Highly Pathogenic Avian Influenza Virus Research

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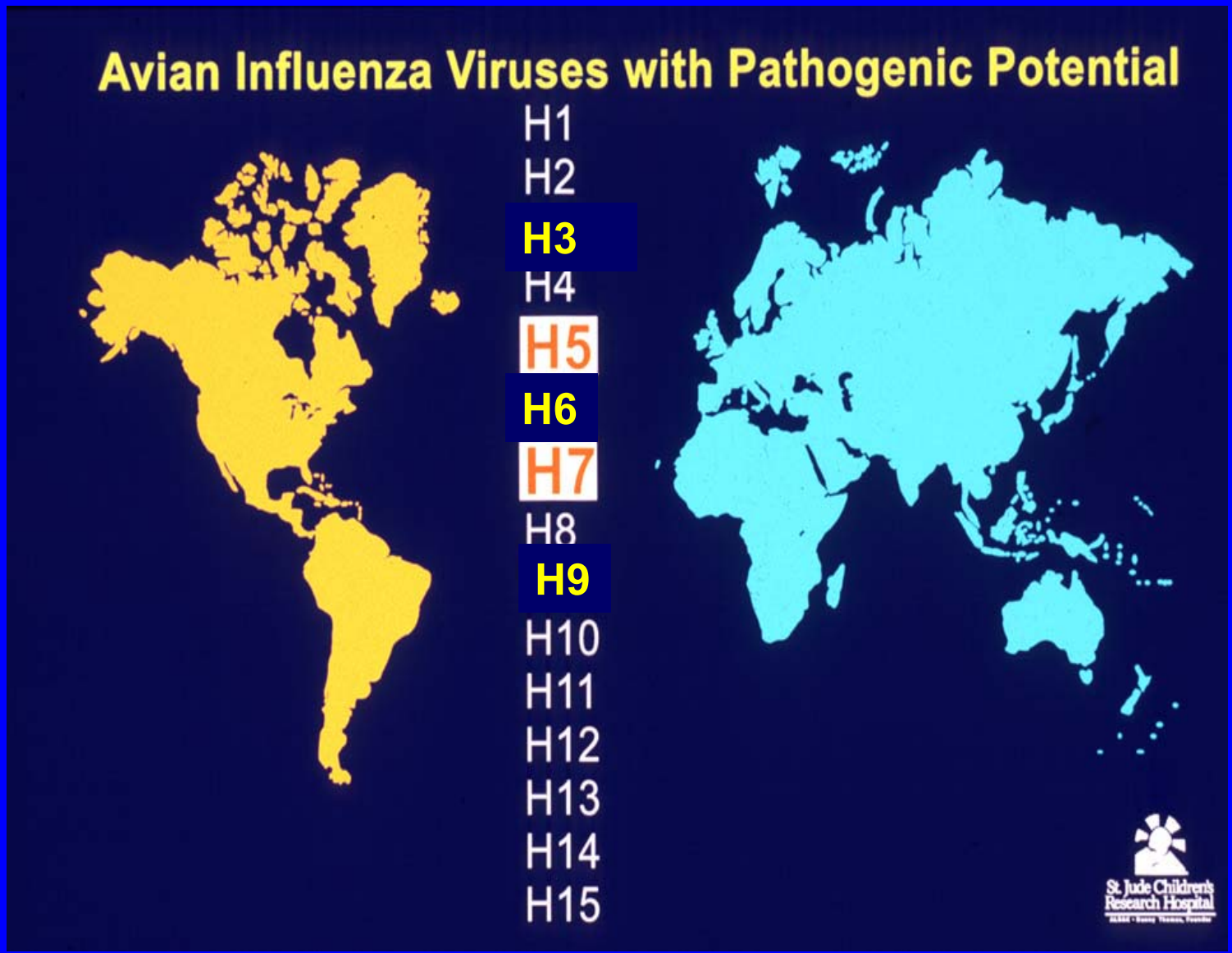
Influenza A Viruses

- 15 HA and 9 NA subtypes – all found in aquatic birds of the world.
- In their natural reservoir species all subtypes of influenza are non-pathogenic and in evolutionary stasis.
- After transfer to other hosts they evolve rapidly.
- H5 and H7 influenza viruses became highly pathogenic


