AI/PI Update
Defense Health Board

LTC Wayne Hachey
Force Health Protection & Readiness

May 2007

Agenda

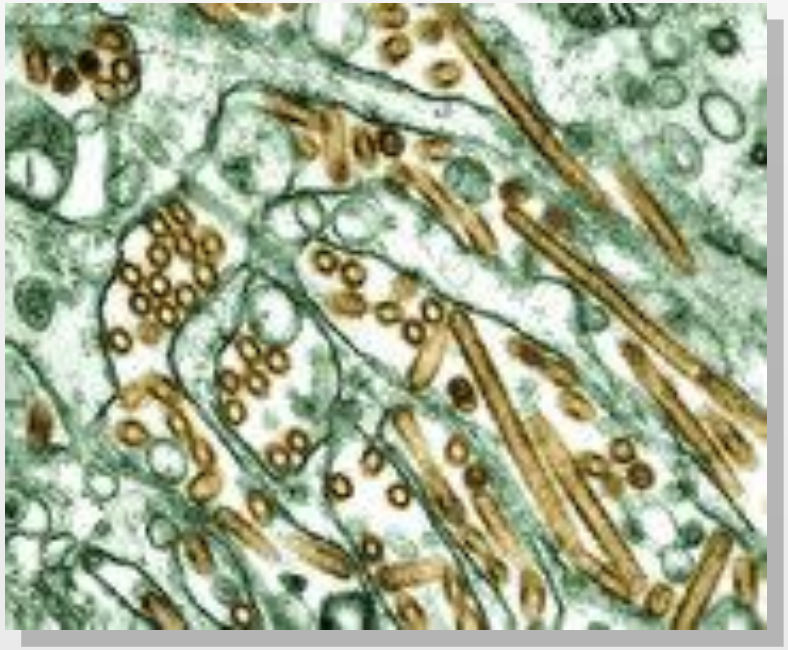
- AI
  - Human and Avian disease
  - Current Epidemiology
  - Recent research activities

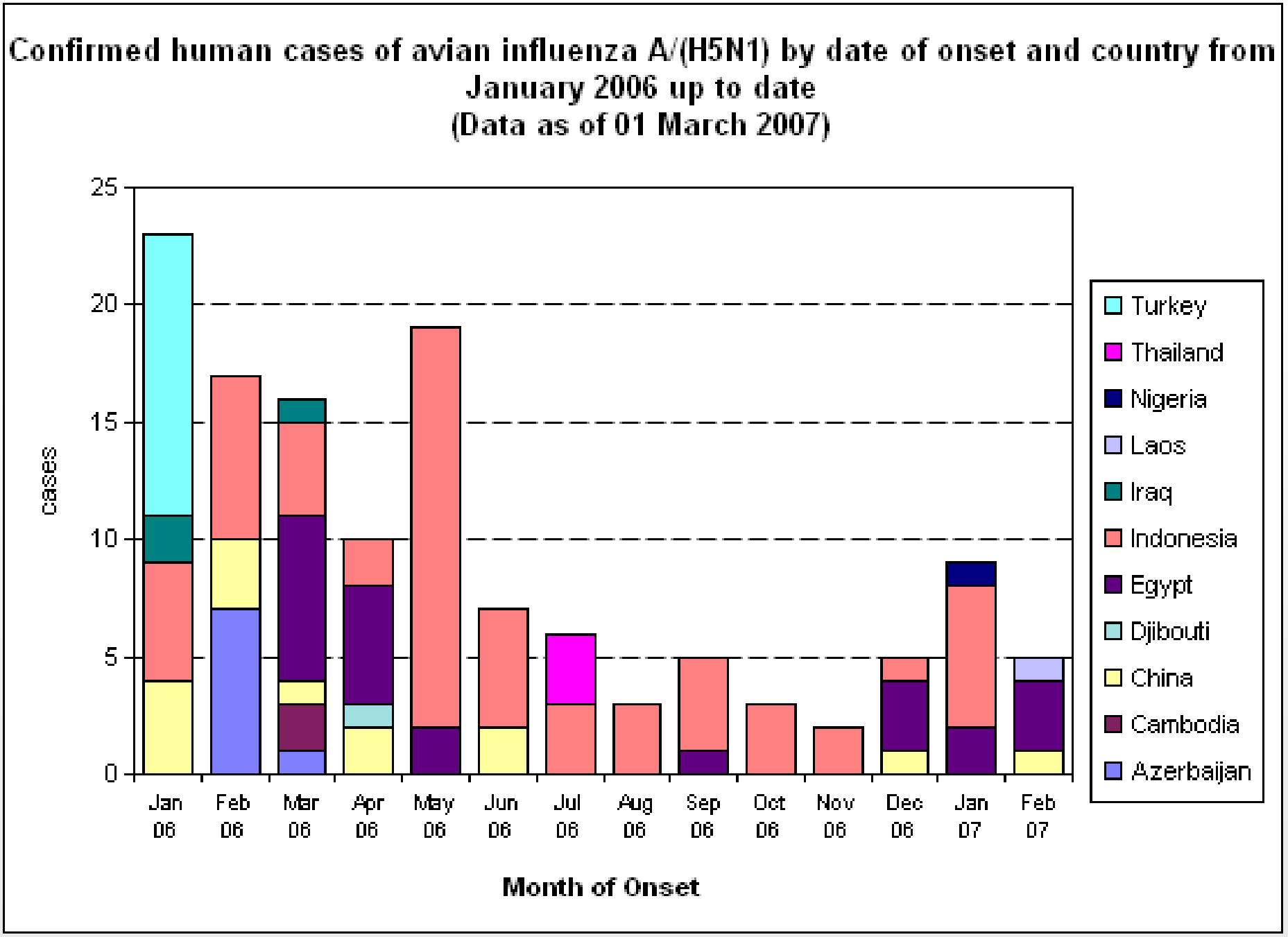
- PI
  - Vaccine
  - Antivirals
  - Community Mitigation
  - Surveillance
  - Communication

H5N1

Human Cases

- 291 Cases, 172 deaths (27 April 07)
- 2006 Indonesia remained the hot spot with 55 cases/45 deaths out of a total global 115 cases and 79 deaths
- Mortality rate
  - 2007 50%
  - 2006 68.9%
  - 2005 43.3%
  - 2004 69.5 %




Confirmed human cases of avian influenza A/(H5N1) by date of onset and country from January 2006 up to date
(Data as of 01 March 2007)
cases
25
20
15
10
5
0
Jan 06
Feb 06
Mar 06
Apr 06
May 06
Jun 06
Jul 06
Aug 06
Sep 06
Oct 06
Nov 06
Dec 06
Jan 07
Feb 07
Month of Onset
Turkey
Thailand
Nigeria
Laos
Iraq
Indonesia
Egypt
Djibouti
China
Cambodia
Azerbaijan

Avian Cases

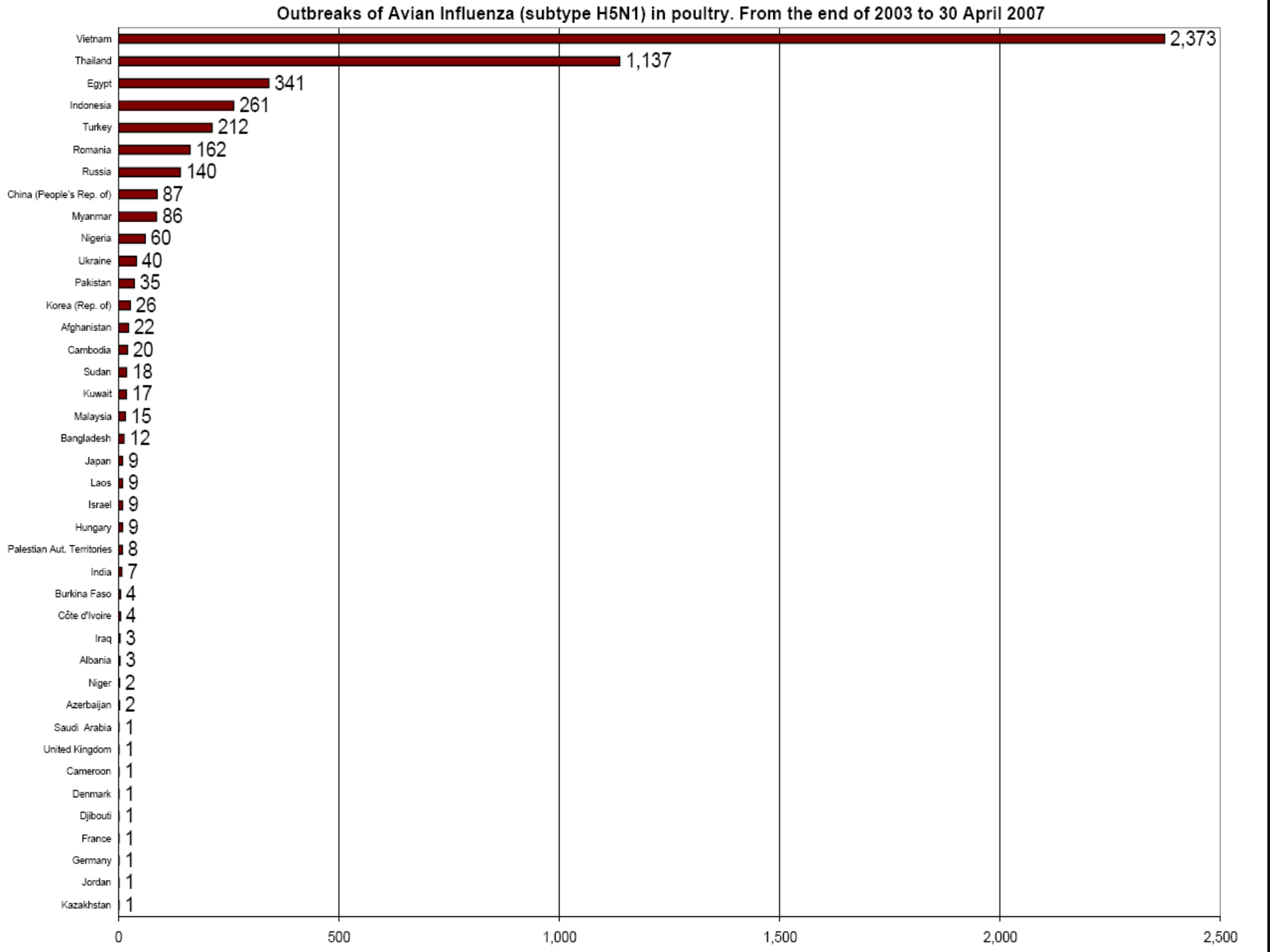
- 63 Countries (12 April OIE)
- Re-emergence of disease
  - Vietnam
  - Russia
  - Myanmar
  - Egypt
  - Kuwait
- Bird migration still plays a less prominent role in comparison with domestic poultry


