Influenza A (H5N1) Epidemiology and Vaccine

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Influenza A (H5N1)

BACKGROUND

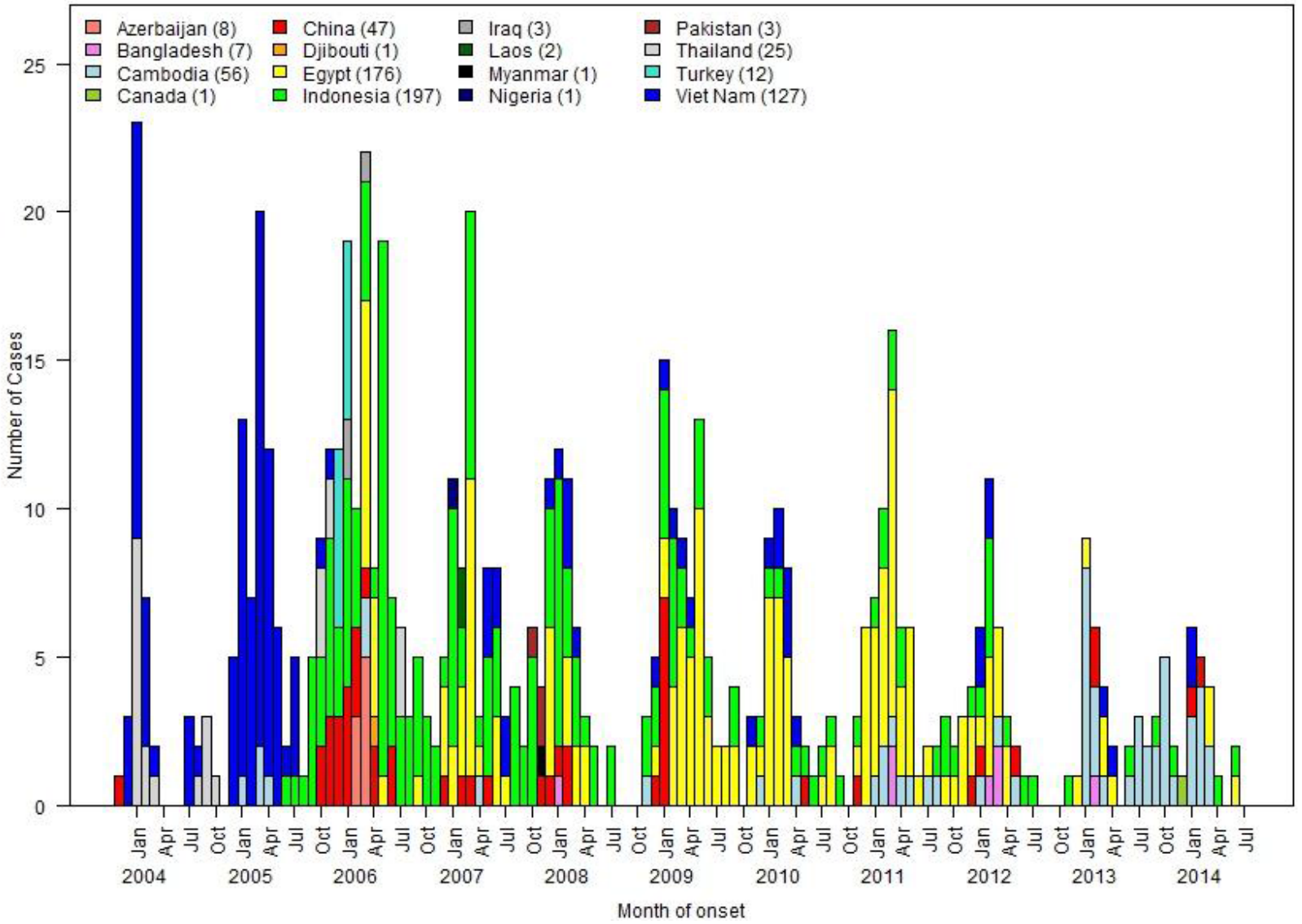
Influenza A (H5N1) in Poultry

- Highly pathogenic avian influenza (HPAI) causes a highly transmissible, severe respiratory disease in birds
- The A(H5N1) subtype virus is endemic in poultry in at least six countries
  - Bangladesh
  - China
  - Egypt
  - India
  - Indonesia
  - Vietnam
- Poultry outbreaks occur frequently in these and nearby countries