Avian Influenza Viruses with Pathogenic Potential
H1
H2
H3
H4
H5
H6
H7
H8
H9
H10
H11
H12
H13
H14
H15
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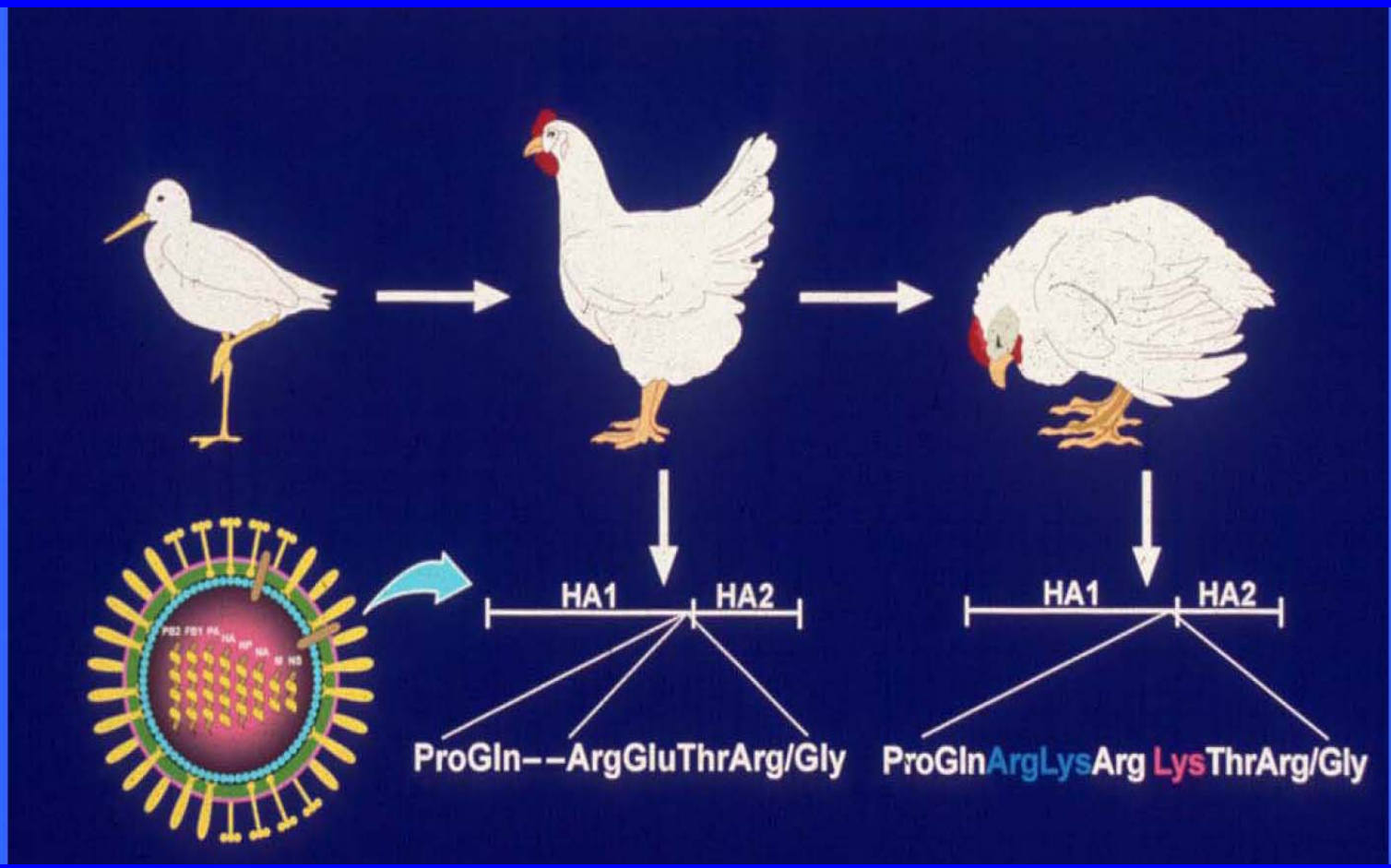
The Ecology of Influenza Viruses

- Influenza viruses in their natural reservoirs are in evolutionary stasis

- Rapid evolution occurs after transfer to new hosts

Emergence of Highly Pathogenic Avian H5N2 Influenza in Mexico in 1995



Recent Highly Pathogenic Avian Influenza Outbreaks

			Humans (Death/Total)	Poultry
H5N1	Hong Kong	1997	6 / 18	Culled
	Hong Kong	2003	1 / 2	———
	Vietnam	2004	20 / 27	Culling
	Thailand	2004	8 / 12	Culling
	Japan, Korea, Laos, Cambodia	2004	———	Culling
	China, Indonesia, Malaysia	2004	———	Culling
H5N2	Texas	2004	———	Culling
H7N7	Holland	2003	1 / 84	Culled
H7N3	Canada	2004	0 / 2	Culled

Conjunctivitis Caused by A/seal/Mass/1/80 (H7N7)

Spread of H5N1 Influenza in Asia

100s of millions of birds culled

Human Cases: 39

Human Deaths: 28

Vietnam:
20 deaths

Thailand:
8 deaths

The Spread of H5N1 in Asia

An unprecedented event in the history of influenza!!