USDA
United States Department of Agriculture
United States Department of Homeland Security
United States Department of the Interior
KEEP
Bird Flu
Out
OF THE UNITED STATES
It's illegal to smuggle birds – wild and domestic – and their products into the United States.
If you do, it will cost you:
Up to $250,000 fine and 5 years in prison for any individual
Up to $500,000 fine and 5 years in prison for any business or organization
CALL 1-800-BE ALERT to report bird smuggling or undeclared bird products brought into the United States.
www.avianflu.gov
USDA is an equal opportunity provider and employer. • May 2007

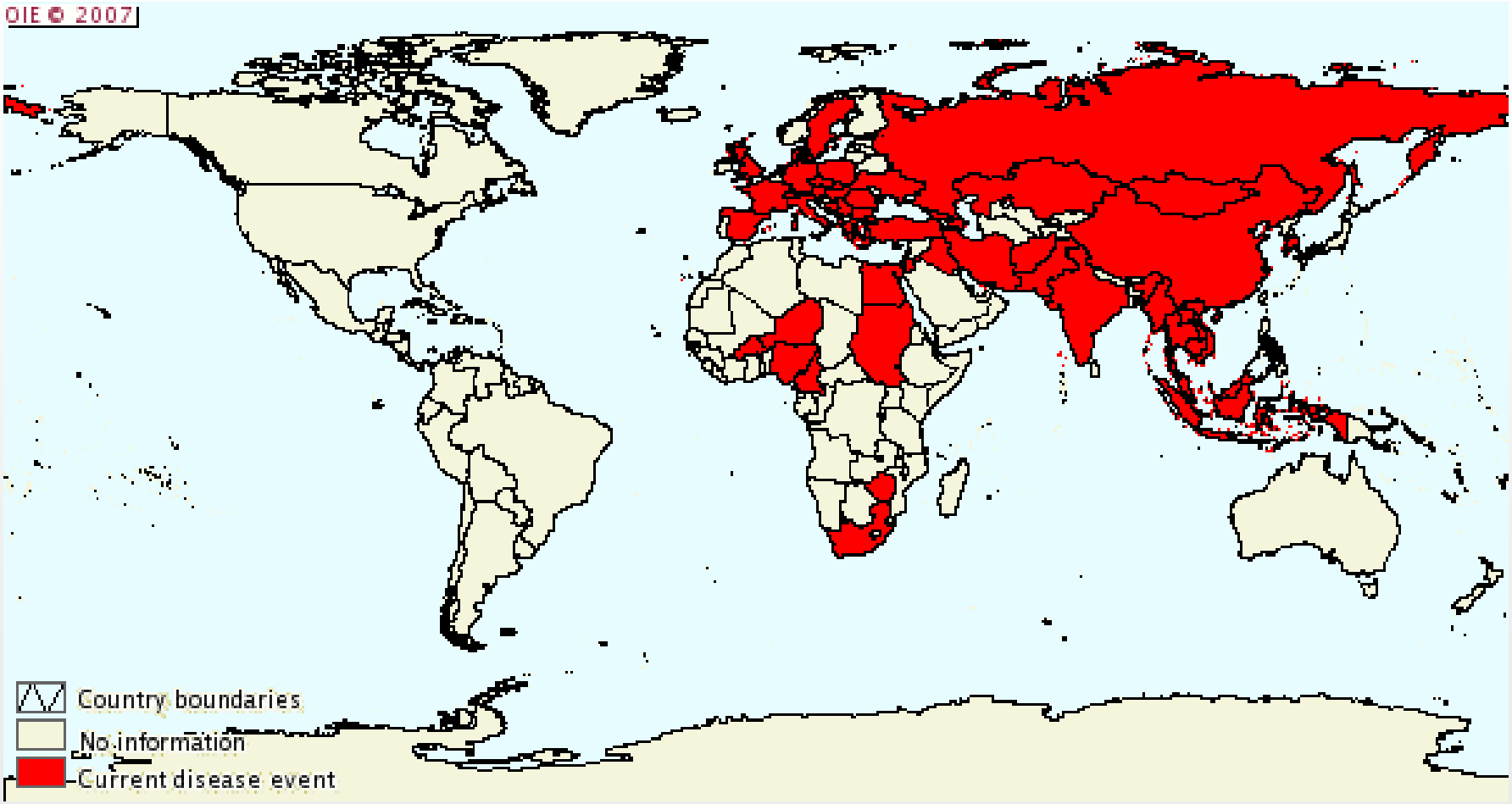
H5N1 Risk via Wild Bird Migration via Asia/Alaska Routes

- Diverse avian hosts from Asia and the Americas overlap in Alaska
- 7 yrs of AI surveillance representing 8,254 samples
  - Yield 5 isolates (H3, H4, H6) with no evidence of Eurasian origin for any virus
- Risk and probably the frequency of intercontinental virus transfer in this region is low
- But close genetic association between H6 in ducks from Alaska and a poultry outbreak in California
  - Reflects real-time connections of migratory ducks between Alaska and California with the vector connection extending into the Russian Far East

Avian influenza restricted zone sign at a road junction close to an infected turkey farm in the United Kingdom (Keith Evans)

