

Pandemic Influenza Workshop for Small to Medium Size Businesses

Bird flu spreads among Java's pigs

Flu in wild birds sparks fears of mutating virus





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CBS photo.

Outline

- Course of influenza disease
- Risk of pandemic influenza
- Use of pharmaceuticals against influenza
- What to expect


Influenza Transmission



- Influenza is highly infectious and easily transmitted.
- The flu spreads in respiratory droplets caused by coughing and sneezing. It usually spreads from person-to-person, although a person may become infected by touching something with virus on it and then touching their mouth or nose.
- Incubation is from 1-4 days

<http://www.cdc.gov/flu/keyfacts.htm>


Influenza Transmission Among Humans



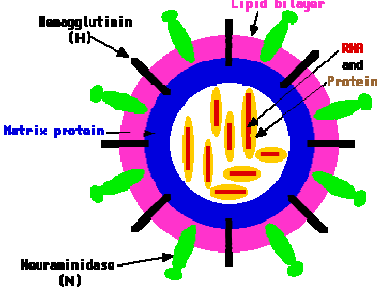
- Adults typically are infectious from the day before symptoms begin through approximately 5 days after illness onset.
- Children can be infectious for >10 days, and young children can shed virus for ≤6 days before their illness onset.
- Severely immunocompromised persons can shed virus for weeks or months.
- Virus can live on non-porous surfaces for 24-48 hrs

MMWR May 28, 2004 / 53(RR06);1-40 J Infect Dis 1982;146:47-51

Influenza Transmission Among Birds



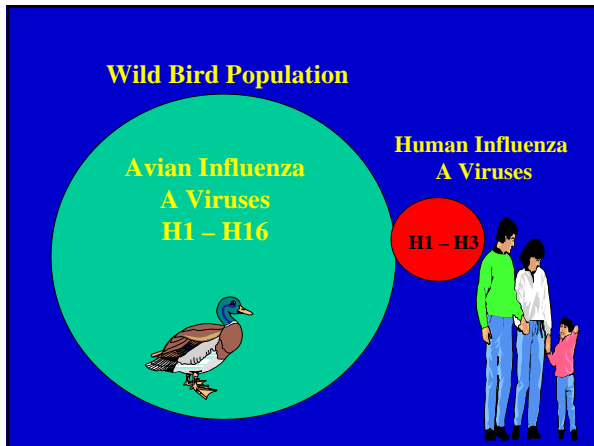
- Birds that survive avian influenza virus (AIV) infections excrete viruses for up to 10 days after infection (www.who.int/mediacentre/factsheets/fs205/en/)
- Rodents, insects (including flies) and wild birds (like sparrows) can act as vectors for AIV (www.aphis.usda.gov/wpa/pa/pubs/sheet_faqs_notice/faq_ahai.html)
- AIV has been cultured from water for up to 100 days (Avian Dis. 1990 Apr-Jun;34(2):412-8)
- AIV can survive in manure for up to 105 days. (www.vetmed.ucdavis.edu/vetext/INF-PO_AI.html)
- AIV have been cultured from poultry houses for up to 100 days after depopulation. (www.nwhc.usgs.gov/pub_metadata/field_manual/chapter_22.pdf)



16 H types – types 1, 2, and 3 in man

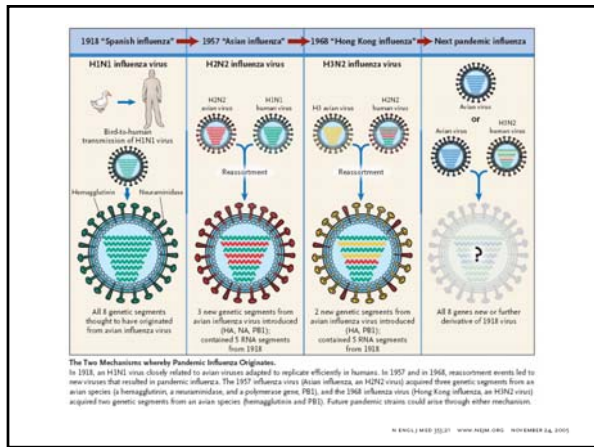
9 N types – types 1 & 2 found in man

From www.ultranet.com/~jkimball/BiologyPages/F/FluVirion.gif



Influenza A

- Key epidemiology features – Influenza epidemics are due to changes in the HA and NA glycoproteins
- a major change (eg change in H type) is termed an antigenic shift (rare event, influenza A only); antigenic shift can lead to pandemics
- a minor change is termed an antigenic drift