Influenza A (H5N1) in Humans

- First cases in Hong Kong in 1997
- Reemerged in Asia in 2003
- Number of infections peaked in 2006
- Sporadic cases with high mortality continue
- Between 2003 and Sept 2014
  - 667 cases in 16 countries
    - Includes 1 fatal case with avian influenza A(H5N6) infection
  - 393 (59%) deaths
- Most cases occur from close contact with infected live or dead birds, or H5N1 virus-contaminated environments
- Human-to-human transmission is extremely rare

Human Infections of Influenza A (H5N1), 2004-2014*



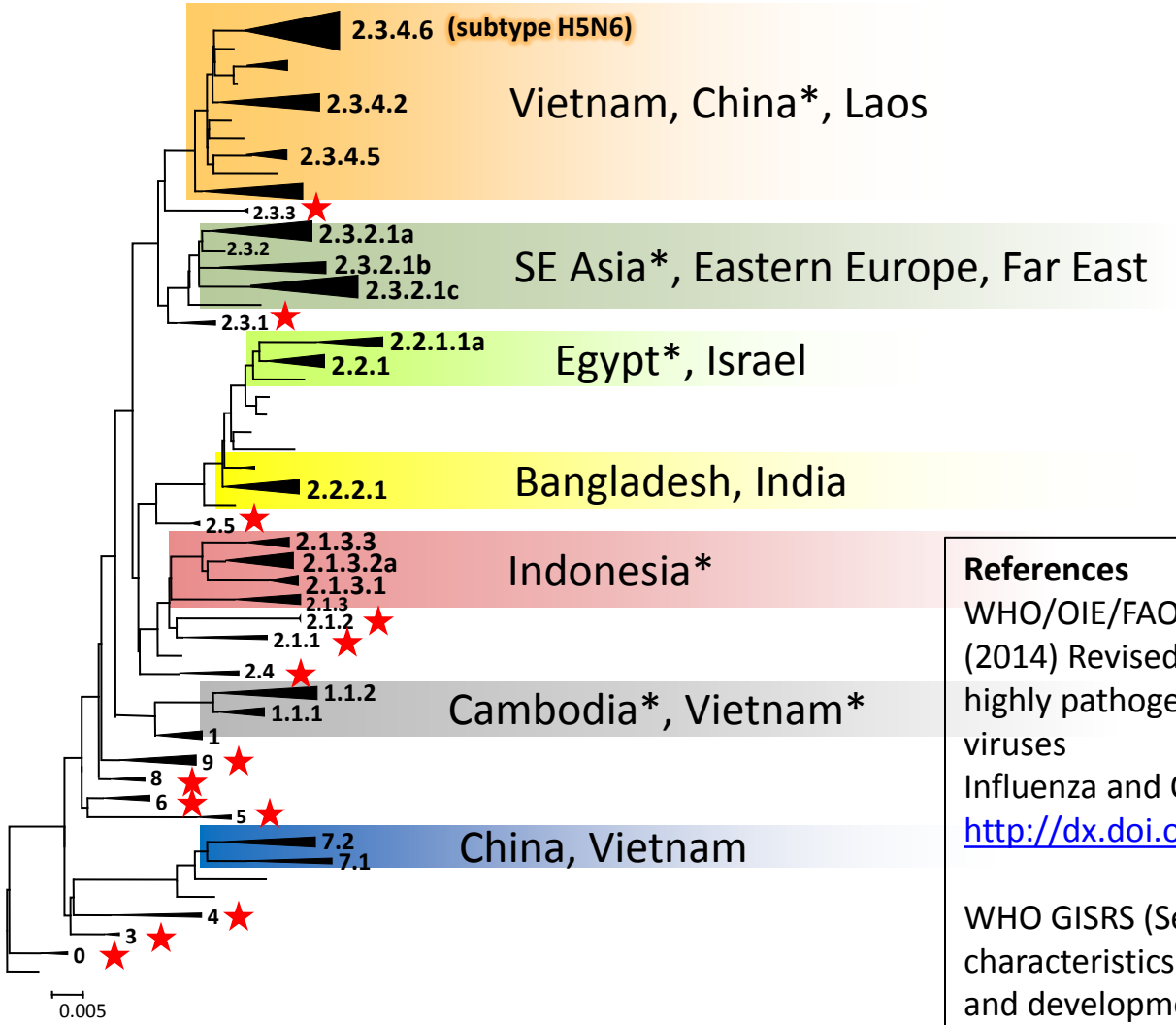
*Includes 1 fatal case of avian influenza A(H5N6) infection in China, 2014.