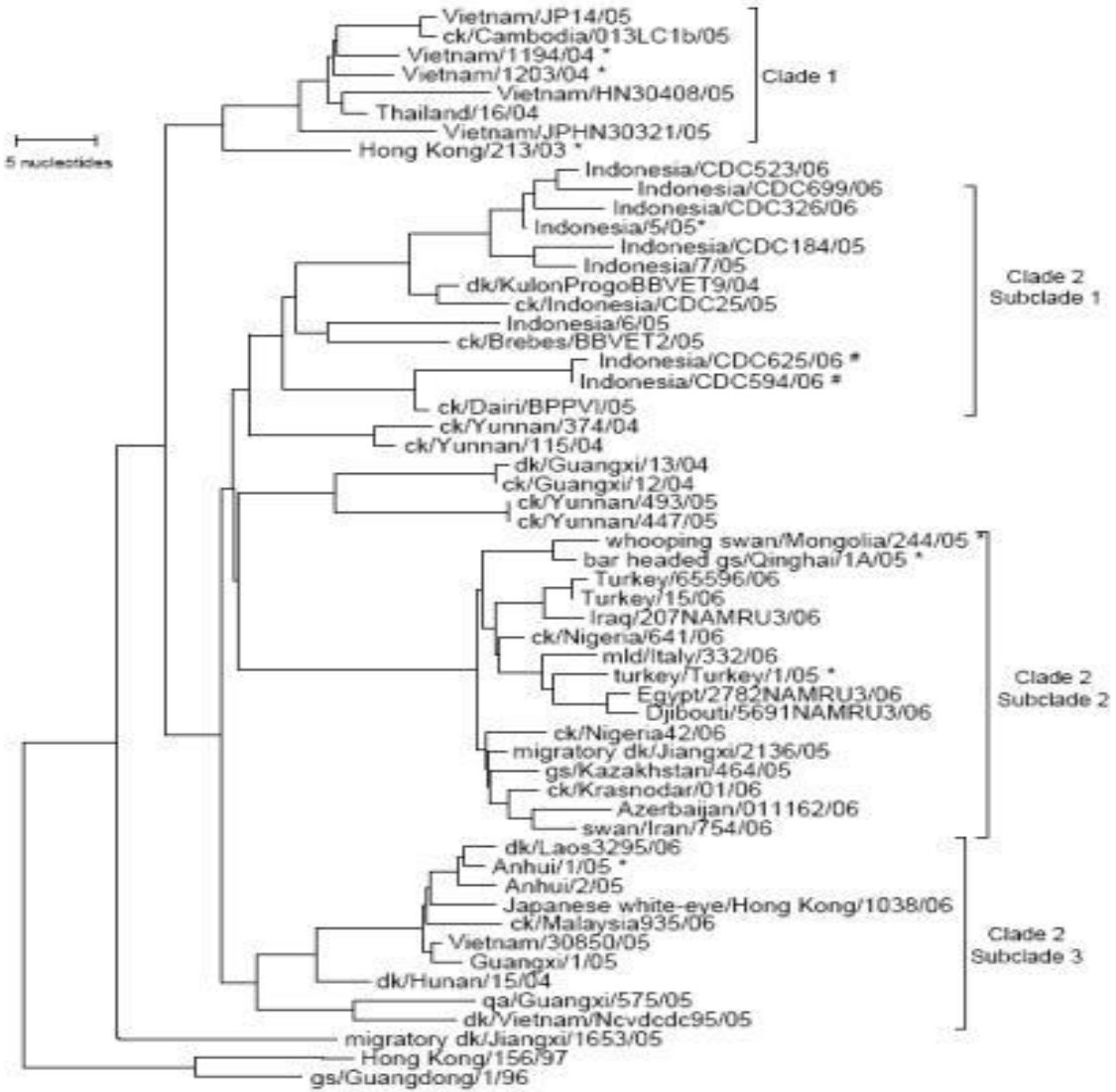

Outbreaks of Avian Influenza (subtype H5N1) in poultry. From the end of 2003 to 30 April 2007
Vietnam 2,373
Thailand 1,137
Egypt 341
Indonesia 261
Turkey 212
Romania 162
Russia 140
China (People's Rep. of) 87
Myanmar 86
Nigeria 60
Ukraine 40
Pakistan 35
Korea (Rep. of) 26
Afghanistan 22
Cambodia 20
Sudan 18
Kuwait 17
Malaysia 15
Bangladesh 12
Japan 9
Laos 9
Israel 9
Hungary 9
Palestian Aut. Territories 8
India 7
Burkina Faso 4
Côte d'Ivoire 4
Iraq 3
Albania 3
Niger 2
Azerbaijan 2
Saudi Arabia 1
United Kingdom 1
Cameroon 1
Denmark 1
Djibouti 1
France 1
Germany 1
Jordan 1
Kazakhstan 1
0
500
1,000
1,500
2,000
2,500

H5N1 Avian Disease Distribution



Clades

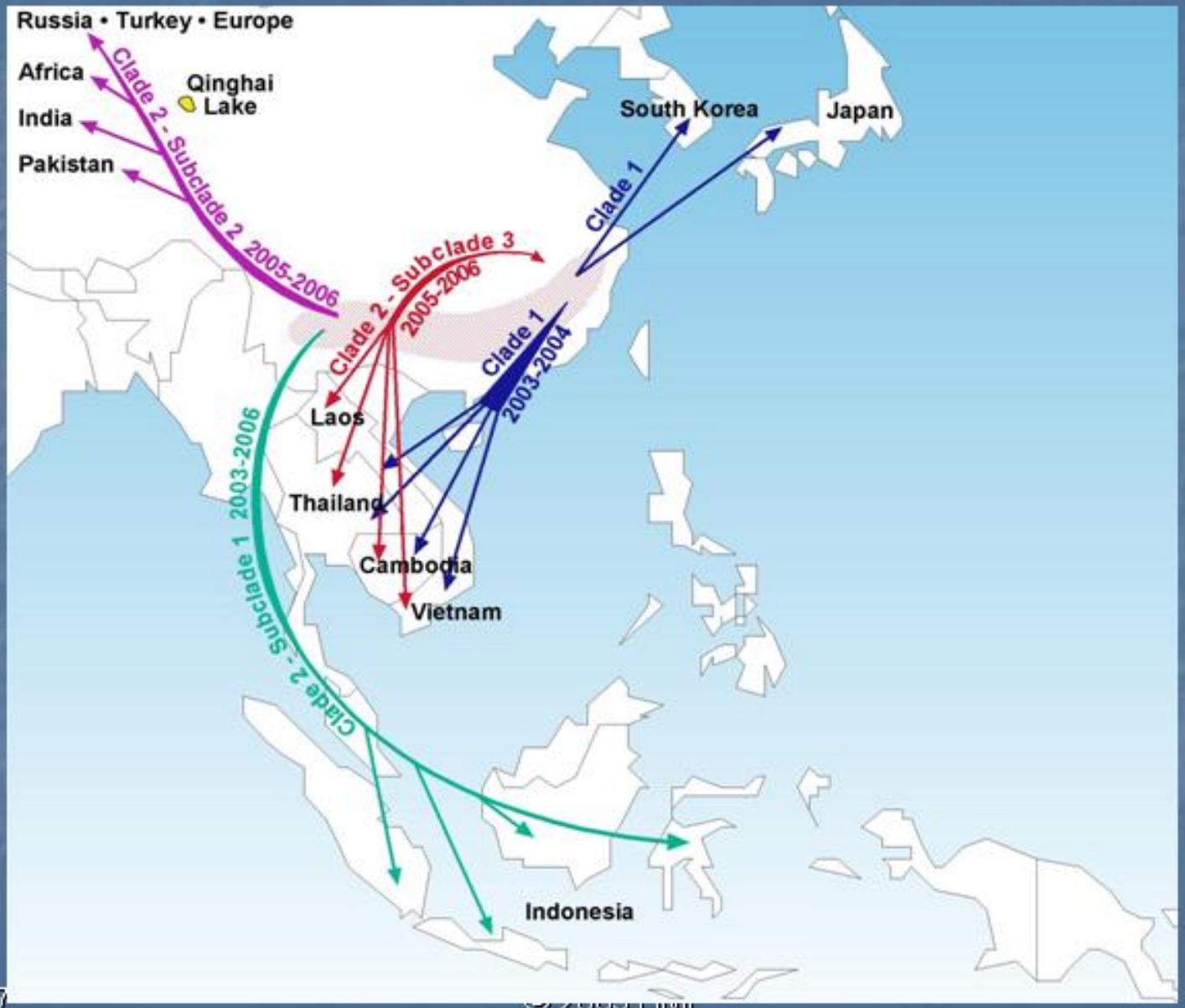
Fig. 1 **Evolution of the H5N1 haemagglutinin gene**



Clades

- 2 discrete lineages resulting in human disease both descended from A/Goose/Guangdong/96
- Clade 1 (2004-5) Vietnam, Thailand, Cambodia (2 cases in Thailand 06)
- Clade 2 circulated in birds in China and Indonesia in 03-04 and spread to Europe, Middle East & Africa in 05-06
  - Six subclades, 3 with distinct geographic distributions & human infections
  - 2.1 Indonesia
  - 2.2 Europe, Middle East, Africa (EMA)
  - 2.3 China
- 2 emerging clades
  - Worrisome lack of avian vaccine cross protection

Antigenic/Genetic Diversity



European-Middle Eastern-African (EMA) Clades (EID Vol 13, May 07, Salzberg et al.)

- Complete genome recently sequenced
- Responsible for several human infection in Egypt & Iraq
- Introduced at least 3 times into the European-African region
- Split into 3 distinct, independently evolving sub lineages
  - One isolate may represent 2 of these sub lineages that have recently reassorted

EMA Clades

- Represent viruses isolated in Europe, the Middle East, and Africa (Côte d'Ivoire, Nigeria, Niger, Sudan, Egypt, Afghanistan, Iran, Slovenia, Croatia, and Italy).
- Shared lineage suggests a single genetic source for introduction- Russia or Qinghai Province origin.
- The broad dispersal throughout these countries during a relatively short period, coupled with weak biosecurity standards, implicates human-related movement of live poultry and poultry commodities as the source of introduction.
- The virus' presence in wild birds leaves open the alternative possibility that migratory birds may have been the primary source, with secondary spread possibly caused by human-related activities.