During the last 100 Years 3 Influenza Pandemics

- **1918-19, "Spanish flu,"** [influenza A(H1N1)] caused 20-40 million deaths worldwide
- **1957-58, "Asian flu,"** [influenza A(H2N2)], caused an estimated 1 million deaths worldwide. Began in China.
- **1968-69, "Hong Kong flu,"** [influenza A(H3N2)], caused approximately 200,000 deaths. This pandemic H3N2 virus was first detected in Hong Kong.

From <http://www.cdc.gov/ncidod/diseases/flu/viruses.htm> and <http://www.zkea.com/news/news031201.html>

The Great Spanish Flu Pandemic of 1918-1919

- 600,000 US deaths in a 10-month period
- 30% of the world's population to become sick and 20-40 million to die
- Intervention measures not effective: Isolation, restricting public meetings, wearing masks




Hong Kong H5N1

- In May 1997, investigations revealed 18 (H5N1) human cases (6 deaths) by the end of 1997, all of them in Hong Kong. Exposure to birds the major risk factor
- This led to the culling of 1.2 million birds and cost the government 245 million in Hong Kong dollars in compensation.




Recent Avian Influenza Outbreaks that have Infected Man (as of 7/28/06)

Years	Avian Influenza A	Country	Number of humans	Number of deaths
1997	H5N1	Hong Kong	18	6
1999	H9N2	Hong Kong	2	
2002	H7N2	Virginia	2	
2003	H5N1	Hong Kong	2	1
2003	H7N7	The Netherlands	89	1
2003	H9N2	Belgium	1	
2003	H7N2	Hong Kong	1	
2003	H7N2	New York	1	
2004	H7N3	Canada	1	
2004	H10N7	Egypt	2	
2004/5	H5N1	Numerous	232	134

Data derived from various CDC and WHO reports

How might a pandemic influenza virus enter the United States?

Influenza Transmission During Air Travel

- In 1979 a passenger jet sat on a runway for 3 hours due to an engine problem. The ventilation system was compromised
- One passenger developed symptoms while on board, exposing 53 other passengers.
- Within 72 hrs, **72% of the passengers and 40% of the crew contracted influenza**

Am J Epidemiol. 1979 Jul;110(1):1-6

Highly Pathogenic H5N1 Influenza Virus in Smuggled Thai Eagles, Belgium

Steven Van Borm,¹ Isabelle Thomas,[†] Germaine Hanquet,[†] Bénédicte Lambrecht,^{1*} Marc Boschmans,² Gerald Dupont,[†] Mireille Decaestecker,³ René Snacken,[†] and Thierry van den Berg

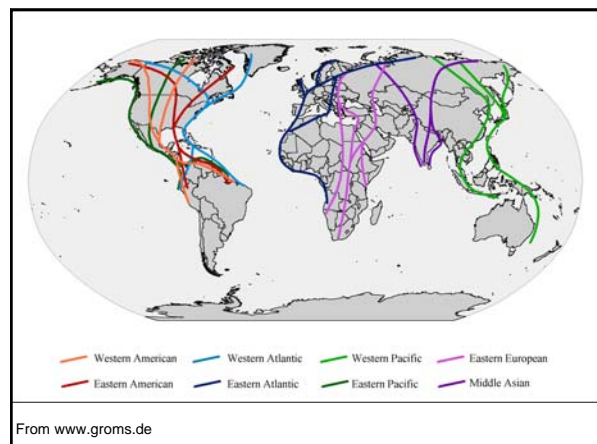
We report the isolation and characterization of a highly pathogenic avian influenza A(H5N1) virus from Crested Hawk-Eagles smuggled into Europe by air travel. A screening performed in human and avian contacts indicated no dissemination occurred. Illegal movements of birds are a major threat for the introduction of highly pathogenic avian influenza.



