

Clinician Update on Avian Influenza

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Outline

- Pandemic influenza versus seasonal flu
- Clinical features of influenza A (H5N1)
- Early recognition and containment of AI
- Resources for clinicians

Recognizing Avian Influenza

Virus kills Vietnamese girl

January 20, 2004

Eight-year-old is fifth victim as fears rise over epidemic

Hanoi, Reuters

An eight-year-old girl has been confirmed as the fifth person to die in Vietnam from an outbreak of bird flu, while nine other children with respiratory ailments are being tested for the virus, doctors said yesterday.

The girl, from the northern province of Ha Tay, died on Saturday. She was taken to hospital in Hanoi on Jan 15 after first showing symptoms on Jan 11, the World Health Organisation (WHO) said yesterday.

"WHO confirms this is the fifth case of death from H5N1," said Robert Dietz, a spokesman for the UN agency, referring to the strain of bird flu.

The WHO says there has been no sign the disease is being spread between humans. Its victims are believed to have caught it from infected chickens and eating cooked chicken and eggs is safe, officials say. But experts are worried there might be a mixing of the avian flu with a human flu and a new, contagious deadly disease could sweep out of Asia, a year after Severe Acute Respiratory Syndrome emerged and killed about 800 people around the world.

South Korea, Japan and Taiwan have



vention (CDC) are expected to arrive in Hanoi last night.

One of the CDC team is an expert on influenza. "We hope we can exchange with the CDC experts about the efficacy of treatment," Nguyen Thanh Liem, director of the children's hospital, told Reuters Television in an interview.

The children are being treated with antiviral drugs and antibiotics, he said.

Dr Liem said it was a "mystery" why the human flu cases were clustered in the north, while the chickens were sick in the south. Possible explanations are differing climate conditions and that some cases in the south may not yet have been diagnosed.

Two hospitals in the south have been treating suspected avian flu patients. Kien Giang General Hospital said on Sunday a man showing symptoms similar to those seen in bird flu victims had died. A woman with the same symptoms was recovering.

Can Tho Paediatric Hospital said yesterday a two-month-old child died on Thursday from respiratory illness.

Can Tho is among the 15 provinces that have declared an outbreak of bird flu. Kien Giang, one of the southernmost provinces in Vietnam, has not reported an outbreak.

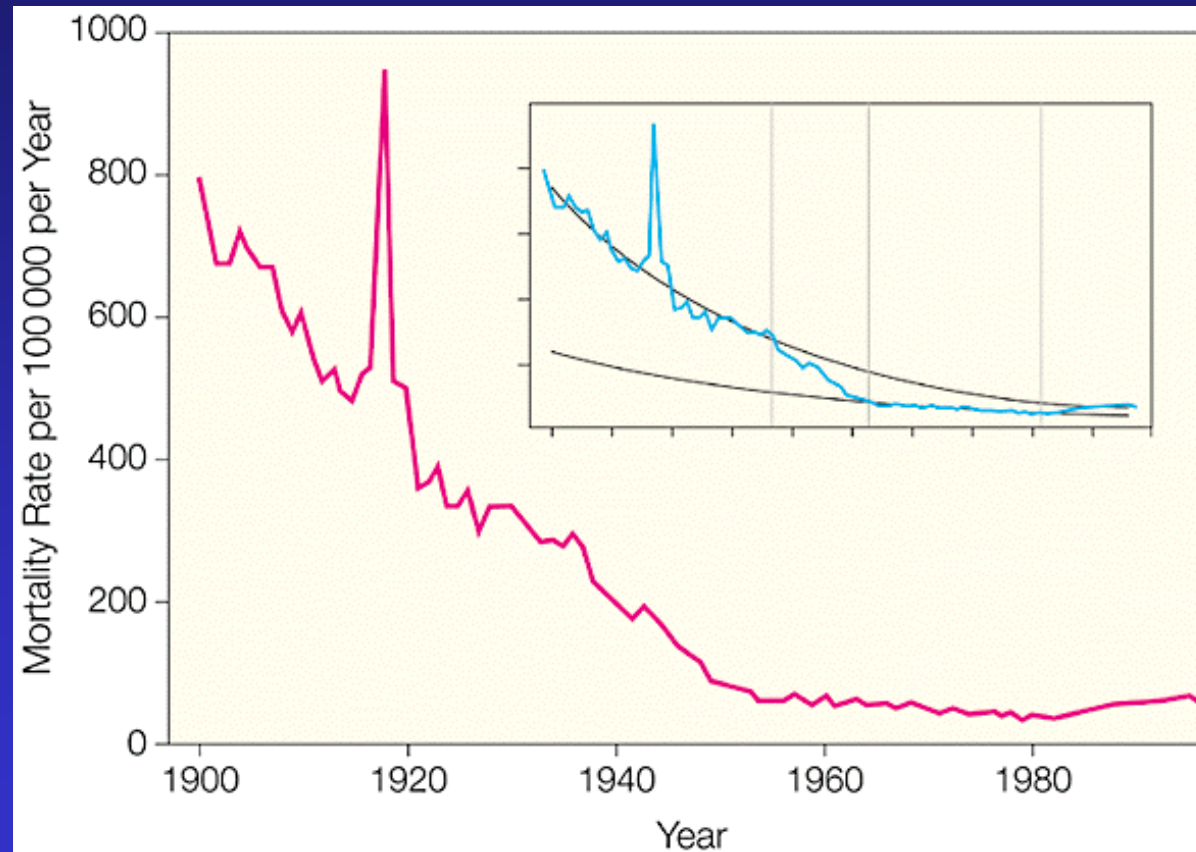
Doctors say bird flu in humans looks similar to common flu, with high fever, sore throat and a dry cough that can deteriorate into severe respiratory prob-