European-Middle Eastern-African Clades

Clades
Vaccine and Antivirals

- Vaccine
  - Non adjuvanted Clade 1 vaccines do not inhibit any Clade 2
  - Non adjuvanted Clade 2.1 vaccine does not inhibit Clade 1 & does not inhibit 2.2 and 2.3 well
- Antivirals
  - Resistance to M2 Channel Blockers
    - Clade 1 resistant
    - Clade 2.1 mixed (80% resistant)
    - Clade 2.2 & 2.3 sensitive
  - Resistance to NA inhibitors
    - Clade 1, 2.1, 2.3 sensitive
    - Clade 2.2 some cases of moderate resistance

What Else Is New?

H5N1

- Higher viral load and wider tissue tropism than seasonal flu
- HPAI cleavage site is not limited to the normal trypsin specific like protease but are ubiquitous proteases
- Suppressive effect for Interferon alpha & gamma and TNF leading to an aberrant immune response – cytokine storm

Viral Replication

- H5N1 has 1-3 log greater viral load than seasonal influenza
  - Increased in fatal vs.. non-fatal cases

Viral Replication		H5N1
Blood	Virus Isolation	17%
	Detectable RNA	56%
Rectum	Virus Isolation	14%
	Detectable RNA	71%

De Jong MD et al Nat Med 2006;12:1203-7

H5N1 HA Cleavability

- HA precursor cleaved into HA1 and HA2
  - Prerequisite for infectivity
- LPAI: single Arg residue
  - Recognized by trypsinlike proteases
- HPAI: multiple basic amino acids
  - Recognized by ubiquitous proteases

Neumann G et al. Emerg Infect Dis 2006;12:881-6

Aberrant Immune Response

- Cytokines increased in fatal vs. non-fatal H5N1 cases
- Cytokines increased in H5N1 infections vs. H3/H1
- INFα,γ and TNFα increased

De Jong MD et al. Nat Med. 2006;12:1203-7

Seo SH et al. Nat Med. 2002;8:950-4

Of Mice and Men

- Humoral immunity elicited by huN1 may provide partial protection against H5N1 (mice and human models)
- Another indication for universal influenza immunization?
- PLos Medicine Feb 07/Vol 4/Issue 2/e59

Mice

- Mice immunized against the NA of a human H1N1 strain
- Naïve mice injected with sera from vaccinated mice
- Both challenged with H5N1 (Vietnam/1204/04)
- 50% survival in both treatment groups
- 100% mortality in control groups

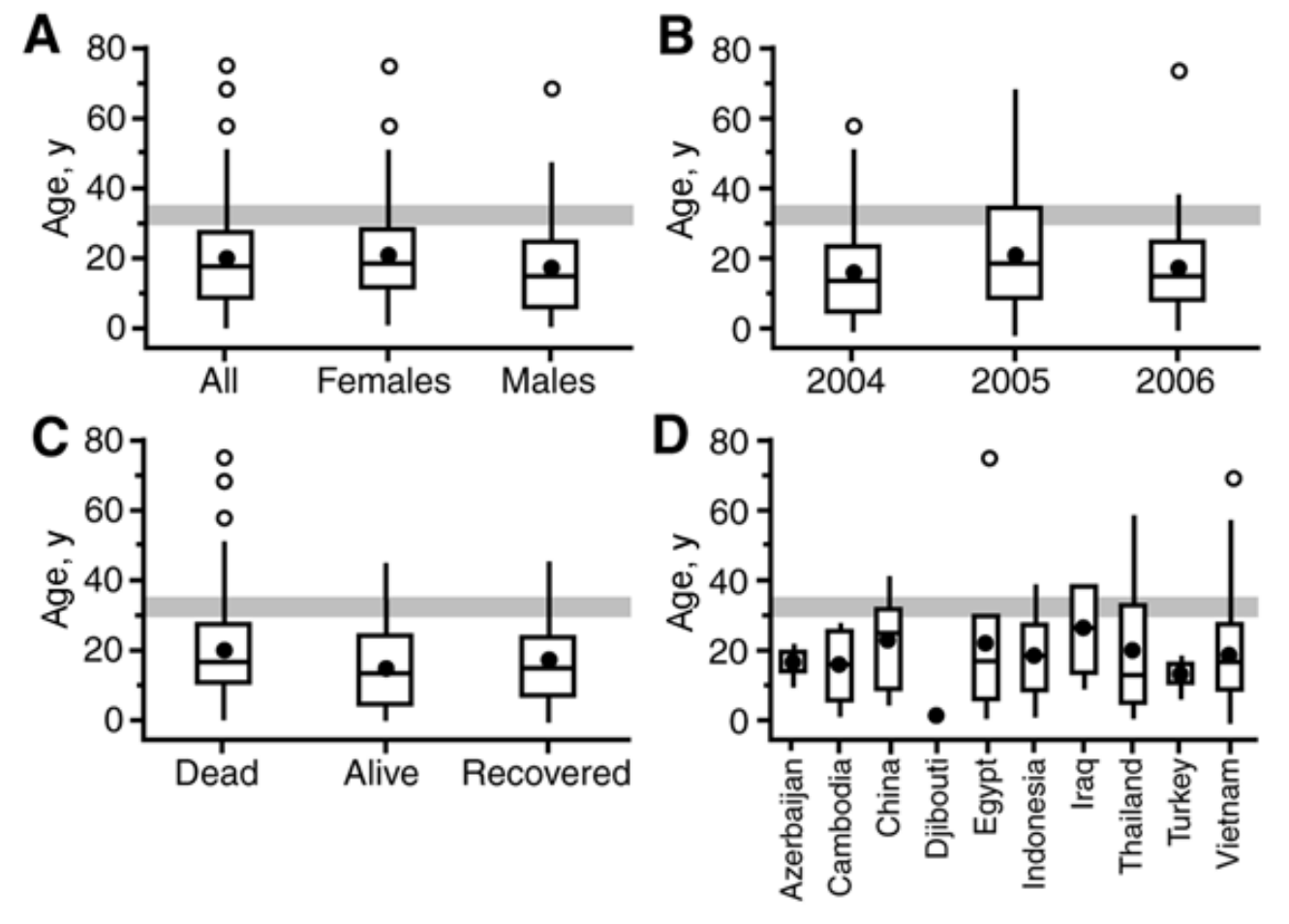
Men

- Human serum samples
- 31/38 demonstrated reactivity with H1N1 A/ New Caledonia/20/99
  - NA inhibition titers ranged from 20->320
- 8/38 had low inhibitory titers (20-80) against the NA of A/Vietnam/1203/03
- Small sample size but some individuals may have functionally significant levels of avN1-reactive antibodies

Is Gray Hair a Possible Protective Factor?

- 229 confirmed cases of H5N1 over 30 months
  - Age skewed toward children and young adults
  - Mean age 19.8 yrs
  - 10-19 yrs 29% vs.. >40 yrs 5.9%
  - Age Specific case rates/million
    - 0-9 yrs & 10-19yrs= 0.15
    - 20-29 yrs = 0.13
    - 30-39 yrs = 0.08
    - ≥ 40 yrs = 0.02

H5N1: a Disease of the Young?



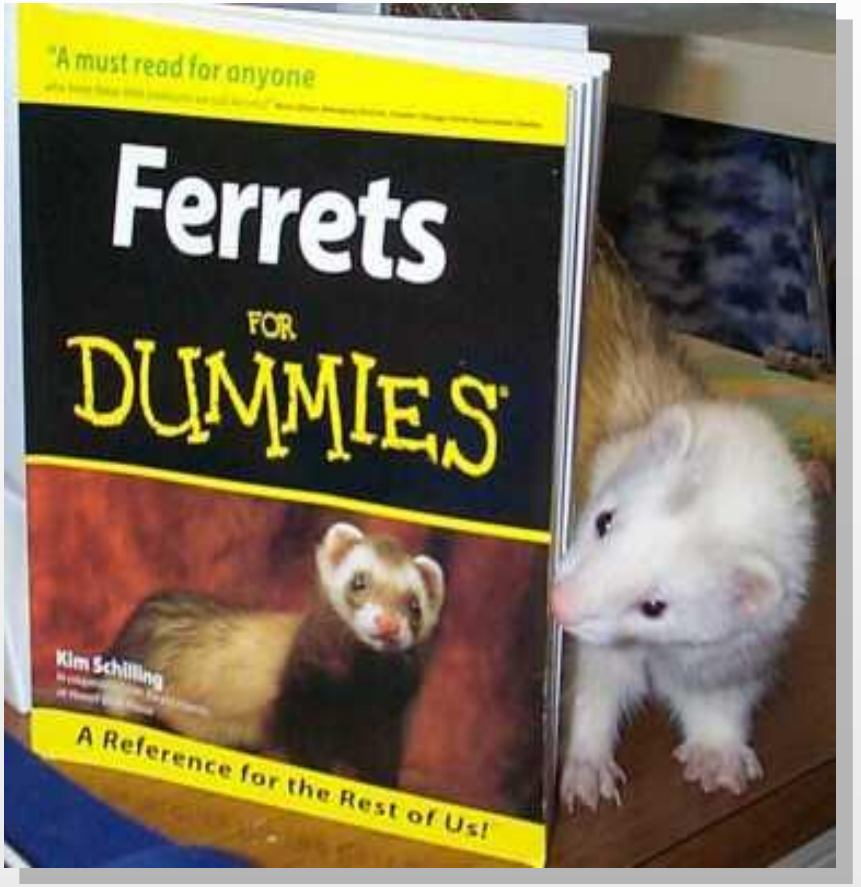
EID: Volume 13, Number 3–March 2007

FR0052

Could Ferrets Lie About Tamiflu?