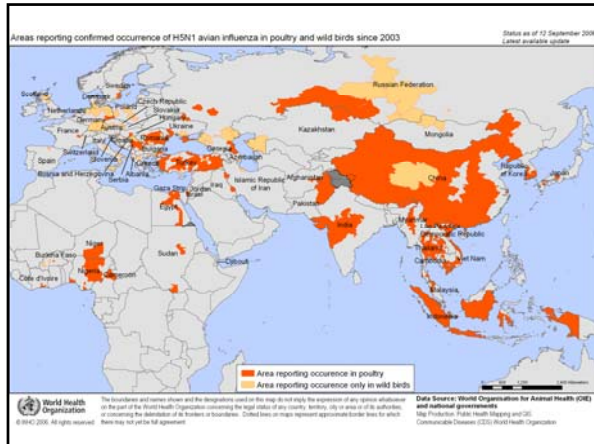
Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 11, No. 5, May 2005



- College of American Pathology, the American Association of Bioanalysts, the American College of Family Physicians and the American College of Physician Services all sent proficiency testing surveys containing one or more samples of A/H2N2 to approximately 6,500 labs in the United States and 17 countries
- Virus was similar to the 1957 pandemic strain
- All viruses recovered or destroyed – no laboratory spread



From www.groms.de



Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to WHO

19 September 2006

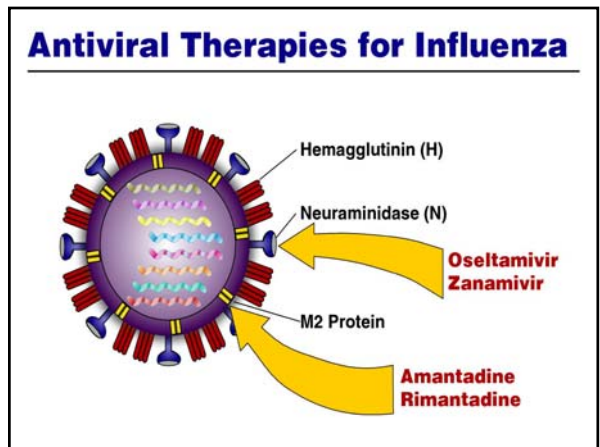
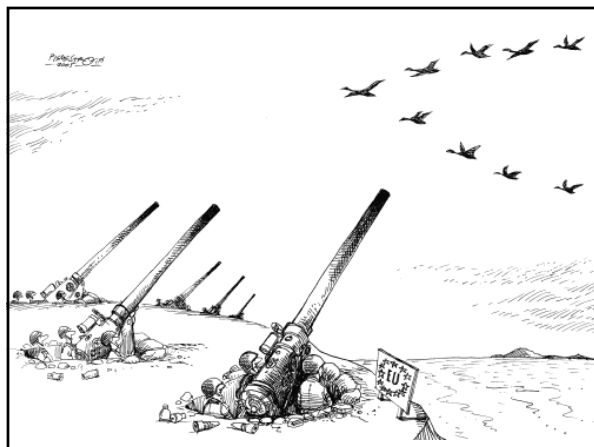
Country	2003		2004		2005		2006		Total	
	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths
Azerbaijan	0	0	0	0	0	0	8	5	8	5
Cambodia	0	0	0	0	4	4	2	2	6	6
China	1	1	0	0	8	5	12	8	21	14
Djibouti	0	0	0	0	0	0	1	0	1	0
Egypt	0	0	0	0	0	0	14	6	14	6
Indonesia	0	0	0	0	19	12	46	37	65	49
Iraq	0	0	0	0	0	0	3	2	3	2
Thailand	0	0	17	12	5	2	2	2	24	16
Turkey	0	0	0	0	0	0	12	4	12	4
Viet Nam	3	3	29	20	61	19	0	0	93	42
Total	4	4	46	32	97	42	100	64	247	144

Total number of cases includes number of deaths.
 WHO reports only laboratory-confirmed cases.

We believe the pandemic threat is **greater now than it has been in decades**," says Nancy Cox, head of the CDC's influenza branch.

Wall Street Journal 9/10/04

How are we preparing for influenza pandemics?



Comparison of Antiviral Drugs for Influenza Table					
Drug	Trade Name	Influenza Virus Type	Approved Use	Treatment Age	Prevention Age
amantadine	Symmetrel®	A	Treatment and Prevention	>1 year	>1 year
rimantadine	Flumadine®	A	Treatment and Prevention	Adults	>1 year
zanamivir	Relenza®	A and B	Treatment	≥7 years	n/a
oseltamivir	Tamiflu®	A and B	Treatment and Prevention	>1 years	>13 years

Source: www.cdc.gov/ncidod/diseases/flu/fluiviral.htm

Composition of the 2005–06 Influenza Vaccine

The Food and Drug Administration's Vaccines and Related Biological Products Advisory Committee has recommended that the 2005–06 trivalent influenza vaccine for the United States contain:

- A/New Caledonia/20/99-like (H1N1),
- A/California/7/2004-like (H3N2), and
- B/Shanghai/361/2002-like viruses.

