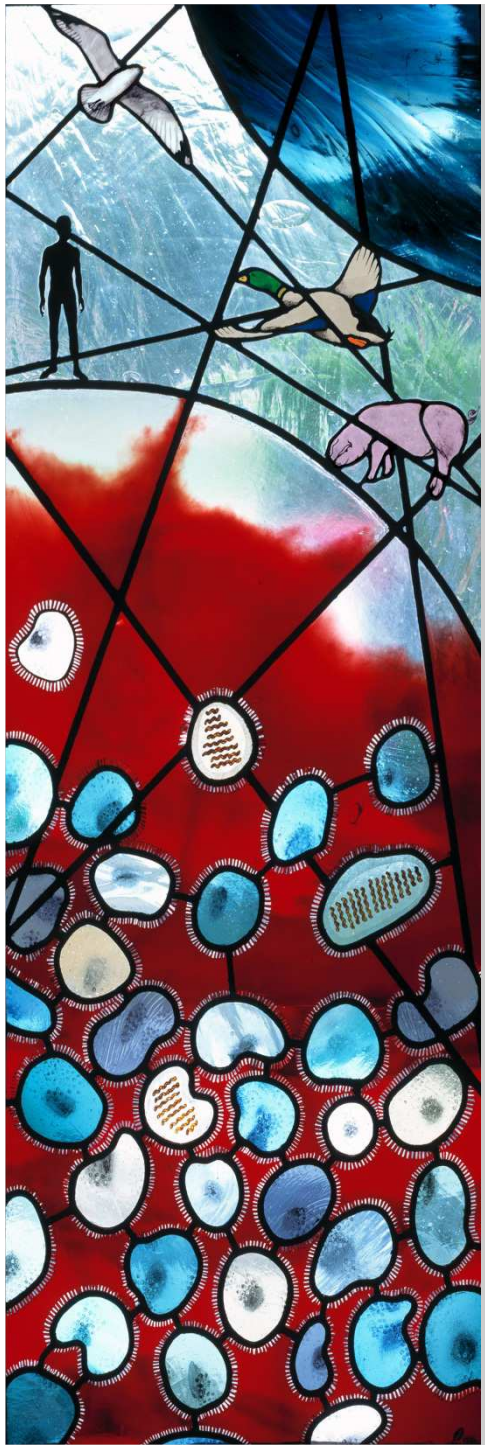

Case Study: H5N1 avian influenza

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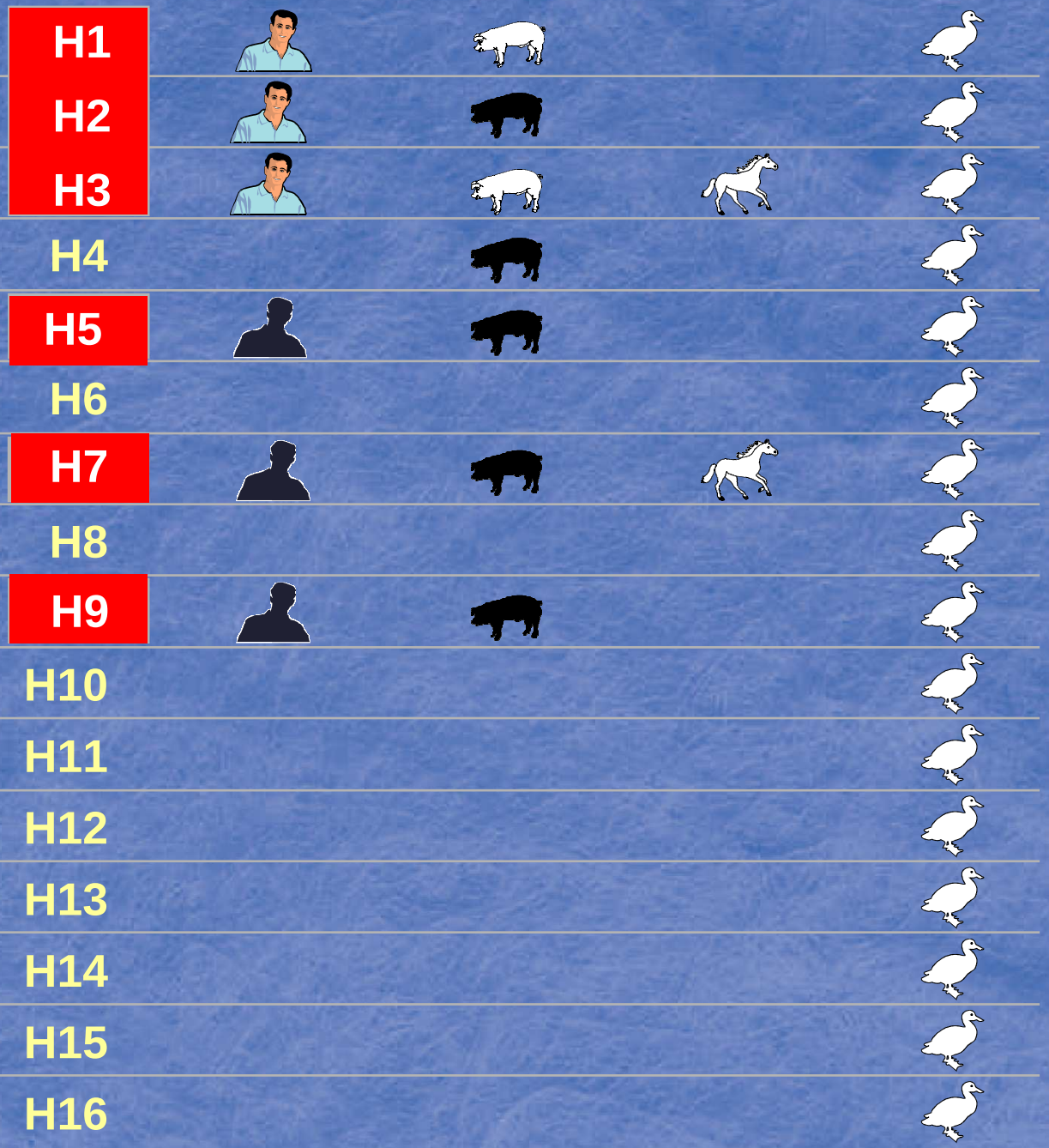
Rose Marie Thomas Endowed Chair
Division of Virology
Department of Infectious Diseases
St. Jude Children's Research Hospital