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

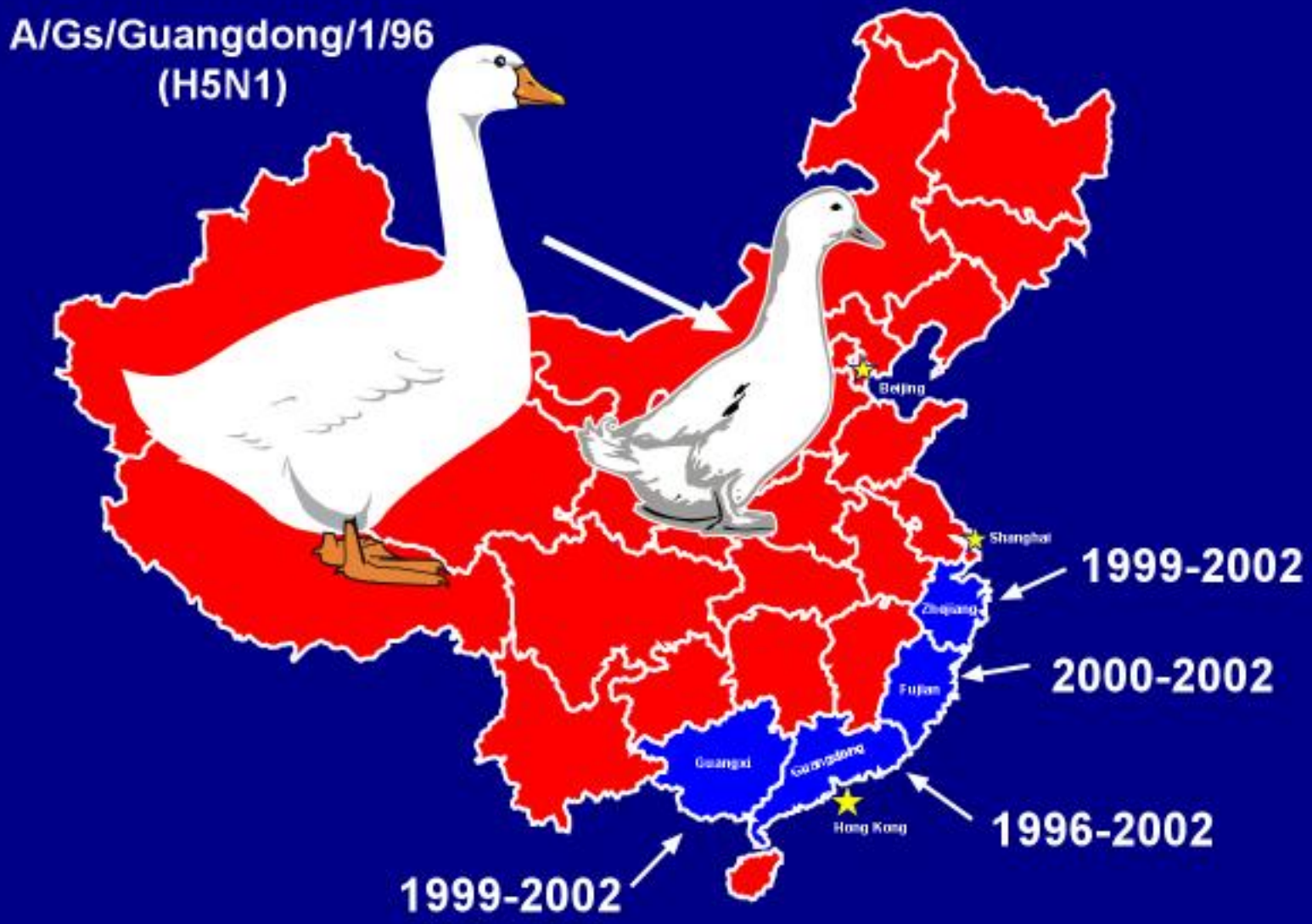
6 of 18 infected persons died

1997-2002 Goose x Multiple mating partners

H5N1

- Antigenically conserved
- Multiple genotypes
- Pathogenic in chickens ***NOT*** in ducks

H5N1 influenza viruses from ducks in China



Chen et al 2004

Genesis of H5N1 Influenza Virus

Nov 2002 Goose x Mating Partner Z Genes

- Isolated from wild migrating birds
- Antigenic drift in HA
- Pathogenic for aquatic birds