Ferrets as Animal Models for Influenza

- Naturally susceptible host
- Receptor in upper airway similar to humans (predominant SA α 2,6 Gal)
- Clinical symptoms closely resemble humans



Early Post-exposure Administration of Tamiflu - Survival Endpoint

Infect with
10 or 100 EID_{50}
A/VN/1203/04

Virus Dose	Experimental Group	No. dead/ Total no.	Day of Death
10 EID_{50}	Treatment	0/3	No
	Control	2/3	10, 10
100 EID_{50}	Treatment	0/3	No
	Control	3/3	7, 7, 9

Day 0 Day 1 Day 2 Day 3 Day 4 Day 5 Day 21

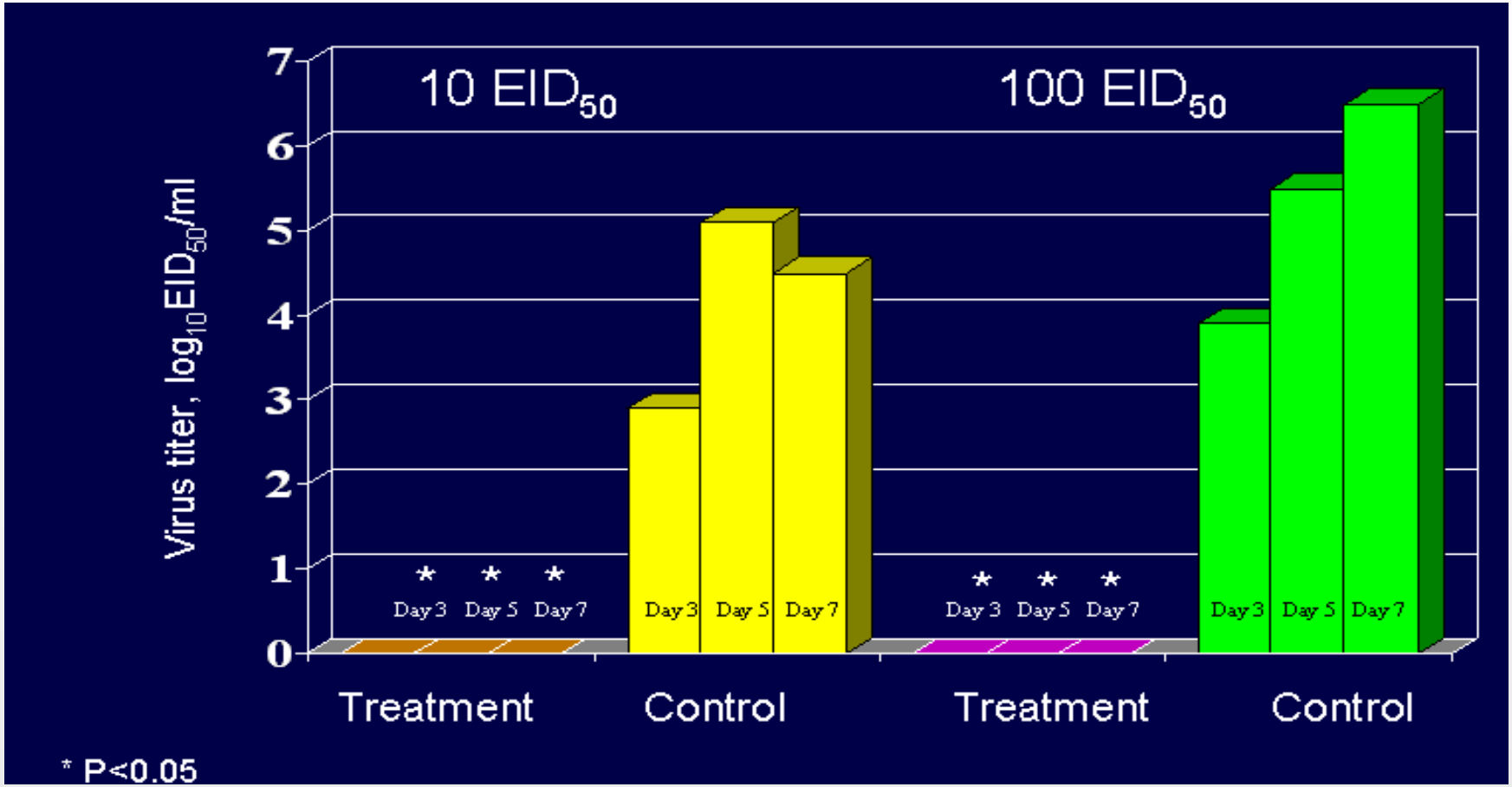
4 hrs 5 mg/kg/d (equiv. to half approved human dose of 75 mg bid)

Oseltamivir 2x daily for 5 days

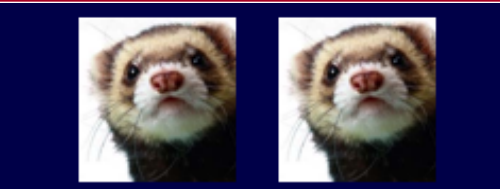
FR0052

Elena A. Govorkova, St Jude Children's Research Hospital
Presented at: Seasonal & Pandemic Influenza 2007

Upper Respiratory Track Viral Titers Tamiflu Tx - Vietnam 1203 Challenge



Late Post-exposure Administration of Tamiflu - Survival Endpoint



Infect with
100 EID_{50}
A/VN/1203/04

Virus Dose	Experimental Group	No. dead/ Total no.	Day of Death
100 EID_{50}	10 mg/kg/d	3/3	7, 7, 8
	25 mg/kg/d	0/3	No
	Control	3/3	6, 7, 8