Influenza A Virus Host Range



Migratory Bird Reservoirs of all Influenza A Viruses

All 16 HA and 9 NA subtypes

Ecology of avian influenza in wild birds

- AI viruses replicate primarily in the intestinal tract.
- Limited overt disease signs (low path)
  - There can be a "cost".
- Only LPAI are perpetuated in wild birds
  - Including H5 and H7 subtypes
  - **Has H5N1 changed this rule?**
- LPAI in wild birds are the reservoir of all influenza A viruses in other species

The H5 and H7 subtypes are unique

- Low pathogenic in wild bird reservoir

-Largely intestinal replication

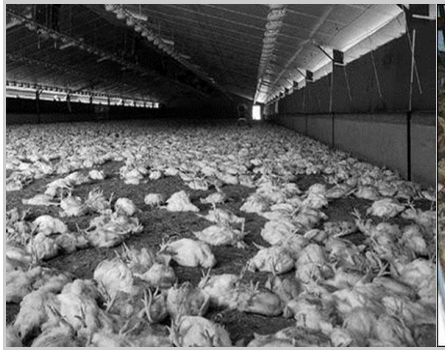
- Evolve rapidly after transmission to domestic poultry

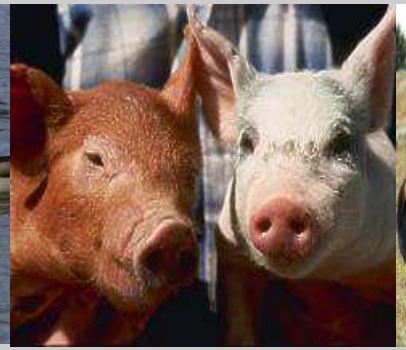
-Host response varies

-Generalized infection, systemic spread-poultry, tigers

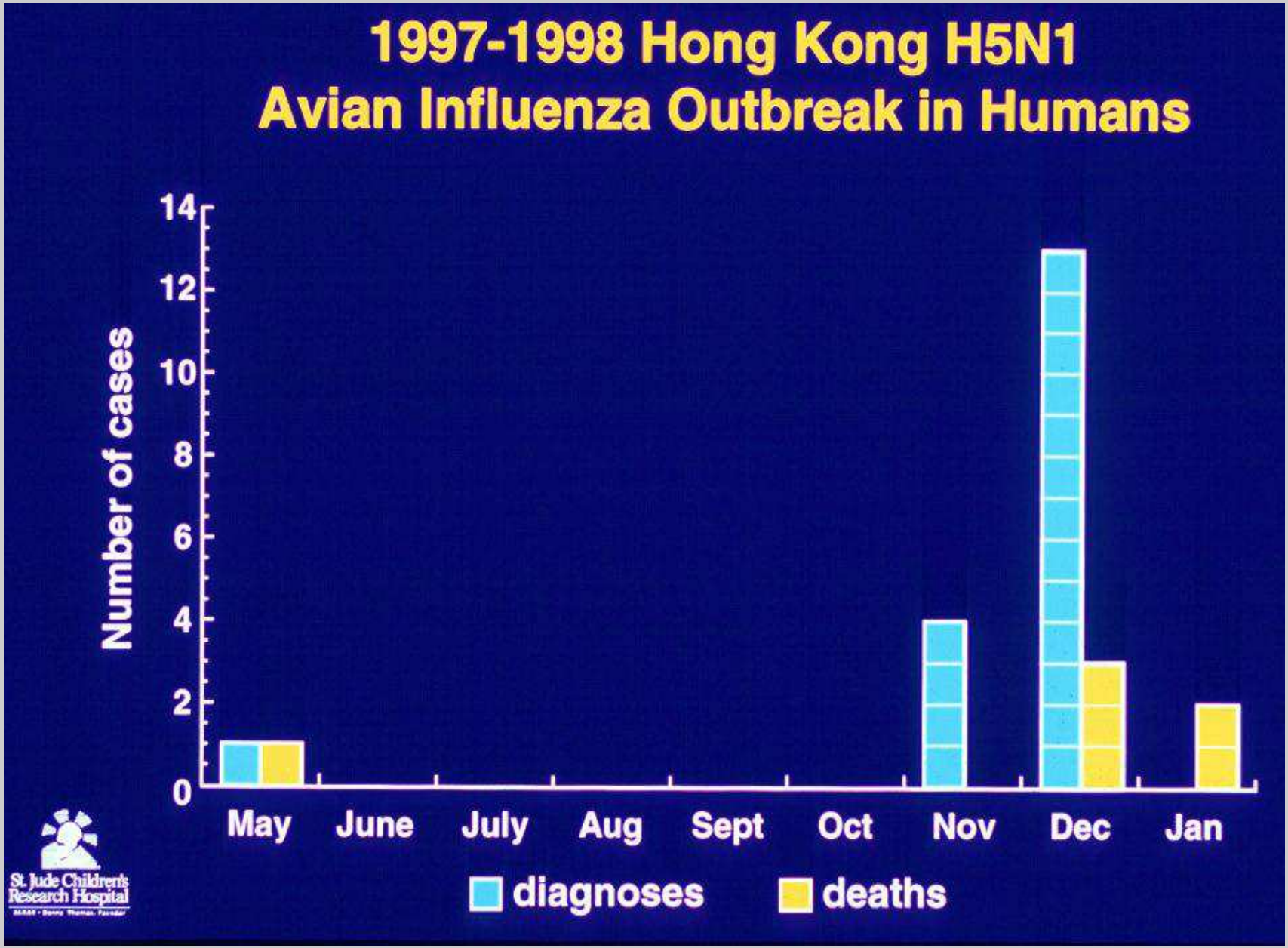
-Replication and spread-ducks pigs horses

LETHAL INFECTION | **INAPPARENT INFECTION**




A child dies in Hong Kong..

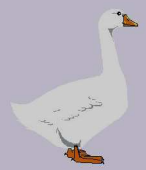


H5N1 – The Starting Point?

