Opening Symposium for the Sustainability Week

Hokkaido University, November 2, 2009

Proposals by Hokkaido University for the Sustainable Development

Global Surveillance is the Key for the Control of Zoonoses

How to control avian, swine, and pandemic influenza as an example

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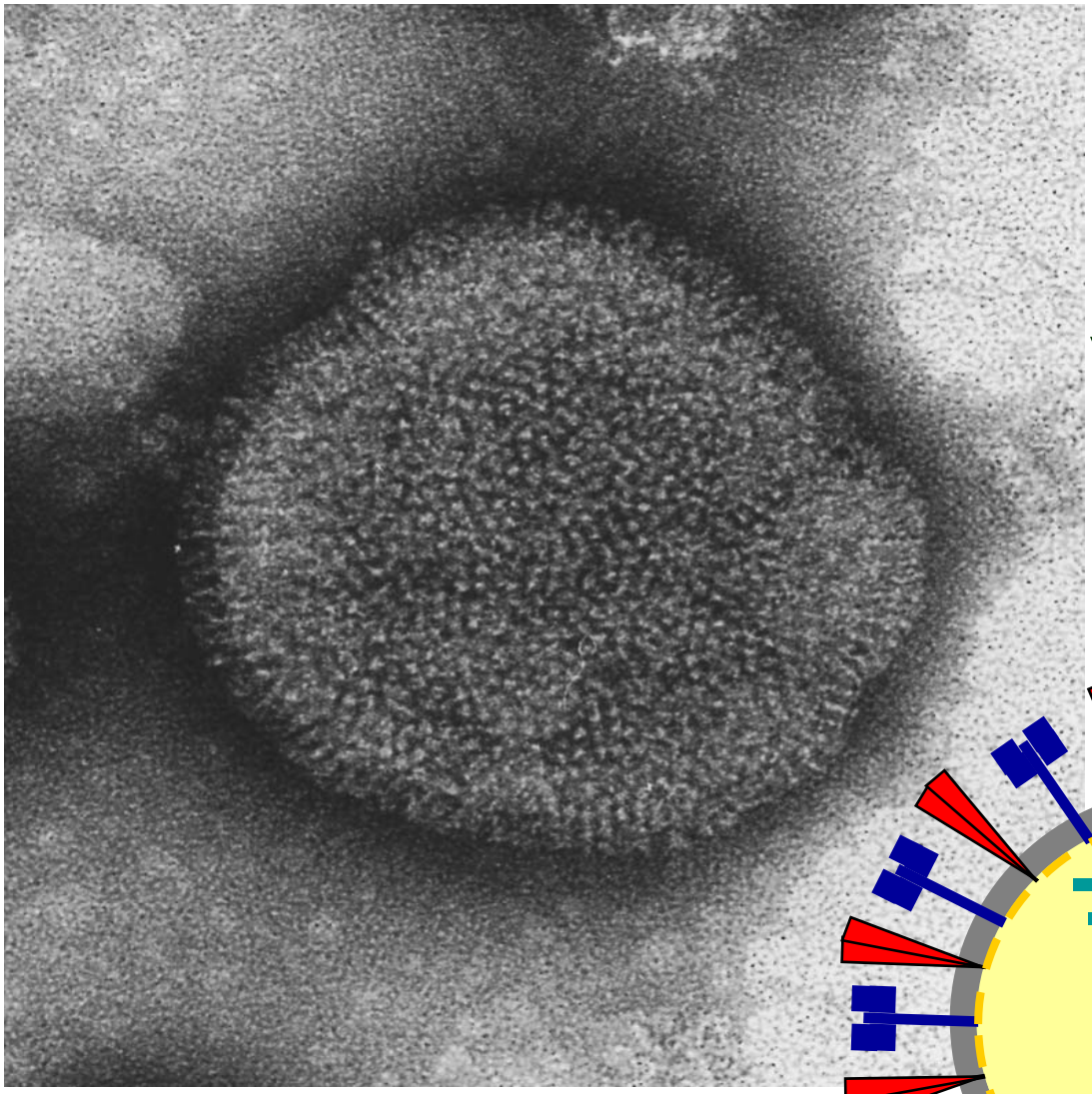
Are we substantially prepared for pandemic influenza ?

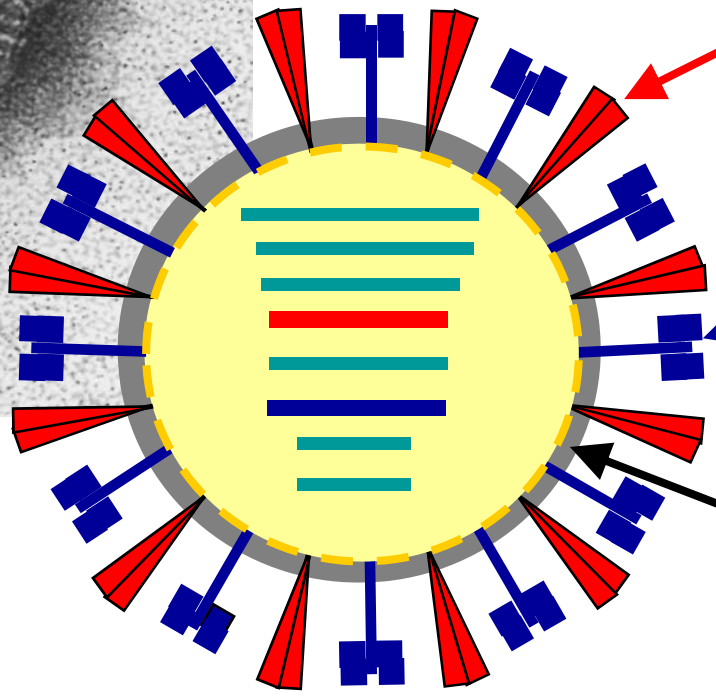
* Why have the H5N1 HPAIVs persisted in poultry for 12 years ?
* Why are antigenic variants selected ?
* Will the HPAIVs returned to migratory birds persist in nature ?
* How should avian influenza be controlled in poultry ?
* What are the advantage and disadvantage of the use of vaccines ?
* Is it OK to forget about H5N1 avian influenza virus strain after the swine-origin H1N1 strain emerged ?
* Are the measures for the control of seasonal flu satisfactory ?

