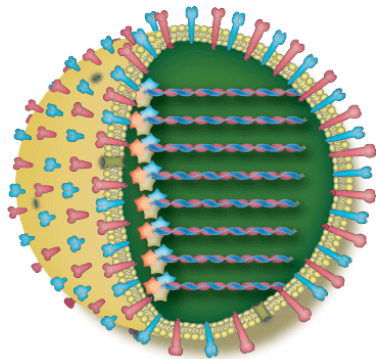

GP Flu Pandemic Symposium (13 & 14 May 2006)



Scientific Update on Avian Influenza (AI)

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- Incidence
- Transmission
- Clinical features
- Pathogenesis
- Management
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Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to WHO

11 May 2006

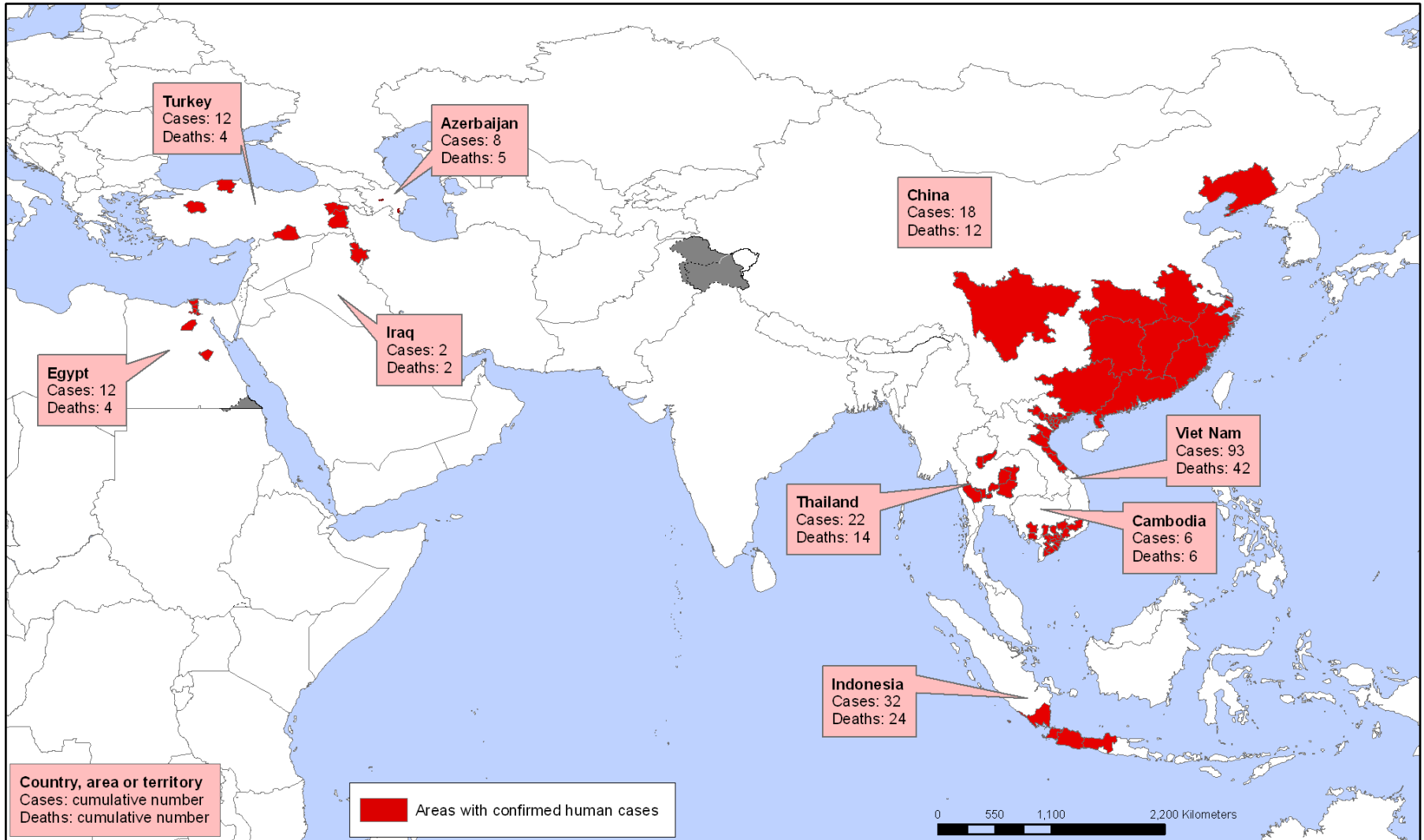
Country	2003		2004		2005		2006		Total	
	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths
Azerbaijan	0	0	0	0	0	0	8	5	8	5
Cambodia	0	0	0	0	4	4	2	2	6	6
China	0	0	0	0	8	5	10	7	18	12
Egypt	0	0	0	0	0	0	13	5	13	5
Indonesia	0	0	0	0	17	11	16	14	33	25
Iraq	0	0	0	0	0	0	2	2	2	2
Thailand	0	0	17	12	5	2	0	0	22	14
Turkey	0	0	0	0	0	0	12	4	12	4
Viet Nam	3	3	29	20	61	19	0	0	93	42
Total	3	3	46	32	95	41	63	39	208	115