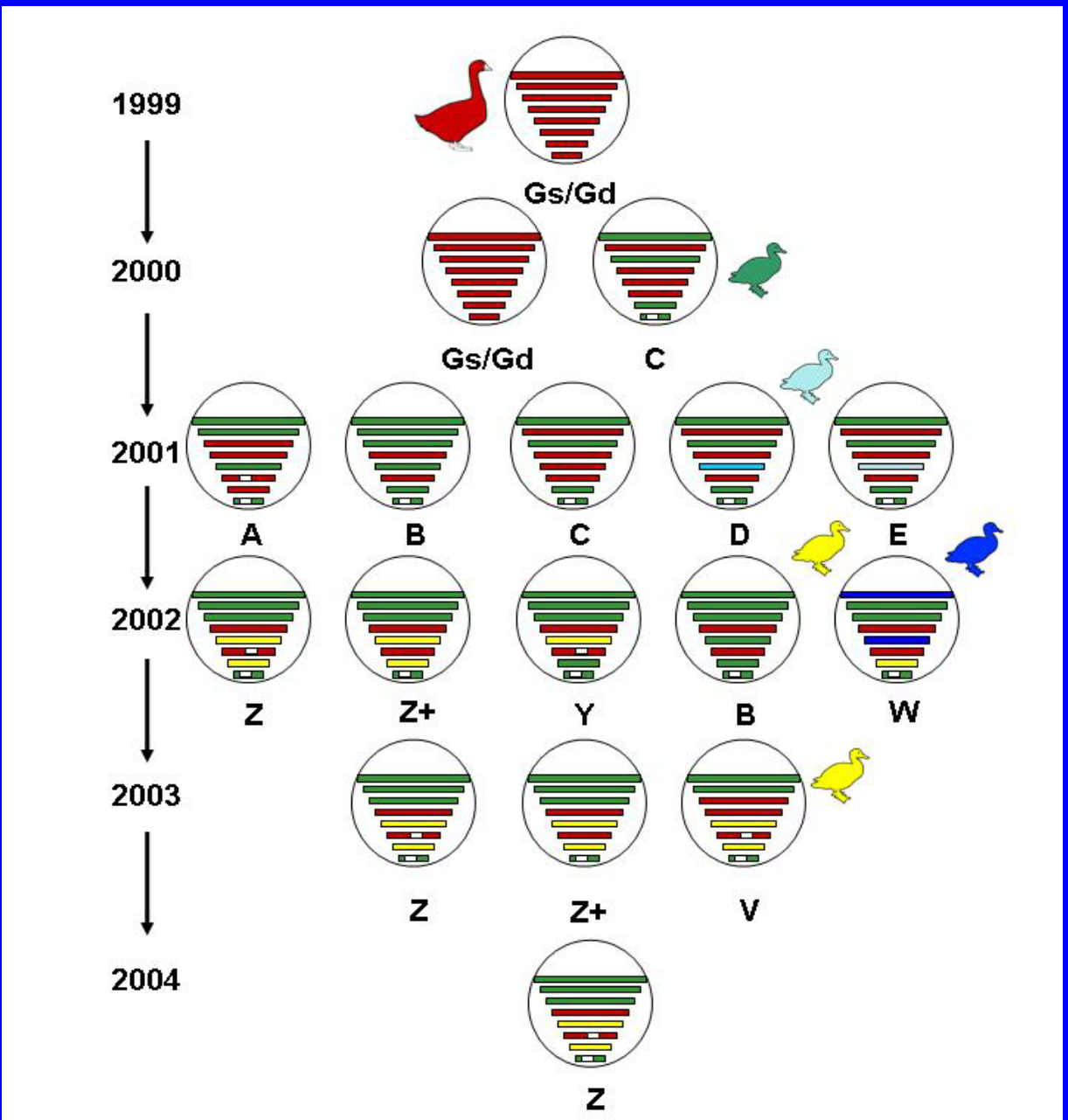
Feb 2003 Family visiting Fujian, China

Daughter died

Father and son infected

(Father died)

Emergence of a Dominant H5N1 Genotype



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 (~14 years)
  - Diarrhea
  - Respiratory symptoms
- High Risk of death in ferrets
  - Respiratory symptoms
  - Diarrhea
  - Hind Leg paralysis