Pandemic Influenza



Photo: The American Red Cross

US Infectious Disease Mortality: The Impact of Influenza and AIDS

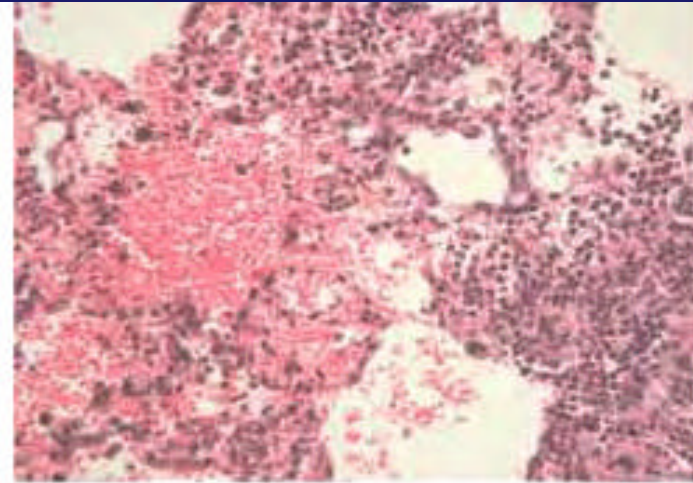
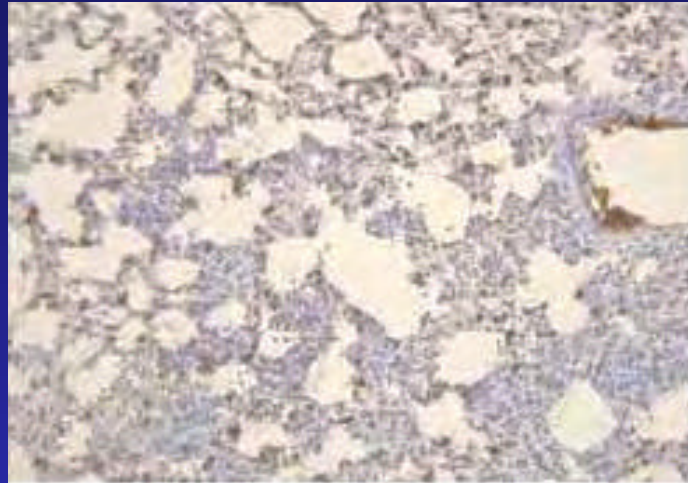


Armstrong. JAMA 1999;281:61

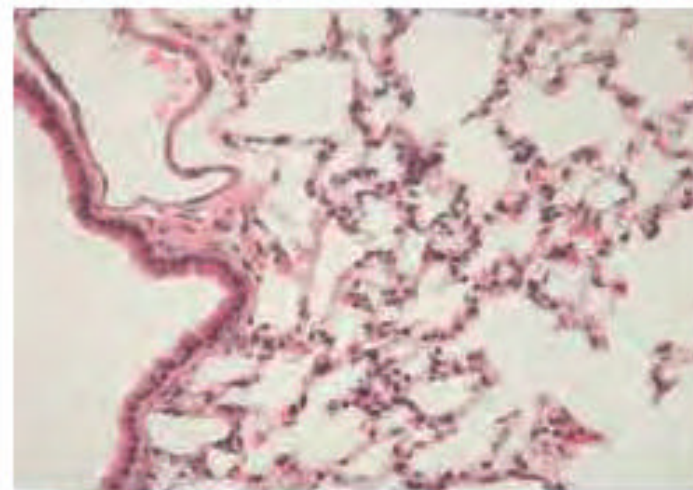
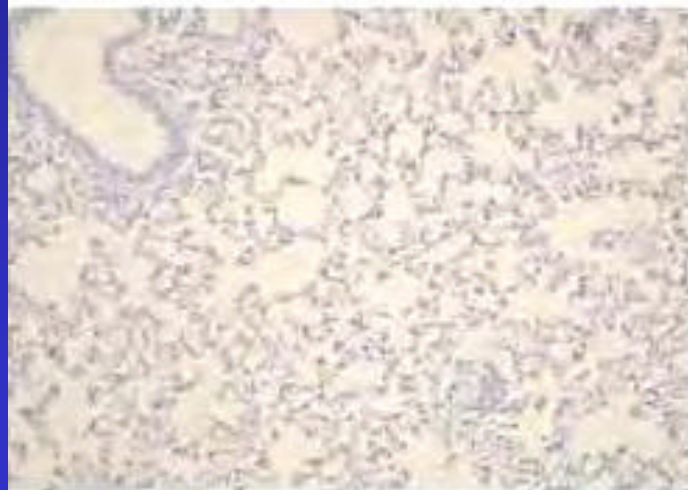