Day 0 Day 1 Day 2 Day 3 Day 4 Day 5 Day 6 Day 21

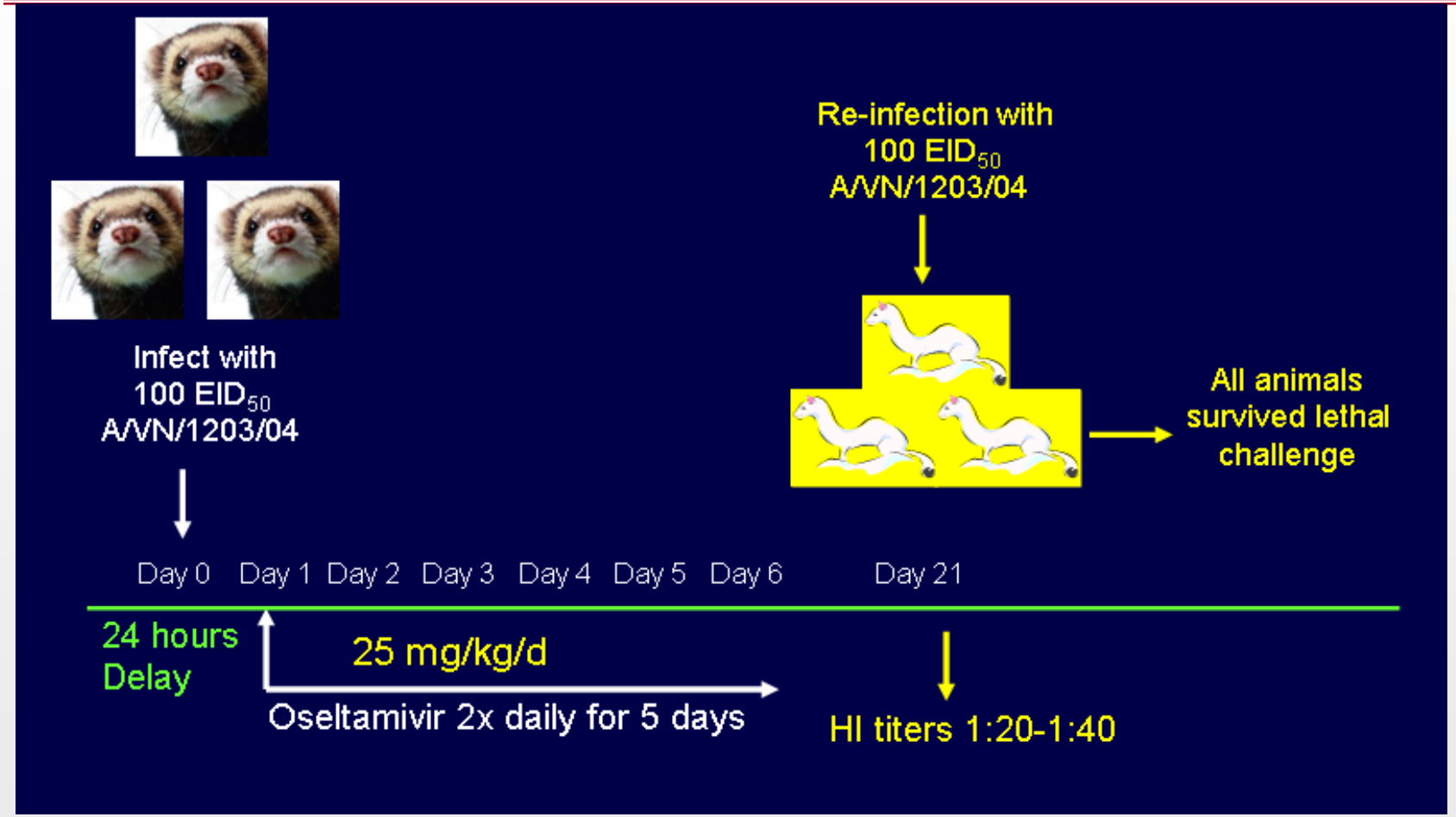
24 hours Delay

10 mg/kg/d (equiv. to approved human dose of 75 mg bid)
or 25 mg/kg/d (equiv. to 2.5x human dose of 75 mg bid)

Oseltamivir 2x daily for 5 days

Elena A. Govorkova, St Jude Children's Research Hospital
Presented at: Seasonal & Pandemic Influenza 2007

Re-infection with a Lethal H5N1 Dose



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Antivirals
The Way Ahead?

- Parenteral Zanomivir:
  - IV Q12 hrs, t1/2 1.8 hrs
  - Protective when administered 4 hours prior to infection
- Peramivir
  - Phase II trials
  - IV and IM
  - Good but not complete protection in ferret and mouse models with Vietnam 1203 challenge
  - Easier to make and easier to achieve higher blood levels

WHO Clinical Recommendations March 07

- Tamiflu
  - Treatment warranted even with late presentation
  - Higher dose & combination therapy with amantadine considered on a case by case basis
  - NO corticosteroids unless septic shock with suspected adrenal insufficiency
  - NO antibiotic prophylaxis
  - Lung protective mechanical ventilation strategies

DoD Antivirals

- Antiviral Guidelines & Release Policy
  - Oseltamivir
    - 3 Million treatment courses ÷ 3 Depots
    - MTF 470,000 treatment courses
  - Zanamivir
    - 242,000 treatment courses
  - Use guidelines based on variable pandemic severity and supply

DoD Antiviral Guidance

- Establishes local use and release for MTF stockpiles
- Primary Stockpile release remains at ASD(HA) level
- Treatment is primary use with limited, targeted prophylaxis
  - Depending on effectiveness of nonpharmacologic measures expanded prophylaxis is an option
    - Post exposure
    - Outbreak/operational
- Uses CDC's Pandemic Severity Index for disease severity metrics and reinforces Community Mitigation Guidelines for case rate reduction and greater antiviral flexibility

Vaccine

Ferrets and Vaccine

- Unadjuvanted vaccine HI data suggest poor cross protection between clades and subclades
- Ferrets given Clade 1 vaccine have cross protection against Clade 2 challenges
  - Survival endpoint
  - Indo 5/05 challenge

Ferrets and Adjuvanted Vaccine

- Clade 1 vaccine – Clade 1 challenge
  - Poor immunogenicity without adjuvant
  - HI titer > 40 with 3.8ug dose of adjuvanted vaccine
  - 90% protective @ 2.9ug
- Heterologous challenge (Indo 5/05)
  - Clade 1 vaccine 3.8ug
    - Neutralization inhibition with Clade 2 challenge 77% vs. 83% with homologous challenge
    - All controls died
    - 1/6 died @ 1.7ug dose all other 100% survival (3.8, 7.5, 15)
    - CD4 T cell response following Clade 1 vaccine and Clade 2 challenge: 4 fold increased response

Clade 3 Vaccine Primer for Clade 1 Challenge (Human)

- "Revaccination Study" n=37 who received 2 doses of a Clade 3 H5 Vaccine in 1998-9 were given a single 90ug dose of Vietnam 1203 Clade 1 vaccine
- Antibody responses in primed subjects compared to H5 vaccine naïve subjects
  - Exceeded those who were unprimed
  - Exceeded those in original 1989-9 study
  - Exceeded those who received two 90ug doses without prime
  - Responses may be due to generation of long-lived memory CD4 cell and/or memory B cells
  - ? Similar effect with Clade 1 primer and Clade 2 boost???

Ali Gogi, N. IDSA 2006

Pre-Pandemic Vaccine

- VRBPAC
  - Recommended FDA approval of Clade 1 Vietnam 1203/04 vaccine
  - FDA approved in April 07
- DoD
  - 1.6M doses
  - Draft Pre-pandemic vaccine policy
    - Includes storage and distribution requirement, AE tracking mechanisms, immunogenicity monitoring

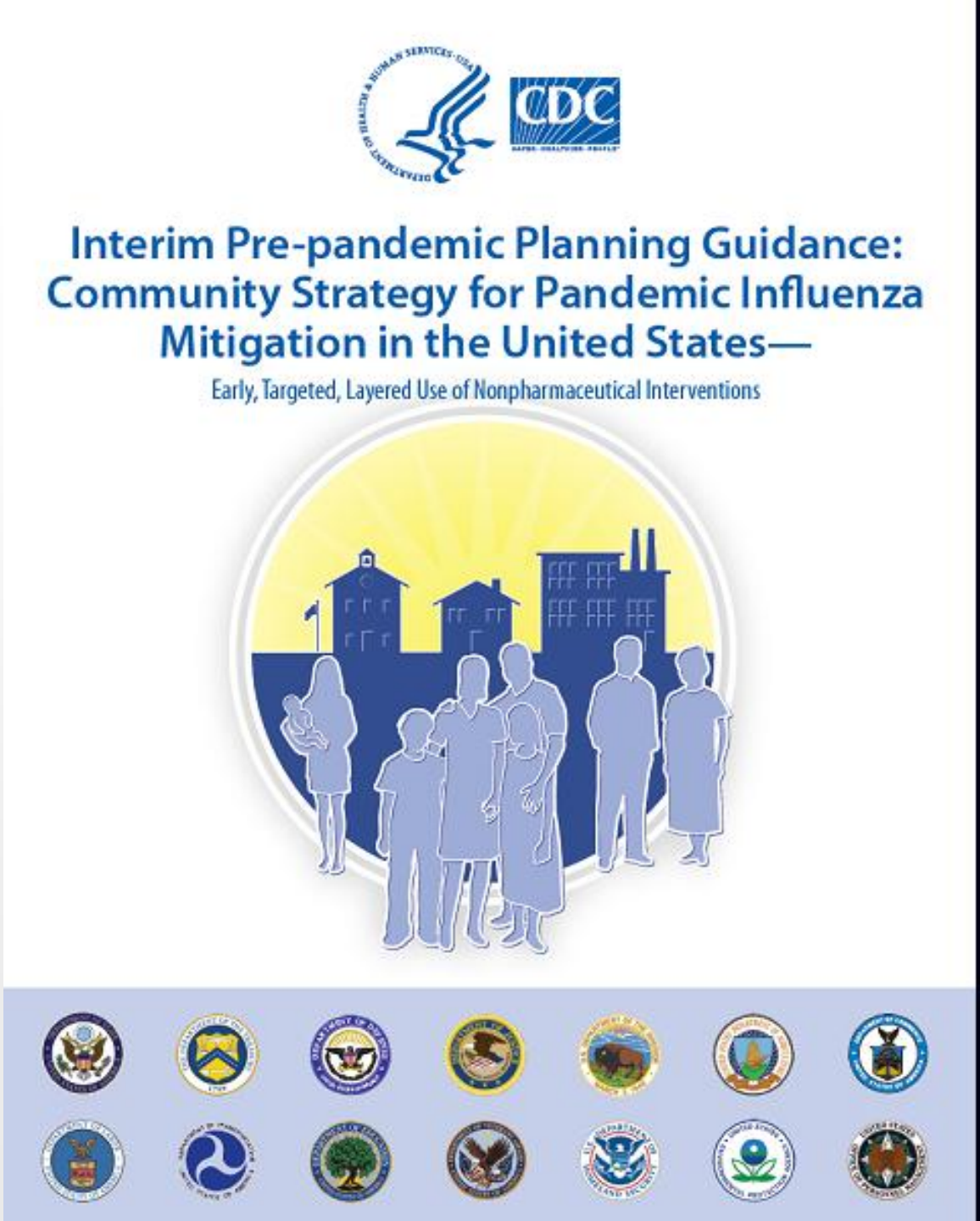
DRAFT DoD Pre-pandemic Vaccine Guidance

- Offer to lab personnel who have direct contact with High Path H5N1
- MILVAX/Service to track administration
- MILVAX/VHC to monitor for AE
- GEIS to coordinate immunogenicity studies
- With impending pandemic JS/NORTHCOM to designate prioritization based on risk, critical role and ability to receive two doses.