Bird flu in Vietnam

February 2004

10 cases – mean age 13.7 years

No pre-existing medical conditions

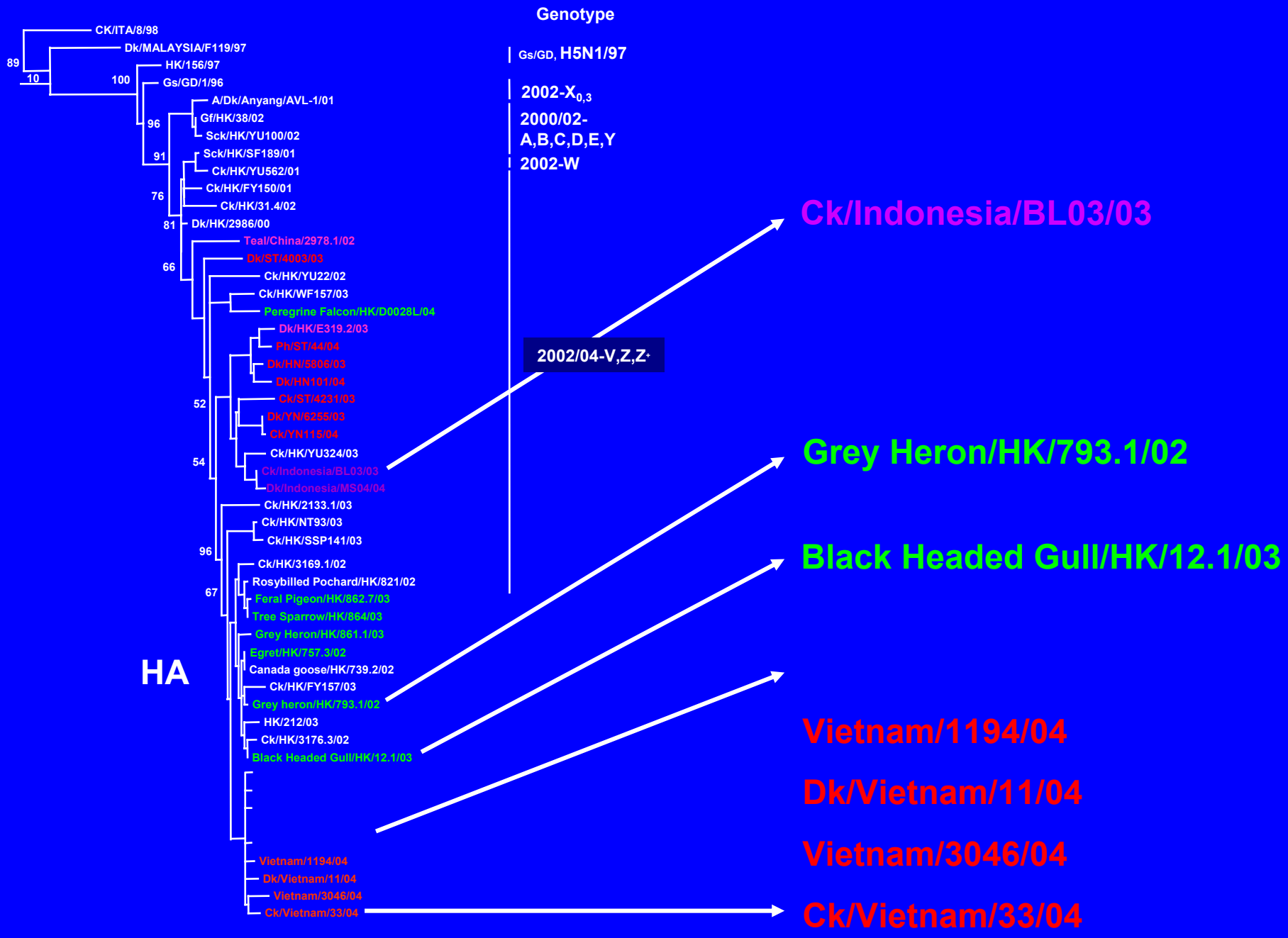
Fever 38.5-40°C

Lymphopenia

7/10 diarrhea

7/10 died

Hien, TT et al. New Eng Med J 2004


Genotype
Gs/GD, H5N1/97
2002-X0,3
2000/02-
A,B,C,D,E,Y
2002-W
2002/04-V,Z,Z-
CK/ITA/8/98
Dk/MALAYSIA/F119/97
HK/156/97
Gs/GD/1/96
A/Dk/Anyang/AVL-1/01
Gf/HK/38/02
Sck/HK/YU100/02
Sck/HK/SF189/01
Ck/HK/YU562/01
Ck/HK/FY150/01
Ck/HK/31.4/02
Dk/HK/2986/00
Teal/China/2978.1/02
Dk/ST/4003/03
Ck/HK/YU22/02
Ck/HK/WF157/03
Peregrine Falcon/HK/D0028L/04
Dk/HK/E319.2/03
Ph/ST/44/04
Dk/HN/5806/03
Dk/HN101/04
Ck/ST/4231/03
Dk/YN/6255/03
Ck/YN115/04
Ck/HK/YU324/03
Ck/Indonesia/BL03/03
Dk/Indonesia/MS04/04
Ck/HK/2133.1/03
Ck/HK/NT93/03
Ck/HK/SSP141/03
Ck/HK/3169.1/02
Rosybilled Pochard/HK/821/02
Feral Pigeon/HK/862.7/03
Tree Sparrow/HK/864/03
Grey Heron/HK/861.1/03
Egret/HK/757.3/02
Canada goose/HK/739.2/02
Ck/HK/FY157/03
Grey heron/HK/793.1/02
HK/212/03
Ck/HK/3176.3/02
Black Headed Gull/HK/12.1/03
Vietnam/1194/04
Dk/Vietnam/11/04
Vietnam/3046/04
Ck/Vietnam/33/04
89
10
100
96
91
76
81
66
52
54
96
67
HA
Ck/Indonesia/BL03/03
Grey Heron/HK/793.1/02
Black Headed Gull/HK/12.1/03
Vietnam/1194/04
Dk/Vietnam/11/04
Vietnam/3046/04
Ck/Vietnam/33/04

Have Pigs Been Infected With H5N1?

- One isolate reported from pigs in Hanoi
- Serology 1/439 positive
- China – two reports virus isolation

