



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



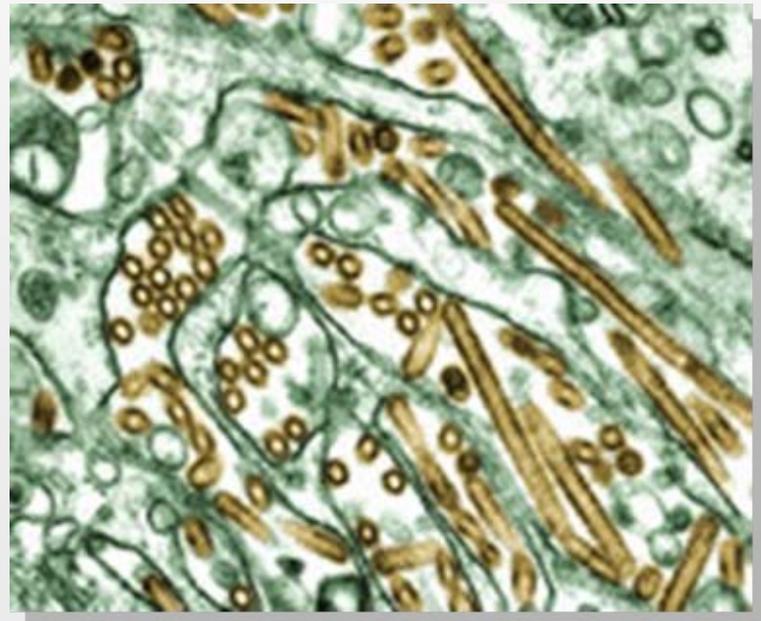
H5N1



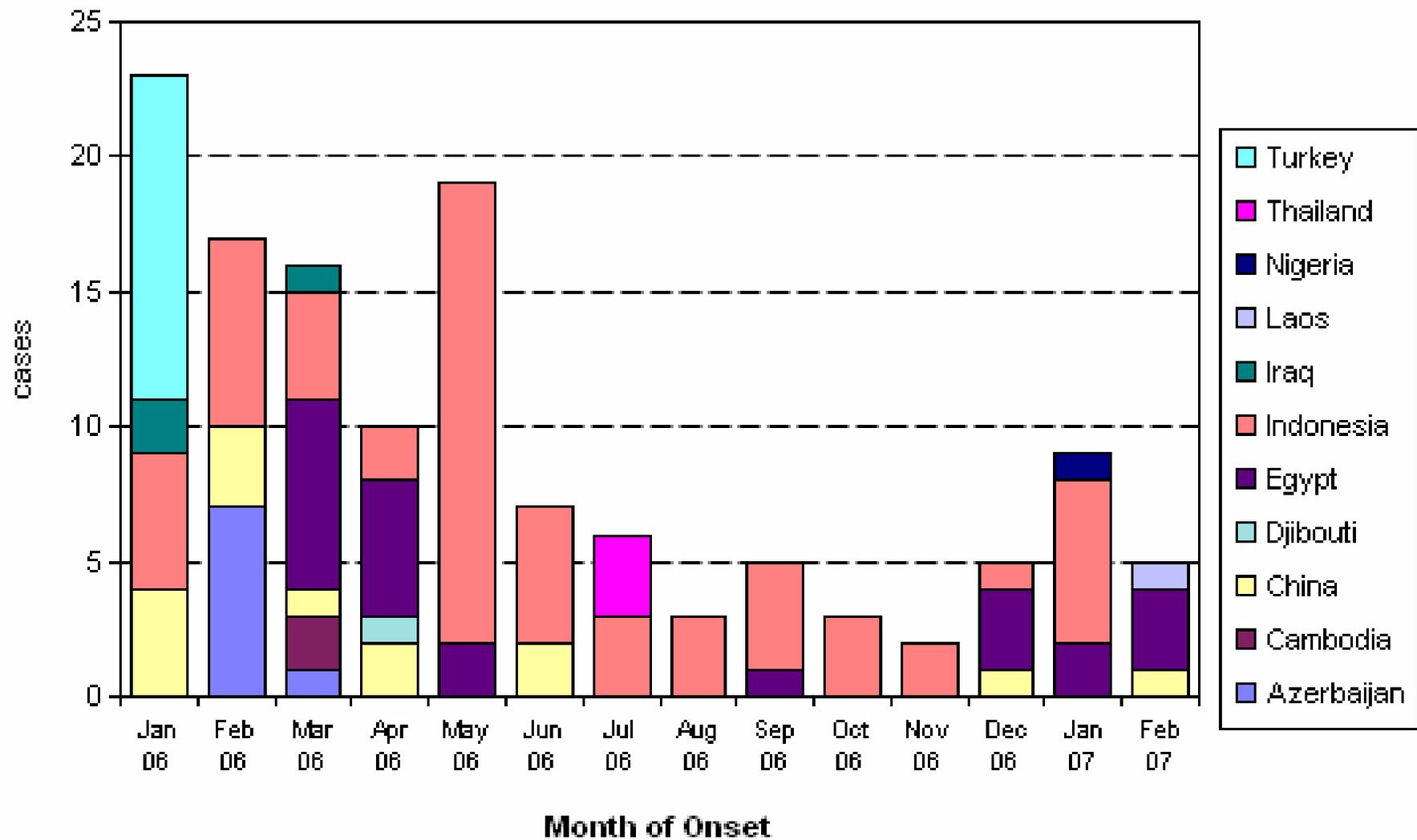


Human Cases

- 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)**





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





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

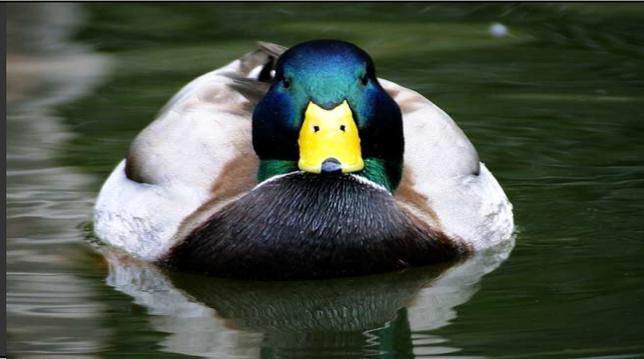
CALL 1-800-BE ALERT to report bird smuggling or undeclared bird products brought into the United States.