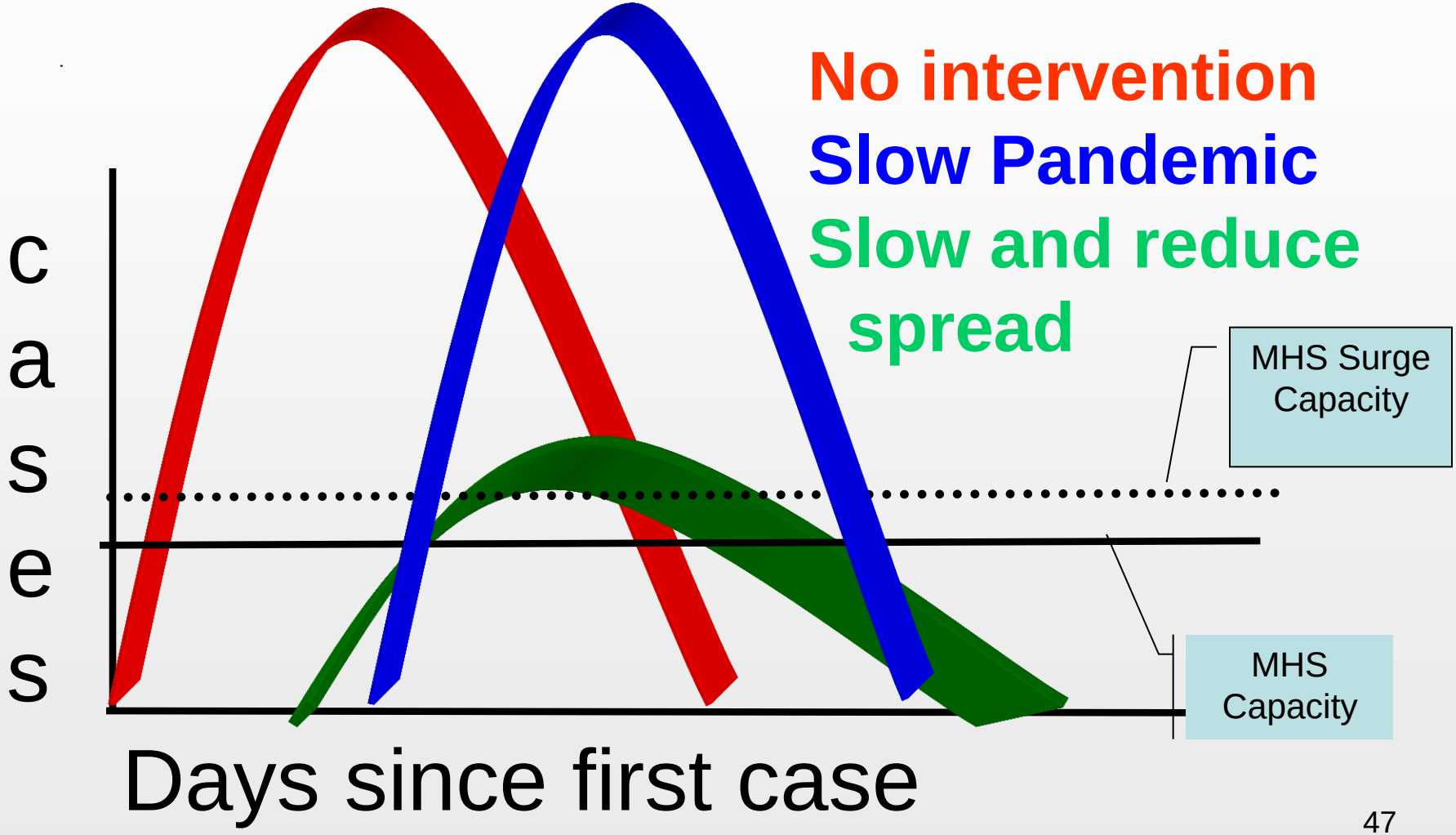
2006-7 Pre-pandemic Vaccine Production

- HHS awarded total of $199M for Clade 2 vaccine (Indo 5/05)
  - $117.9M Sanofi Pasteur 3.7M doses (90ug)
  - $40.95M Novartis 800K doses (90ug)
  - $40.6M GSK 800K doses (90ug)
  - Actual number of doses yet to be determined pending reagent development & production yield
- Distribution allocation recommendations being developed by interagency work group for pandemic and pre-pandemic vaccine prioritization
- DOD to pursue acquisition of pre-pandemic vaccine to vaccinate 1.3M personnel as required in the National Pandemic Implementation Plan

Community Mitigation Guidelines



Response Goals

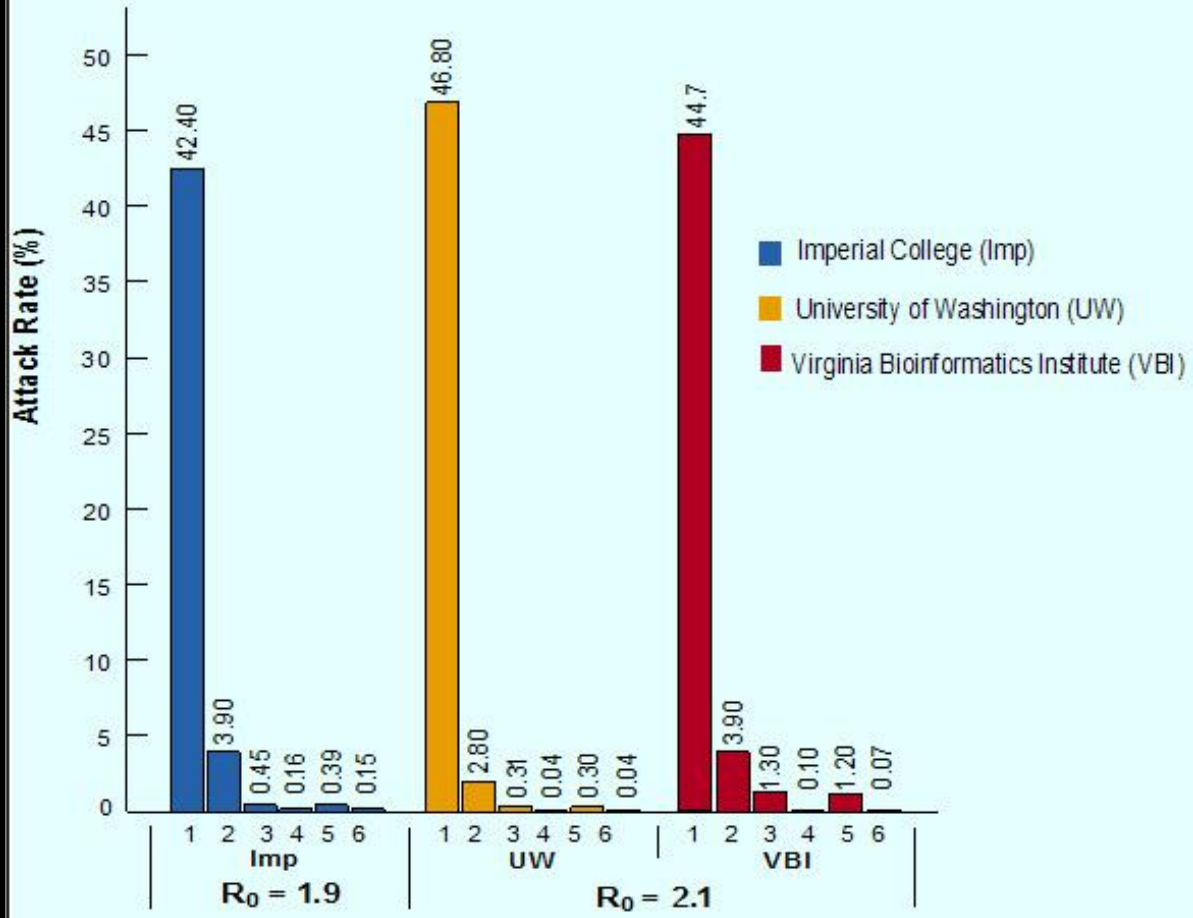


FR0052

TLC Interventions

- Voluntary Isolation & Quarantine
- Infection Control Measures
- Social Distancing
  - School closure
  - Reduce adult social contact
- All included in DoD CPG (community mitigation strategies)
  - Uses Pandemic categories as triggers
  - TLC to be employed EARLY by installations

Mathematical Models Predict a Reduction in Attack Rate When Multiple Community Mitigation Interventions are Used*



Attack Rate is the proportion of an exposed population at risk who either become infected or develop clinical illness during the epidemic period.