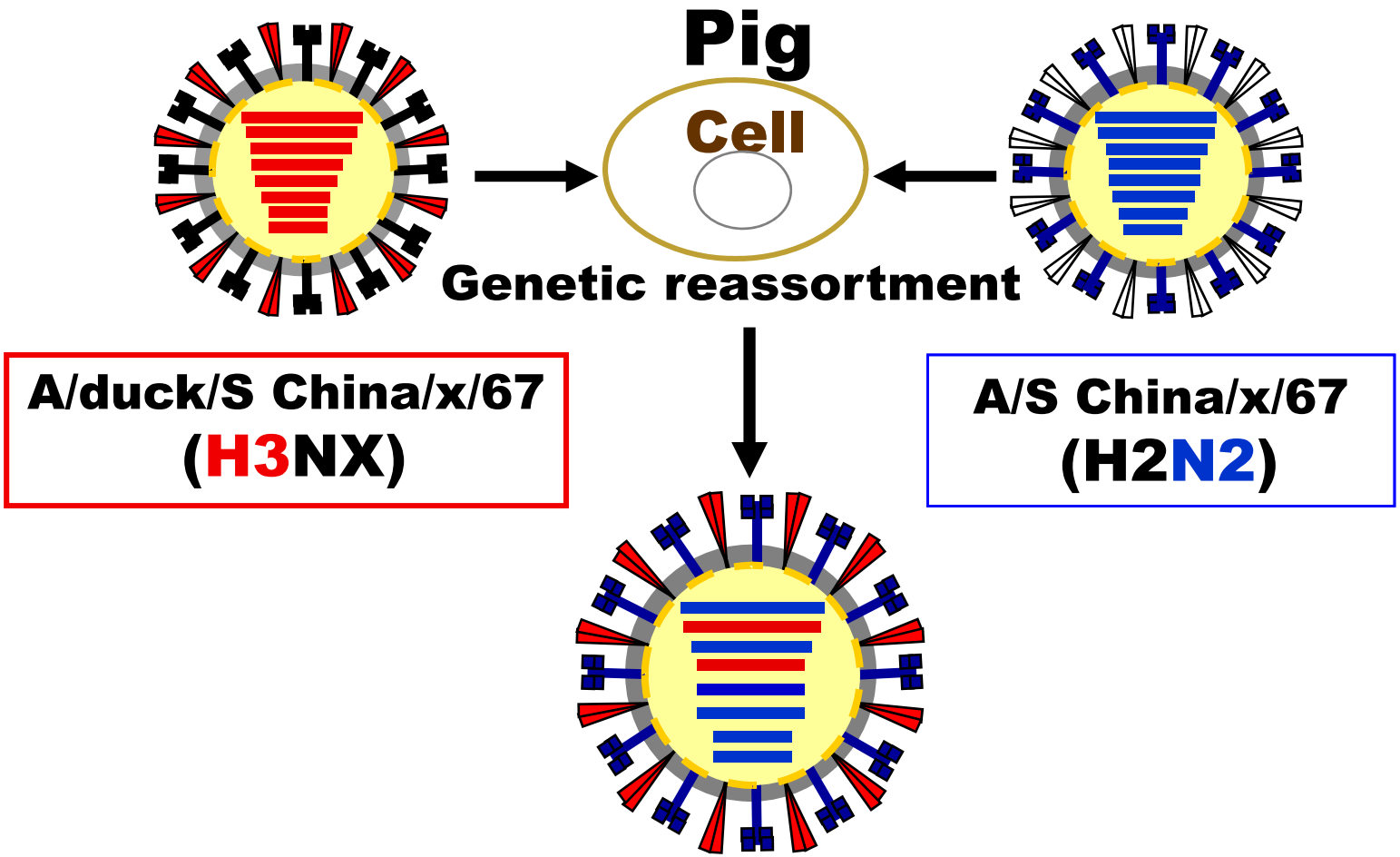
Ecology of influenza viruses in nature, birds and mammals;

* Origin, evolution, and perpetuation of influenza virus in nature.
* Mechanism of the emergence of highly pathogenic avian flu virus and human pandemic strains.
* Antigenic variation and genetic reassortment of influenza viruses.

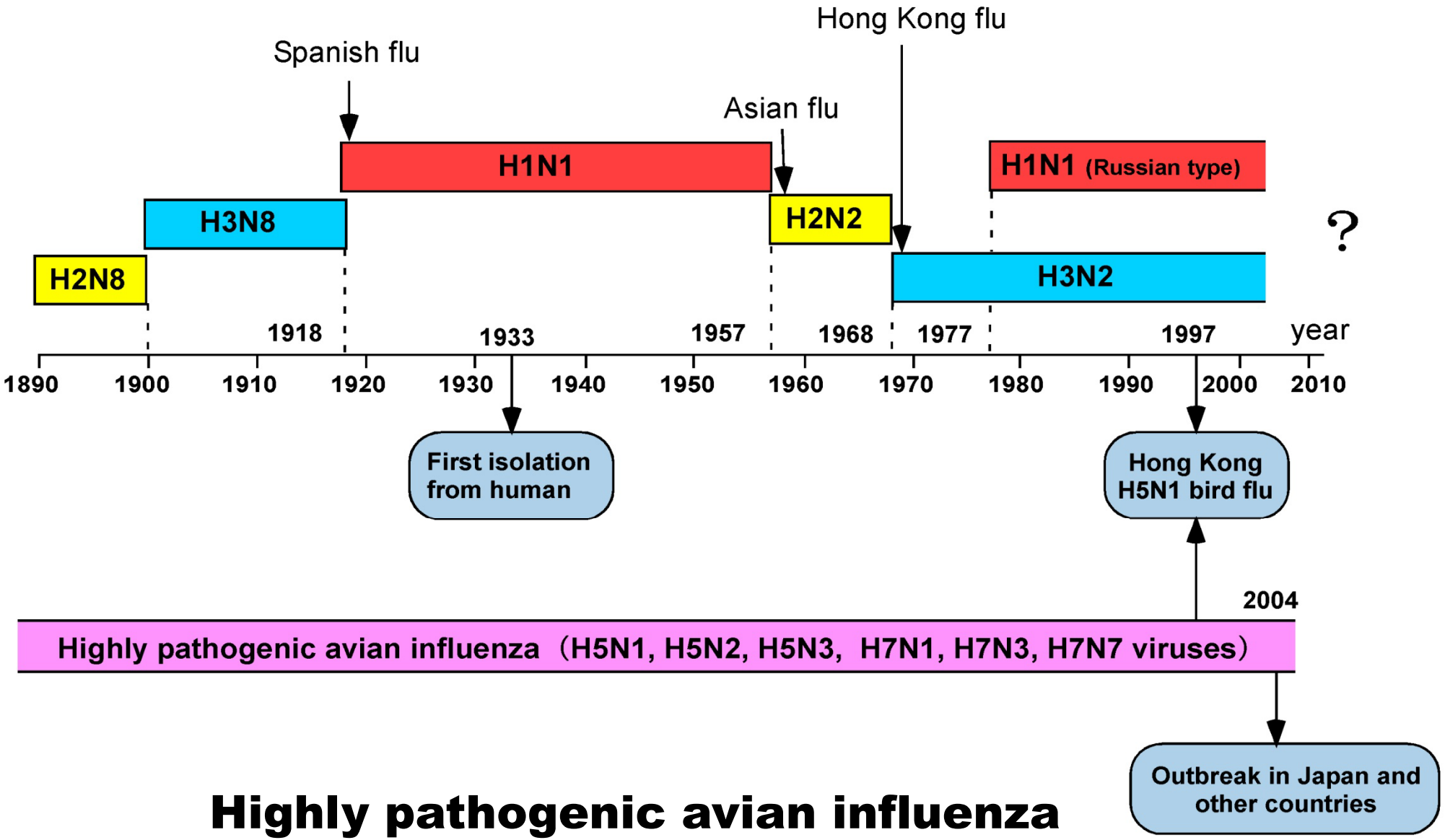


Influenza virus particle



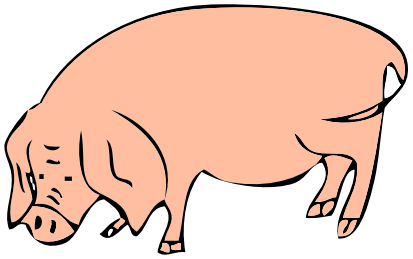

Pig
Cell
Genetic reassortment
A/duck/S China/x/67
(H3NX)
A/S China/x/67
(H2N2)
A/Hong Kong/1/68 (H3N2)
Humans

Pandemic influenza in humans

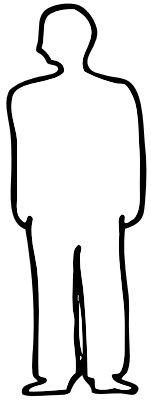


Highly pathogenic avian influenza

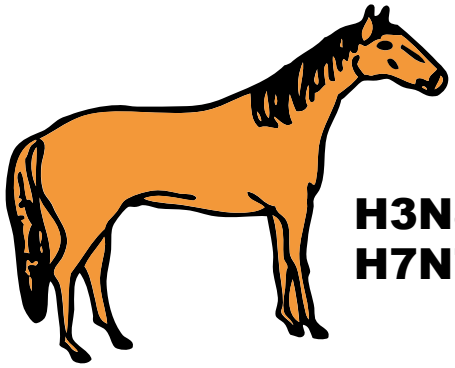
Host range, and HA and NA subtypes of influenza A virus



