


Pediatric Challenges and Opportunities in the 21st Century
 21 - 22 April, 2006

Avian Flu: The Risks of Pandemic Outbreak

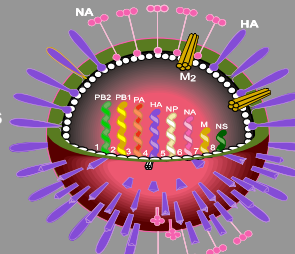

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www.Cure4Kids.org


Avian Flu: The Risks of Pandemic

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- Negative sense RNA virus segmented genomes
- Each segment encodes a different protein
- Smallest RNAs encode 2 proteins



The Influenza Epidemics of Great Britain

First epidemic in Britain 1510

Epidemics Of:	1588	★ 1729	1775	1833
	1658	1737	★ 1782	1836
	1675	1743	1789	1837
	1688	1758	1790	
	1693	1762	1803	
	1709	1767	★ 1831	

Annals of Influenza in Great Britain (1850)

1918 Spanish Influenza

- 50 – 100 million persons killed
- Total sequence now known – **Taubenberger**
- Closely related to classic H1N1 swine influenza
- Avian source of all gene segments

Brevig Mission – 1918 Spanish Influenza



- Letter carrier taken home by dog team.
- Nov 15 - 20: 72 of 80 people in Brevig died.
- Children survived

1918 Spanish Influenza



Jeffery Taubenberger



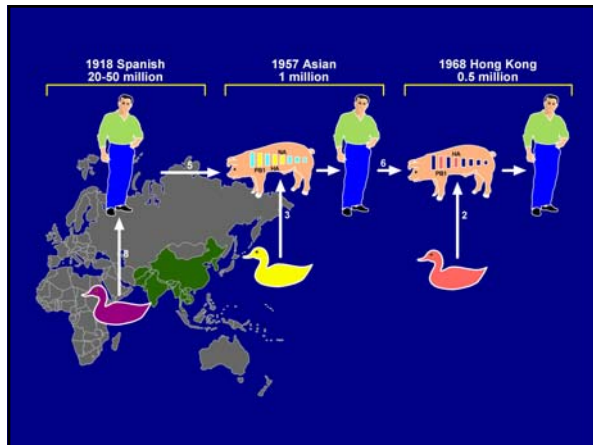
Johan Hultin

Brevig Mission –
The Complete
Sequence

Reconstructed 1918 Spanish Influenza

- Lethal for mice and embryonated eggs
- Replicates in the absence of trypsin
- High growth in human bronchial epithelial cells

Tumpey et al., Science, October 2005

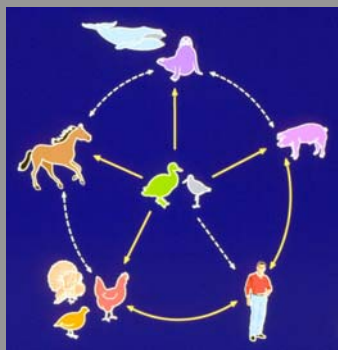


Influenza A Virus Host Range

H1	Human	Pig	Bird
H2	Human	Pig	Bird
H3	Human	Pig	Horse
H4	Human		Bird
H5	Human		Bird
H6	Human		Bird
H7	Human		Horse
H8	Human		Bird
H9	Human		Bird
H10			Bird
H11			Bird
H12			Bird
H13			Bird
H14			Bird
H15			Bird
H16			Bird

The Ecology of Influenza Viruses

- That there are a limited number of host specific lineages of influenza viruses
- There is geographical separation into Eurasian and American lineages



Spread of H5N1 Influenza in Asia 2004-2005



100s of millions of birds culled
Human Cases: 194
Human Deaths: 109
 Vietnam: 42 deaths
 Thailand: 14 deaths
 Cambodia: 6 deaths
 Indonesia: 23 deaths
 China: 11 deaths
 Turkey: 4 deaths
 Iraq: 2 deaths
 Azerbaijan: 5 deaths
 Egypt: 2 deaths