Culling of all poultry in Hong Kong

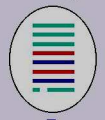
-No more human infections

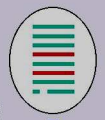
Time Line of Emergence of H5N1 Influenza

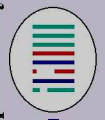


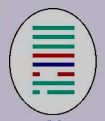
Culling of all poultry in Hong Kong.

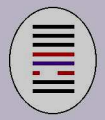
Multiple Genotypes











Penfold and Kowloon Park die off of exotic waterfowl.

Daughter dies in Fujian, father dies in Hong Kong, and son recovers.

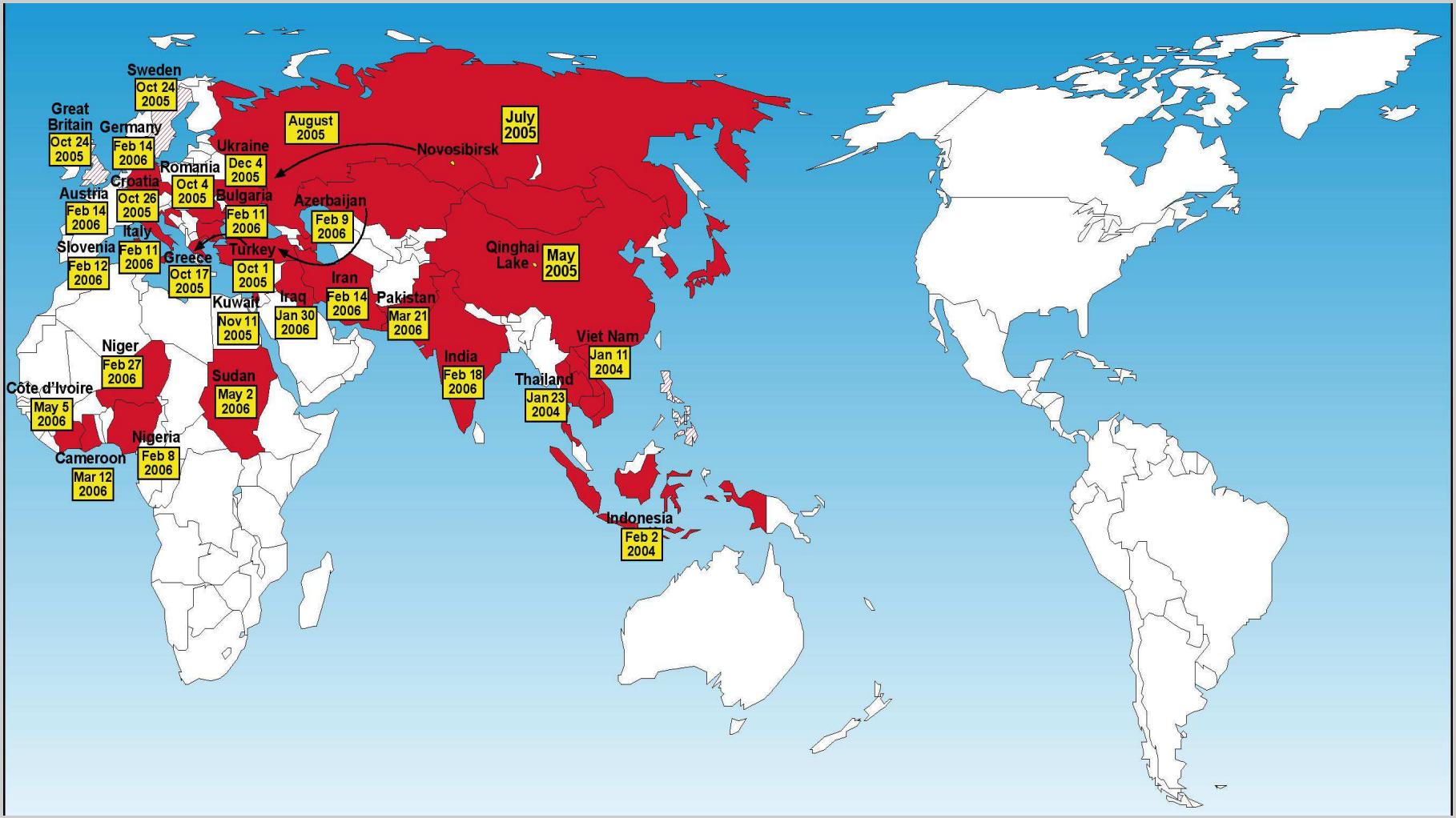
S.E. China	Hong Kong	Hong Kong	Hong Kong	Hong Kong	Fujian Hong Kong	S. Korea Japan	Vietnam Thailand Laos Cambodia
1996	May 1997	Dec. 1997	1998-2002	Dec. 2002 ↓ Jan. 2003	Feb. 2003	Dec. 2003 ↓ Jan. 2004	Jan. 2004