www.avianflu.gov

USDA is an equal opportunity provider and employer. • May 2007



H5N1 Risk via Wild Bird Migration via Asia/Alaska Routes

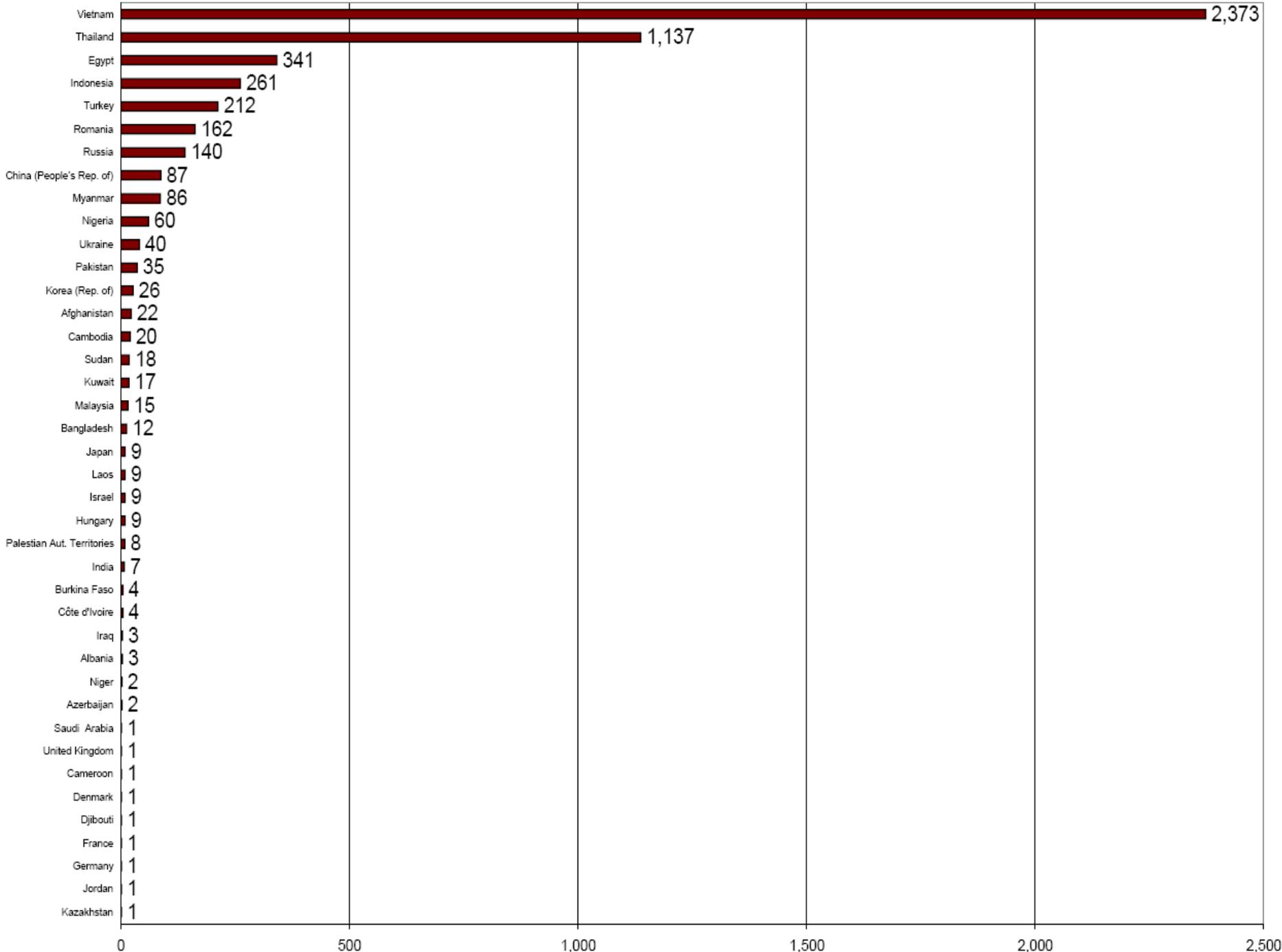


- Diverse avian hosts from Asia and the Americas overlap in Alaska
- 7 yrs of AI surveillance representing 8,254 samples
 - Yield 5 isolates (H3, H4, H6) with no evidence of Eurasian origin for any virus
- Risk and probably the frequency of intercontinental virus transfer in this region is low
- But 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)

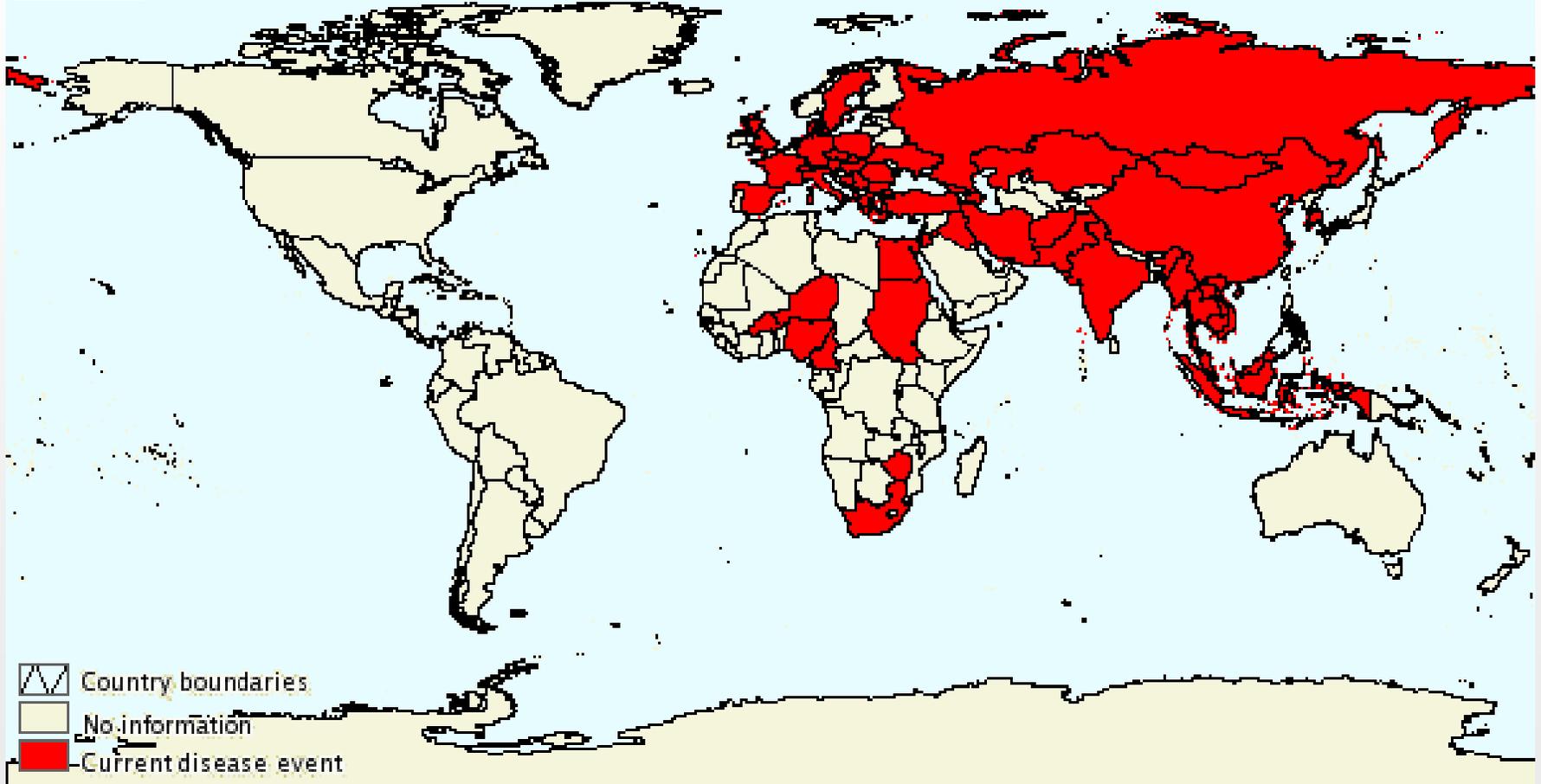
Outbreaks of Avian Influenza (subtype H5N1) in poultry. From the end of 2003 to 30 April 2007





