and executing research, development and acquisition of public health emergency MCMs
- Supports advanced development, stockpile procurement, & mfg. infrastructure building of MCMs for **CBRN Threats, Pandemic Influenza, and Emerging Diseases**

ROLES of BARDA

- Advanced development; acquisitions of medical countermeasures for Bioterror attacks and emerging diseases.
- Bridge the 'Valley of Death' for drugs without markets (beyond phase I studies).
- Technical, Contractual, Clinical, Regulatory components.
- Countermeasure component of the ASPR; Collaborate with NIH, CDC, FDA and others.

National Pandemic Influenza Strategy Plans



U.S. Pan Flu MCM Goals

- **Vaccines**
 - Goal #1: Establish and maintain a dynamic pre-pandemic influenza vaccine stockpile available for 20 M persons (2 doses/person) *or more persons depending on vaccine mfg. capacity & results of dose-sparing adjuvant studies and prime-boost immunization studies: H5N1 vaccine stockpiles*
 - Goal #2: Provide pandemic vaccine to all U.S. citizens within 6 months of a pandemic declaration: pandemic vaccine (600 M doses)
- **Antivirals**
 - Goal #1: Provide influenza antiviral drug stockpiles for pandemic treatment of 25% of U.S. population (75 M treatment courses) *and antivirals for prophylactic usage as a community mitigation measure*
 - Goal #2: Provide influenza antiviral drug stockpiles for strategic limited containment at onset of pandemic (6 M treatment courses)
- **Diagnostics**
 - Goal #1: Develop new high-throughput laboratory & point-of-care (POC) influenza diagnostics for pandemic virus detection
- **Respiratory Disease Countermeasures**
 - Goal #1: Develop and acquire other CMs including syringes/needles, masks/respirators, ventilators, antibiotics, & other supplies

National Strategy for Pandemic Influenza (Nov 2005) and HHS Pandemic Influenza Plan (Nov 2005)

www.pandemicflu.gov

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IEDD Program Portfolio Approach: 2004-2008

30+ contracts & 3 grants totaling ~\$4B; >20 companies	Vaccines	Antivirals	Diagnostics/ Respiratory CM
Advanced Development	Cell-based, Antigen-sparing Next Generation Recombinant Egg-based Supply	Peramivir, Next generation AntiVirals	<u>Diagnostics</u> Point of Care, Clinical Lab Next Generation <u>Ventilators</u>
Acquisitions	H5N1 Pre-Pandemic Vaccine and adjuvant Stockpiles	<u>Tamiflu & Relenza</u> Federal Stockpiles State Stockpiles	Masks & Respirators
Infrastructure/ Capacity Building	Retrofit Existing Mfg Facilities; Build New Cell-based Mfg Facilities; International support		

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HHS Pandemic Vaccine Initiatives at a Glance:

- **Year-round egg supply** with associated reagents/testing for pandemic influenza vaccine production and development of pandemic-like vaccine candidates
- **Commercial scale manufacturing for stockpiles** Six contracts for, storage, and testing of H5N1 vaccines awarded from 2004-2007 establishment of the national pre-pandemic influenza vaccine stockpile.- 3 new contracts just awarded
- Six contracts for development of **cell-based influenza vaccines** towards U.S.-licensure were awarded in 2005-06 at a total investment is \$1.3 B. The goal is to develop commercial-scale production for 600M doses in 6 months by 2012
- Three contracts for development of **antigen-sparing pandemic** influenza vaccines towards U.S.-licensure were awarded in 2007-total investment of \$133 M.

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HHS Pandemic Vaccine Initiatives at a Glance:

- Two contracts for **retrofitting existing U.S. manufacturing facilities** for egg-based influenza vaccine production were awarded in 2007- total investment of \$133 M.
- Solicitation for proposals was issued in 2007 for development of **next-generation recombinant influenza vaccines**, contract award(s) is expected soon.
- Solicitation “**Building Domestic Cell-based Influenza Manufacturing Facilities**” to support detailed design, construction, commissioning, validation, and clinical bridging studies of new U.S.-based facilities to manufacture cell-based influenza vaccines. Contract award anticipated in December 2008.
- Support for **international vaccine tech transfer and capacity building**. WHO and Vietnam.

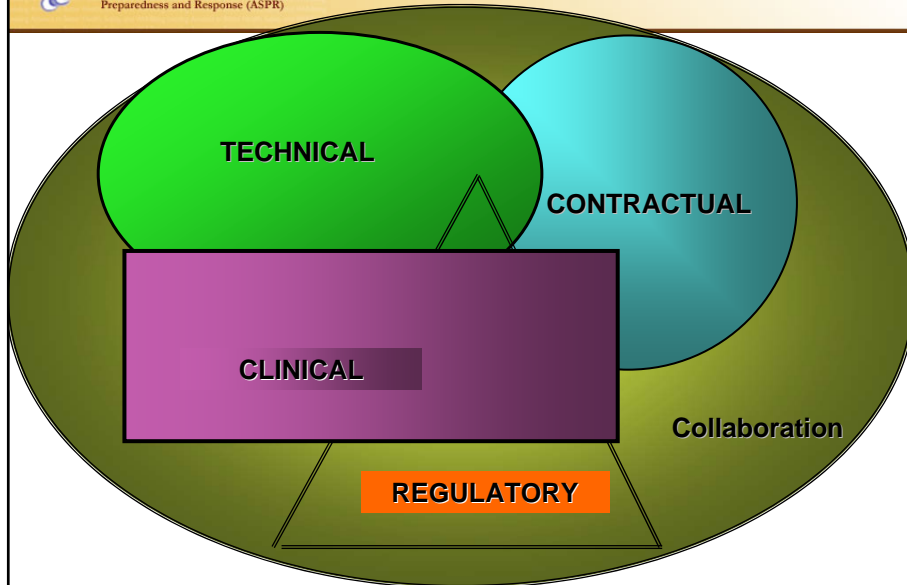
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IEDD sponsored 'Mix-n-Match' studies

- Use stockpiled H5N1 vaccine(s) from one company to mix (bedside) with adjuvants from other companies.
- Developed as an approach within BARDA-test case.
- Preclinical studies Tox, immuno in animals nearly complete.
- Human phase 1 trials to begin in December at NIH

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IEDD Team Elements



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- Thank you...