Clade 1

Index Case

Index Cluster

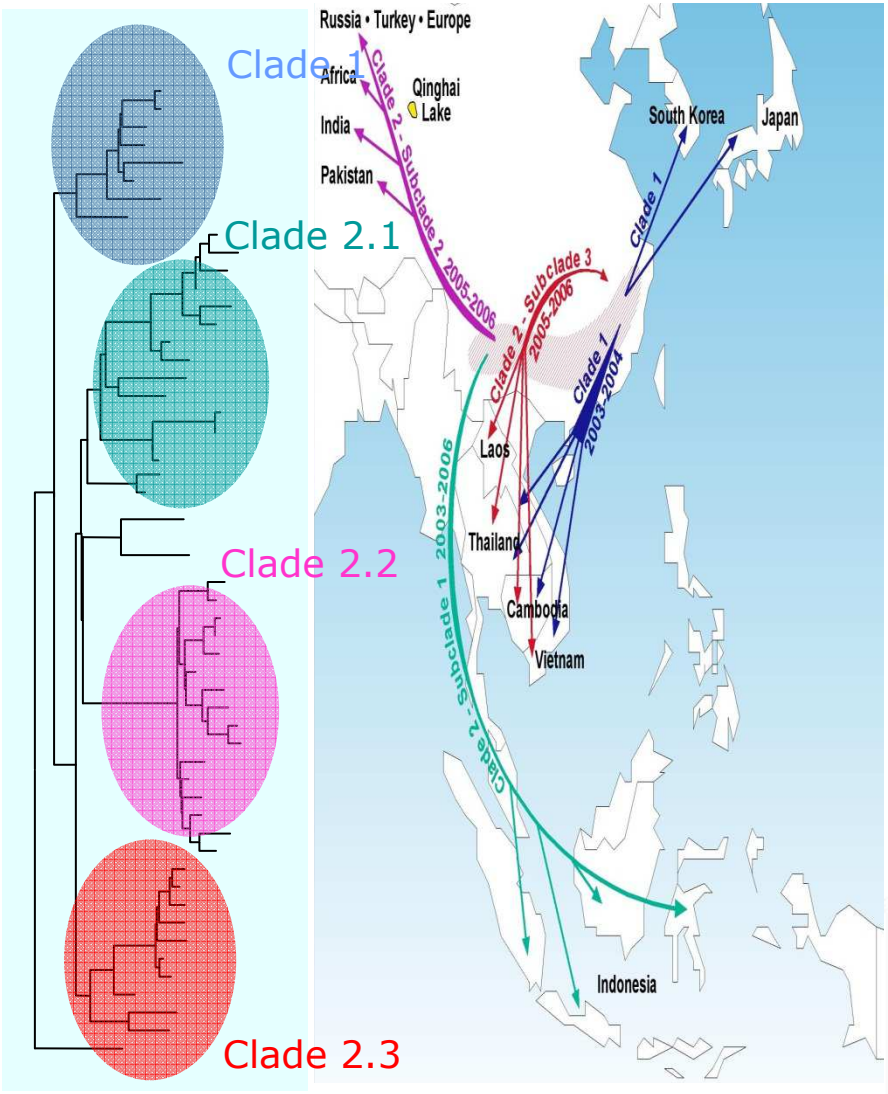
Initial Spread of H5N1: 2004 →

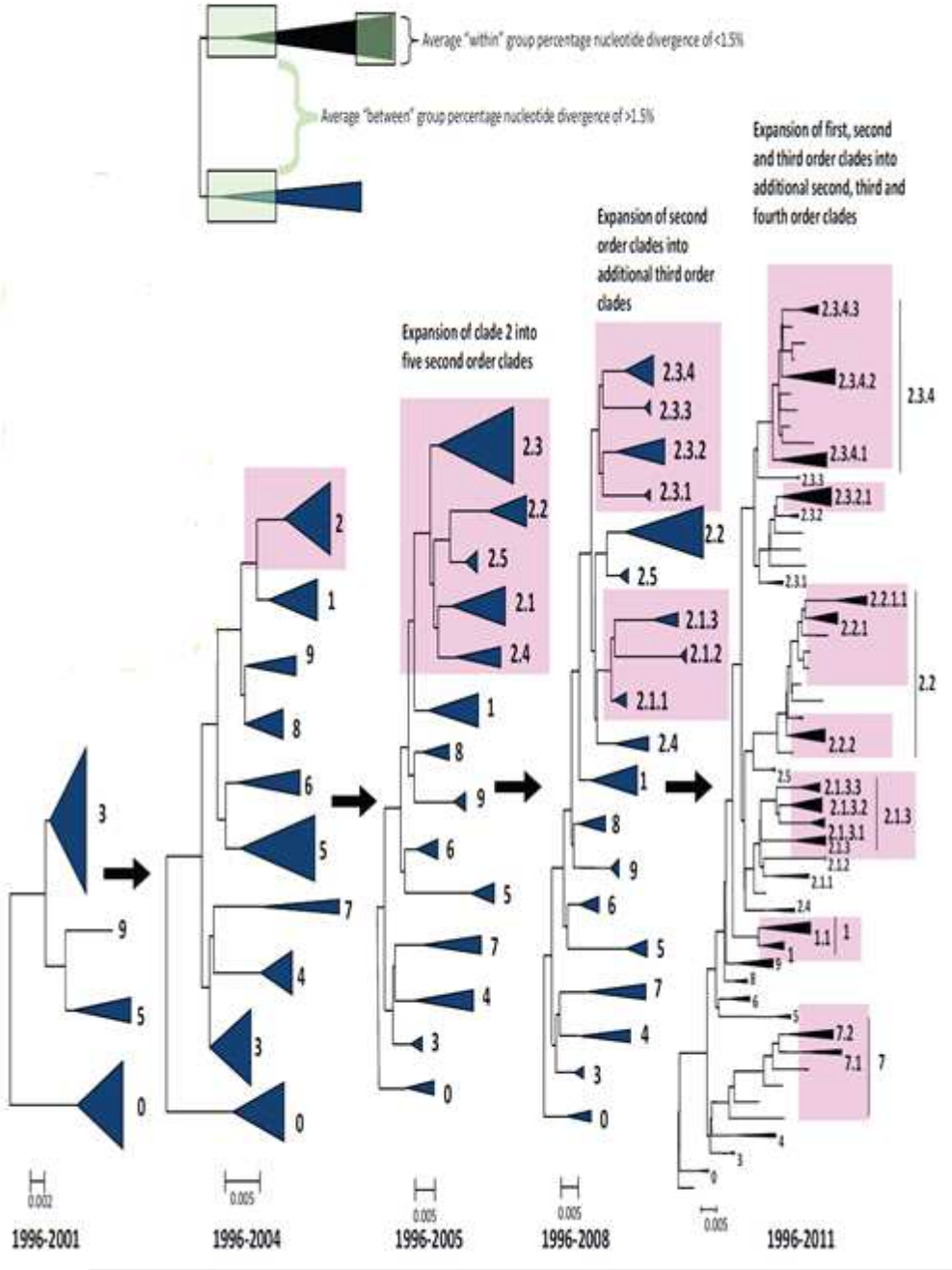


Current status:

Poultry: +500 million Human Cases: 602 Human Deaths: 355

Continuing evolution of H5 hemagglutinin

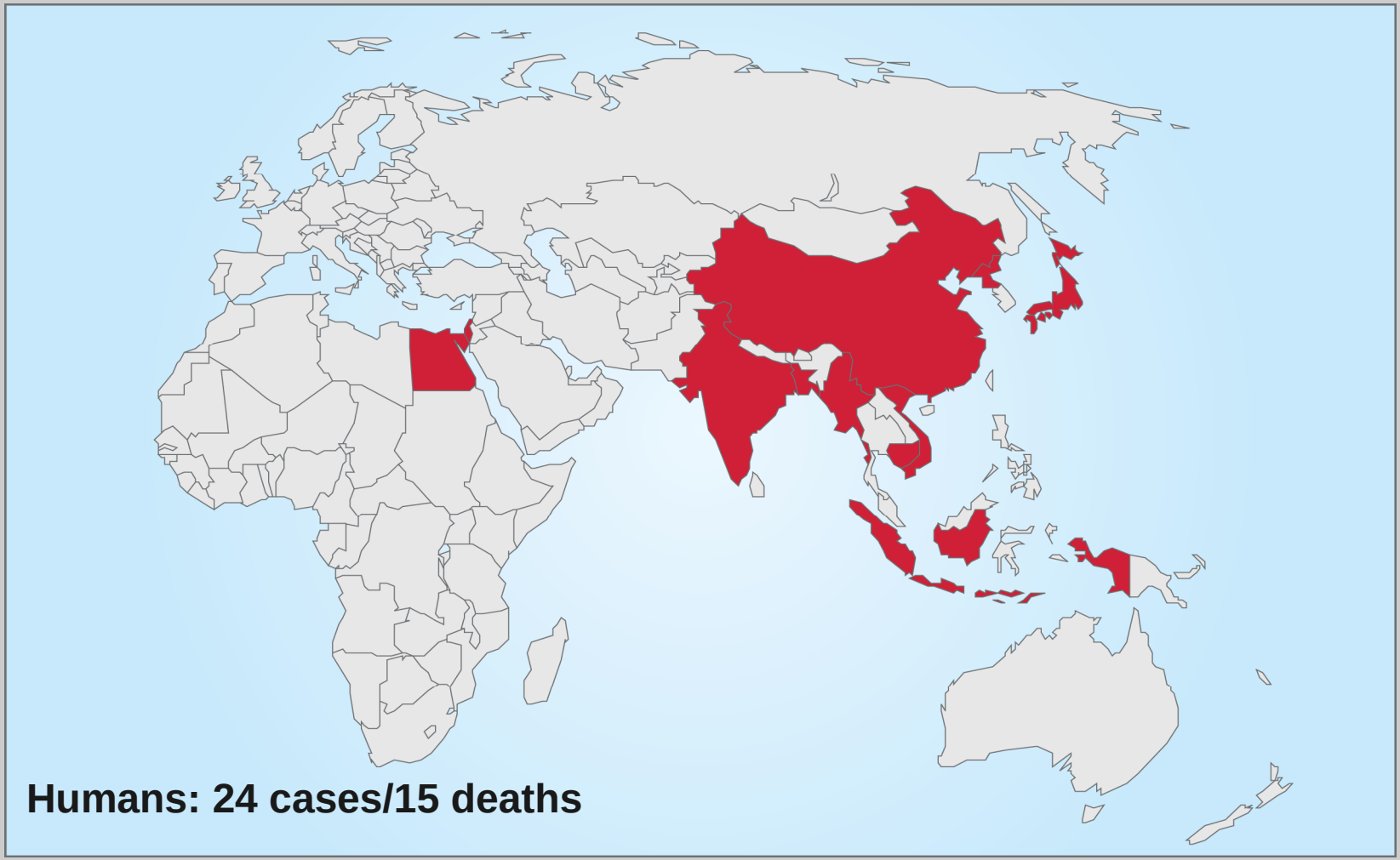




Control Strategies

- Stamping out-compensation- successful
- Vaccination, reduces disease signs- fails to eradicate