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

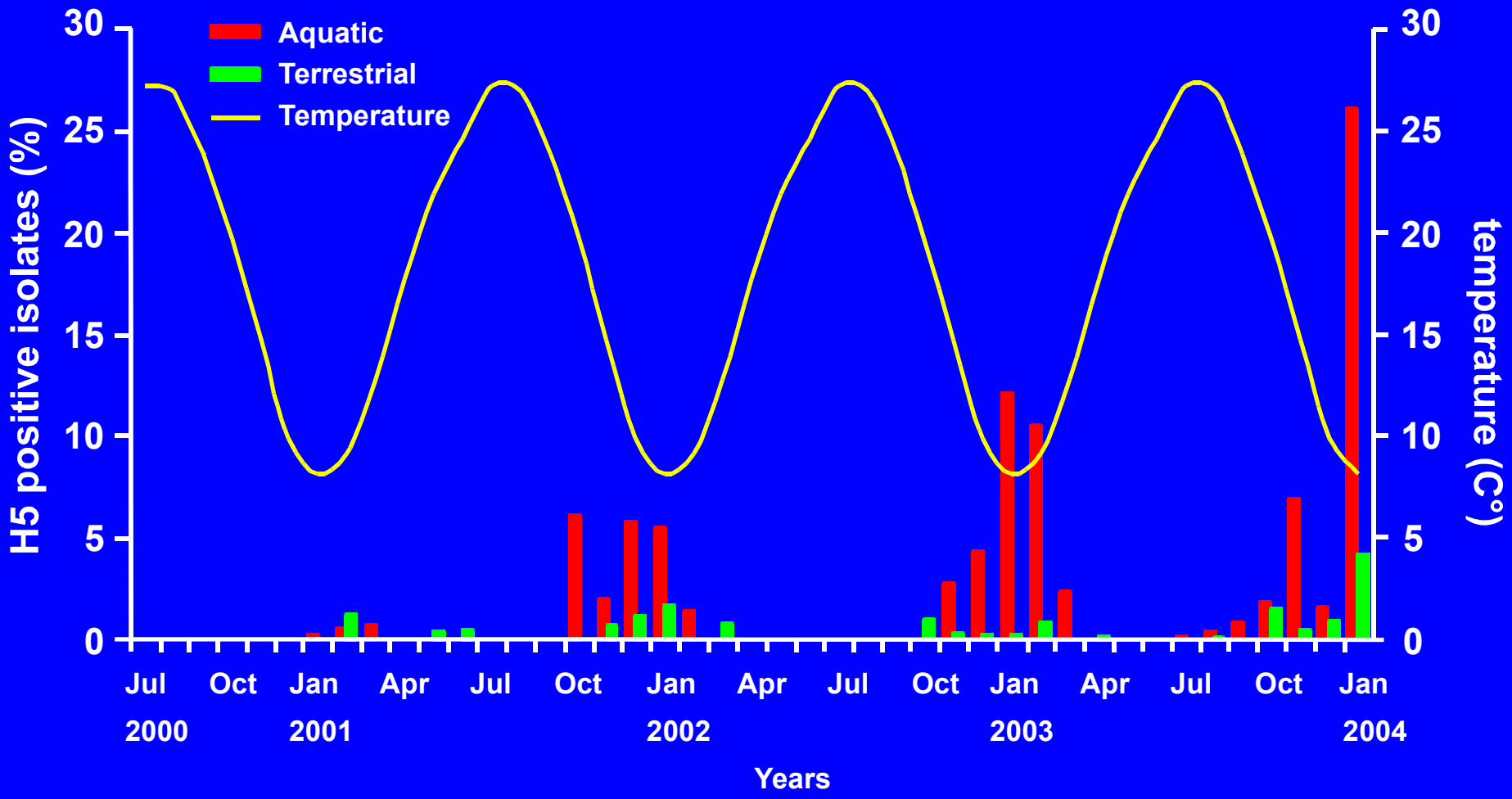
Expanding Host Range for Influenza

Experimental transmission in domestic cats

H5N1 in Thailand

Kuiken et al, Science 2004

Seasonality of H5N1 influenza in China



Were Migrating Birds The Spreaders?

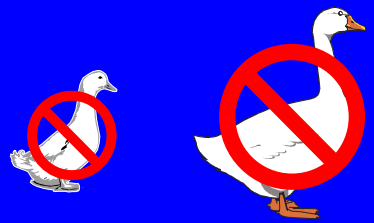
- Isolation of virus from wild birds in Hong Kong