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

Incidence (2)

Affected areas with confirmed human cases of H5N1 avian influenza since 2003

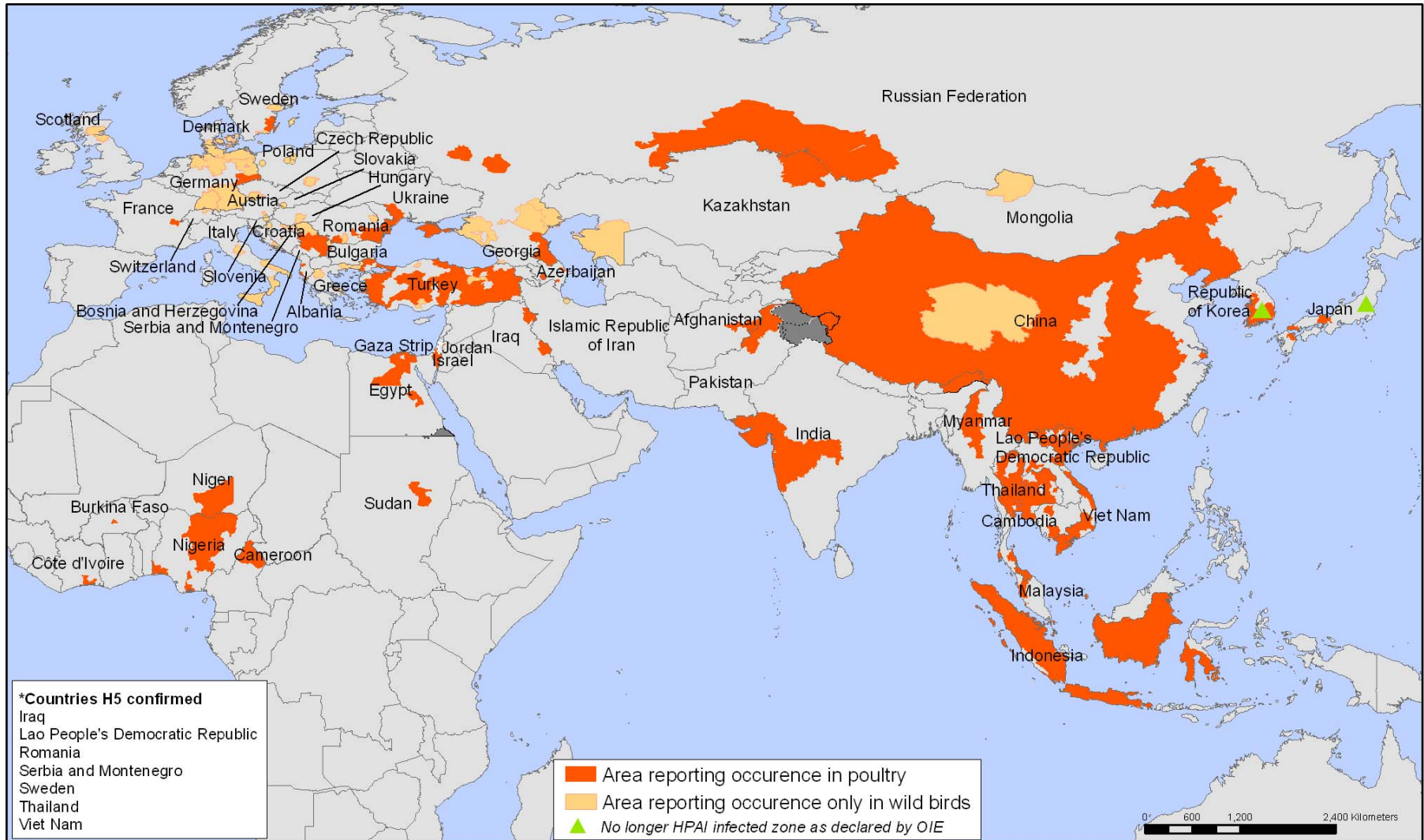
Status as of 27 April 2006



Incidence (3)