http://www.who.int/influenza/human_animal_interface/Influenza_Summary_IRA_HA_interface_27June14.pdf?ua=1

H5N1 Virus Evolution

- H5N1 viruses continue to evolve
- Evolution is monitored using sequence of HA gene
- Viruses are grouped into clades based on phylogenetic characterization and sequence homology
- Knowledge of currently circulating clades and antigenic distance from existing candidate vaccine viruses is relevant to updating pre-pandemic vaccine recommendations

H5 Clades, 1996-2014



★Not detected since at least 2008 (n=13)

*Reported in 2014

References

WHO/OIE/FAO H5N1 Evolution Working Group (2014) Revised and updated nomenclature for highly pathogenic avian influenza A (H5N1) viruses
Influenza and Other Resp Vir 8(3):1750-2659
http://dx.doi.org/10.1111/irv.12230

WHO GISRS (Sep 2014). Antigenic and genetic characteristics of zoonotic influenza viruses and development of candidate vaccine viruses for pandemic preparedness.
http://www.who.int/influenza/vaccines/virus/201409_zoonotic_vaccinevirusupdate.pdf?ua=1

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GLOBAL VACCINE RECOMMENDATIONS

Global Recommendations for Use of Licensed H5N1 Vaccine During Inter-Pandemic Periods

- Strongly recommended
  - Laboratory workers involved in certain high-risk activities
    - Large-scale production or manipulation of, or work over a long period of time with, HPAI H5N1 virus strains
    - Work with drug-resistant HPAI H5N1 viruses or viruses that have the potential for increased transmissibility to mammals
- Recommended
  - First responders to human or animal HPAI H5N1 cases or outbreaks
  - HCWs who evaluate or manage patients with suspected or confirmed HPAI H5N1 virus infection in designated referral facilities
- Not recommended
  - Persons who may only potentially come in contact with infected animals
  - Essential workers in areas where HPAI H5N1 virus is enzootic
  - General population

http://www.who.int/immunization/sage/meetings/2013/november/SAGE_WG_H5vaccine_background_paper_16Oct2013_v4.pdf

Which Vaccine to Use?

- Viral evolution necessitates development of representative candidate vaccine viruses (CVV)
- WHO recommends countries consider CVV for pandemic preparedness purposes based on their assessment of public health risk and need
- Candidate vaccine viruses for H5
  - 26 in development
  - 4 in preparation

http://www.who.int/influenza/vaccines/virus/201409_zoonotic_vaccinevirusupdate.pdf?ua=1

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VACCINE IN THE UNITED STATES

Four H5N1 Vaccines in HHS Stockpile

Virus	Clade	FDA licensure
A/Vietnam/1203/2004	1	Yes (Sanofi)
A/Indonesia/5/2005	2.1.3.2	Yes (GSK)
A/bar-headed goose/Qinghai/1A/2005	2.2	No
A/Anhui/1/2005	2.3.4	No

- Use of vaccine in HHS Stockpile is limited
  - Permit use during pandemic or for clinical studies
  - Permit strain change only during an emergency
- Use of vaccines in HHS Stockpile not possible during in inter-pandemic times

http://osp.od.nih.gov/sites/default/files/4_Donabedian_BARDA.pdf

Vaccine Produced Post-Licensure

- One FDA-licensed vaccine (Q-Pan) is being produced post-licensure
  - HHS/BARDA supported additional vaccine production, post-licensure
  - Manufacturer producing one lot (~100,000 doses)
  - Vaccine will be ready early 2015
  - A portion of this will be stored at NIH and made available to investigators

Q-Pan H5N1 Vaccine

- Made by ID Biomedical Corporation of Quebec (subsidiary of GSK)
- Emulsion
  - 3.75µg HA of the influenza virus strain A/Indonesia/05/2005
  - $AS03_A$ adjuvant emulsion (full dose, 11.86mg tocopherol)
- 2 doses (0.5mL each), administered 21 days apart
- Intramuscular injection only
- Approved for use in persons ≥18 years of age at increased risk of exposure to the influenza A virus H5N1 subtype contained in the vaccine

AS03-adjuvant

- Q-Pan is the first vaccine with AS03 to be licensed in the United States
- There are no adjuvanted SEASONAL influenza vaccines licensed in the US
- AS03 is an oil-in-water emulsion adjuvant
- Reasons to use AS03 in influenza vaccines include
  - Increase immunogenicity
  - Antigen dose sparing
  - Influenza cross-strain neutralization
- AS03 was used in H1N1pdm09 monovalent vaccines
  - Pandemrix (Made by GSK in Germany)
  - Arepanrix (Made by ID Biomedical Corp in Quebec)