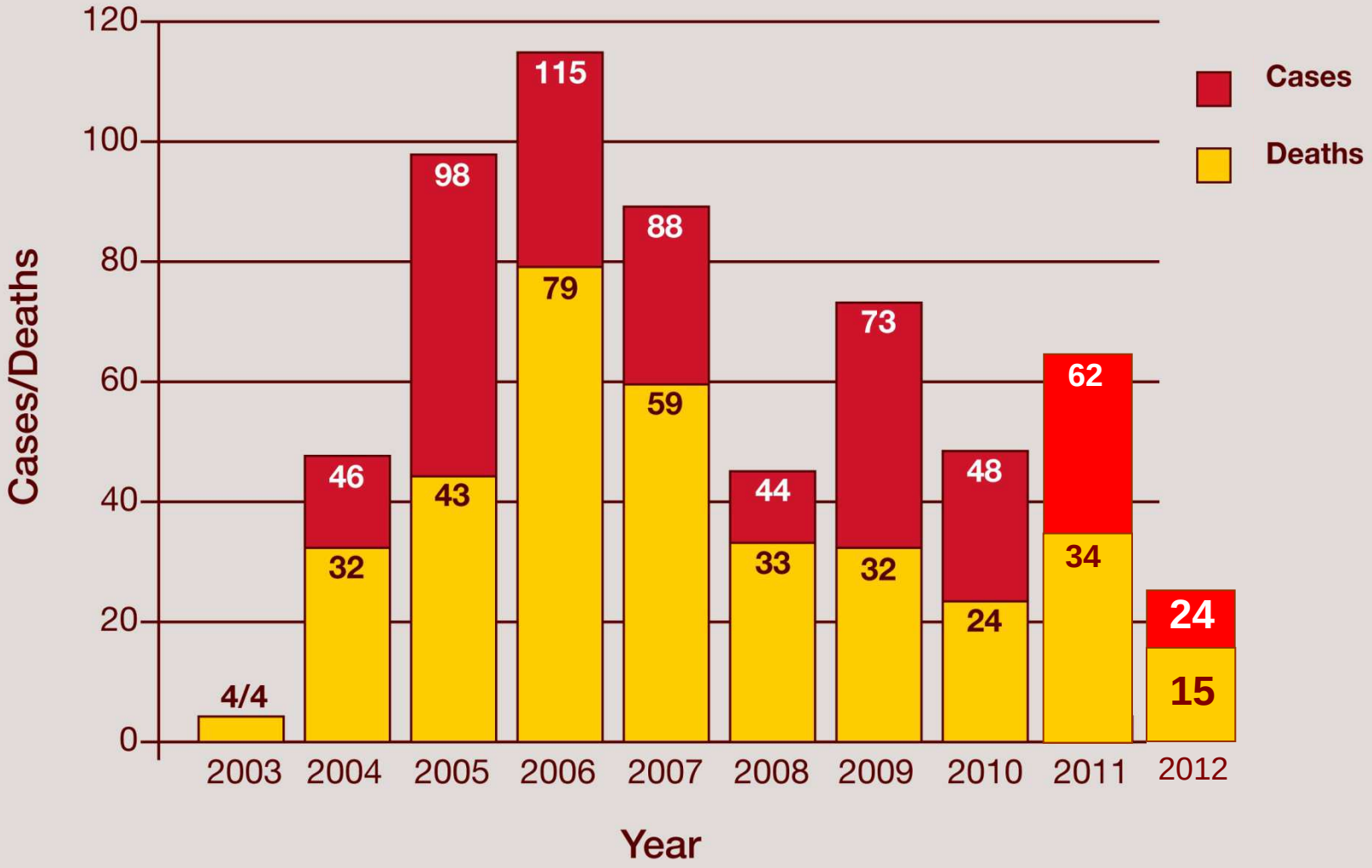
H5N1 Influenza 2012



Ongoing outbreaks of highly pathogenic H5N1 in domestic poultry &wild birds

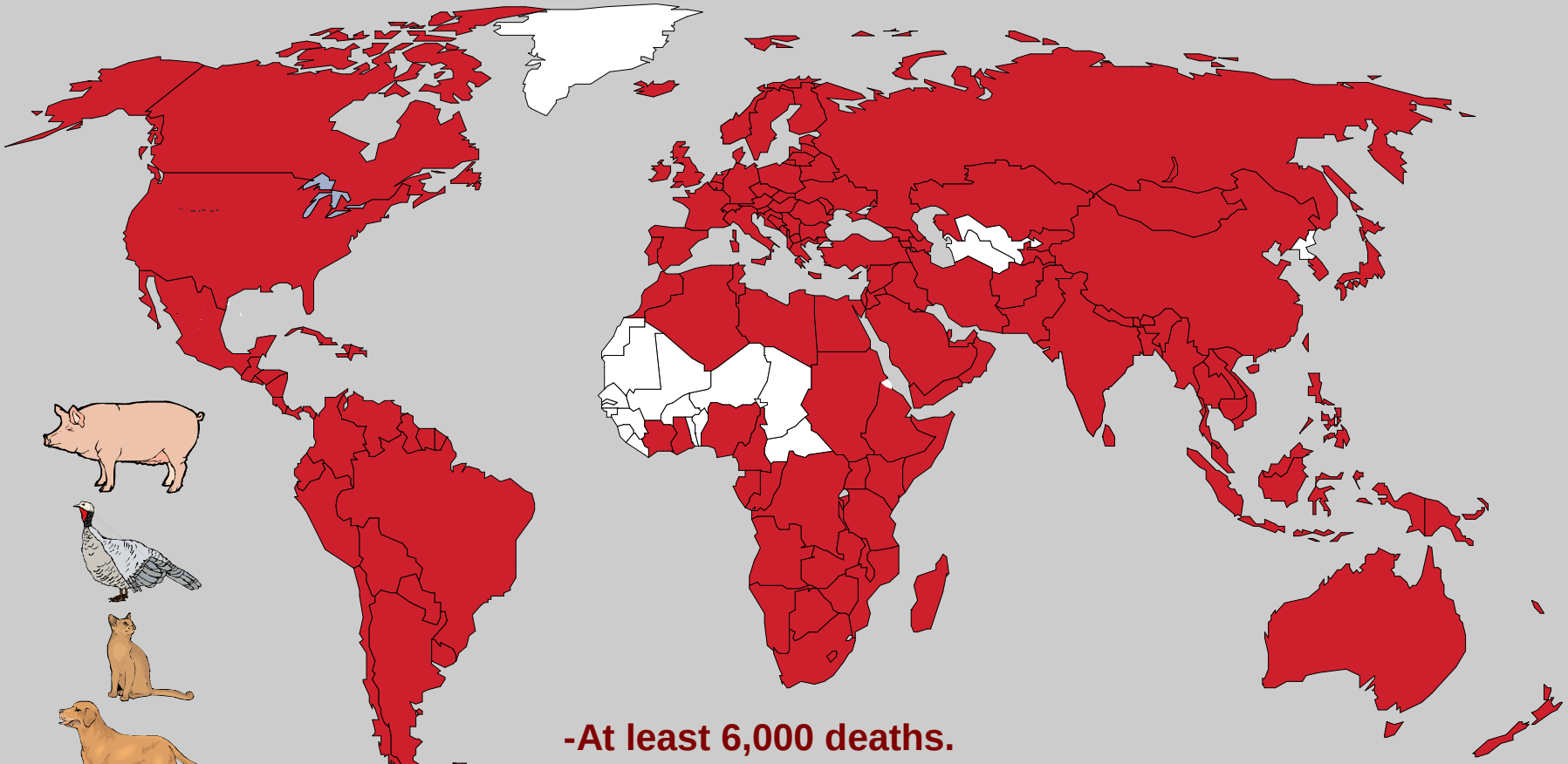
Bangladesh	Hong Kong	Israel	Nepal	Egypt
Bhutan	India	Indonesia	Myanmar	Vietnam
China				

Human H5N1 Cases



Pandemic Preparedness

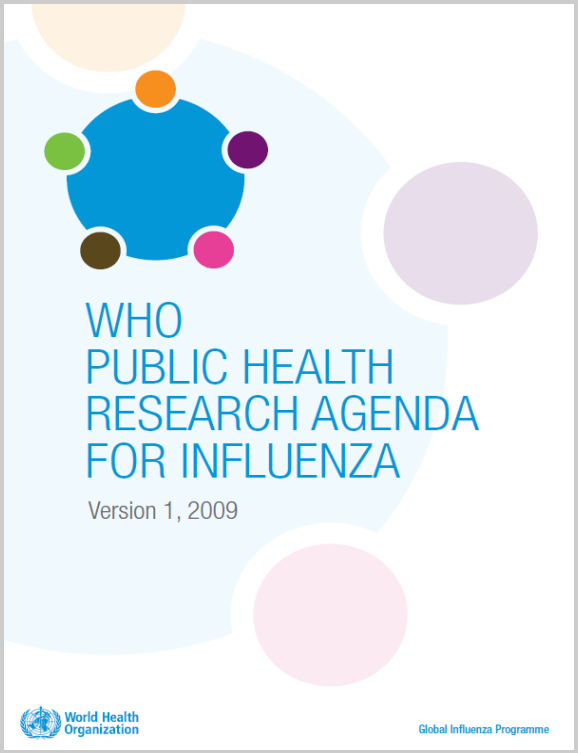
The Spread of Pandemic H1N1
April - November 2009