Areas reporting confirmed occurrence of H5N1* avian influenza in poultry and wild birds since 2003

Status as of 4 May 2006



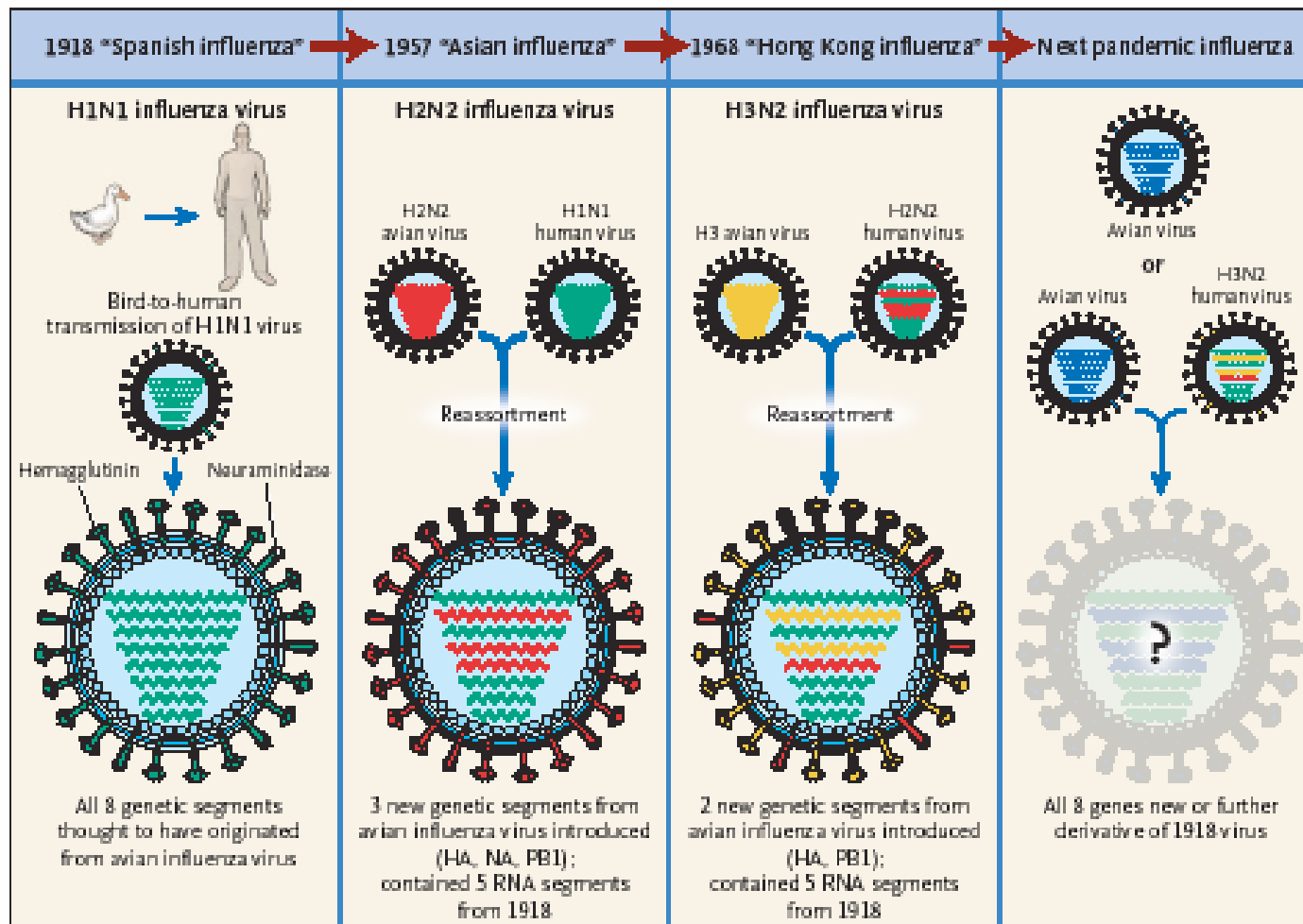
10 Things you need to know about pandemic influenza