AS03-adjuvanted pH1N1 vaccines and narcolepsy

- Pandemrix (used in many European Union countries)
  - Studies in several European countries have found an increased risk of narcolepsy in all age (mostly in children and adolescents)
  - No studies to date with a negative finding
  - Attributable risk as high as 6.25 cases per 100,000 vaccinated
- Arepanrix (used in Canada and Brazil)
  - A population-based study in Quebec found a relative risk similar to that observed in European studies of Pandemrix
  - The attributable risk was 1 case per 1,000,000 doses (this is lower than the AR observed in Europe, but the baseline incidence of narcolepsy was also lower than in Europe)
- Adjuvanted H1N1pdm09 vaccines were not used in the US
- A CDC-sponsored international study on adjuvanted H1N1pdm09 vaccines (Arepanrix and MF59-adjuvanted vaccines) and narcolepsy is in progress
  - Preliminary results expected in late 2015

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INCREASED RISK OF EXPOSURE

Defining Persons at Increased Risk of Exposure to H5N1*

Occupational exposure group	Includes (not an exhaustive list)	Work involves	Risks contemplated
Laboratory worker	• H5N1 vaccine manufacturer • Antiviral drug developer • Diagnostic test developer • Investigator • Laboratory technician • Student or post-doctoral candidate	Contact or works with live influenza A (H5N1) virus or clinical samples from suspect cases	Mechanical malfunction, human error, accidents, natural disasters, gaps in respiratory or other protections
Experimental animal study worker	• Veterinarian • Animal care technician	Contact with or care for influenza A (H5N1)-inoculated or infected animals, secretions or products	Unexpected animal behavior, bites, injuries, gap in respiratory and other protections
Public health responder (human health)	• EIS officer • Epidemiologist • Infection control specialist • Environmental specialist	Investigating or managing suspected or confirmed human case(s) of influenza A (H5N1) infection	Gaps in respiratory protection due to malfunctions, accidents
Public health responder (animal health)	• Field veterinarian • Field animal health technicians (e.g., diagnostic sampling) • EIS officer • Epidemiologist	Investigating suspected or confirmed avian case(s) of influenza A (H5N1) infection or suspected cases in other species	Gaps in respiratory protection due to malfunctions, accidents or unexpected animal behavior.
Other	• Ancillary staff entering laboratory (e.g., service technician, janitor, informatics technician)	Potential for contact with live influenza A (H5N1) virus or inoculated/infected animal in a laboratory	Gaps in respiratory protection due to malfunctions, accidents or unexpected animal behavior

*H5N1 is used herein to denote any H5 subtypes with the A/goose/Guangdong/96 lineage H5

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ESTIMATE OF VACCINE DEMAND

Estimating Size of Population at Increased Exposure

Risk group	Estimated number	Total persons	Vaccine doses (x2)
Laboratory worker or experimental animal study worker	In 2014, 173 PIs with USDA license to work with HPAI (x15 staff per PI laboratory)	2,595	5,190
Public health responder (human and animal health)	Epidemiologists (100) Veterinarians (100) Other (50)	250	500
Total		**2,845**	**5,690**

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ASSESSING RISK

Assessing Risk to Laboratory Workers

- Highly pathogenic avian influenza viruses are regulated by USDA as select agents under Code of Federal Regulation (Title 9, Part 121)
- The select agent regulations require entities in the United States to do the following:

  "An individual or entity must immediately notify APHIS or CDC upon discovery of a release of a select agent or toxin causing occupational exposure or a release of a select agent or toxin outside of the primary barriers of the biocontainment area."

Reported Laboratory Incidents in the United States

- Between 2007 and 2013
  - 44 reported incidents (average 6/year)
  - Needle stick, animal bite, leak, work outside containment, equipment/PPE failure
  - Incident does not equal exposure
- Estimated annual frequency of incidents per laboratory worker was <1% per year
- Zero persons infected

Summary

- H5N1 remains a global concern
- United States has licensed vaccine
- Total population at increased risk of occupational exposure is small
- Data suggests risk of transmission through occupational exposure is extremely low
  - Limitations
    - Laboratory events
      - Could have gone unreported
      - Not restricted to H5N1 (included all HPAI subtypes)
    - No systematic data collected on public health responders

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