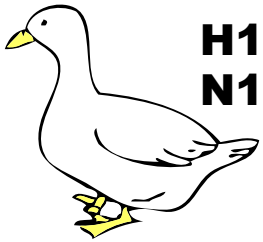
H1N1
H1N2
H3N2
H2N3, H3N1, H3N3,
H3N8, H4N6, H5N1,
H5N2, H9N2



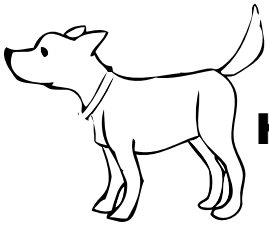
H1N1
H2N2
H3N2
(H2N8,H3N8)
H5N1,H7N7,
H9N2



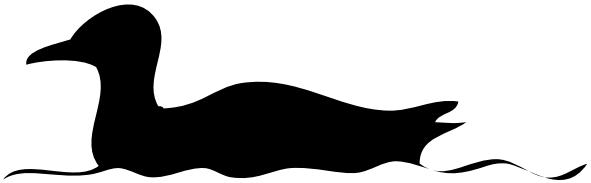
H3N8
H7N7



H1-H12
N1-9

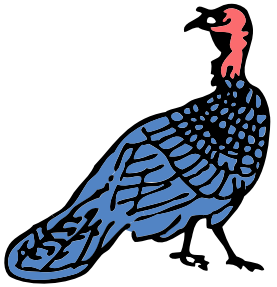


H3N8,H5N1

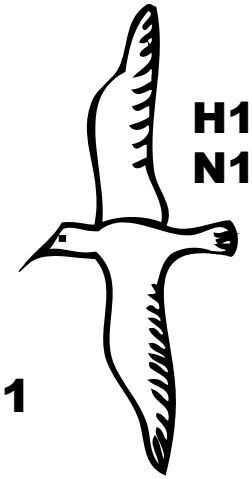


H1-16
N1-9

H5N1

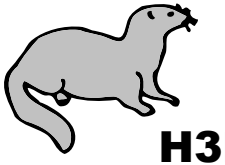


H1-10
N1-9

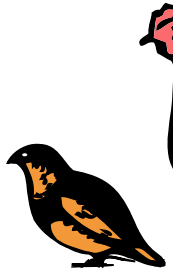


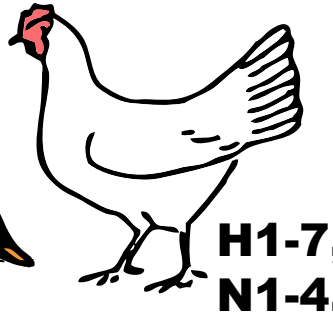
H1-7, H9-16
N1-9

H3N3
H4N5
H7N7

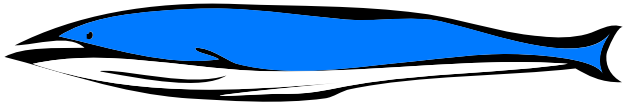


H3N2
H5N1
H10N4





H1-7, H9-11
N1-4, N6-8



H1N3, H13N2, H13N9

Duck influenza

- Each of the known subtypes (H1-16, N1-9) of influenza A virus has been isolated from ducks.
- In ducks, viruses replicate in the colon, being shed with feces in a week, and non-pathogenic.
- Water-borne fecal-oral transmission
- Ducks carry and provide viruses during migration and over-wintering.

→ Migratory duck is the NATURAL HOST of influenza A viruses.

Kida H et al (1980) Infect Immun

Influenza viruses are antigenically and genetically highly conserved in ducks.

- Viruses replicating in the intestine are not under the serum antibody selection pressure.
- 40 to 50 % of population of migratory ducks are juvenile birds that hatched in the summer.
- Preserved in frozen water of the lakes, where they nest in summer, in winter.

Kida H et al (1987) Virology; Ito et al (1995) Arch Virol

HAs of H3N2 viruses isolated from pigs in southern China

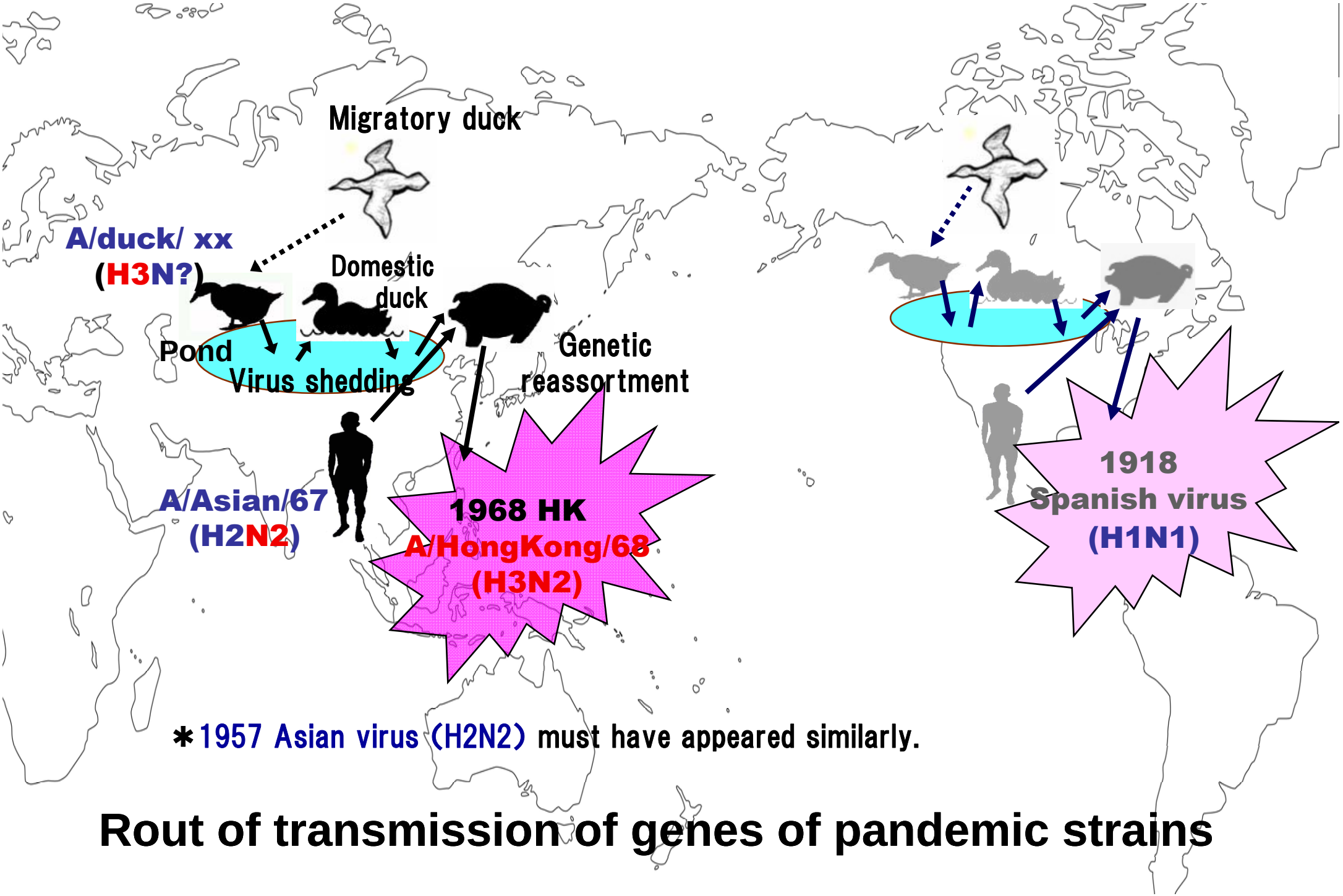
- Closely related with those of A/Hong Kong/68 (H3N2) and H3 viruses isolated from migratory ducks.
- Amino acid sequences at the receptor-binding site on the HA indicate either specificity to human or avian type receptors.
- Both types of receptoer were found on the surface of the epitherial cells lining the upper respiratory tract of pigs.