1918 Hemagglutinin Causes Severe Lung Damage

M88/H^{sp}

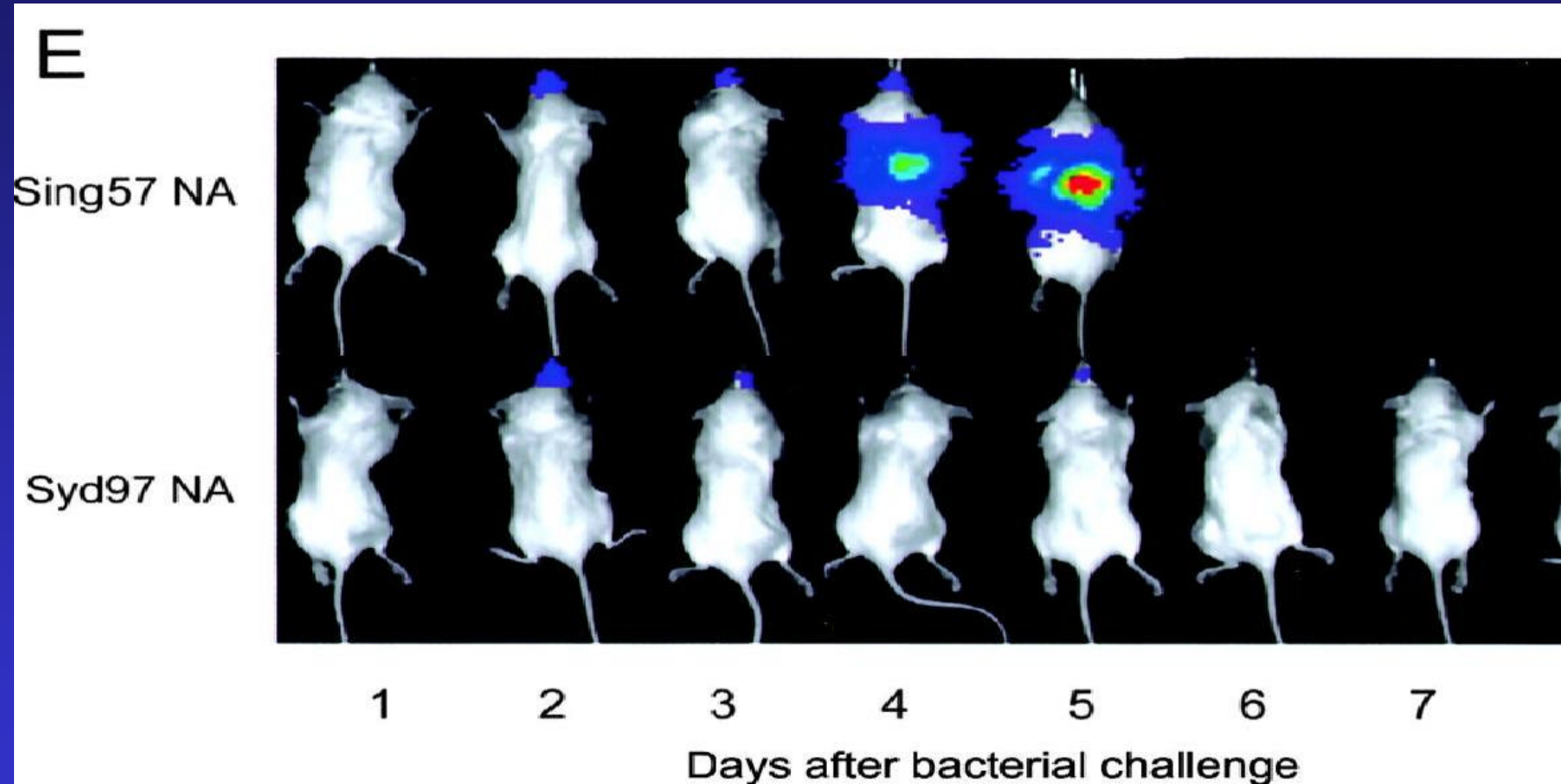


M88



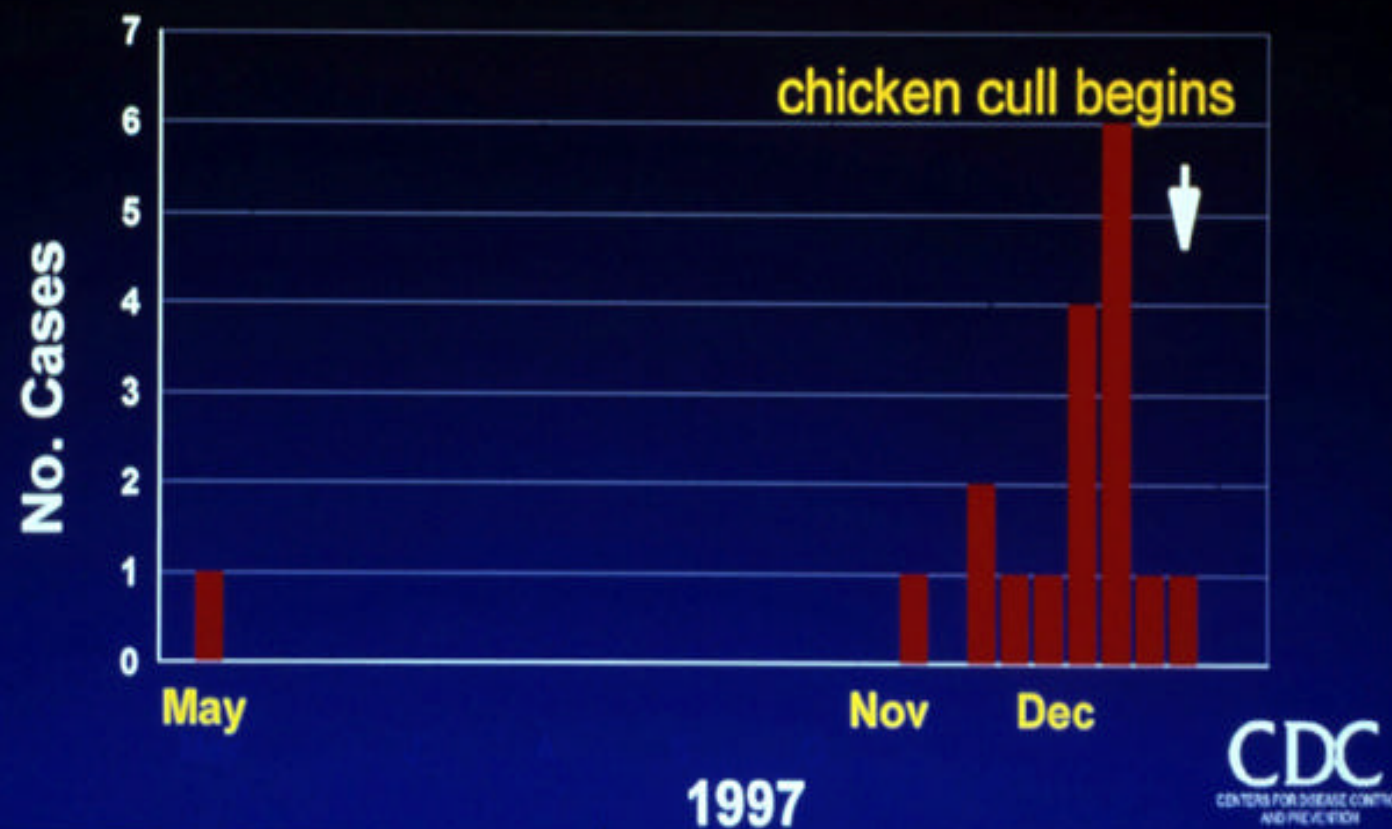
Kobasa et al. Nature 2004;431:703

Neuraminidase Sets Up Bacterial Pneumonia



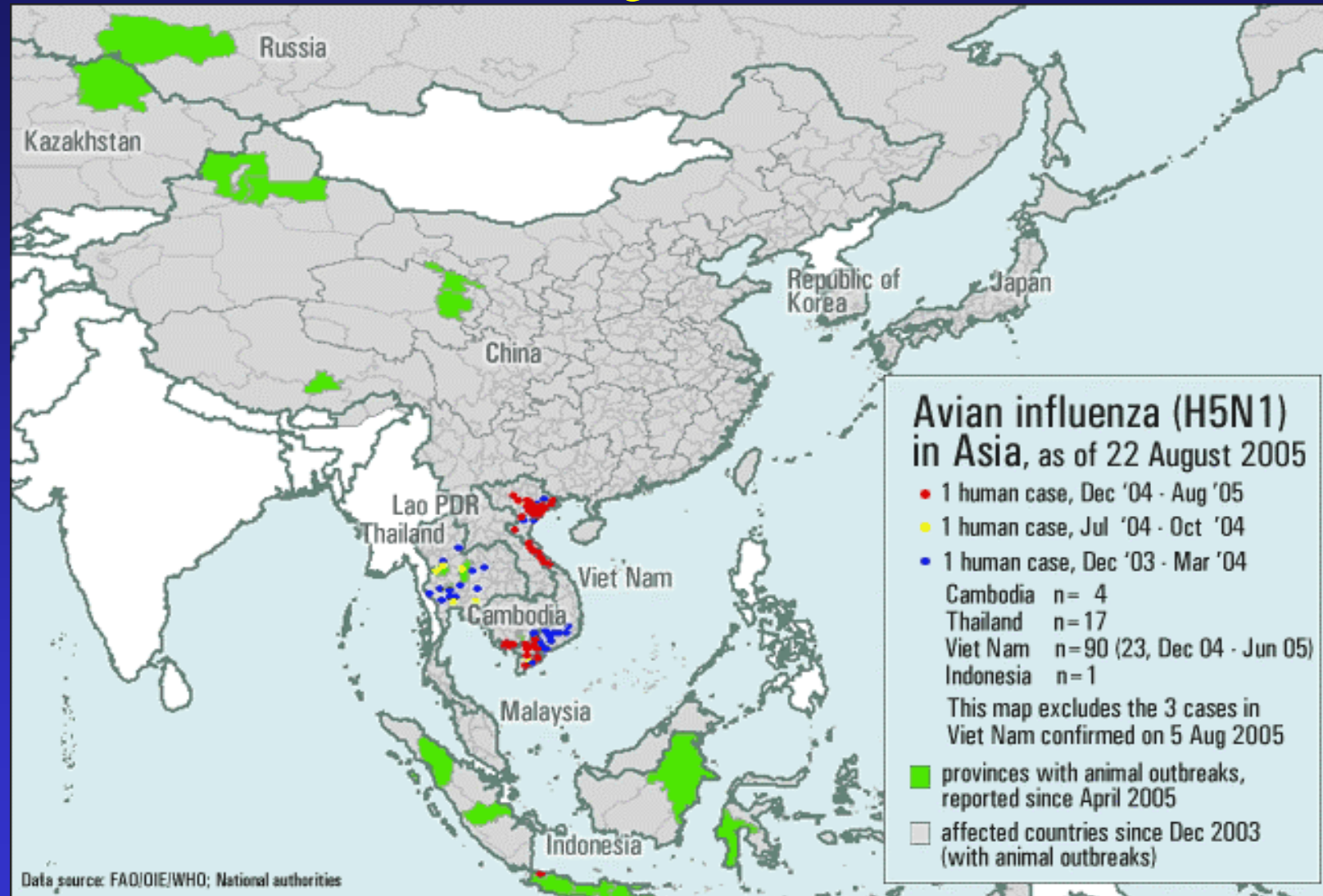
Peltola et al. JID 2005;192:249

Influenza A(H5N1) Cases by Week of Illness Onset, Hong Kong, 1997



Avian Influenza in Asia

(22 August, 2005)



Disclaimer: The presentation of material on the maps contained herein does not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or areas or its authorities of its frontiers or boundaries.



Human H5N1 Most Common in Children

Age	Sex	Onset	Exposure	Outcome
7	M	3 Jan	Dead poultry at neighbors	Died
6	M	6 Jan	Dead poultry at neighbors	Died
6	M	7 Jan	Sick poultry at neighbors	Died
58	F	19 Jan	Sick poultry in backyard	Died
27	F	20 Jan	Purchased, cooked chicken from affected area	Recovered
4	M	21 Jan	Sick/dead fighting cocks, poultry in backyard	Died
6	M	24 Jan	Dead poultry in backyard	Died
2	M	25 Jan	Sick poultry in backyard	Recovered
13	M	26 Jan	Sick poultry in backyard	Died
47	F	3 Feb	Sick/dead fighting cocks in backyard	Recovered
29	M	13 Feb	Sick/dead fighting cocks, chicken in backyard	Recovered
39	F	1 Mar	Dead fighting cock at neighbors	Died
18	M	31 Aug	Sick/dead fighting cock in backyard	Died

Thai Children at Risk for H5N1 Infection

Knowledge, attitudes, and practices*	Before	After	p-value
Thought it was safe to touch sick or dead poultry with bare hands	78 (40)	27 (14)	<0.01
Thought it was safe for children to touch sick or dead poultry with bare hands	45 (23)	9 (5)	<0.01
Children in your household touched sick or dead poultry with bare hands	12 (6)	7 (4)	0.4
Took dead chicken or poultry from your yard and prepared it to eat	24 (12)	17 (9)	0.3

* Before and after a public education campaign
Olsen et al. EID 2005;11:



TABLE. Clinical features, treatment, and outcomes in five patients with laboratory-confirmed influenza A (H5N1), by sex and age of patient — Thailand, 2004