H5N1 Avian Disease Distribution

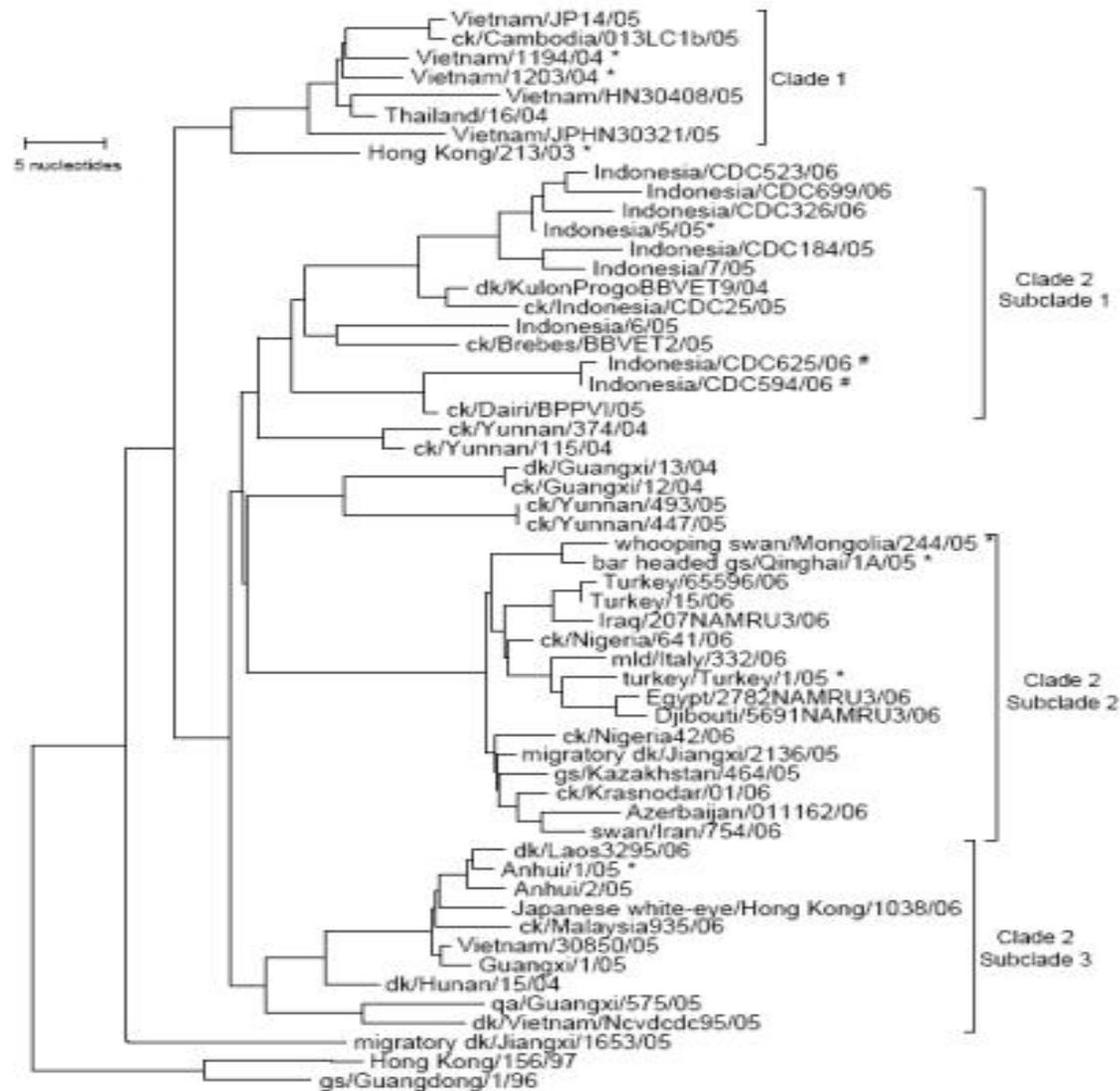
OIE © 2007





Clades

Fig. 1 Evolution of the H5N1 haemagglutinin gene

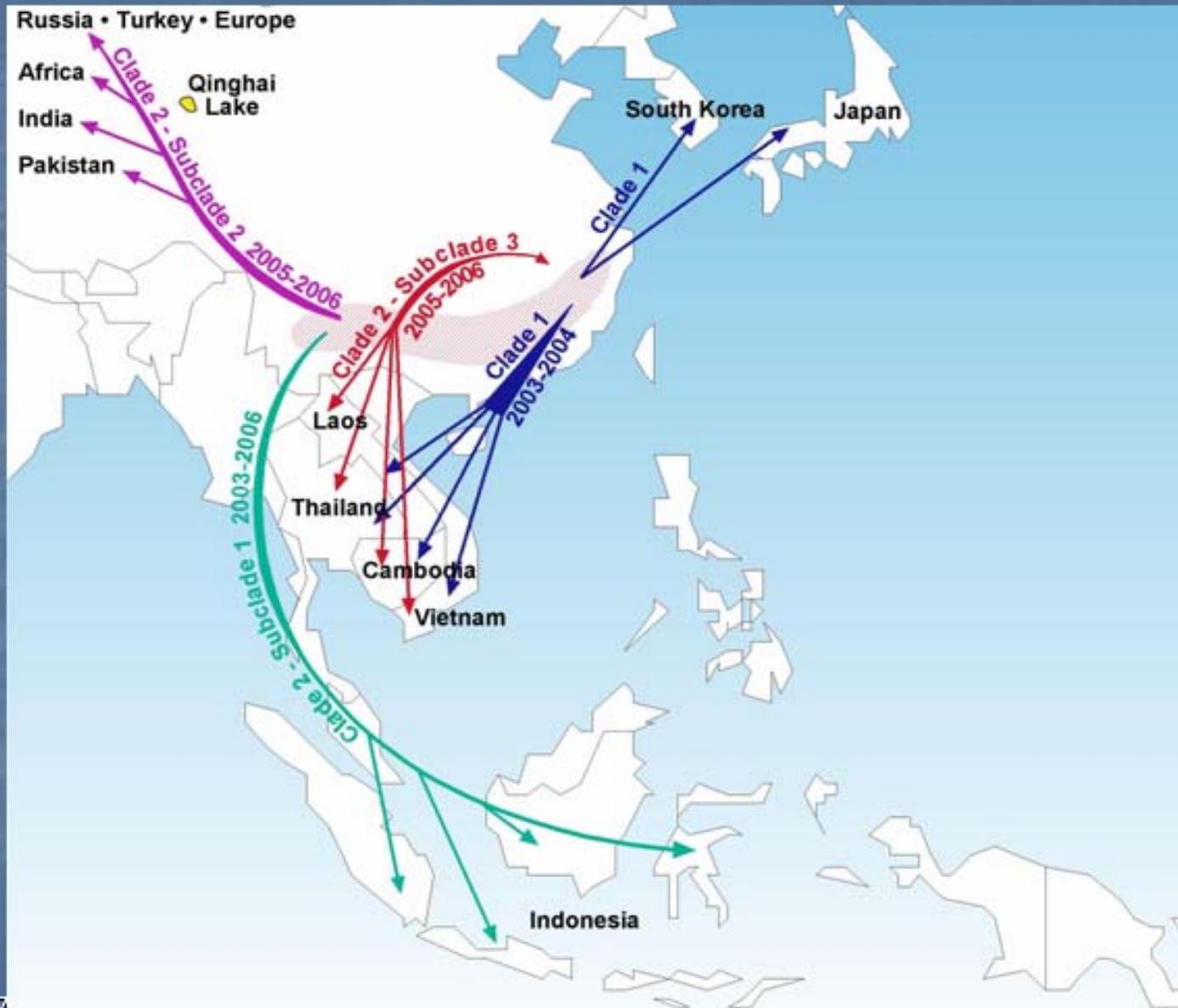




Clades

- 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

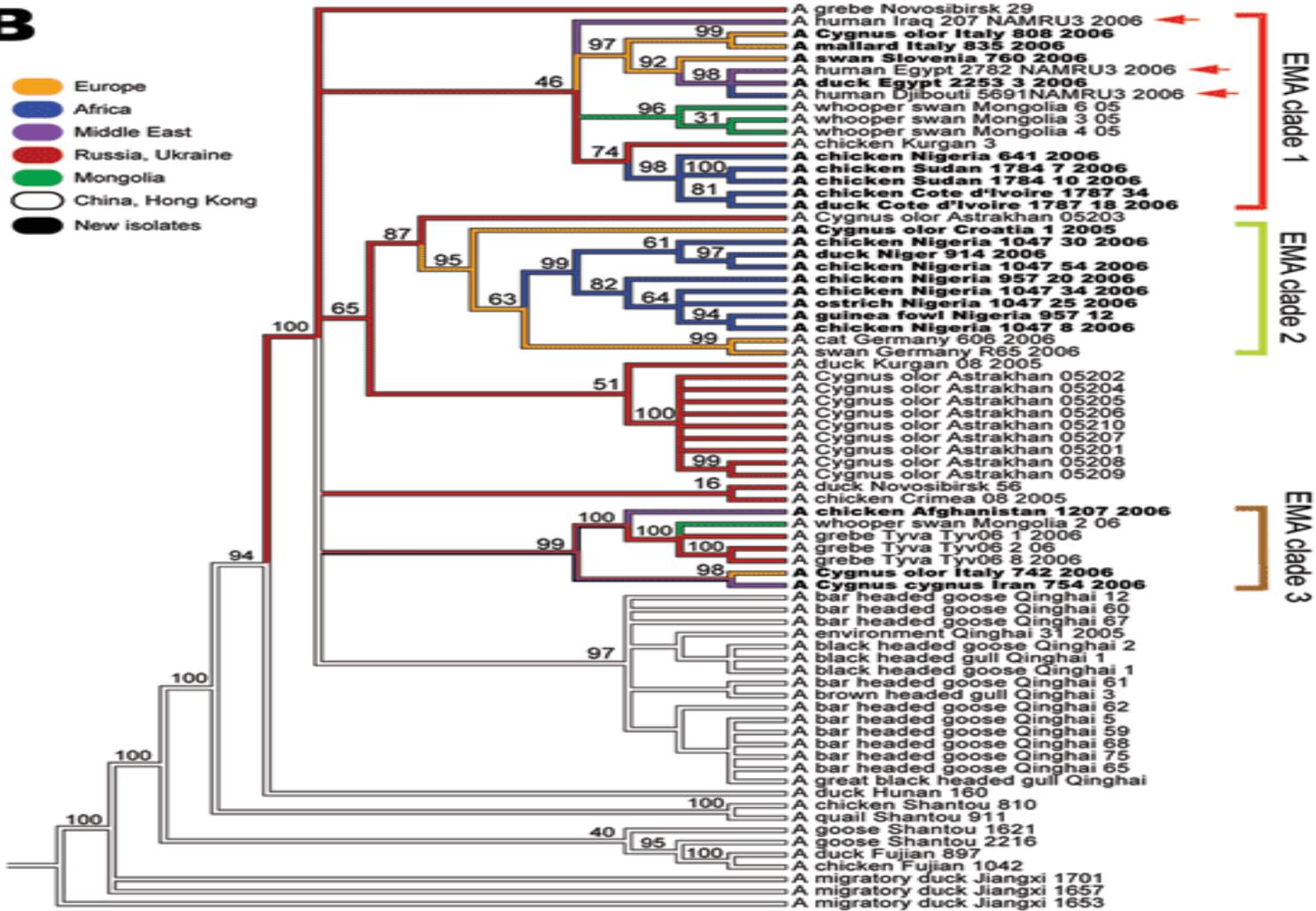
- Represent viruses isolated in Europe, the Middle East, and Africa (Côte d'Ivoire, Nigeria, Niger, Sudan, Egypt, Afghanistan, Iran, Slovenia, Croatia, and Italy).
- Shared lineage suggests a single genetic source for introduction- Russia or Qinghai Province origin.