(WHO 14 October 2005)

1. **Pandemic influenza is different from avian influenza (AI)** - An influenza pandemic happens when a new subtype emerges that has not previously circulated in human
2. **Influenza pandemics are recurrent events** – 3 pandemics occurred in the previous century:
 - a) “Spanish influenza” - H1N1, 1918 (estimated 40-50million deaths)
 - b) “Asian influenza” - H2N2, 1957 (estimated 2 million deaths), &
 - c) “Hong Kong influenza” – H3N2, 1968 (estimated 1 million deaths)
3. **The world may be on the brink of another pandemic** - ?H5N1 strain:
 - a) First infected human cases in Hong Kong 1997
 - b) Since mid-2003 has caused the most severe outbreaks in poultry in record
 - c) To-date over 200 human cases have been lab confirmed & more than half of these people have died (mostly previously healthy children & young adults)
4. **All countries will be affected** – Once fully contagious virus emerges, its global spread is inevitable
5. **Widespread illness will occur** – Because most people will have no immunity to the pandemic virus, infection & illness rates are expected to be higher than during seasonal epidemics of normal influenza

10 Things you need to know about pandemic influenza (2)

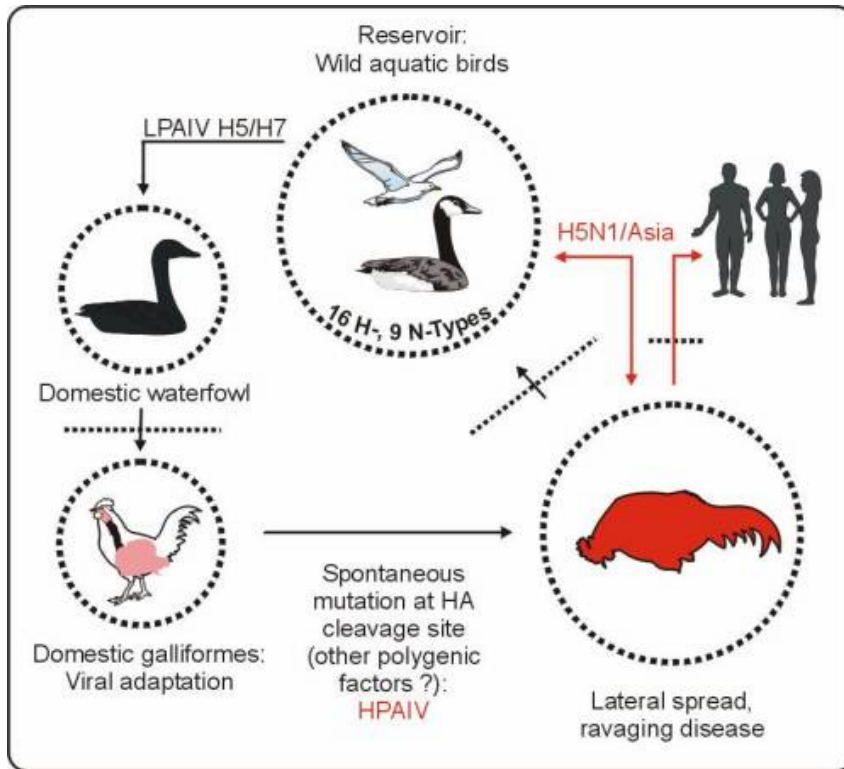
6. **Medical supplies will be inadequate** – Supplies of vaccines & antiviral drugs will be inadequate in all countries at the start of a pandemic & for many months thereafter
7. **Large numbers of death will occur** – Death rates are largely determined by 4 factors:
 - a) Number of people who become infected
 - b) Virulence of the virus
 - c) Underlying characteristics & vulnerability of affected populations
 - d) Effectiveness of preventive measures
8. **Economic & social disruption will be great** – High rates of illness & worker absenteeism are expected
9. **Every country must be prepared** – Strategic actions to provide different layers of defence
10. **WHO will alert the world when the pandemic threat increases**