Sex	Age (yrs)	Signs and symptoms on admission*	Subsequent complications	Initial investigative findings	Treatment and outcome
Male	7	Fever, cough, sore throat for 6 days. Dyspnea on day 6; CXR [†] bilateral interstitial infiltrates.	Respiratory failure on day 10; cardiac failure, pneumothorax, ARDS [§] , gastrointestinal bleeding.	Leukocytes: 4,100/ μ L Lymphocytes: 1,440/ μ L Platelets: 304,000/ μ L AST [¶] : 120, ALT ^{**} : 52	Oseltamivir on days 18–22. Died on day 29.
Male	6	Fever, cough, rhinorrhea for 5 days. Dyspnea on day 6; CXR patchy infiltrates in right lower lobe.	Respiratory failure on day 8; hepatitis, ARDS.	Leukocytes: 1,200/ μ L Lymphocytes: 624 / μ L Platelets: 89,000/ μ L AST: 790, ALT: 150 Proteinuria: \geq 3	Oseltamivir on days 18–20. Died on day 20.
Male	6	Fever, cough, rhinorrhea, sore throat for 4 days. Dyspnea on day 5; CXR multifocal patchy infiltrates.	Respiratory failure on day 6; pneumothorax, ARDS.	Leukocytes: 2,200/ μ L Lymphocytes: 638/ μ L Platelets: 150,000/ μ L AST: 175, ALT: 43	Died on day 18.
Female	58	Fever, cough, sore throat, myalgia for 2 days. Dyspnea on day 2; CXR multifocal patchy infiltrates.	Respiratory failure on day 4; cardiac failure, renal failure, ARDS.	Leukocytes: 5,680/ μ L Lymphocytes: 454/ μ L Platelets: 185,000/ μ L BUN ^{††} : 39 mg/dL Creatinine: 2.3 mg/dL	Died on day 8.
Male	6	Fever, cough, sore throat, myalgia for 4 days. Dyspnea on day 5; CXR multifocal patchy infiltrates.	Respiratory failure on day 5; cardiac failure, renal failure, ARDS.	Leukocytes: 2,900/ μ L Lymphocytes: 696/ μ L Platelets: 87,000/ μ L AST: 280, ALT: 50 BUN: 54 mg/dL Creatinine: 4.6 mg/dL	Oseltamivir on days 5–8. Died on day 8.

* No patients had an underlying illness reported.

[†] Chest radiograph.

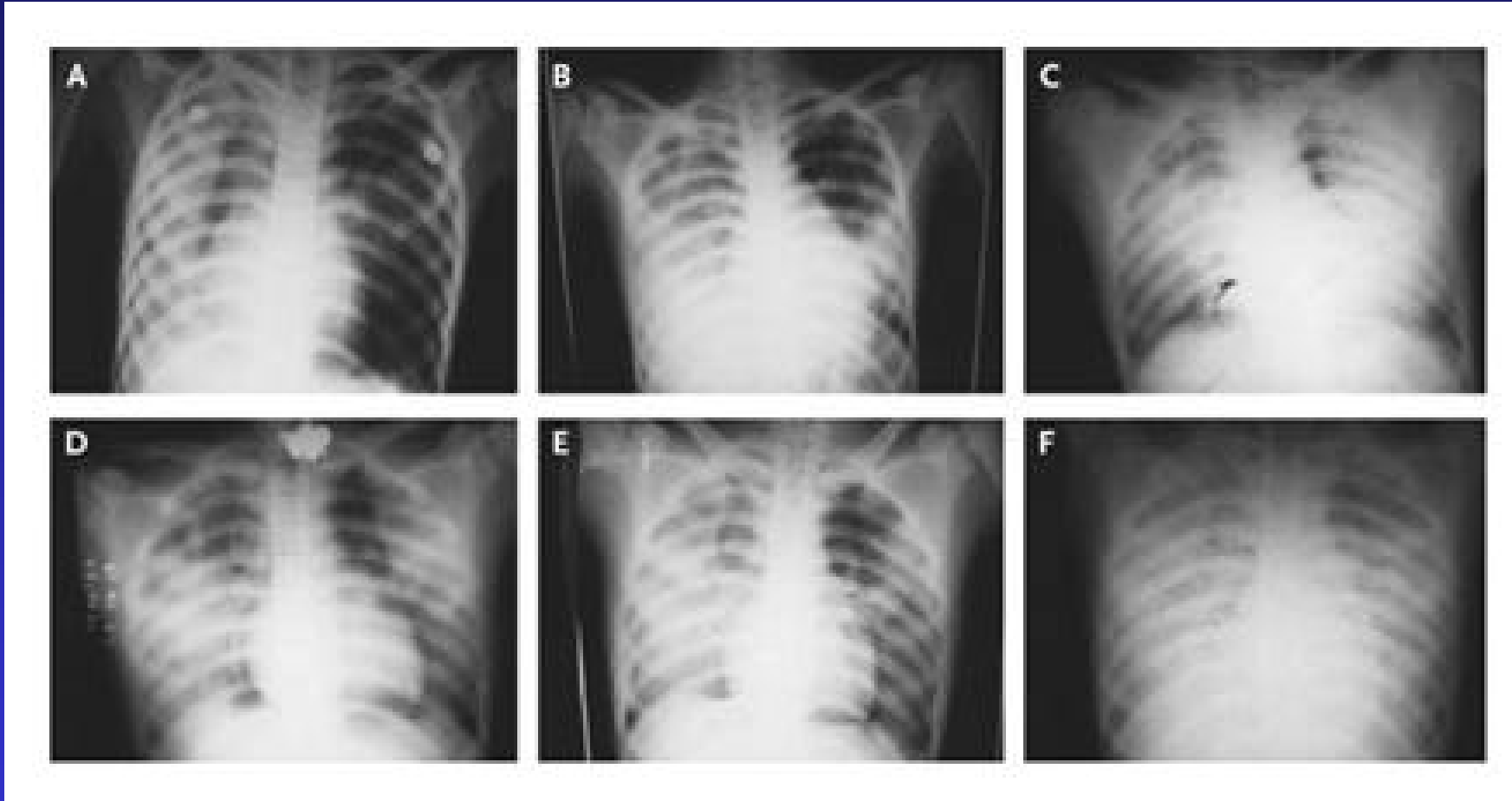
[§] Acute respiratory distress syndrome.

[¶] Aspartate aminotransferase.

^{**} Alanine aminotransferase.