Genesis of H5N1 Influenza In Asia



1996 Goose/Guangdong/1/96 (H5N1)

1997 Emergence of H5N1 Bird Flu

A reassortant

Goose X Quail X Duck

H5N1 H9N2 H6N1

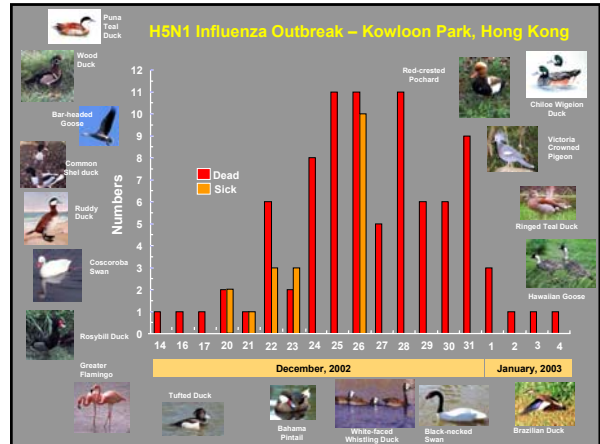
6 of 18 infected persons died

1997-2002 ► Multiple genotypes

2003-2005 ► Pathogenic for aquatic birds

► Spread across Asia

H5N1 Influenza Outbreak – Kowloon Park, Hong Kong



The Spread of H5N1 in Asia



Poultry Market Surveillance Southern China 2004-2005



H5N1 Influenza Viruses Isolated From Live Poultry Markets In Southern China 2004 - 2005



1.9%



1.8%

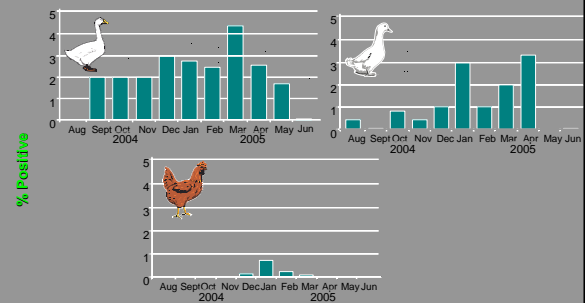


0.5%

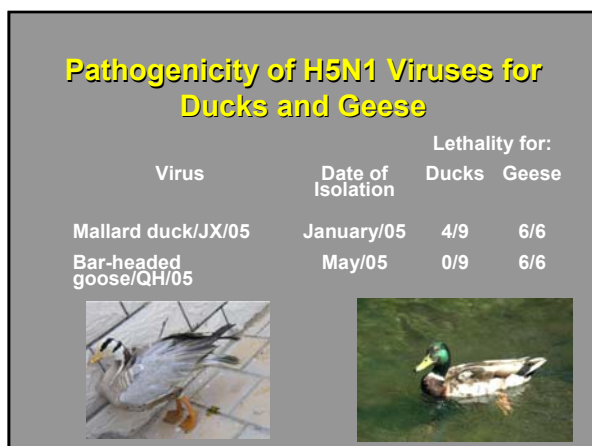
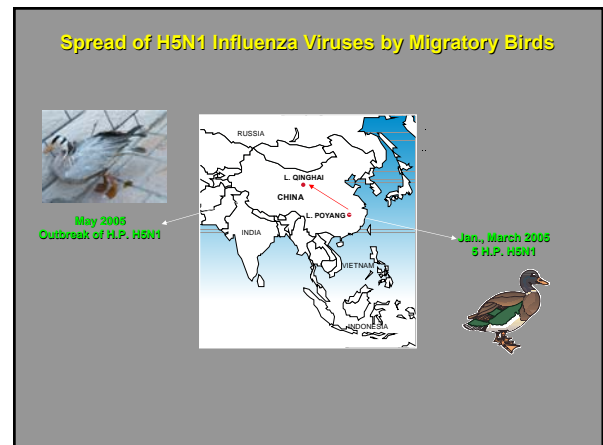
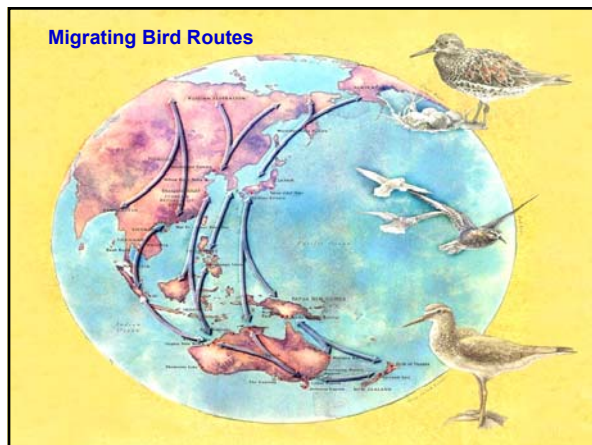
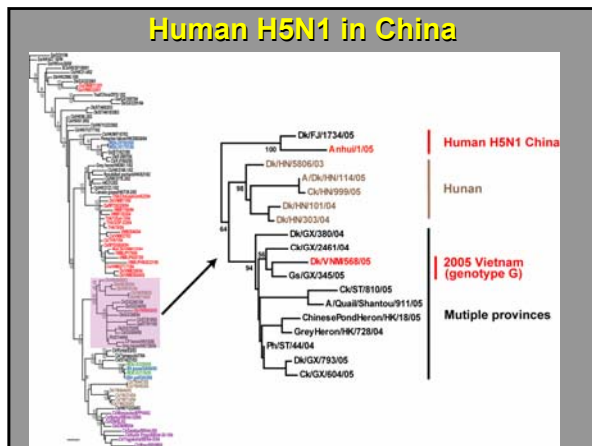