The Two Mechanisms whereby Pandemic Influenza Originates.

In 1918, an H1N1 virus closely related to avian viruses adapted to replicate efficiently in humans. In 1957 and in 1968, reassortment events led to new viruses that resulted in pandemic influenza. The 1957 influenza virus (Asian influenza, an H2N2 virus) acquired three genetic segments from an avian species (a hemagglutinin, a neuraminidase, and a polymerase gene, PB1), and the 1968 influenza virus (Hong Kong influenza, an H3N2 virus) acquired two genetic segments from an avian species (hemagglutinin and PB1). Future pandemic strains could arise through either mechanism.

Transmission



Bird-to-human:

- Exposure to ill poultry & butchering of birds
- Plucking & preparing of diseased birds
- Handling of fighting cocks
- Playing with poultry
- Consumption of duck's blood & undercooked poultry

Bird-to-felids:

- Feeding raw infected chickens to tigers & leopards in zoos in Thailand

Human-to-human

- (Thailand) apparent child-to-mother (& child's aunt) transmission – intimate contact without use of precautions
- limited & has not continued beyond one person

Environment-to-human

- (Theoretical possibility) Oral ingestion of contaminated water
- Conjunctival inoculation
- Contamination of hands from infected fomites & subsequent self-inoculation

Transmission (2)

- Most strains of AI virus are found in the respiratory & GI tract of infected birds
- The HPAI (e.g. H5N1) spread to virtually to all parts of an infected bird, including the meat
- AI survives in contaminated raw poultry meat (fresh or frozen)
- Low temperatures maintain the viability of the AI virus
 - Low temp 4C: at least 35 days (in wet faeces)
 - At 25C: 7 days (in wet faeces)
 - At 37C: 6 days (in wet faeces)
- AI virus can also survive on surfaces (poultry house environment) for several weeks
- (Current H5N1 strains survive longer in faeces at warmer temperatures)



Transmission (3)

- Environmental exposure scenarios in human (theoretical possibilities) via faecal-oral & respiratory routes:
 - Consumption of drinking water contaminated by the virus
 - Recreational use (e.g. swimming or bathing) in contaminated water
 - Exposure to virus in sewage or surface water
 - Occupational exposure to excreta & infected animals (e.g. sewage treatment, agricultural practices)



Clinical Features

- Incubation period: 2 – 4 days (up to 8 days)
- Symptoms presentation:
 - High fever (Temp > 38C)
 - Influenza-like illness (cough, sore throat, & muscle aches)
- Other symptoms presentation:
 - GI: diarrhoea, vomiting, abdominal pain
 - Pleuritic pain
 - Epistaxis & gum bleeding
- (Reported cases of 2 patients) Encephalopathy & diarrhoea without apparent respiratory symptoms
- Respiratory distress, tachypnoea, & inspiratory crackles
- Clinically apparent pneumonia with progression to respiratory failure, ARDS, multi-organ failure
- Radiographic changes: diffuse, multifocal, or patchy infiltrates; interstitial infiltrates; & segmental or lobar consolidation



Clinical Features (2)

- Lab findings:
 - Leucopenia, particularly lymphopenia
 - Mild-to-moderate thrombocytopenia
 - Slightly or moderately elevated aminotransferase levels
- Virologic Diagnosis:
 - Viral isolation/culture (“gold standard”)
 - Immunofluorescent antibody staining (IFA)
 - Detection of H5-specific RNA (RT-PCR assays)
 - Serological assay, haemagglutination inhibition (Commercial rapid antigen tests)
- Duration of viral shedding in children <12yrs with human influenza
 - can last up to 21 days
 - may also be protracted in children & adults with avian influenza H5N1