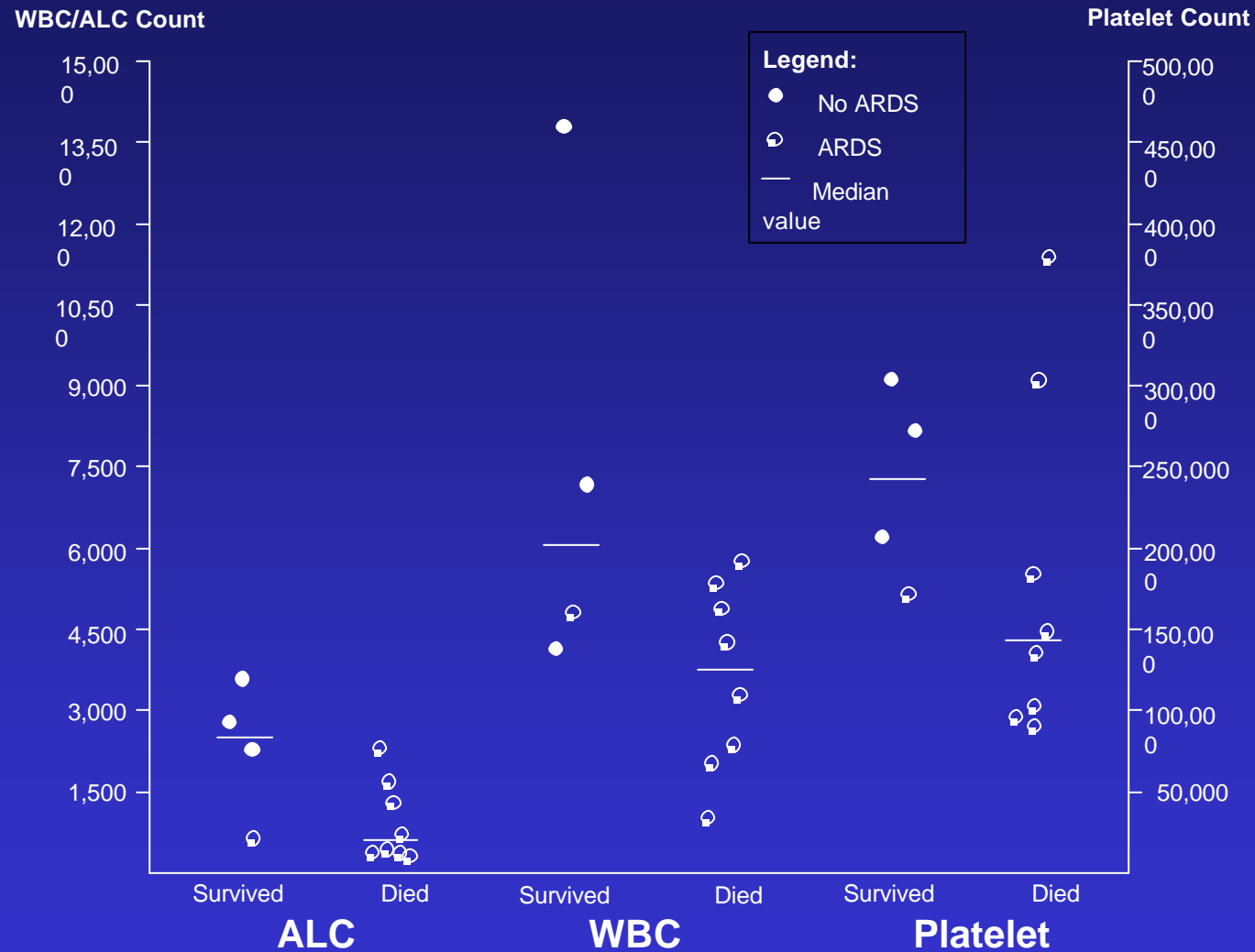
^{††} Blood urea nitrogen.