- The broad dispersal throughout these 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

B

- Europe
- Africa
- Middle East
- Russia, Ukraine
- Mongolia
- China, Hong Kong
- New isolates





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
- $\text{INF}_{\alpha,\gamma}$ and TNF_{α} 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

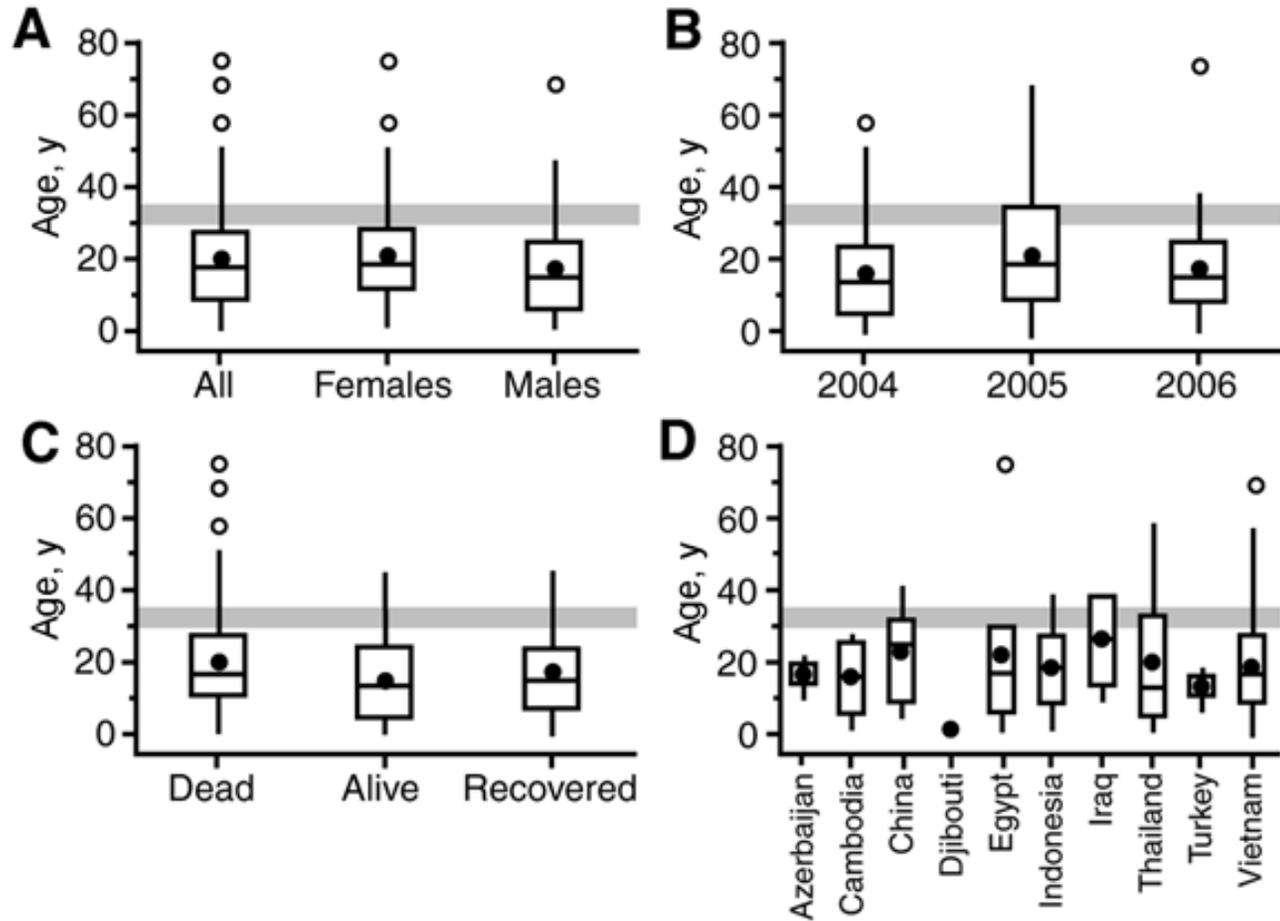


Is Gray Hair a Possible Protective Factor?

- 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
 - \geq 40 yrs = 0.02



H5N1: a Disease of the Young?





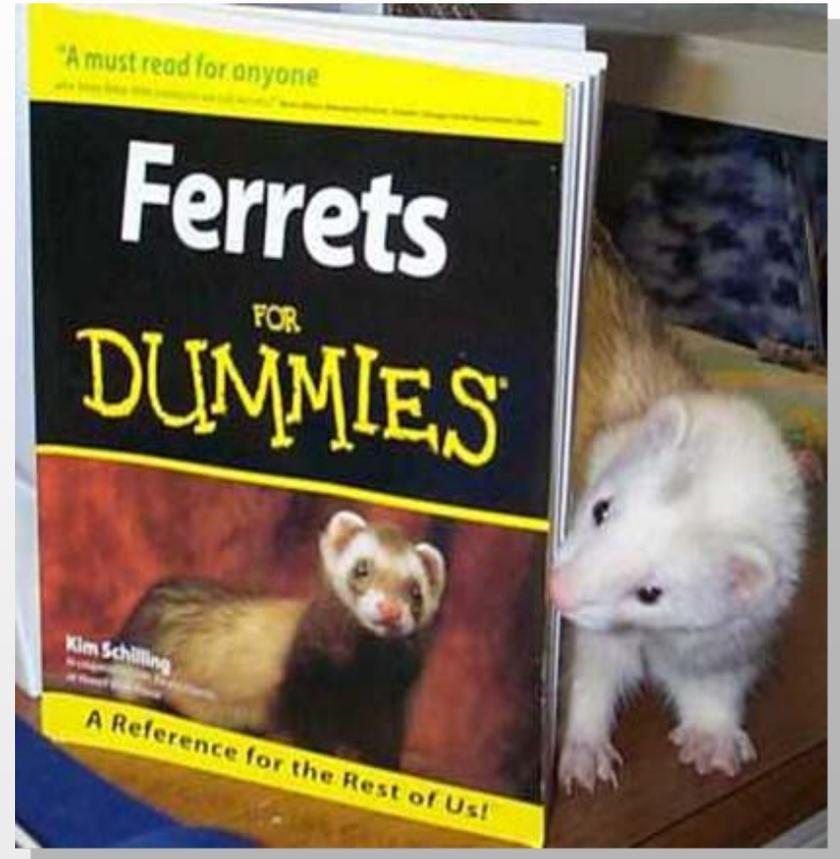
Could Ferrets Lie About Tamiflu?