Kida H et al (1988) Virology

Influenza viruses isolated from domestic ducks in southern China

- HAs of influenza viruses isolated from domestic ducks in southern China closely related with those of viruses isolated from migratory ducks, pigs, and A/Hong Kong /68 antigenically and genetically.
- Each of the viruses was isolated on the Pacific Flyway of migratory ducks.
- Migratory duck → domestic duck → pig → humans

Yasuda J (1991) J Gen Virol



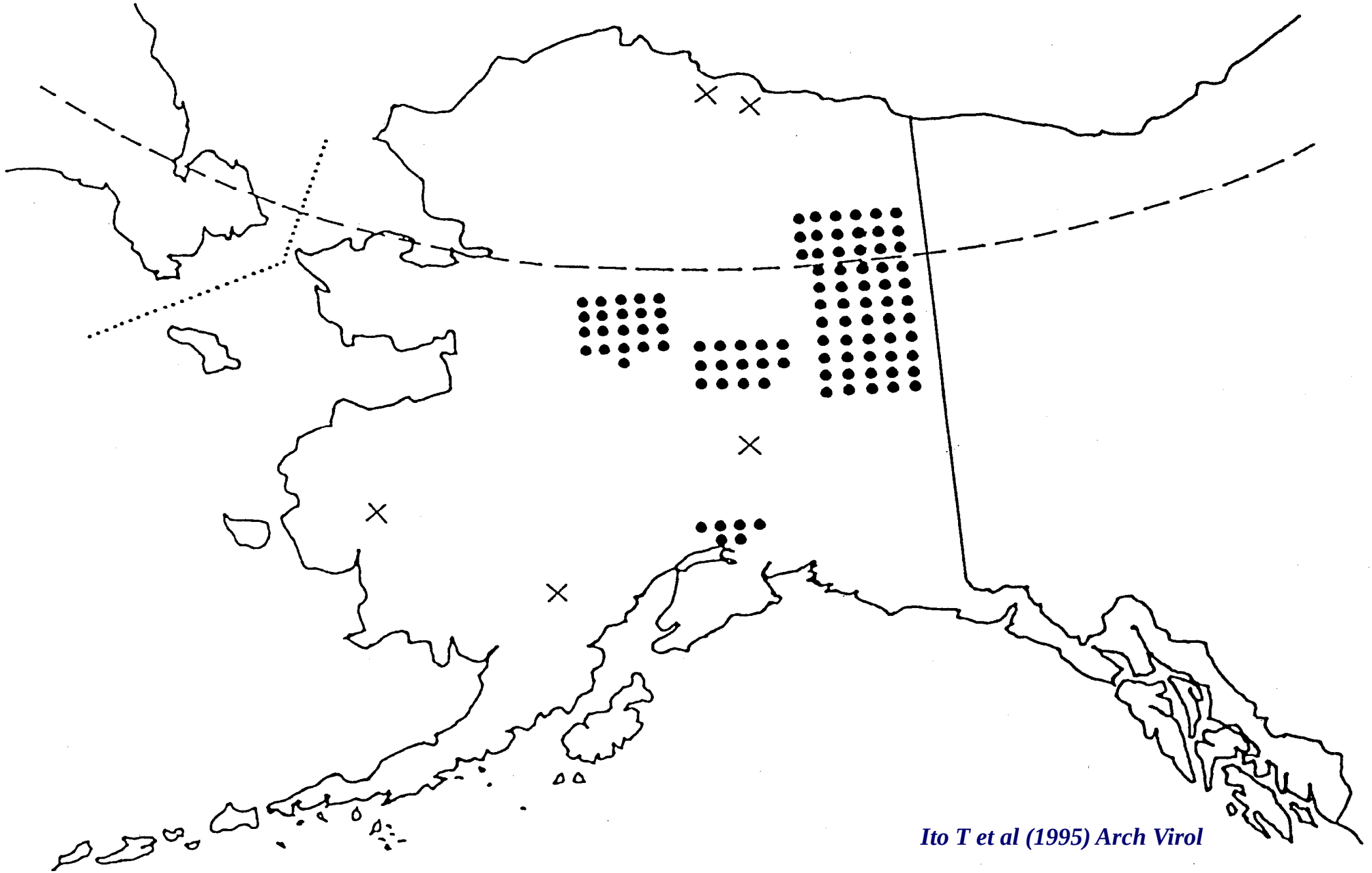
＊1957 Asian virus (H2N2) must have appeared similarly.

Rout of transmission of genes of pandemic strains

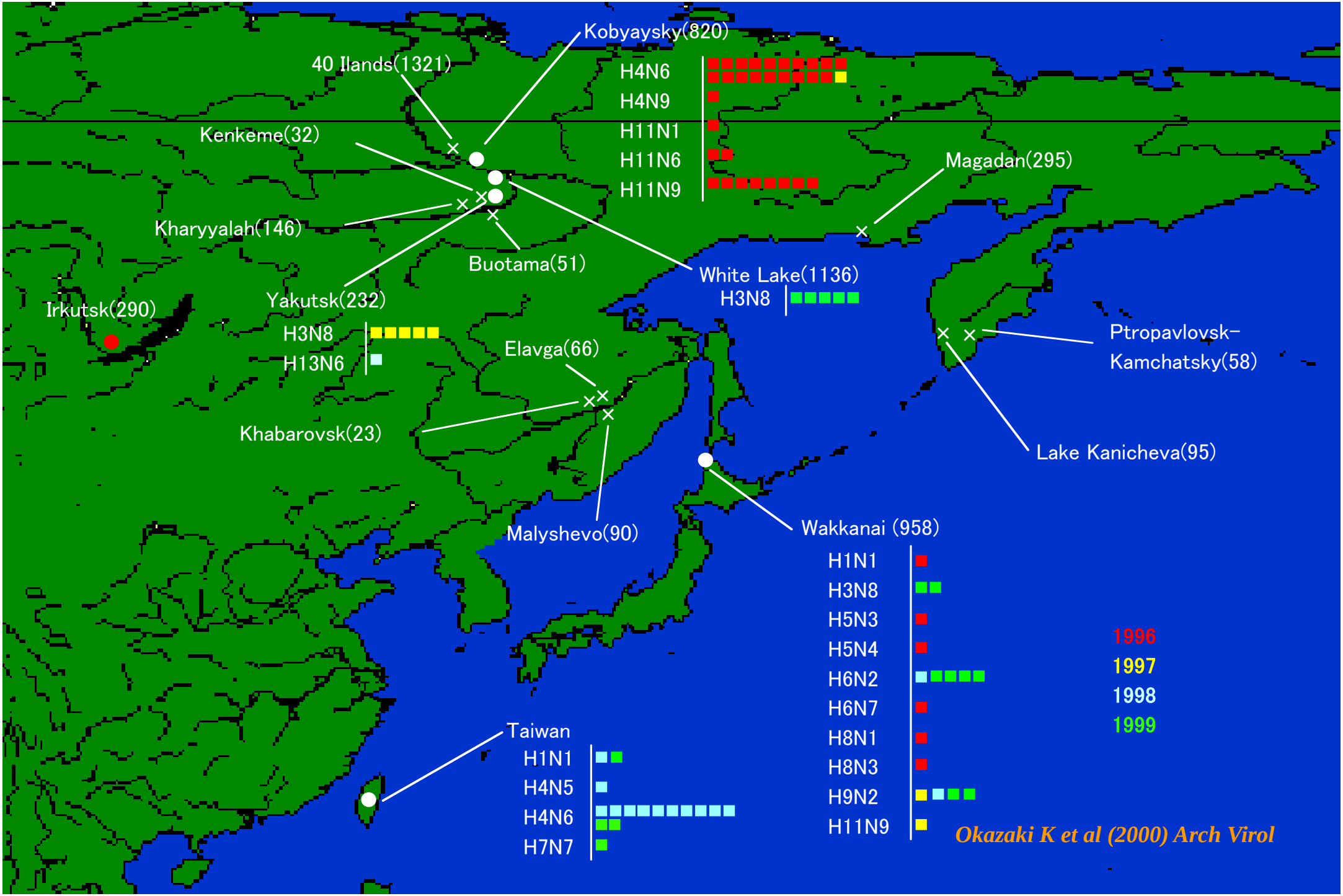
The role of pigs in the emergence of pandemic influenza virus strains

- Pigs are susceptible to avian influenza viruses of each of the HA subtypes.
- Genetic reassortants were generated in the cells lining upper respiratory tract of pig upon concurrent infection with mammalian and avian strains.