Influenza A (H5N1) Pneumonia



Hien. NEJM 2004;350:1179

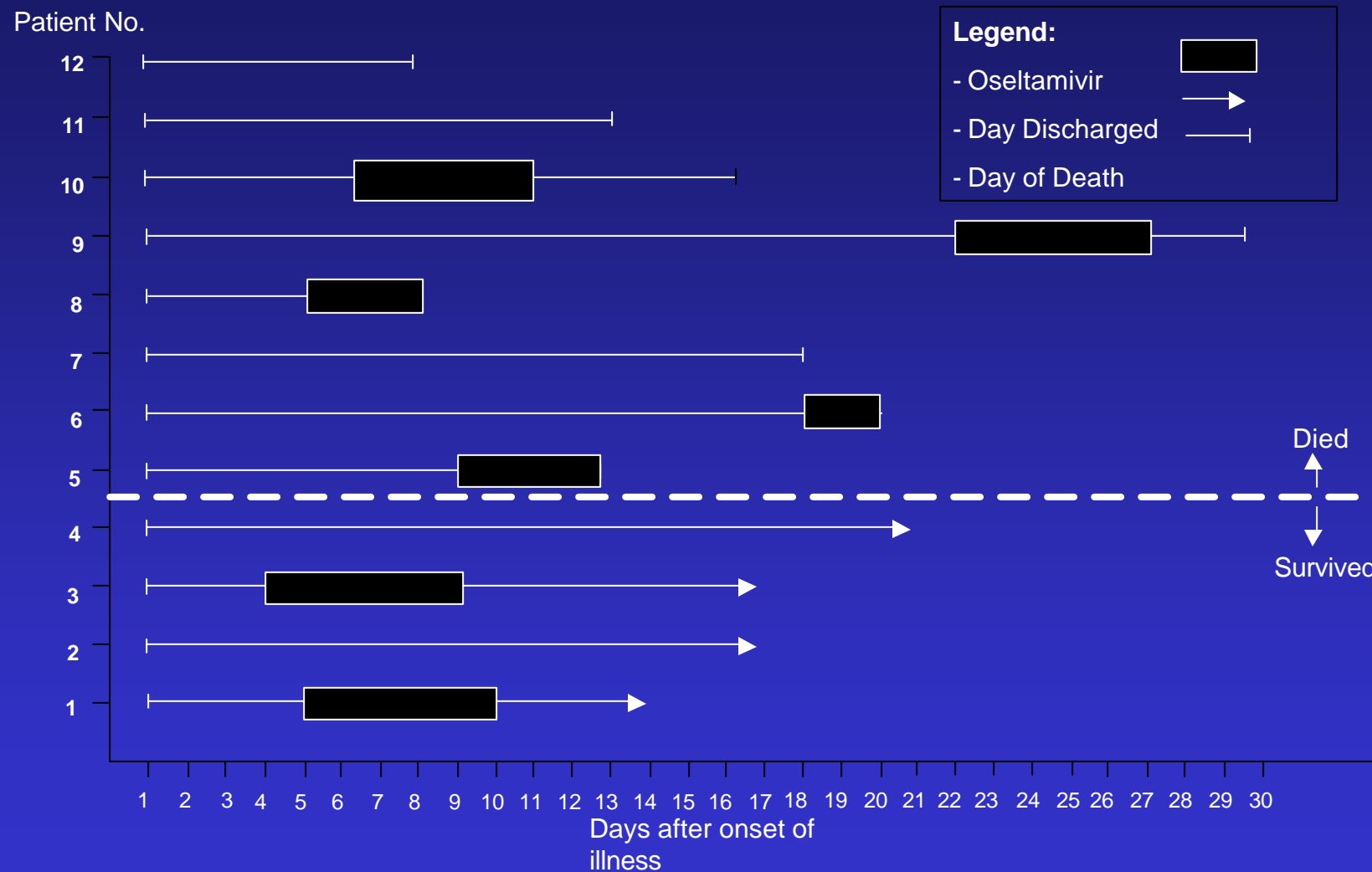
Lymphopenia Predicts Mortality



Chotpitayasunondh et al. EID 2005;11:201



Early Oseltamivir Associated with Survival



Chotpitayasunondh et al. EID 2005;11:201



H5 in 2004 is More Virulent and Requires More Oseltamivir

- Mouse model of lethal H5 infection
- '04 virus more lethal than '97 virus
- Oseltamivir was protective
 - Higher dosages needed
 - 8-day regimen better than 5-day

Yen et al. JID 2005;192:665



Clinical Features of Avian Influenza

- Persistent fever, lymphopenia
- Severe pneumonia or ARDS
 - unusual presentations possible
- Exposure to sick poultry
- Exposure to affected areas or persons
 - Clustering may be an emergency

Investigating Person-to-Person Spread



Timeline of Exposures and Illness

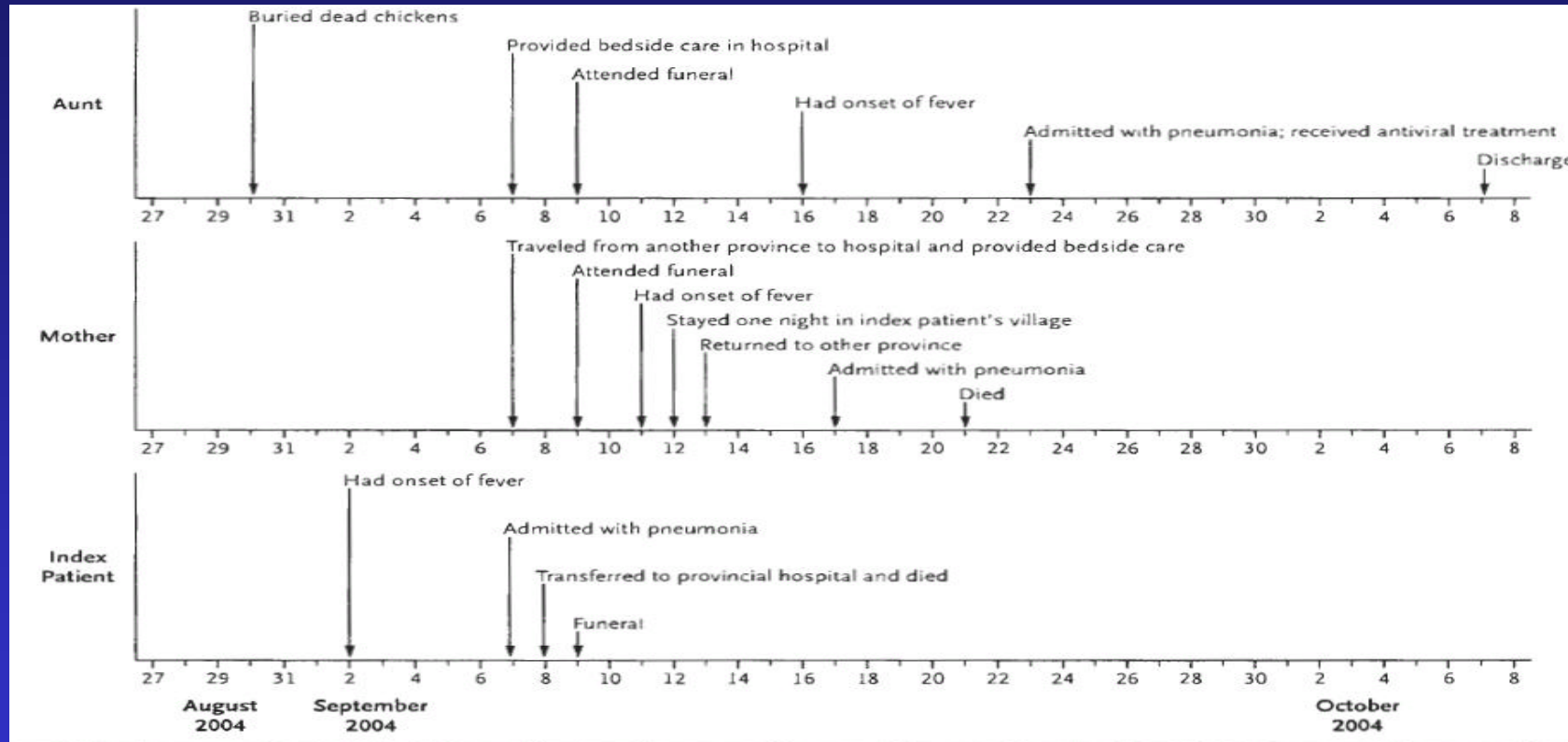


Figure 2. Timeline of Pertinent Exposures and Dates of Illness in the Three Patients.

The index patient, who lived with her aunt, was not known to have had direct contact with the sick or dying chickens, but she played and slept in an area where the chickens were also often present. The mother lived and worked in a province four hours' drive from the index patient's village. The three-night funeral took place in a different, unaffected village.