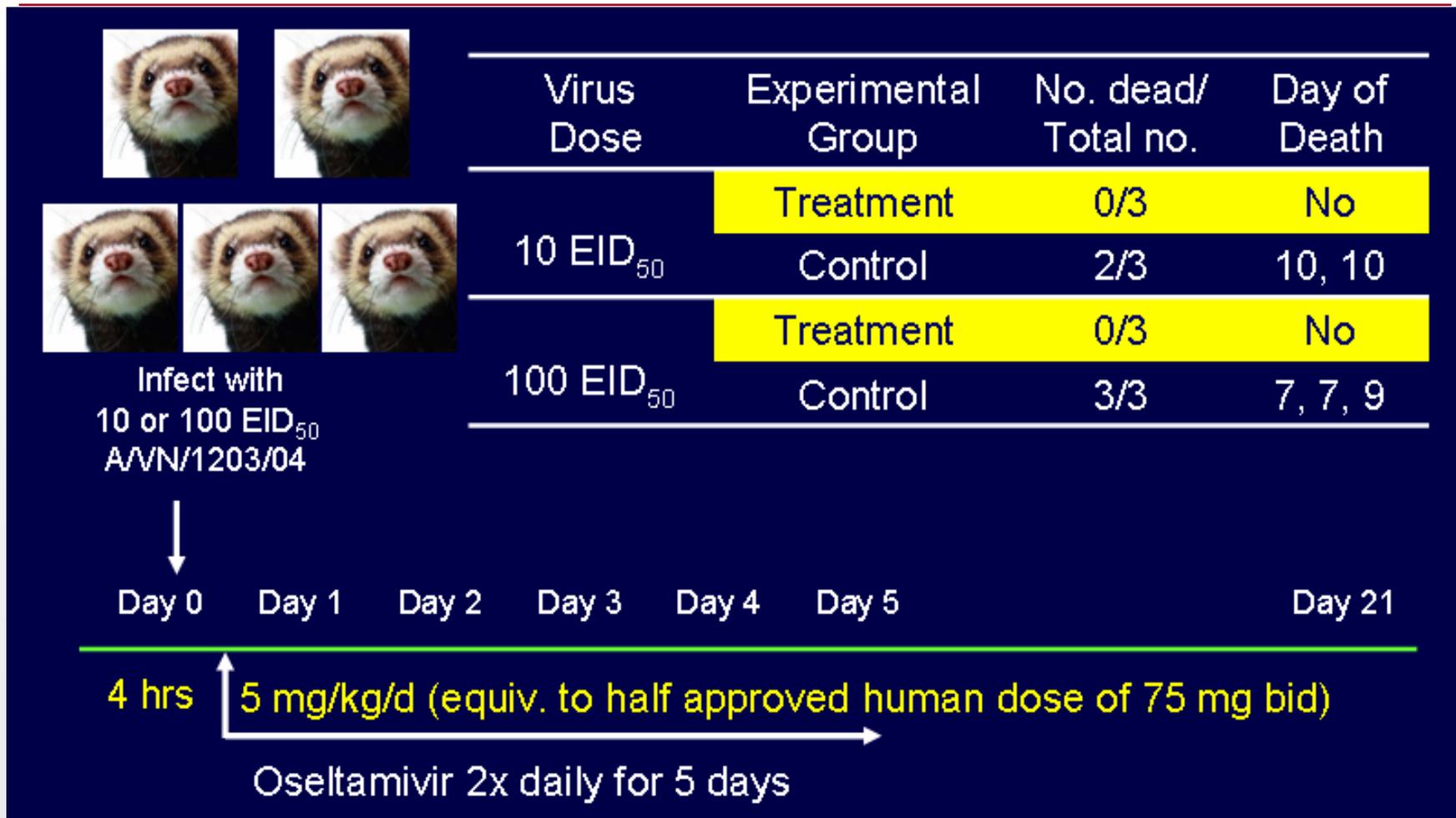
Ferrets as Animal Models for Influenza

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



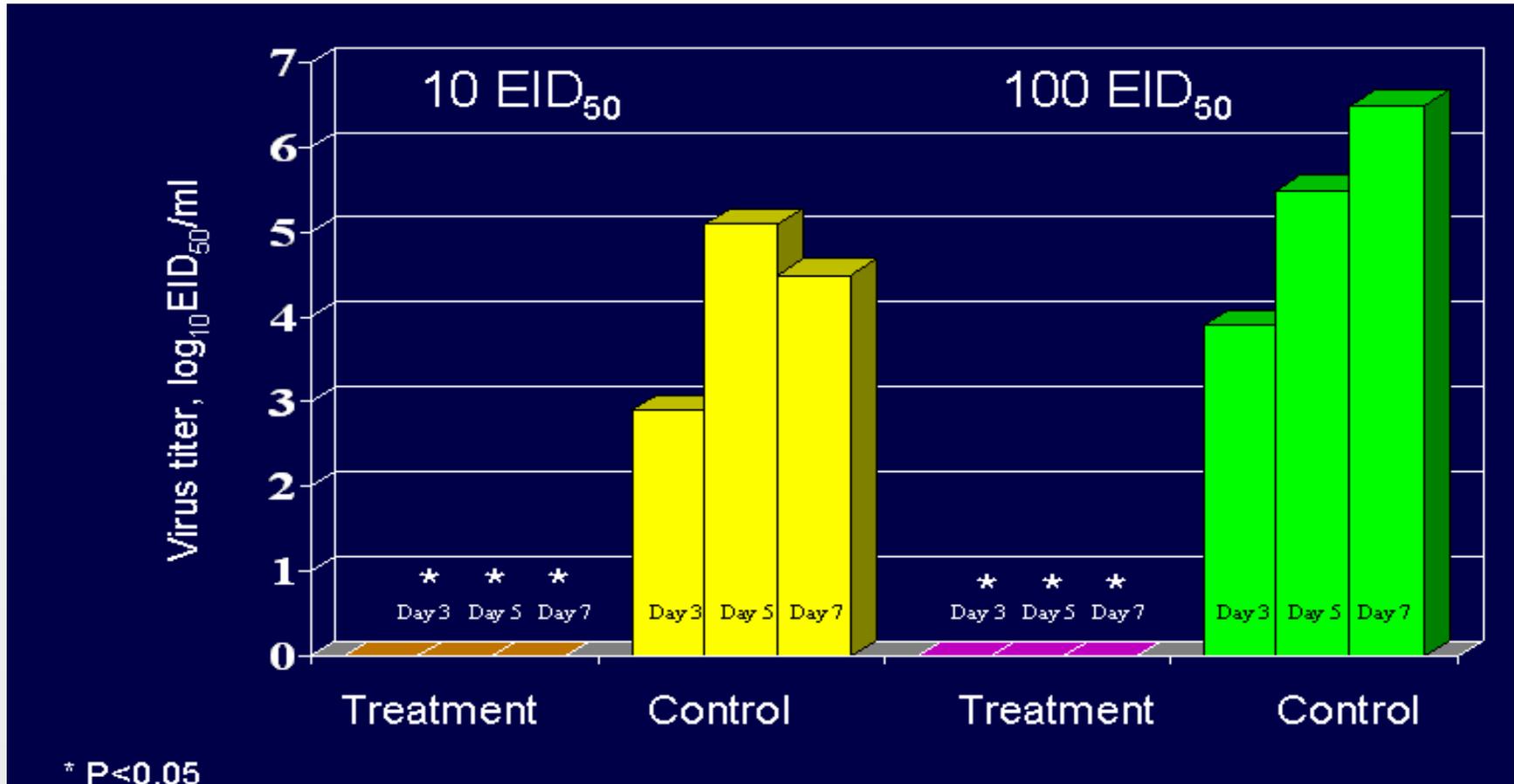


Early Post-exposure Administration of Tamiflu - Survival Endpoint





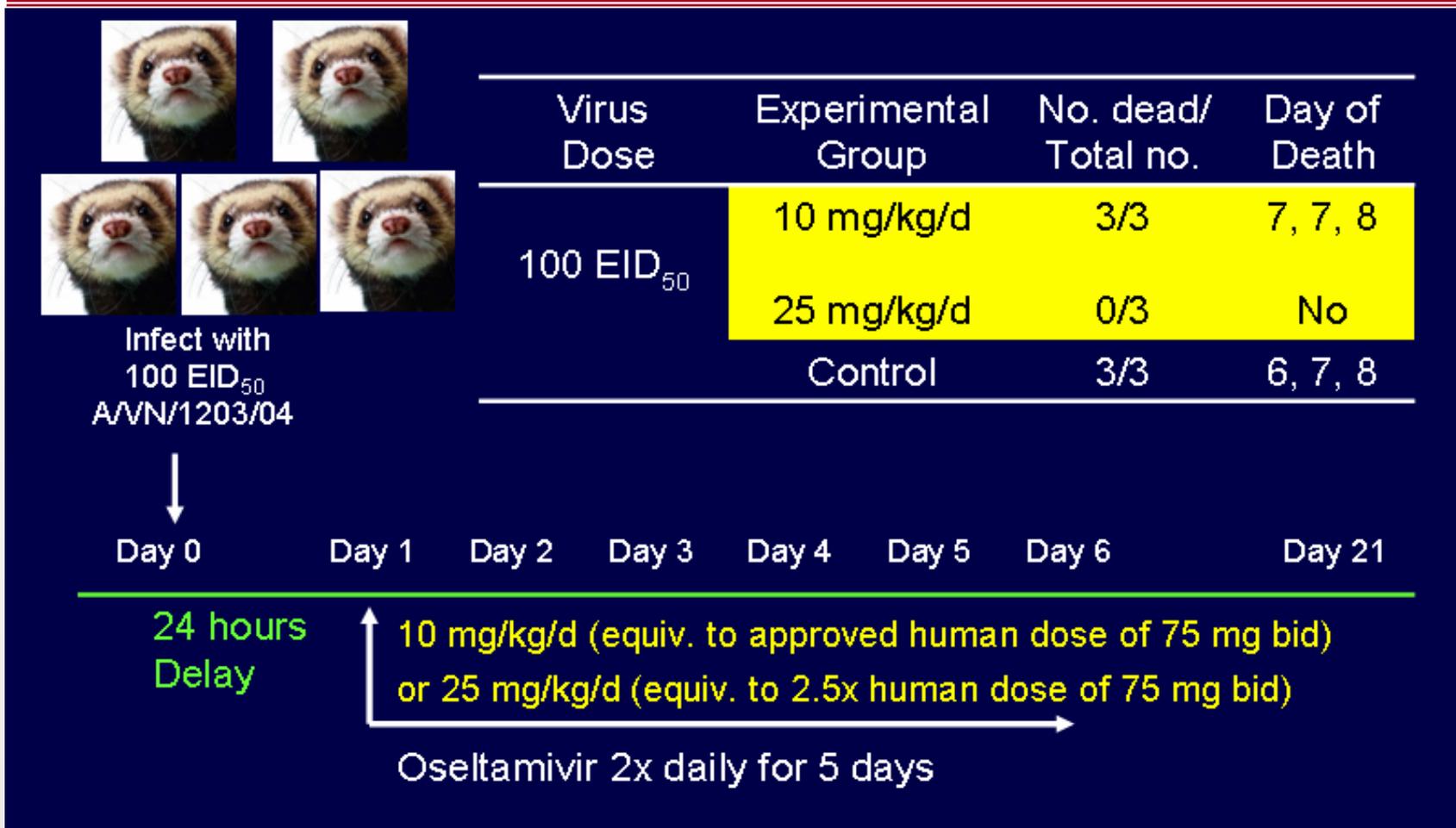