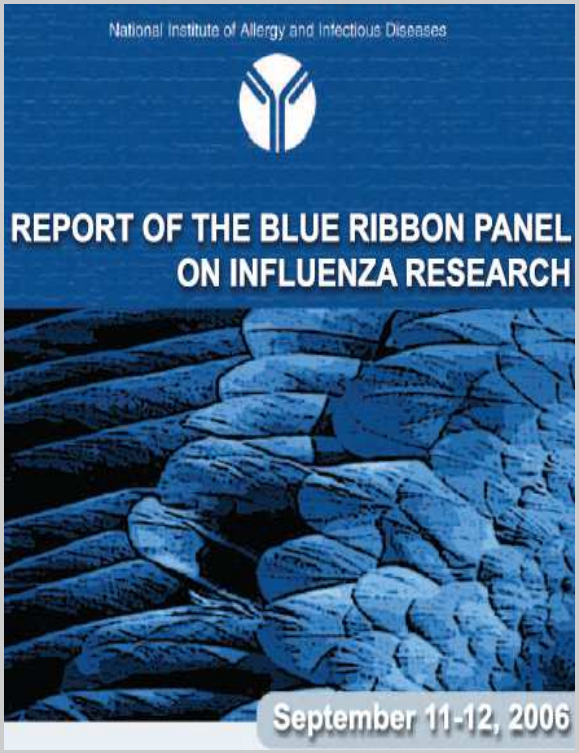


-At least 6,000 deaths.
-Modest severity except in young adults

-Decreased relevance of H5N1

Rationale for research on pathogenicity and transmissibility of H5N1





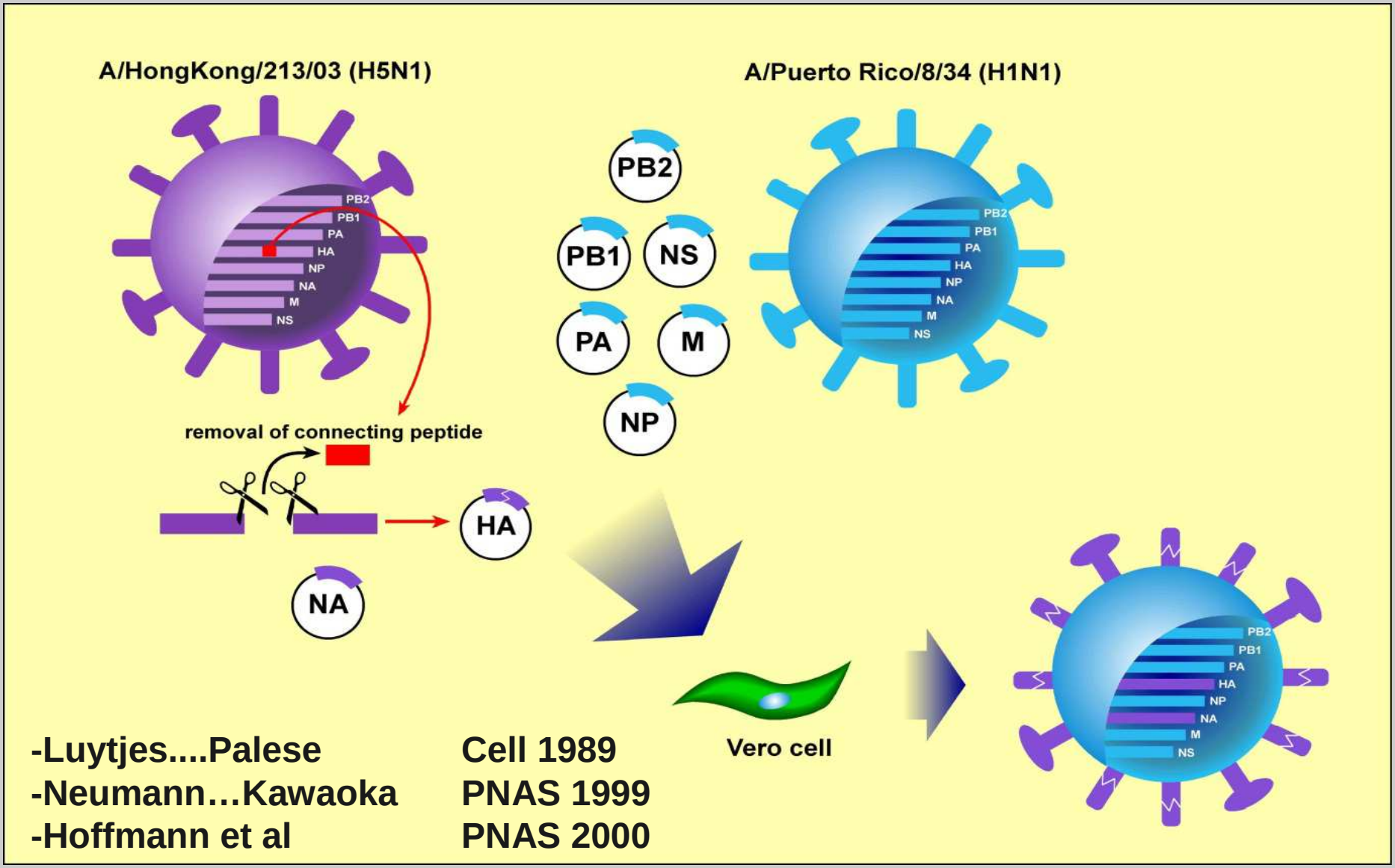
"…the genetic processes and external factors leading to the emergence of pandemic influenza viruses remain incompletely understood (e.g. the potentials for mutation and genetic reassortment, as do factors associated with infectivity, transmissibility and pathogenicity"

"**Research Recommendations**:

1.1.1 Investigate virus-specific factors associated with zoonotic and pandemic potential (e.g. infectivity, transmissibility and pathogenicity)"

"Learning more about how influenza viruses circulate between animal reservoirs and about the evolutionary pressures that lead to the emergence and spread of new viral sub-types—**especially the factors that favor transmission from animals to humans**—are urgent research priorities."