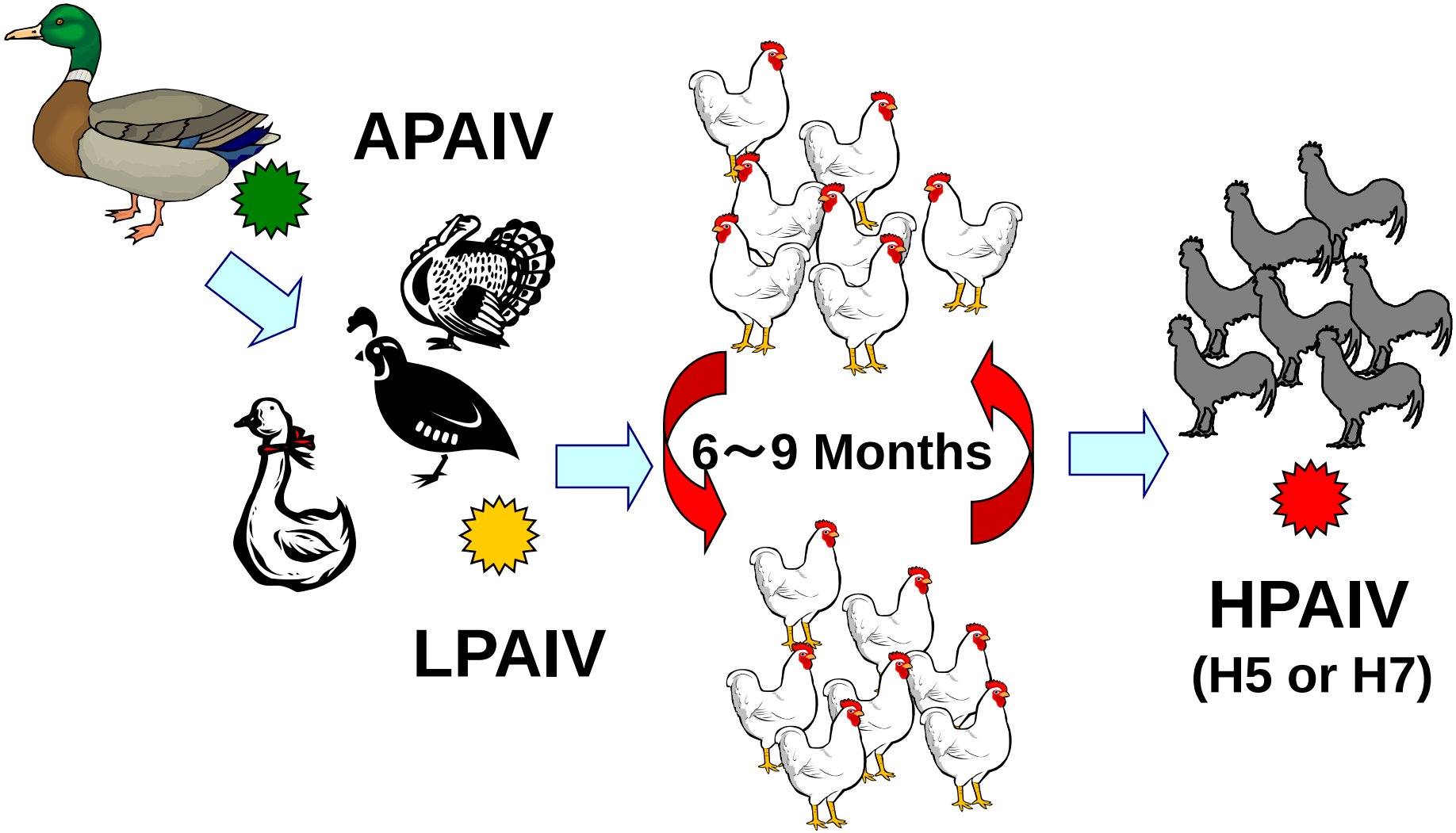
Kida H et al (1994) J Gen Virol



Ito T et al (1995) Arch Virol

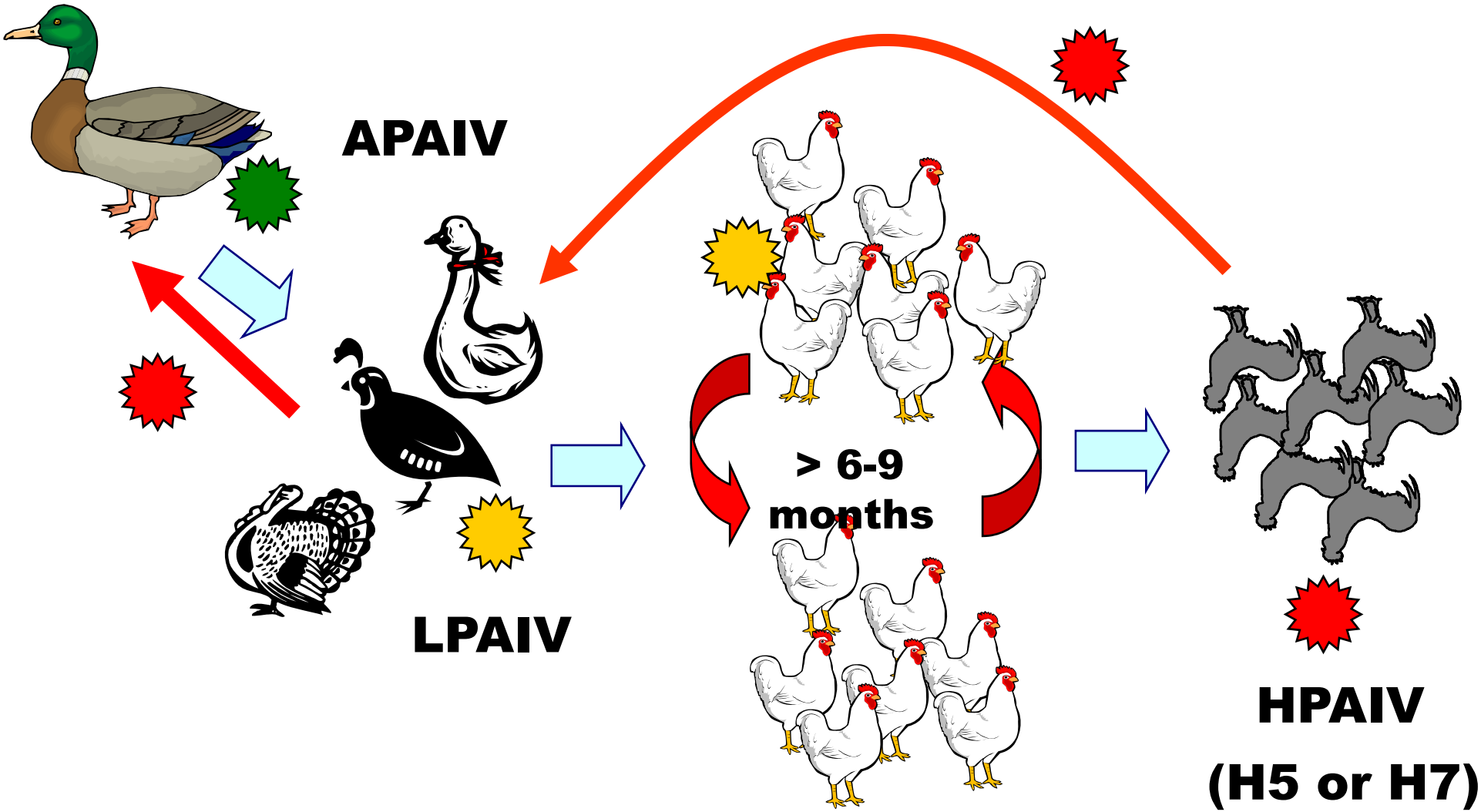

Kobyaysky(820)
H4N6
H4N9
H11N1
H11N6
H11N9
40 Ilands(1321)
Kenkeme(32)
Magadan(295)
Kharyyalah(146)
Buotama(51)
White Lake(1136)
H3N8
Irkutsk(290)
Yakutsk(232)
H3N8
H13N6
Elavga(66)
Ptropavlovsk-
Kamchatsky(58)
Khabarovsk(23)
Lake Kanicheva(95)
Malyshevo(90)
Wakkanai (958)
H1N1
H3N8
H5N3
H5N4
H6N2
H6N7
H8N1