  - Black headed gulls
  - Feral pigeon
  - Little Egret

  - Grey Herons
  - Peregrine Falcon

Prevention and Control

Changes in poultry marketing in Hong Kong

1998



2000 One clean day per month

2001

2002

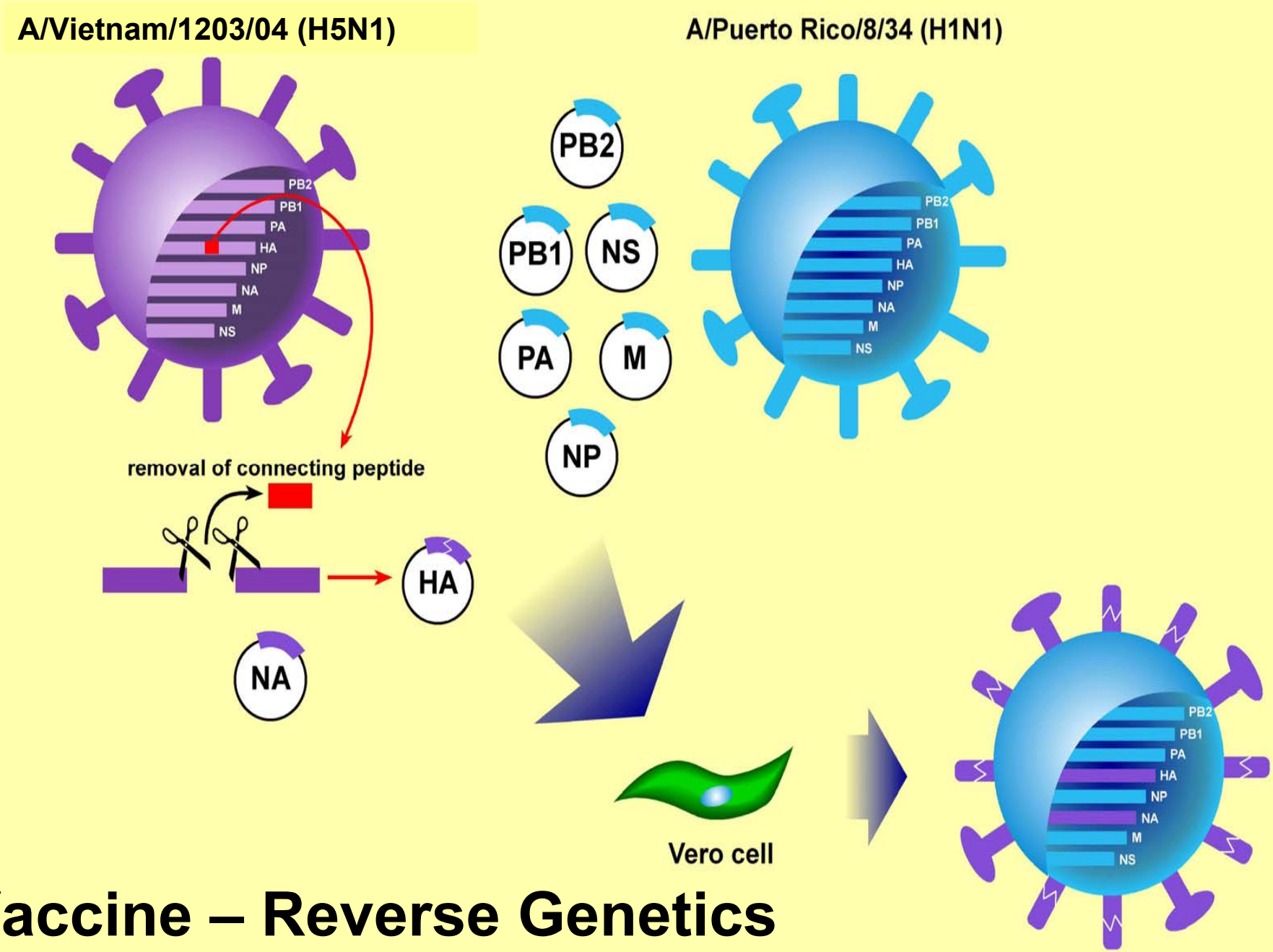
- Inactivated vaccine used to ring vaccinate H5N1 infected farms
- Additional clean day per month