Upper Respiratory Track Viral Titers Tamiflu Tx - Vietnam 1203 Challenge



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

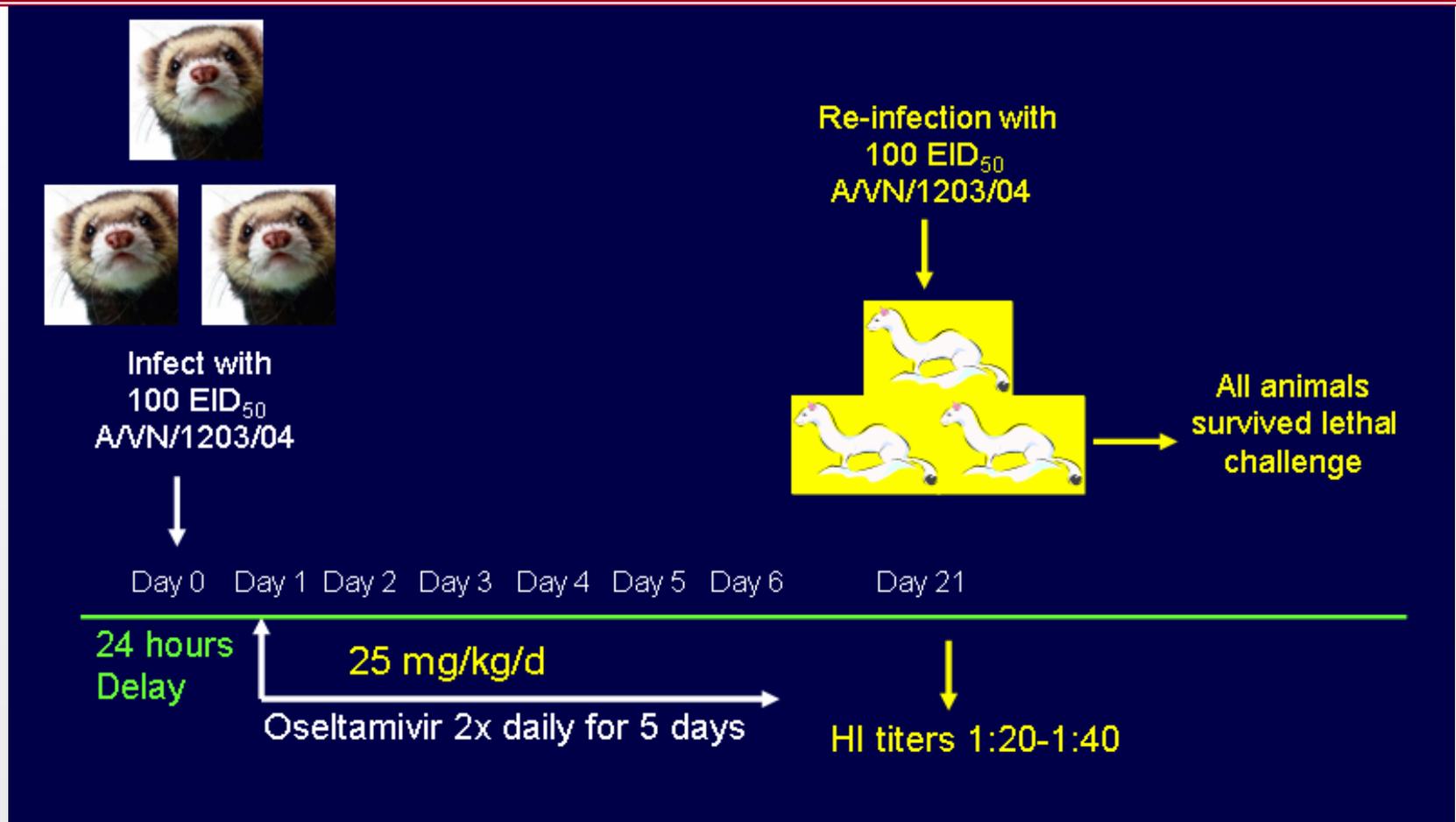


Late Post-exposure Administration of Tamiflu - Survival Endpoint





Re-infection with a Lethal H5N1 Dose





Antivirals

The Way Ahead?