Getting the Virus

- Urgent effort to get specimens to WHO network
- Index patient dead, cremated
 - Mother's body embalmed
 - Lung and other tissues tested by RT-PCR and IHC
- Aunt survived
 - NP and OP swabs tested by cell culture, RT-PCR
 - Acute and convalescent serum (neutralization, ELISA)

Containing Pandemic Influenza With Antiviral Agents

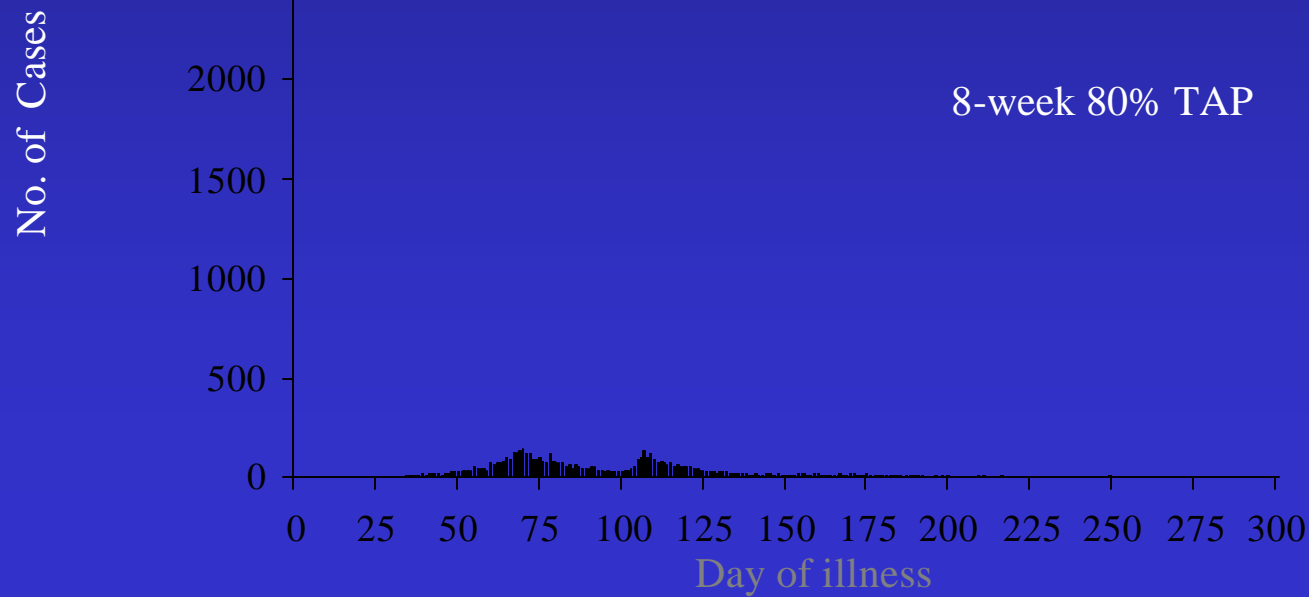
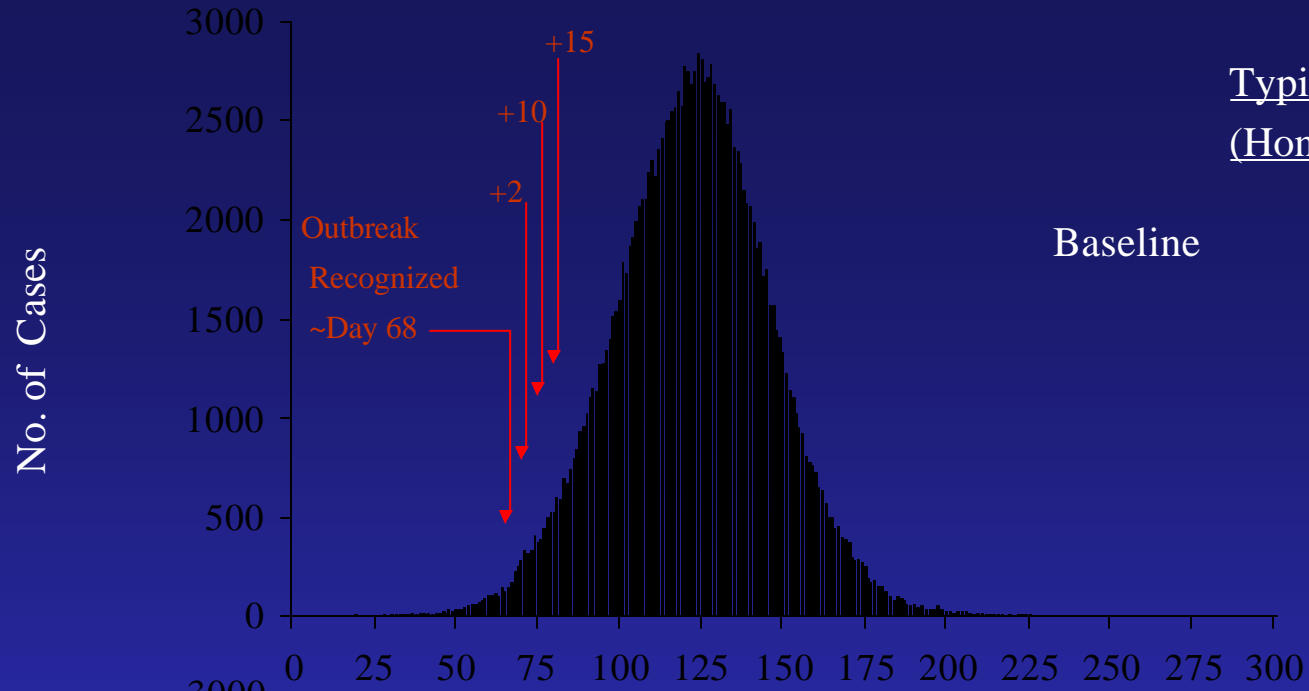
- Theoretical models using Thailand data
- Contacts of suspected cases take antiviral agents
- Pandemic contained if R_0 low
- Prophylaxis with quarantine more effective
- Critical is speed of detecting cases and response

Longini IM et al. Science 2005

Ferguson et al. Nature 2005



Typical "Large" Outbreaks
(Hong Kong Calibration)



An Influenza Pandemic and the Clinician

- Know clinical and epidemiological features
- Teach your colleagues
 - Have a pandemic plan
 - Have antivirals and protective equipment
- Be prepared to lead
 - Confirm the diagnosis
 - Get the virus
 - Get a lot of help, fast

Resources for Clinicians

- www.cdc.gov
 - U.S. public health guidelines
- www.pandemicflu.gov
 - U.S. pandemic plan
- www.who.int
 - Global updates and official case reports
- More coming