2003 Inactivated vaccine used on all farms

- increased biosecurity
- sentinal unvaccinated poultry

2004 No H5N1

Vaccine



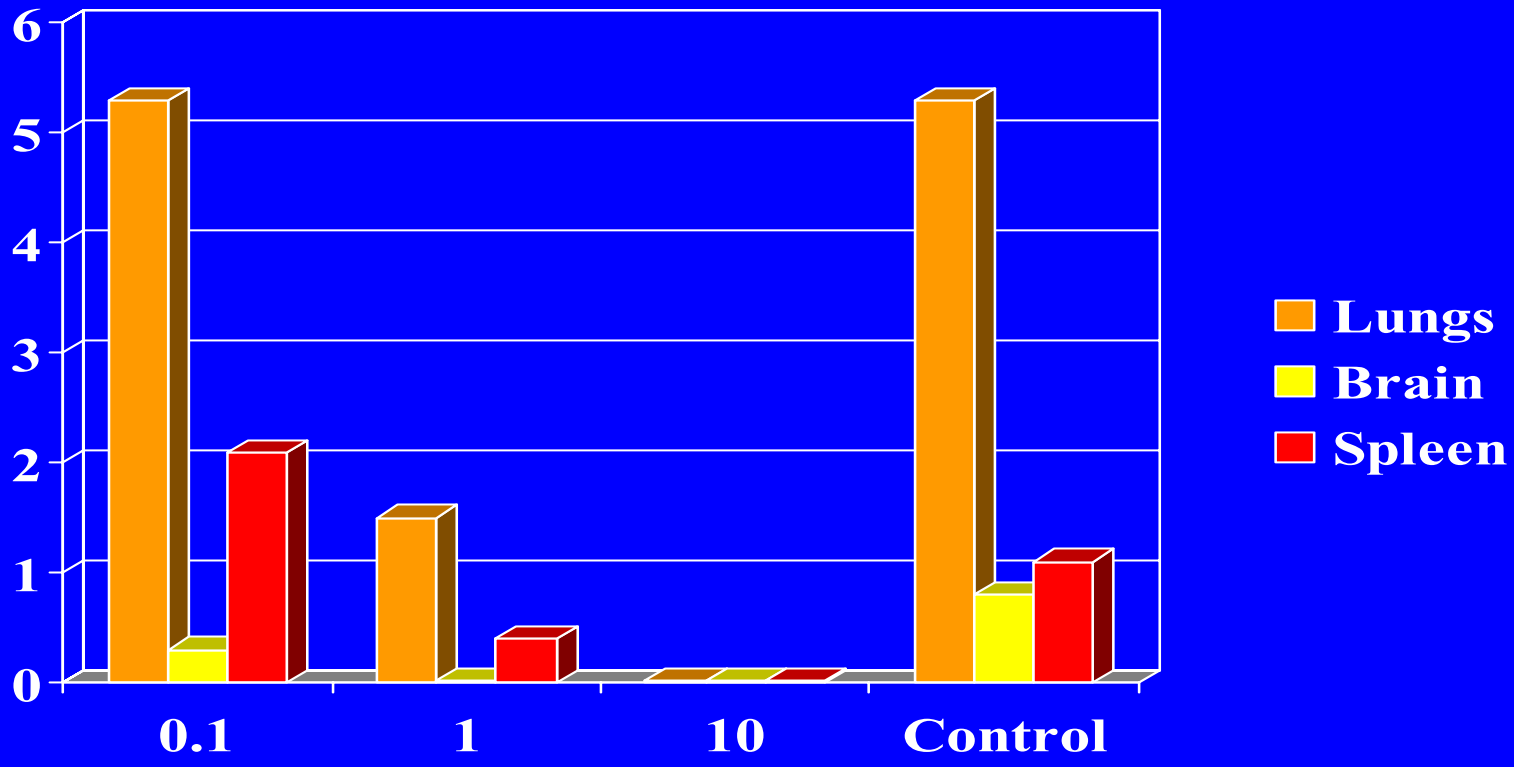
Vaccine – Reverse Genetics

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

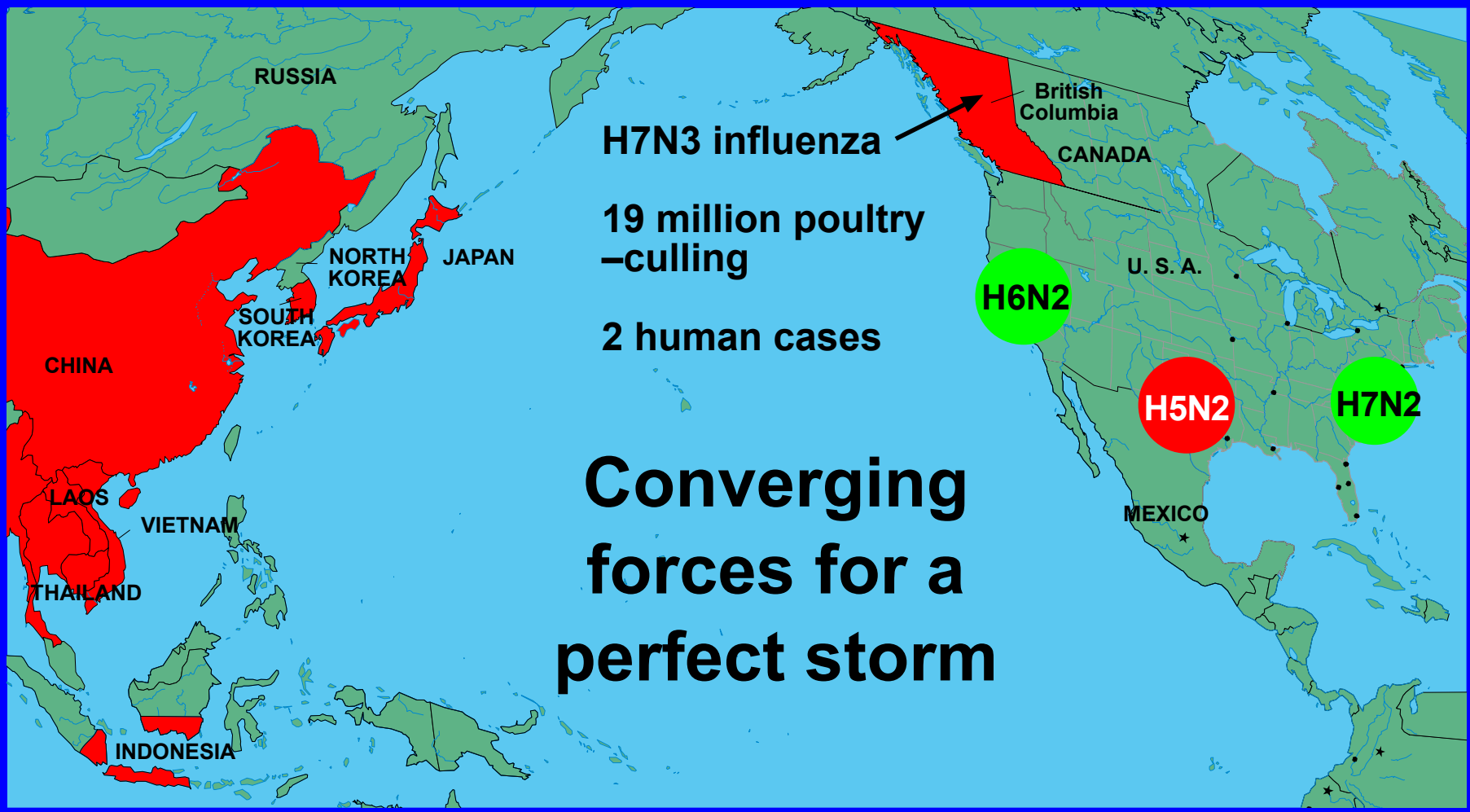
Reduction of A/Vietnam/1203/04 (H5N1) Virus Replication after Prophylactic Treatment of Mice with Oseltamivir



www.timeasia.com

FEBRUARY 9, 2004

TIME


RUSSIA
British Columbia
CANADA
H7N3 influenza
19 million poultry –culling
2 human cases
NORTH KOREA
JAPAN
SOUTH KOREA
CHINA
U. S. A.
H6N2
H5N2
H7N2
LAOS
VIETNAM
THAILAND
MEXICO
INDONESIA
Converging forces for a perfect storm

Facilities

Non-pathogenic avian	BL2	
Pathogenic avian	BL3	
Pathogenic avian with human transmissions	BL3	-- Augmented with PAPR -- With isolators
Pathogenic avian with gene exchange or gene modification	BL3	-- Augmented with PAPR -- With isolators

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