- Parenteral Zanomivir:
 - IV Q12 hrs, $t_{1/2}$ 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

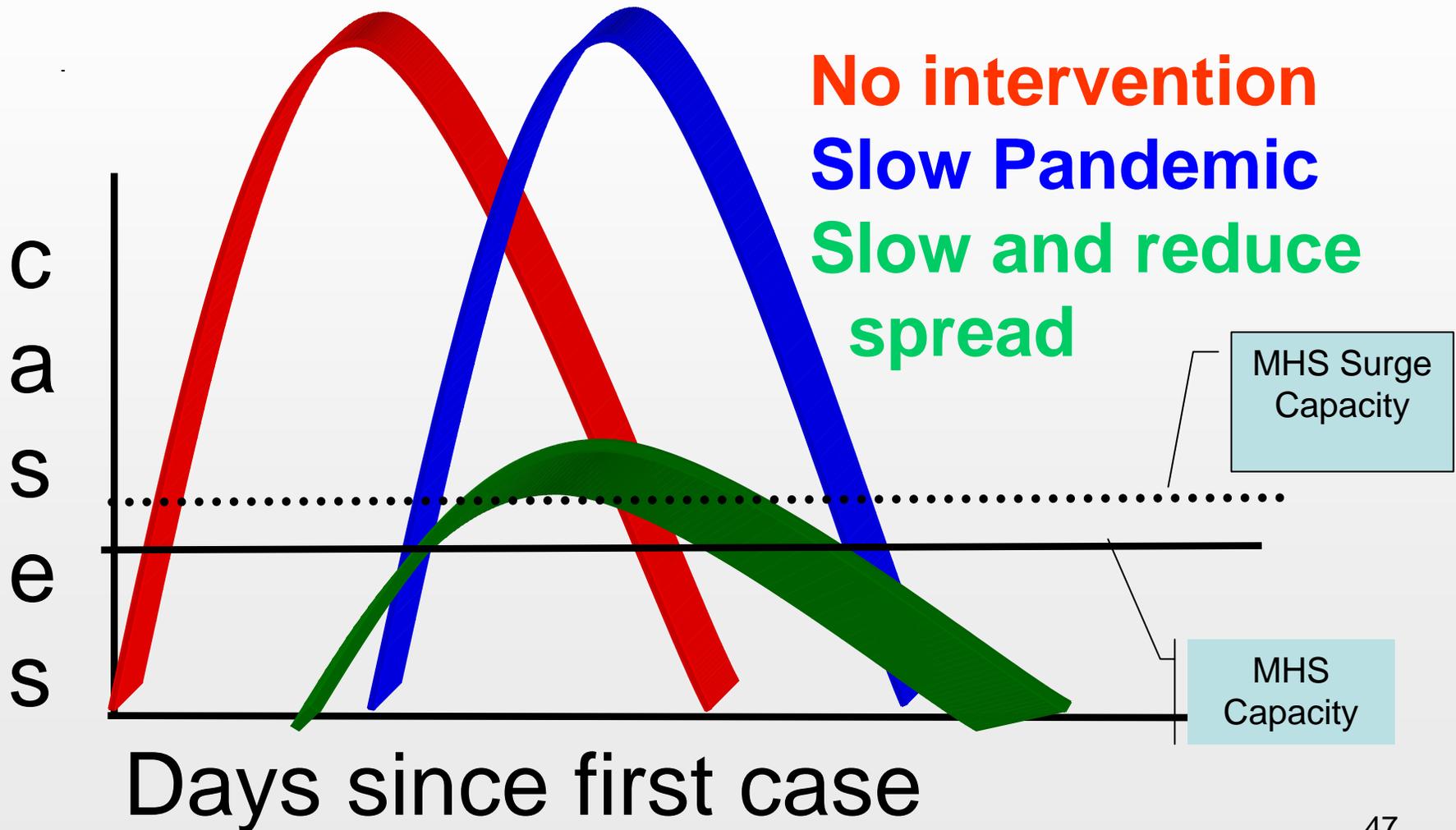


Interim Pre-pandemic Planning Guidance: Community Strategy for Pandemic Influenza Mitigation in the United States— Early, Targeted, Layered Use of Nonpharmaceutical Interventions





Response Goals

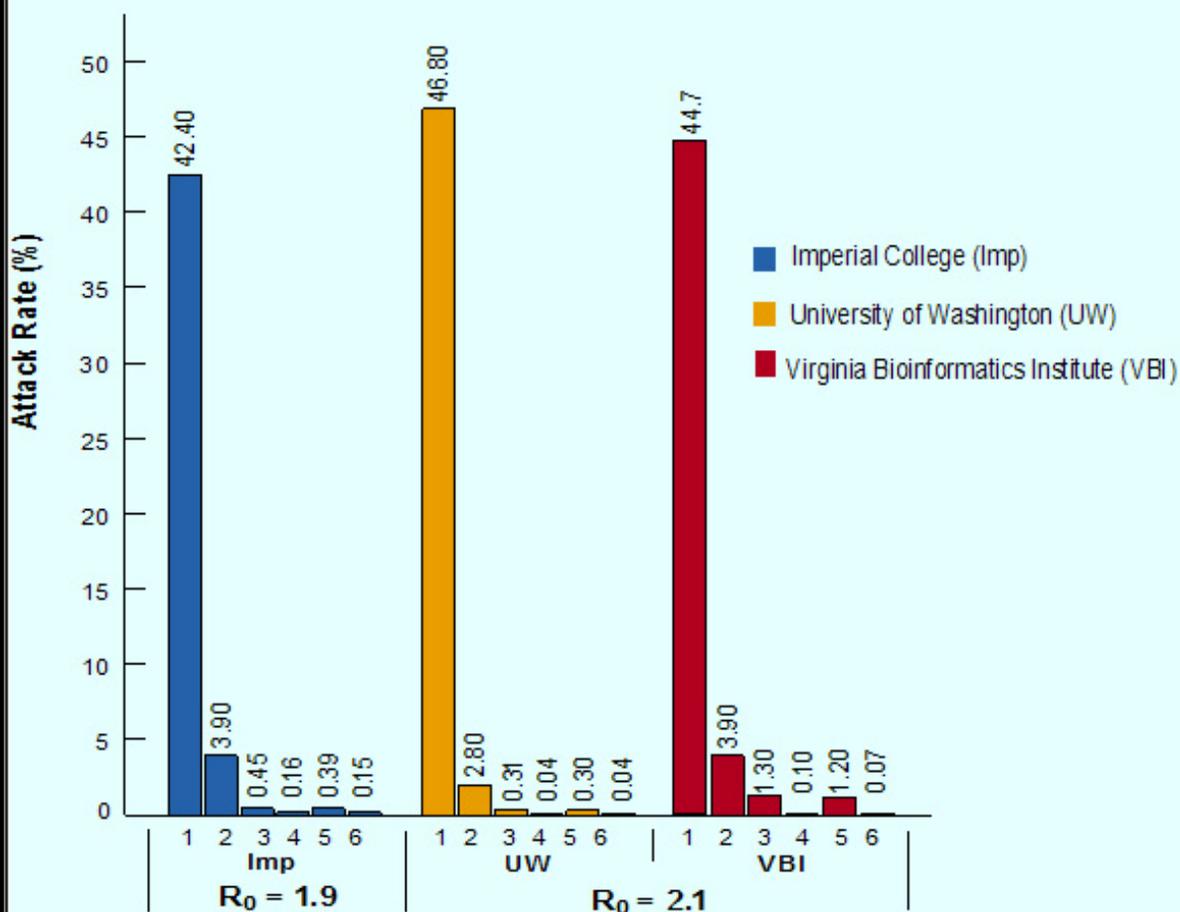




TLC Interventions

- 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.