0.3%

Isolation of H5N1 Viruses From Live Poultry Markets in S. China



Based on numbers (%) from August 2004 to June 2005



The Role of Ducks

- Domestic
- Migratory

"The Trojan Horses"

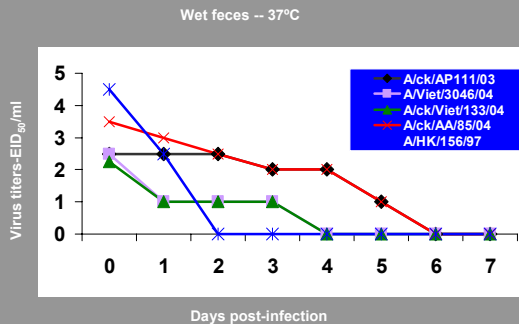


Rapid Evolution of H5N1 in Ducks

- Long term shedding despite antibody
- Retain HPAI characteristics
- Antigenic drift
- Increased environmental stability



H5N1 Stability in Fecal Samples



H5N1 – Thermal Stability



H5N1 in cooling coils remained viable for 45 days

Chantane Buranathai
Thailand

How Pathogenic Is This Virus?

A/Vietnam/1203/04 (H5N1)

- Kills chickens in less than one day
- Kills ducks in 1-2 days
- High risk of death in humans
 - Diarrhea
 - Respiratory symptoms
- High Risk of death in ferrets
 - Respiratory symptoms
 - Diarrhea
 - Hind Leg paralysis

Human H5N1 Cases in Vietnam

- Multiple organ dysfunction
- More virus in the lower respiratory tract
- Diarrhea in majority of patients
 - Virus isolation 1/7
 - RNA 5/7
- Detection of RNA in human serum 4/7
- Median virus load 6 days for H5N1, 2 days for H3N2



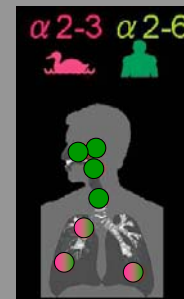
Menno de Jong, Ho Chi Minh City, Vietnam,
Oxford University Clinical Research Unit

Human H5N1 Influenza in Vietnam

- High levels of cytokines (IP10, IL6, IL8, INT γ)
- IP10 and IL8 correlates with virus load

Menno de Jong, Ho Chi Minh City, Vietnam,
Oxford University Clinical Research Unit

Receptor Distribution in Humans



Shinya et al Nature 2006

Does H5N1/04 Replicate and Transmit in Pigs?

	Infected	Contact	
Vietnam/1203/04	—	0	
Ck/Vietnam/C-58/04	—	0	
DK/TH/D4AT/04	—	0	
GS/TH/G7CS/04	—	0	

Choi et al 2005

Expanding Host Range for Influenza



H5N1 in Thailand



Experimental transmission in domestic cats

Kuilken et al, Science 2004

Prevention and Control



Control Strategies: H5N1 Poultry

ERADICATION

Culling — Quarantine — Biosecurity



The Hong Kong Model

- 1998 
- 2000 One clean day per month
- 2001 
- 2002
- Inactivated vaccine used to ring vaccinate H5N1 infected farms
 - Additional clean day per month
- 2003
- Inactivated vaccine used on all farms
 - increased biosecurity
 - sentinel unvaccinated poultry
- 2004 No H5N1

Control Strategies: H5N1 Poultry

Vietnam: The ongoing experiment.

Vaccination → Eradication of Virus
→ Eradication of Symptoms

Residual Virus



Control Strategies: H5N1 Poultry

China: Changing strategies?
(Indonesia)

Vaccination → Disease control - Poultry
→ Continued low level virus circulation — no disease
→ New vaccine strategies? (Biosecurity??)