High Levels of Adamantane Resistance Among Influenza A (H3N2) Viruses and Interim Guidelines for Use of Antiviral Agents — United States, 2005–06 Influenza Season

- Among the 120 influenza A (H3N2) viruses tested, 109 (91%) demonstrated the S31N substitution in the M2 protein that confers resistance to amantadine and rimantadine
- On the basis of available antiviral testing results, CDC recommends that neither amantadine nor rimantadine be used for the treatment or chemoprophylaxis of influenza A infections in the United States for the remainder of the 2005–06 influenza season.

January 17, 2006 / 55(Dispatch);1-2

THE NEW ENGLAND JOURNAL OF MEDICINE

BRIEF REPORT

Oseltamivir Resistance during Treatment of Influenza A (H5N1) Infection

Memmo D. de Jong, M.D., Ph.D., Tran Tan Thanh, M.Sc., Trung Huu Khanh, M.D., Vo Minh Hien, M.D., Gavin J. D. Smith, Ph.D., Nguyen Vinh Chau, M.D., Bach Van Cam, M.D., Phan Tu Qui, M.D., Do Quang Ha, M.D., Ph.D., Yi Guan, M.D., Ph.D., J.S. Malik Peiris, D.Phil., M.D., Tran Tinh Hien, M.D., Ph.D., and Jeremy Farrar, D.Phil., F.R.C.P.

SUMMARY

Influenza A (H5N1) virus with an amino acid substitution in neuraminidase conferring high-level resistance to oseltamivir was isolated from two of eight Vietnamese patients during oseltamivir treatment. Both patients died of influenza A (H5N1) virus infection, despite early initiation of treatment in one patient. Surviving patients had rapid declines in the viral load to undetectable levels during treatment. These observations suggest that resistance can emerge during the currently recommended regimen of oseltamivir therapy and may be associated with clinical deterioration and that the strategy for the treatment of influenza A (H5N1) virus infection should include additional antiviral agents.

N Engl J Med 2005;353:2667-72.

Combination chemotherapy, a potential strategy for reducing the emergence of drug-resistant influenza A variants

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Abstract

Rapid development of resistant influenza variants after amantadine treatment is one of the main drawbacks of M2 blockers. On the other hand, the emergence of variants with low susceptibility to the neuraminidase (NA) inhibitor is limited. In the present study we examined whether combination therapy with two classes of anti-influenza drugs can affect the emergence of resistant variants in vitro. We observed that virus yields of human A/Nanchang/1/99 (H1N1), A/Panama/2007/99 (H3N2), and A/Bangkok/1/04/99 (H1N1) viruses in MDCK cells were significantly reduced ($P < 0.005$) when the cells were treated with the combination of amantadine and low doses of oseltamivir carboxylate ($\leq 1 \mu\text{M}$). After five sequential passages in MDCK cells, the M2 protein of viruses cultivated with amantadine alone mutated at positions V27A and S31N. Viruses cultivated with oseltamivir carboxylate ($\geq 0.001 \mu\text{M}$) possessed mutations in the hemagglutinin (HA) protein. These variants showed reduced efficiency of binding to sialic acid receptors and decreased sensitivity to NA inhibitor in plaque reduction assay. Importantly, no mutations in the HA, NA, and M2 proteins were detected when the drugs were used in combination. Our results suggest that combination chemotherapy with M2 blocker and NA inhibitor reduced the emergence of drug-resistant influenza variants in vitro. This strategy could be an option for the control of influenza virus infection, and combination with other novel drugs should be explored.

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Keywords: Influenza A virus; Oseltamivir; Amantadine; Drug resistance

doi:10.1016/j.antiviral.2006.01.012

What to expect if a pandemic occurs?

- Expectations in a Pandemic**
- Avoidance of poultry
 - Black markets for antiviral therapy, masks, and vaccines
 - False claims of therapies/prophylaxis by charlatans
 - Reduction in public services
 - Restrictions in travel
 - Economic distress