Reverse genetics for influenza viruses



-Luytjes....Palese Cell 1989
-Neumann…Kawaoka PNAS 1999
-Hoffmann et al PNAS 2000

Approval processes for a “typical” H5N1 transmission experiment

Approvals based on “science”

- Peer review of grant funding
- NIH Office of Biotechnology Activities (for some experiments)
- Institutional Biosafety Committee
- Institutional Animal Care and Use Committee

Approvals based on “facilities”

Select Agent registration
Requires
-Specific HPAI enhancements to standard BSL3
-USDA and/or CDC registration paperwork
-Multiple inspections for facilities, security, inventory, etc.
-Renewed every three yrs

Personnel requirements
-Dept. Justice personnel clearance
-Documented personnel training and proficiency

Approvals based on “material transfer”

Importation permits
Requires
-USDA permit
-CDC permit
-USDA facility inspections

Export permits
Requires
-Dept. of Commerce License

Biosecurity–

to prevent loss, theft, or misuse of microorganisms and biological material

Accomplished by limiting access to facilities, research materials, and information

- All personnel undergo FBI Security Risk Assessment
- Access granted through biometric reader

- Inventory and tracking of virus strains is strictly controlled
- Inventory is inspected/verified biannually by USDA

Biosafety

- to reduce or eliminate exposure of individuals and the environment to potentially hazardous biological agents

Accomplished by **four** primary controls

1. PPE:

Powered-Air Respirator (PAPR), Scrub Suit, Tyvek Coverall, Dedicated Shoes, Booties, Disposable Gown, 2 Pair Nitrile Gloves

2. Work Place Practices:

Entry and Exit Process, Decontamination, Emergency Procedures, Handling Sharps, Working in Class II Biosafety Cabinets

3.Administrative:

Immunizations, Security Clearance, Training, Supervision

4.Engineering:

Directional Air Flow, HEPA Filtration, BSCs, Entry and Access Point Control

The Fouchier/Kawaoka reports

- Avian HP H5N1 viruses have the potential to become mammalian transmitted
- Identification of specific markers in HA
  - Receptor binding
  - Stability
  - Glycosylation
- Multiple strategies to become mammalian transmissible
- Confusing information provided to NSABB

The doomsday agent report

The New York Times
SundayReview | The Opinion Pages

January 7, 2012

An Engineered Doomsday

Scientists have long worried that an influenza virus that has ravaged poultry and wild birds in Asia might evolve to pose a threat to humans. Now scientists financed by the National Institutes of Health have shown in a laboratory how that could happen…

The New York Times
SundayReview | The Opinion Pages

April 21, 2012

The Latest on the Doomsday Virus

We can worry less that a newly created bird flu virus might kill tens or hundreds of millions of people if it escaped from the laboratory. But there is still some residual danger….

Global influenza program for influenza WHO/Indonesia/Vietnam

Sharing of influenza viruses and knowledge

H5N1:The continuing global threat

Indonesia
Humans:188 cases/156 deaths
Endemic in poultry

Egypt
Humans: 167 cases/60 deaths
Endemic in poultry

Bangladesh
Humans:6 cases/0 deaths
Poultry-over 2 million dead

Wild birds: Clade 2.3.2.1
Whooper swan, Grebes, Tufted duck, passerines
China, Japan, Mongolia, Israel, Vietnam, South Korea,

Nature is the greatest bioterrorist threat

Benefits

Public Health:

- **Knowledge that H5N1 virus can adapt to become efficiently transmissible in mammals/ humans.**
  - Pandemic preparedness for H5 is needed: viruses persistently endemic in poultry in many countries, such as China, Indonesia, Egypt and Vietnam.
  - Continued monitoring of H5N1 antigenic changes in the field.
  - Control measures for blocking transmission from avian species to mammalian species (such as swine) to prevent further adaptation. (> 500 millions pigs in China)
- **Provide the knowledge to determine which of the multitude of influenza viruses have pandemic potential – risk assessment**
  - Which clade of H5N1 is acquiring the necessary mutations for transmissibility?
  - Vaccine seed stock preparation - need to keep updating the vaccine seed.
  - Stamping out – with international assistance .

Science:

- **Look for the mutations that would confer such functionality (they may already exist!!!):**
  - Need for increased surveillance and rapid sequencing and sharing.
  - Importance of deep sequencing of all human H5N1 original isolates.

More Science to be addressed…

- Is there a required sequence of events for the transmission to occur; i.e. are the receptor binding mutations a critical first step during the adaptation?
- Does the virulence of transmissible H5N1 increase or decrease for mammals (as a result of tissue tropism change)?
- Do the changes in the receptor binding domain alter the antigenicity and immunogenicity of H5N1 viruses?
- Does the transmissible H5N1 possess the capacity to spread in wild birds or in swine?
- Do the transmissible H5N1 viruses have a higher propensity to reassort with the circulating pandemic H1N1? (it most likely occurs in China, Thailand, Vietnam)

Risks

- **High lethality in humans?**
- **Laboratory escape: intentional or accidental**
- **Development of bioterrorist agent – possible but less likely**
  - **H5N1 continues to evolve and spread, including in countries with high terrorist threat.**
  - **Shutting down research in US will not necessarily be followed globally.**
- **Pandemic influenza will definitely emerge again. Will it be H5? (Nature poses the greatest bioterrorist threat.)**
- **Life is not risk free.**

The future… Risk management

- "The cat is out of the bag." Things cannot be undone.
- Managing the risk instead of avoiding the risks
  - Managing the risk instead of thinking that stopping US research will make the risk disappear
- Are the risks manageable?
  - Assess the risk of research projects and receive pre-approval
    - Dual Use Research of Concern (DURC)
  - Inspections, inspections…
  - "Real-time" communication between principle investigators with funding agency; avoid surprises…
  - Can the questions be addressed using low-path viruses?
    - Yes partially but not the high pathogenic aspects
  - Education of the scientists and younger generations.

“Risk free?”

Acknowledgements

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University of Alberta, Canada

WHO Collaborating Centers and
CEIRS Collaborators