H8N3
H9N2
H11N9
1996
1997
1998
1999
Taiwan
H1N1
H4N5
H4N6
H7N7
Okazaki K et al (2000) Arch Virol

Acquisition of pathogenicity of avian influenza virus in chicken



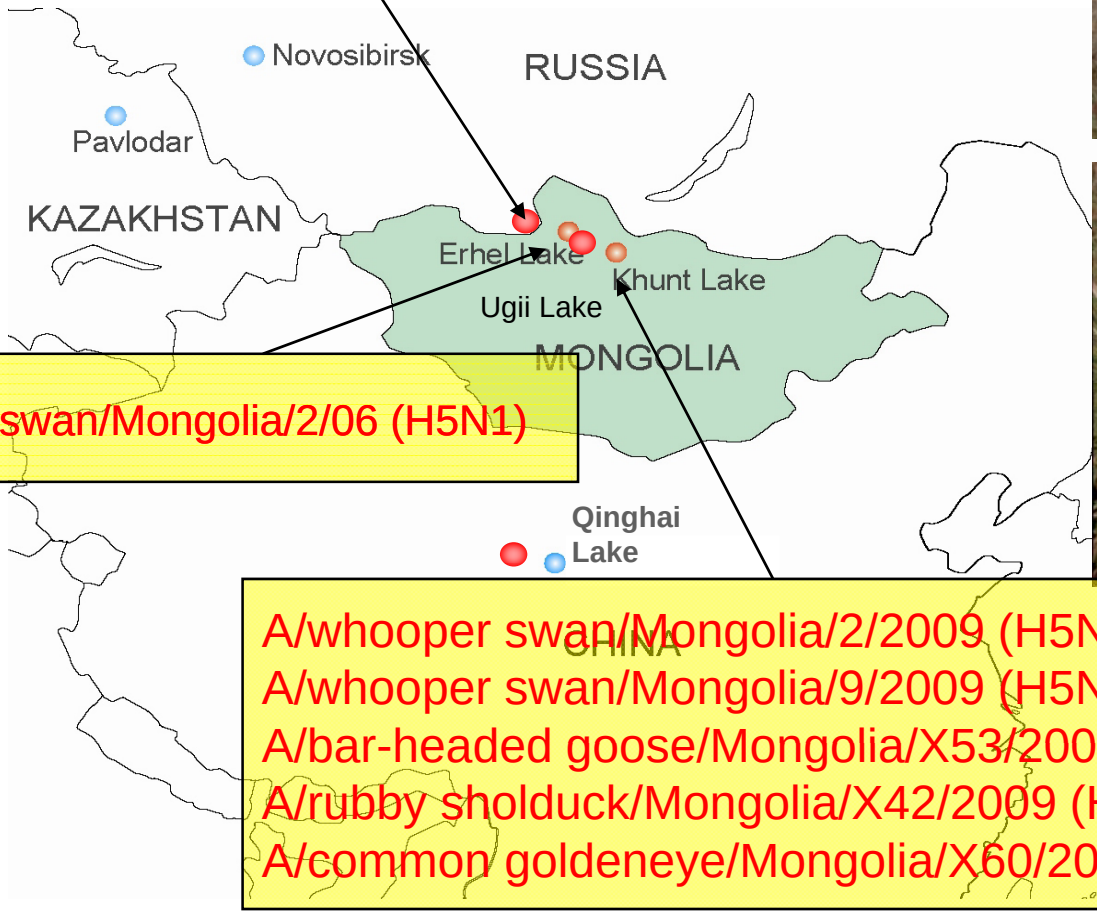

禁猎野生鸟类

Return of the HPAIV from domestic poultry to migratory water birds



HPAI viruses isolated from wild birds in Mongolia

A/whooper swan/Mongolia/3/05 (H5N1)
A/bar-headed goose/Mongolia/1/05 (H5N1)
A/common goldeneye/Mongolia/12/06 (H5N1)