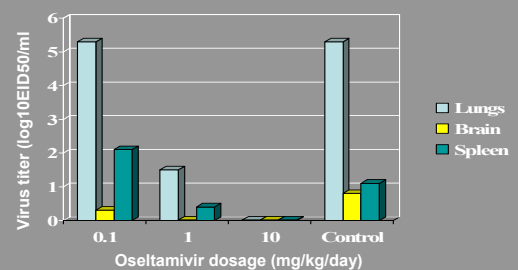


Antivirals

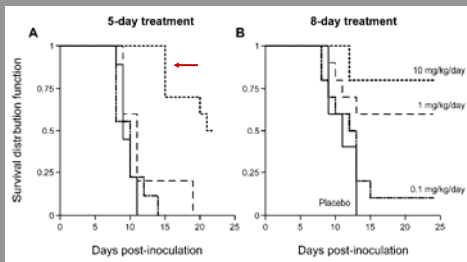
Sensitivity of Human H5N1 Influenza Viruses to Amantadine

Year	Virus	Sensitivity	Amino acid change on M2 protein
1997	A/HK/156/97	Yes	Ser31
2003	A/HK/213/03	No	Ser31→Asn
2004	A/Vietnam/1203/04	No	Ser31→Asn
	A/Vietnam/1194/04	No	Ser31→Asn

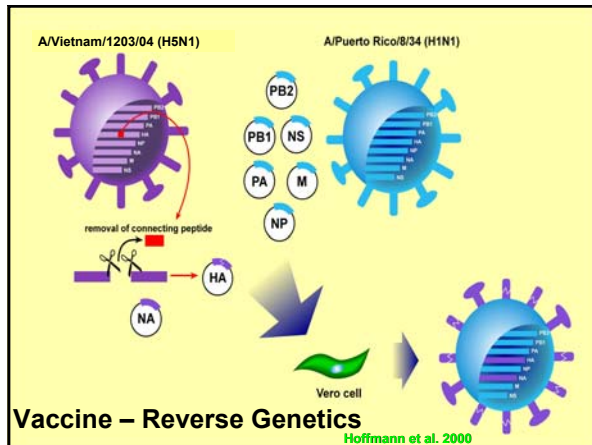
Reduction of A/Vietnam/1203/04 (H5N1) Virus Replication after Prophylactic Treatment of Mice with Oseltamivir



Survival of Mice After A/Vietnam/1203/04 (H5N1) Infection



Vaccines



Studies on r.g. H5N1 Vaccines in Ferrets

- r.g. Hong Kong/213/04 (H5N1)
- Complete protection from homologous challenge
- Cross protection from challenge with A/Vietnam/1203/04
 - Virus shedding reduced
 - Weight loss
 - No virus in brain
 - No disease signs

Poultry Vaccines

Good Ones

- Provide protection despite antigenic drift
- Can reduce virus load below level of transmission

Bad Ones

- Protect against disease signs
- Birds shed transmissible levels of virus

Efficacy of H5N3 Vaccine in Khaki Campbell Ducks

Treatment	Outcome		
	Disease/Death /Total	Virus Shedding	Transmission to Non-vaccinated Contacts
Vaccine-1x	0/0/10	0/10	0/10
Vaccine -- boost	0/0/10	0/10	0/10
Control	10/8/10	10/10	

Thaweesak Songserm-SJCRH

Vaccine: Chicken/Vietnam/C58/04 (H5); dk/Germany/1215/73 (N3); PR/8/34 internal genes

Dose: 0.25µg HA antigen

Schedule: Vaccinate day 0, boost day 14, challenge 28 days

Challenge: DK/Thailand/D4AT/04 (H5N1)

Ducks: 4 weeks old at day 0

The Current Situation

- Humans → New human cases in:
Indonesia, Turkey, Azerbaijan, Egypt, Iraq, Cambodia, China
► Antigenically and genetically different viruses in Indonesia, China, Europe (3 clades)
- Poultry → H5N1 causing asymptomatic infection in ducks but killing swans
- Wild birds → Highly pathogenic H5N1 is endemic and spreading globally

Duck Blood Salad

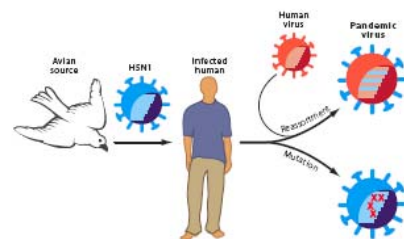


Leuad Peng Pet

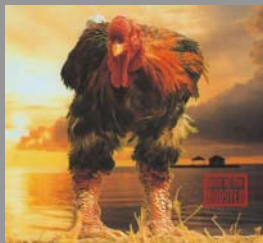
The Consequence of a H5N1 Influenza Pandemic

- **Collapse of the global economy**
 - Exhaustion of all materials made off shore!!!
 - ↓ Vaccines
 - ↓ Antivirals
 - ↓ Masks
 - ↓ Needles
 - ↓ Much more!!

Will H5N1 Acquire Transmissibility?



HAPPY NEW YEAR OF THE DOG



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Dr. Thaweesak Songserm





Questions and Answers

Some questions were asked without a microphone nearby and may be difficult to hear, but they are presented here.




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End

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