Commercial Influenza Rapid Diagnostic Tests

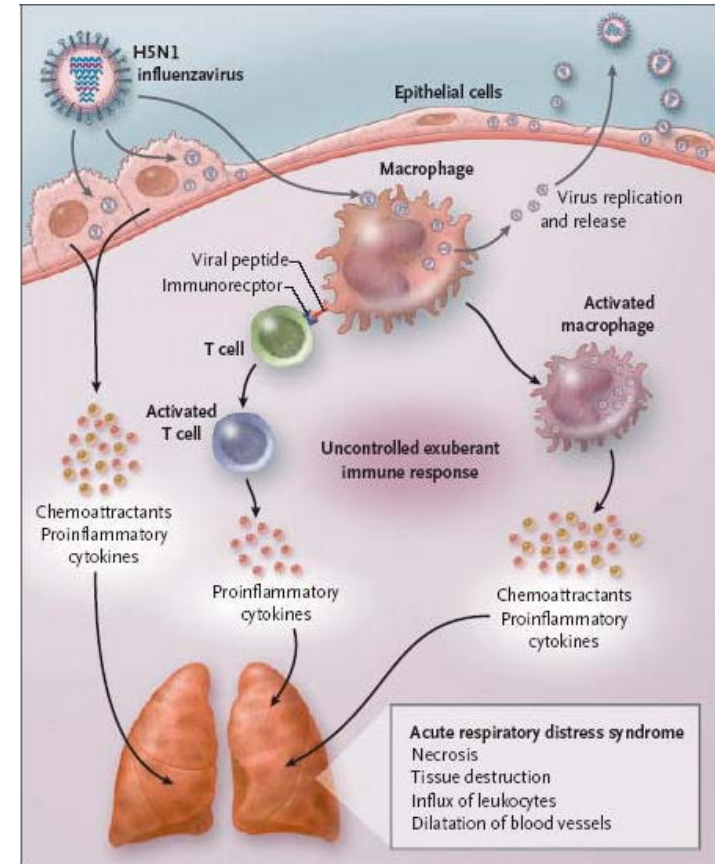
WHO recommendations on the use of rapid testing for influenza diagnosis, July 2005

- Screening tests for Influenza A & B virus infections
- Also referred to as 'near patient' or 'point-of-care' tests
- Largely immunoassays that detect influenza viral antigens or viral neuraminidase activity:
 - a. Detect & distinguish between influenza A & B infections
 - b. Detect but do not distinguish between influenza A & B infections
 - c. Detect influenza A only
- In suspected human infection of AI:
 - Rapid tests **will not differentiate** between human & AI A virus subtypes
 - Use of rapid test should be **in combination** with **clinical findings** & **exposure history**
 - Rapid tests should only be used where clinical guidelines exists, & confirmatory RT-PCR test are available (or prior arrangement made with national /WHO H5 Reference Lab)



Pathogenesis

- Innate immune response to Influenza (H5N1) may contribute to disease pathogenesis
- Plasma level of inflammatory mediators (certain interleukins, IL) were found to be higher among patients who died than among those who survived
- Proposed mechanism of cytokine storm: an uncontrolled exuberant immune response to the virus with an outpouring of pro-inflammatory cytokines & chemoattractants
- Such response may be responsible in part for the sepsis syndrome, ARDS, & multi-organ failure



Osterholm, Michael T. *Preparing for the next pandemic.*
NEJM 352;18 5 May 2005: 1839-1842

Management

- Patient with suspected or proven H5N1 infection should be hospitalised in isolation
- Supportive care
- Supplemental oxygen & ventilatory support
- Nebulisers & high-air flow oxygen masks should be used only with strict airborne precautions
- Use of anti-viral agents for treatment:
 - **Neuraminidase inhibitor:** the H5N1 virus is susceptible in vitro to oseltamivir (Tamiflu) & zanamivir (Relanza)
 - Recent H5N1 isolates are **highly resistant** to the M2 inhibitors amantadine & rimantadine
- (? role of other neuraminidase inhibitors, inteferon alfa, & immunomodulators)