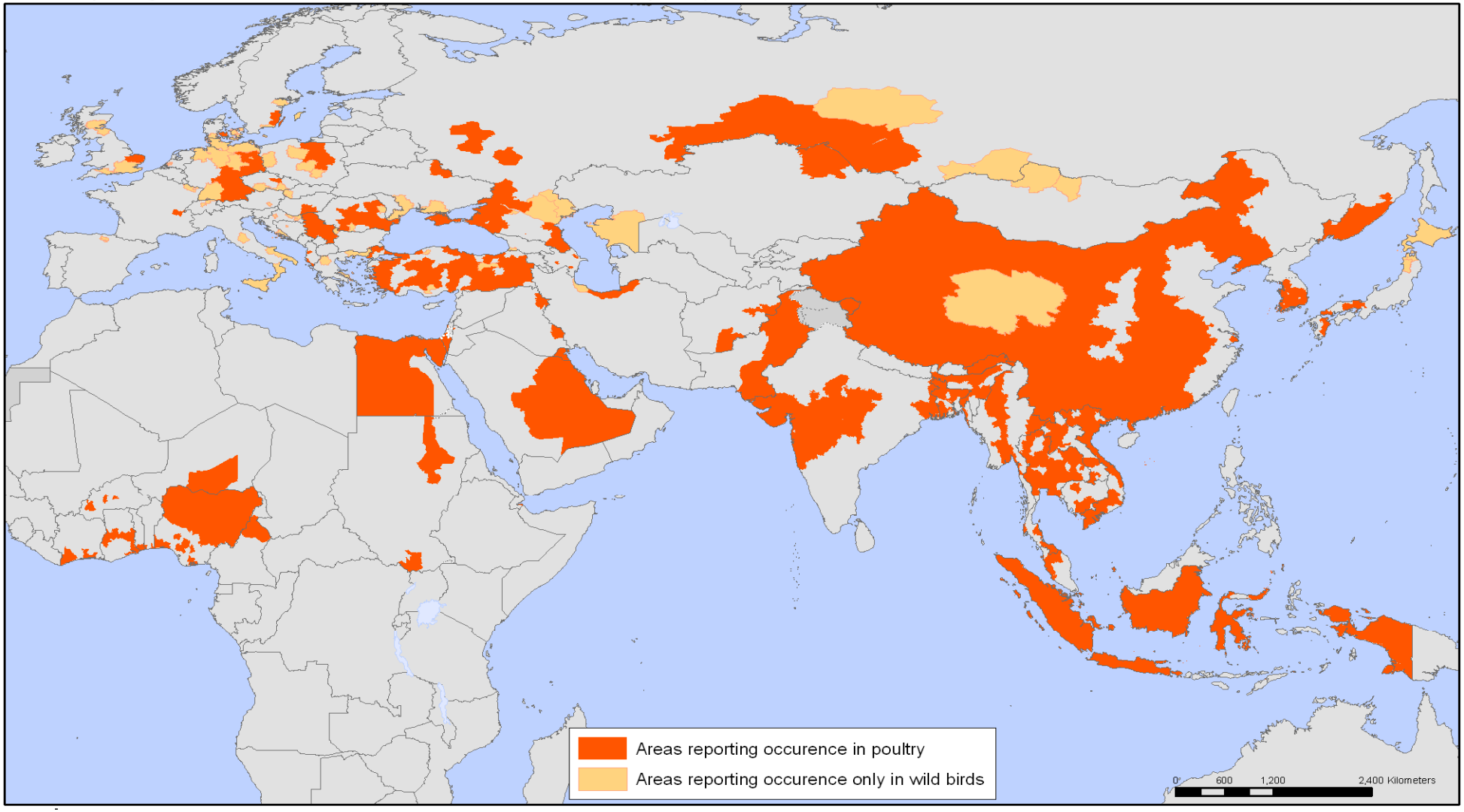


A/whooper swan/Mongolia/2/06 (H5N1)

A/whooper swan/Mongolia/2/2009 (H5N1)
A/whooper swan/Mongolia/9/2009 (H5N1)
A/bar-headed goose/Mongolia/X53/2009 (H5N1)
A/rubby sholduck/Mongolia/X42/2009 (H5N1)
A/common goldeneye/Mongolia/X60/2009 (H5N1)

Areas reporting confirmed occurrence of H5N1 avian influenza in poultry and wild birds since 2003

Status as of 12 December 2008
Latest available update

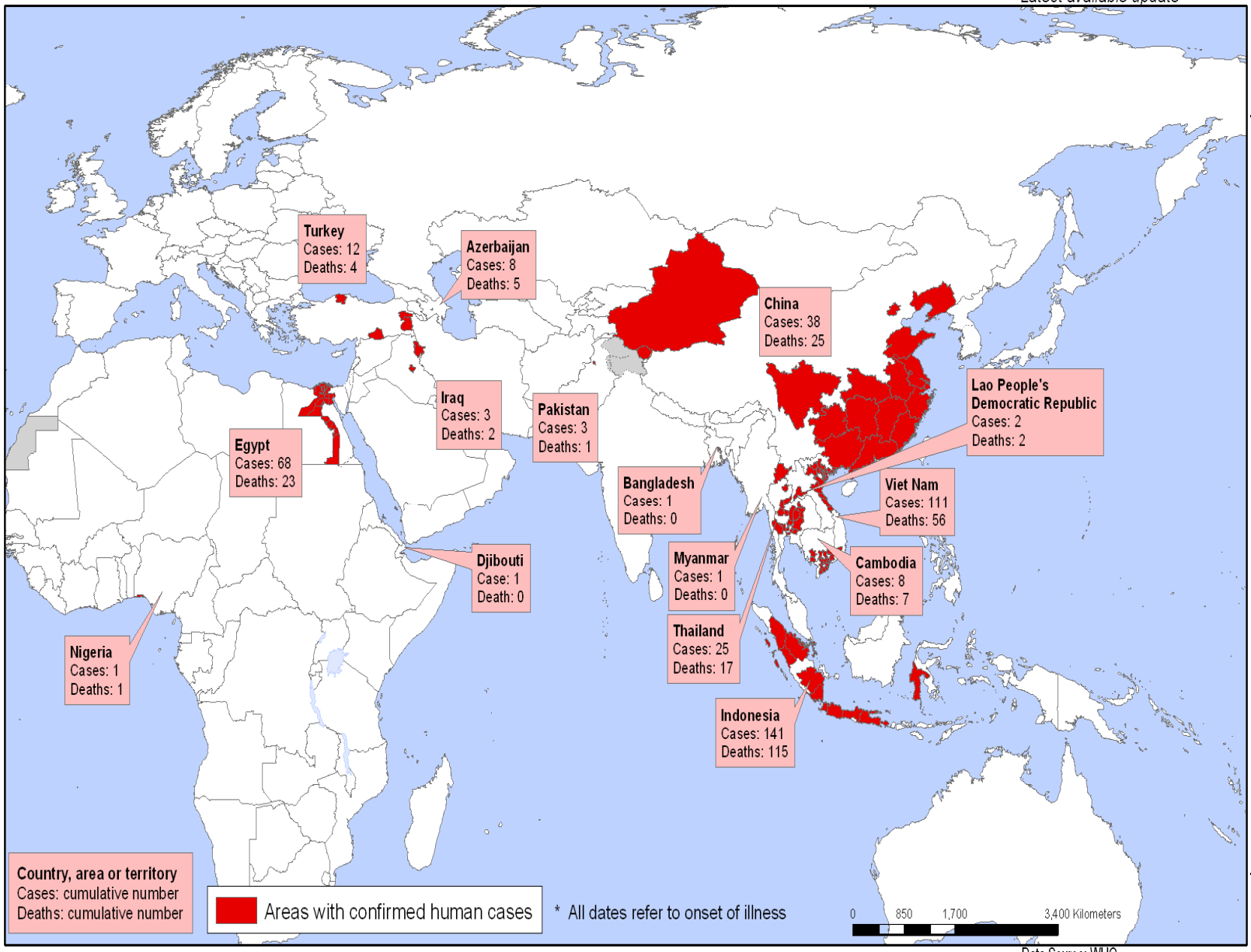


62 Countries where H5N1 HPAIV infections were reported in wild birds, poultry, and both

Japan, Republic of Korea, China, Mongolia, Myanmar, Lao PDR, Thailand, Cambodia, Viet Nam, Malaysia, Indonesia, Bangladesh, India, Pakistan; Afghanistan, Iran, Azerbaijan, Georgia, Iraq, Kuwait, Saudi Arabia, Turkey, Israel; Russian Federation, Kazakhstan, Ukraine, Romania, Bulgaria, Albania, Serbia, Hungary, Slovakia, Czech Republic, Croatia, Poland, Slovenia, Bosnia & Herzegovina; Greece, Switzerland, Austria, France, Italy, Germany, Netherlands, Denmark, Sweden, Spain, England, Ireland; Djibouti, Gaza Strip, Egypt, Sudan, Nigeria, Niger, Cameroon, Burkina Faso, Cote d'Ivoire

Areas with confirmed human cases of H5N1 avian influenza since 2003 *

Status as of 6 May 2009
Latest available update



Country	Deaths / Cases
China	25/ 38
Viet Nam	56/111
Indonesia	115/141
Egypt	27/ 87
Cambodia	7/ 8
Lao PDR	2/ 2
Thailand	17/25
Iraq	2/ 3
Azerbaijan	5/ 8
Turkey	4/12
Djibouti	0/ 1
Nigeria	1/ 1
Myanmar	0/ 1
Pakistan	1/ 3
Bangladesh	0/ 1
Total	**262/442**