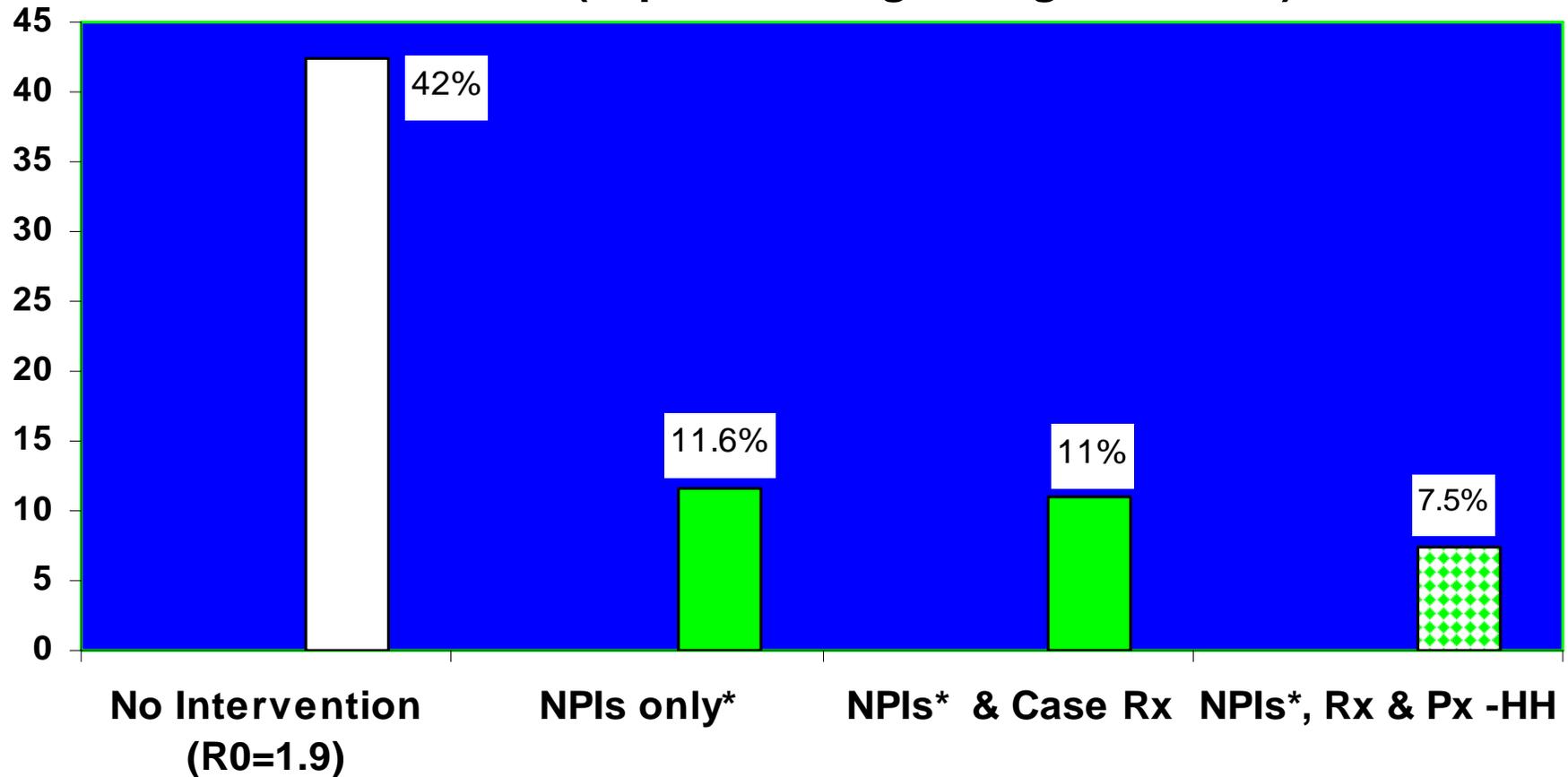
Removing one source of transmission may make other sources relatively more important.

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



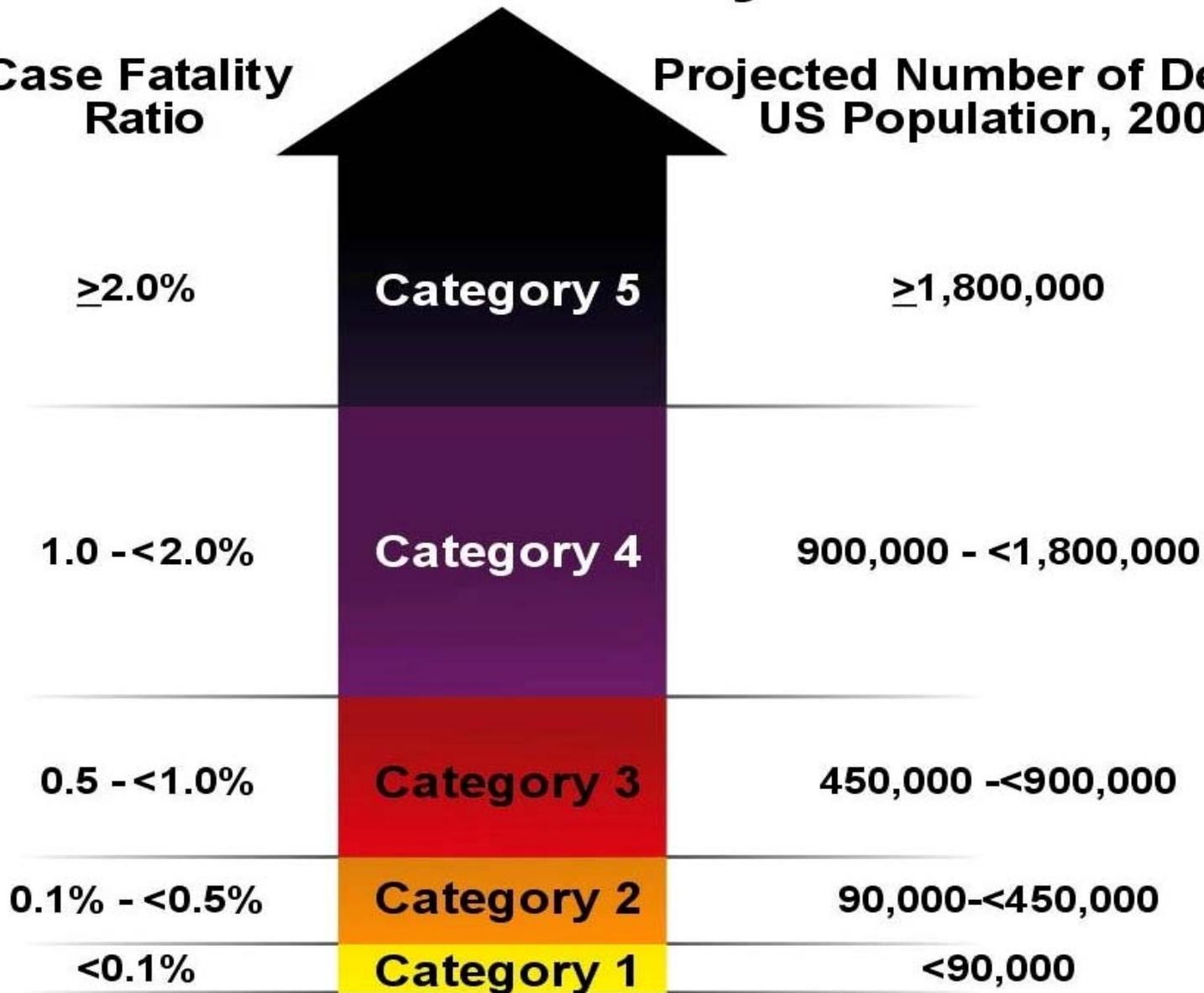
Pandemic Severity Index

- 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



* 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 -reduce out-of school social contacts and community mixing	Generally not recommended Generally not recommended	Consider: ≤4 weeks †† Consider: ≤4 weeks ††	Recommend: ≤12 weeks §§ Recommend: ≤12 weeks §§
Workplace / Community Adult social distancing -decrease number of social contacts (e.g., encourage teleconferences, alternatives to face-to-face meetings) -increase distance between persons (e.g., reduce density in public transit, workplace) -modify, postpone, or cancel selected public gatherings to promote social distance (e.g., stadium events, theater performances) -modify work place schedules and practices (e.g., telework, staggered shifts)	Generally not recommended Generally not recommended Generally not recommended Generally not recommended	Consider Consider Consider Consider	Recommend Recommend Recommend 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



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