Prevention



- **No Influenza A (H5) vaccines** are currently commercially available for humans - several candidate vaccines are under study
- **Household & close contacts:**
 - hand-hygiene, do not share utensils, avoid face-to-face contact with patients, consider donning high-efficiency masks & eye protection
 - post-exposure prophylaxis with oseltamivir
- **Travellers**
 - immunised with the available trivalent human vaccine, at least 2 weeks before travelling
 - avoid all direct contact with poultry, & farms or live-animal markets with poultry
 - avoid touching surfaces contaminated with poultry faeces or secretions
 - practise good hand hygiene & by not ingesting undercooked eggs or foods from poultry
 - to consult health care provider if fall ill with fever + respiratory symptoms within 10 days of return from an affected area



Prevention (2)



■ Isolation precautions in health care facilities

- combination of standard, contact, droplet, & airborne isolation precautions
- isolation in a negative-pressure room, if available
- limit number of healthcare workers with direct contact patients & limit access to the environment of patients
- restrict visitors to a minimum & give them proper PPE & instructions on its use

■ Healthcare workers (HCW)

- PPE (personal protective equipment): N-95 mask or equivalent, long-sleeved cuffed gowns, face shield or eye goggles, & gloves
- daily temperature surveillance & to report any febrile event
- post-exposure chemoprophylaxis with oseltamivir
- pre-exposure chemoprophylaxis with oseltamivir to be considered for HCW involved in high-risk procedures (e.g. aerosol-generating procedures)



Food Safety Implications

WHO, International Food Safety Authorities Network (INFOSAN), 4 November 2005

- Conventional cooking (temp at or $> 70^{\circ}\text{C}$ in all parts of a food item) will inactivate the H5N1 virus
- H5N1 virus, if present in poultry meat, is not killed by refrigeration or freezing
- Home slaughtering & preparation of sick or dead poultry for food is hazardous
- Eggs can contain H5N1 virus both on the outside (shell) & the inside (whites & yolk)
- Uncooked eggs should not be used in foods that will be cooked, baked or heat-treated in other ways
- No epidemiological evidence to indicate that people have been infected with H5N1 virus following consumption of properly cooked poultry or eggs
- Greatest risk of exposure to virus is through the handling & slaughtering of live infected poultry



Recommended good hygiene practices

WHO, International Food Safety Authorities Network (INFOSAN), 4 November 2005

- Separate raw meat from cooked or ready-to-eat foods to avoid contamination
- Keep clean & wash hands after handling frozen or thawed raw chicken or eggs
- Wash hands thoroughly with soap
- Cook thoroughly - poultry meat reaches 70C at the centre of the product; egg yolks should not be runny or liquid
- Do not eat raw poultry parts or raw eggs



Oseltamivir

(WHO Advice on Use of Oseltamivir, 17 March 2006) (NEJM 353;13, Sep 29, 2005)

- Recommended for use for both treatment & prophylaxis of influenza
- Evidence of effectiveness in human H5N1 disease is based on available virological data, animal models, & limited human studies
- Optimal dose & duration of treatment is uncertain in H5N1 disease
- Doses used for seasonal human influenza continue to be recommended

- Dosage for **treatment**:
 - Adult: 75 mg, twice daily for 5 days
 - Children **1 year of age or older**: (weight adjusted dose for 5 days)
 - 30mg twice daily for 15kg or less
 - 45mg twice daily for > 15 to 23kg
 - 60mg twice daily for > 23 to 40kg
 - 75mg twice daily for > 40kg
 - Children up to 1 year of age: **not recommended**

Prospective studies needed: ? 150mg twice daily in adults for 7 to 10 days duration in treating severe infections



Oseltamivir (2)

(WHO Advice on Use of Oseltamivir, 17 March 2006) (NEJM 353;13, Sep 29, 2005)