A combination of interventions, even with poor compliance, may reduce the attack rate.

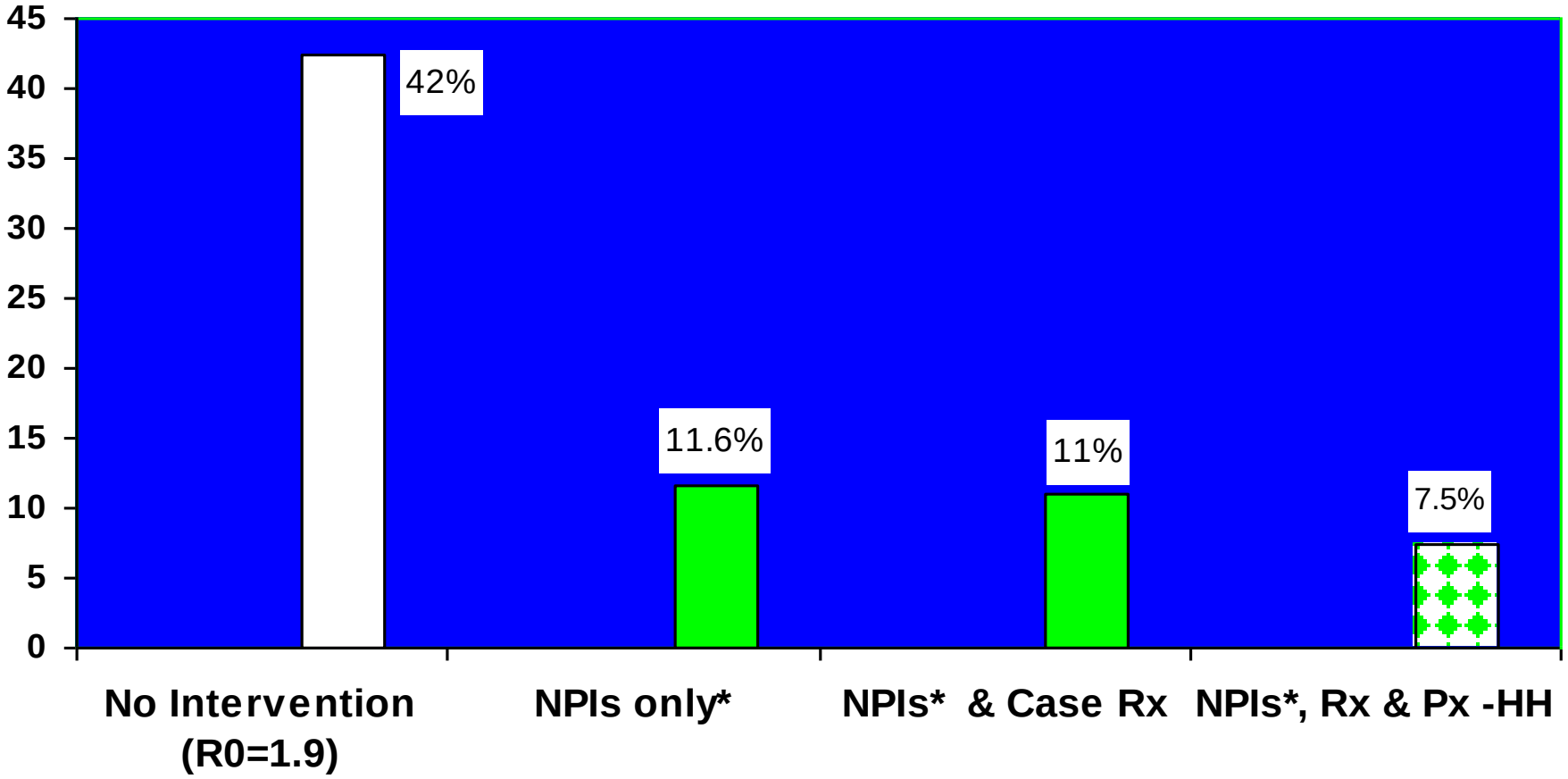
Sensitivity analyses point to school closure, workplace and generic social distancing as significant components.

Removing one source of transmission may make other sources relatively more important.

When schools are closed, the primary source of transmission shifts to the home.

*Based on multiple mathematical models that included various assumptions of compliance (30%, 60%, 90%) and the percentage of ill individuals and household contacts identified and treated with antiviral medications (60%, 80%).

Pandemic Influenza Illness Rates With and Without TLC Interventions
Source: MIDAS (Imperial College- Ferguson et al.)



*All identified cases isolated, full school closure, 50% adult social contact reduction
30% compliance HH Quarantine, 60% case identification,
NPI=Nonpharmaceutical intervention
Rx= antiviral treatment, Px= antiviral prophylaxis for household (HH) contacts

Effect of Public Health Measures on 1918 Pandemic (Bootsma & Ferguson PNAS 6 April 2007)

- Unlike Europe in 1918 U.S. employed Public Health measures
- City specific per-capita mortality was correlated with how early interventions were introduced
- Modeling reproduced the observed epidemic patterns
  - Time limited interventions reduced mortality by 10-30%
  - Cities with the most effective interventions reduced rates by up to 30-50%

Public Health Interventions and Epidemic Intensity During the 1918 Pandemic (Hatchett, Mecher & Lipstich, PNAS Apr 06)

- Used data on the timing of 19 classes of NPI in 17 cities during the 1918 pandemic
- Cities that implemented multiple interventions at an early phase had peak death rates~50% lower than those that did not
- Also had a trend toward lower cumulative excess mortality ~ 20%
- Few cities maintained NPI > 6 weeks

Pandemic Severity Index

- Community mitigation trigger points based on severity index
- Based on hurricane categories
- Range 1-5
- Category 1 similar to seasonal influenza
- Category 5 mild version is 1918 type
- Interventions vary with pandemic severity

Pandemic Severity Index

Case Fatality Ratio		Projected Number of Deaths* US Population, 2006
≥2.0%	Category 5	≥1,800,000
1.0 -<2.0%	Category 4	900,000 - <1,800,000
0.5 -<1.0%	Category 3	450,000 -<900,000
0.1% - <0.5%	Category 2	90,000-<450,000
<0.1%	Category 1	<90,000

* Assumes 30% Illness Rate

Strategies by Severity Index

Interventions* by Setting	Pandemic Severity Index		
	1	2 and 3	4 and 5
Home			
Voluntary isolation of ill at home (adults and children); combine with use of antiviral treatment as available and indicated	Recommend†§	Recommend†§	Recommend †§
Voluntary quarantine of household members in homes with ill persons¶ (adults and children); consider combining with antiviral prophylaxis if effective, feasible, and quantities sufficient	Generally not recommended	Consider **	Recommend **
School			
Child social distancing			
-dismissal of students from schools and school based activities, and closure of child care programs	Generally not recommended	Consider: ≤4 weeks††	Recommend: ≤12 weeks§§
-reduce out-of school social contacts and community mixing	Generally not recommended	Consider: ≤4 weeks ††	Recommend: ≤12 weeks§§
Workplace / Community			
Adult social distancing			
-decrease number of social contacts (e.g., encourage teleconferences, alternatives to face-to-face meetings)	Generally not recommended	Consider	Recommend
-increase distance between persons (e.g., reduce density in public transit, workplace)	Generally not recommended	Consider	Recommend
-modify, postpone, or cancel selected public gatherings to promote social distance (e.g., stadium events, theater performances)	Generally not recommended	Consider	Recommend
-modify work place schedules and practices (e.g., telework, staggered shifts)	Generally not recommended	Consider	Recommend

Triggers

Pandemic Severity Index	WHO Phase 6, U.S. Government Stage 3*	WHO Phase 6, U.S. Government Stage 4 and First human case in United States	WHO Phase 6, U.S. Government Stage 5 and First laboratory-confirmed cluster in State or region¶
1	Alert	Standby	Activate
2 and 3	Alert	Standby	Activate
4 and 5	Standby**	Standby/Activate ††	Activate

FR0052

Traders at Onipanu poultry market in Lagos, February 2007 (AFP)

Surveillance

Capability	FY 05	FY 06	FY 07	
Total # Countries in Network	30	56	65	S America, Africa, Mid East, SE Asia
Sampling Capacity # specimens/year	~9000	~16000	~18000	Increased surge capacity and analytical capability
# BSL 3 labs	3	4	8	USAMRIID, LRMC, AFRIMS, NHRC
Data Integration	No	Yes	Yes	Coord Center 24/7

Communication

- Health Affairs pandemic flu watchboard now evolved into DoD Pandemic flu site
- Easier URL www.dod.mil/pandemicflu
- Content expanded to include non-medical guidance
  - MARFORPAC, NORTHCOM, PACOM, DoD Education Activity, Civilian Personnel Management Service

Questions