- The evidence for effectiveness for prophylaxis of H5N1 disease is based on the results of trials of preventing human influenza in healthy & elderly patients & children
- Dosage for **prophylaxis**:
 - Adults & teenagers 13 years of age or older:
 - 75 mg once daily for 7-10 days
 - (from the last day of a potentially infective exposure)
 - Children from **1 year to 13 years of age**: (weight adjusted dose 7 -10 days)
 - 30 mg daily for 15kg or less
 - 45 mg daily for > 15 to 23kg
 - 60 mg daily for > 23 to 40kg
 - 75 mg daily for > 40kg
- For people with repeated or prolonged exposure such as HCW or personnel involved in bird culls: pre-exposure courses / repeat post-exposure courses / continuous treatment may be necessary
- Continuous treatment for up to 6 weeks with 75 mg/day is generally well-tolerated
- Efficacy & safety of post-exposure prophylaxis have been shown in children 1 year & older



Oseltamivir (3)

- Menno D. de Jong et al. Oseltamivir resistance during treatment of Influenza A (H5N1) infection. NEJM 353; 25, December 22, 2005: 2667 - 2672
- Oseltamivir treatment failure in Influenza A (H5N1)
 - Institution of treatment late in the course of the illness
 - Primary infection with overwhelming viral replication
 - Altered pharmacokinetics in severely ill patients (e.g. diarrhoea)
 - Oseltamivir-resistance mutant virus with H274Y substitution in the neuraminidase gene
- Rapid decline in viral load to undetectable levels in those patients who survived
- Further evaluation needed to improve antiviral efficacy:
 - Higher doses, longer duration of therapy, or combination therapy
 - Oseltamivir-resistant influenza virus: Inclusion of other antiviral agents in the treatment arsenals (e.g. Zanamivir)

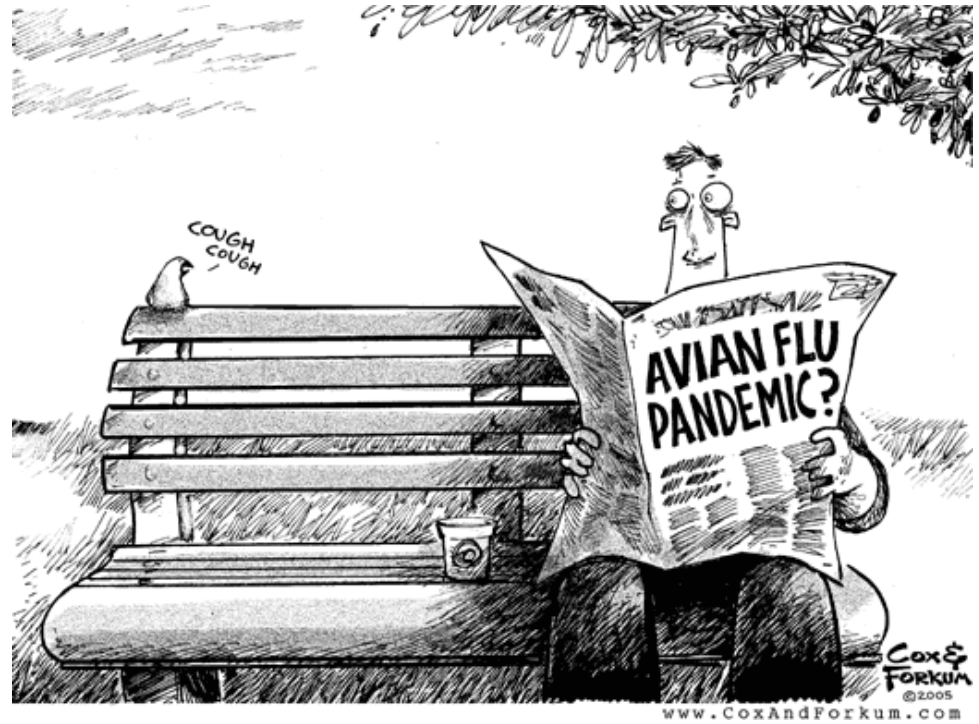
Conclusions

- Infected birds have been the primary source of Influenza (H5N1) infections in humans
- Transmission between humans is very limited at present
- H5N1 in human differs in multiple ways from human strain influenza including: Routes of transmission, Clinical severity, Pathogenesis, Response to treatment
- Detailed contact & travel histories, & knowledge of viral activity in poultry are essential for case detection
- Recent human isolates are fully resistant to M2 inhibitors
- Knowledge of the epidemiology, natural history, & management of H5N1 disease is incomplete



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Thank You