As of 24 September 2009

World Health Organization

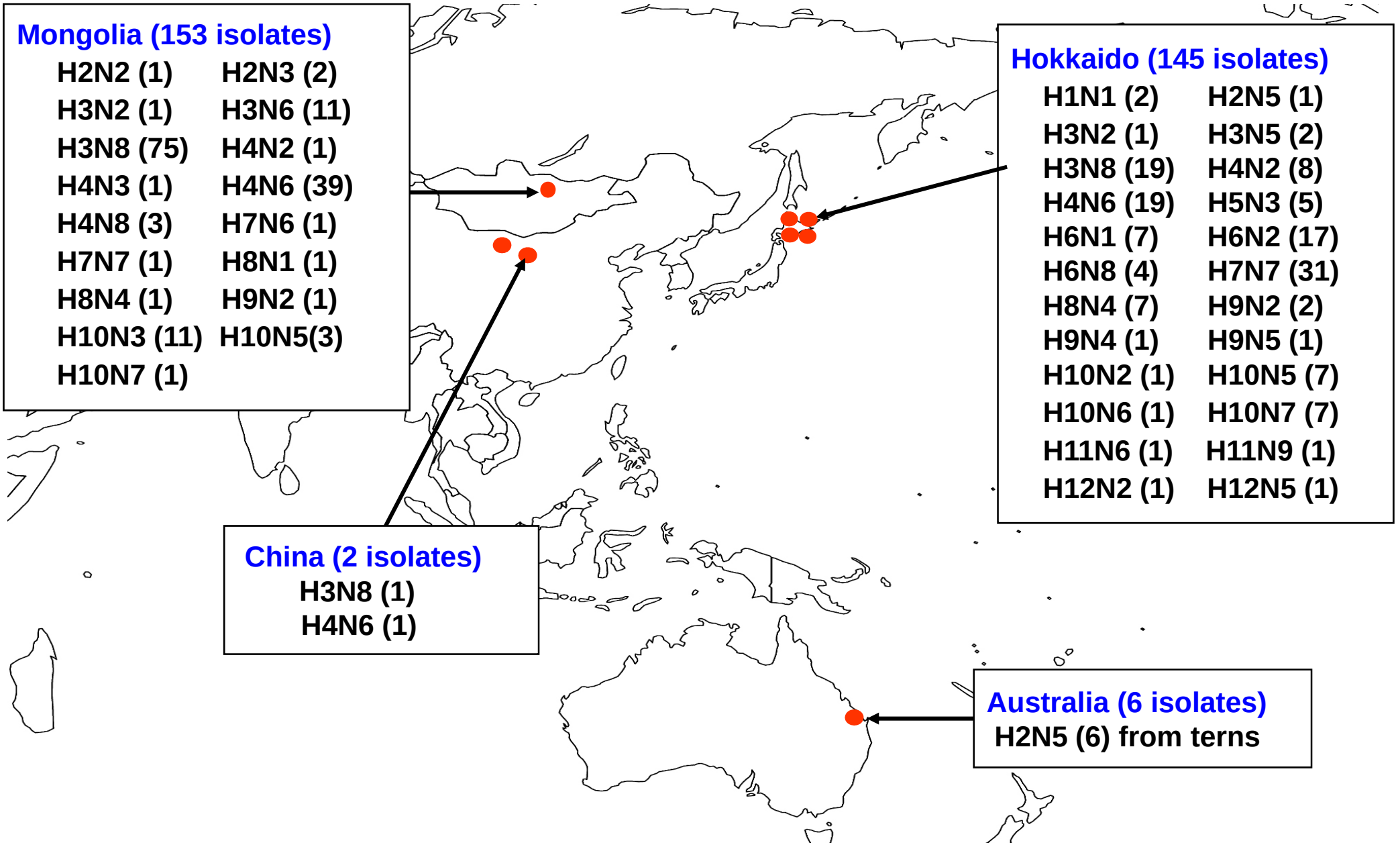
Data Source: WHO
Map Production: Public Health Information and Geographic Information System (GIS)
World Health Organization

Influenza Vaccine for bird flu

- may prevent manifestation of disease signs and decrease the amount of virus shed, but does not confer protective immunity from infection.
- is produced with inactivated virus, not live virus.
- "Test and culling or stamping-out policy" is recommended for the control of avian influenza.
- Vaccination is not recommended but one of the options applied only under DIVA (differentiating infected from vaccinated animals) based strategy as a tool is, in addition to, not instead of test and culling policy.
- Country where vaccine is used is not designated as HPAI-free.

→ must lead silent spread of virus.

Surveillance of avian influenza in migratory ducks in 2004-2008

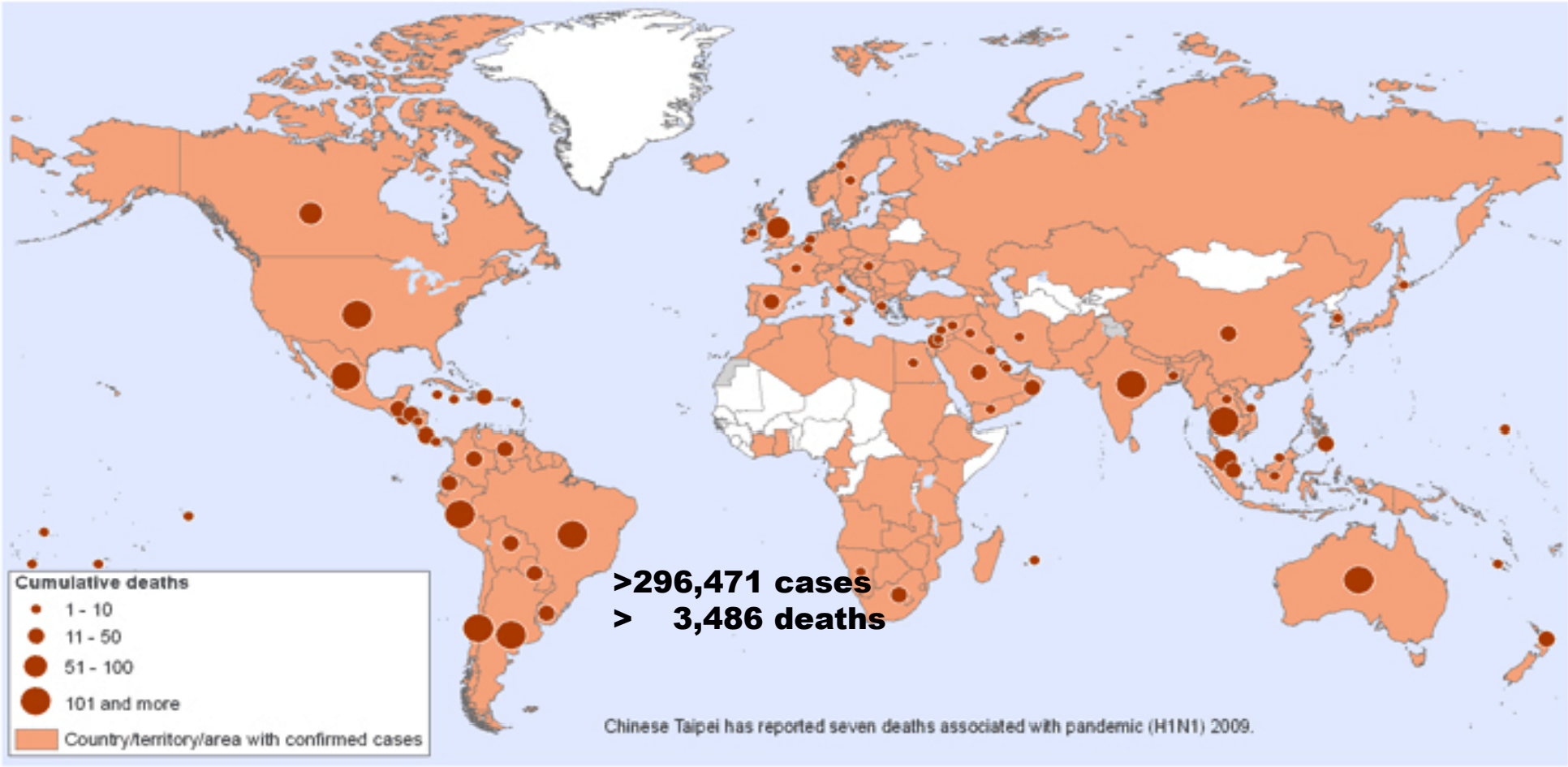


World Health Organization

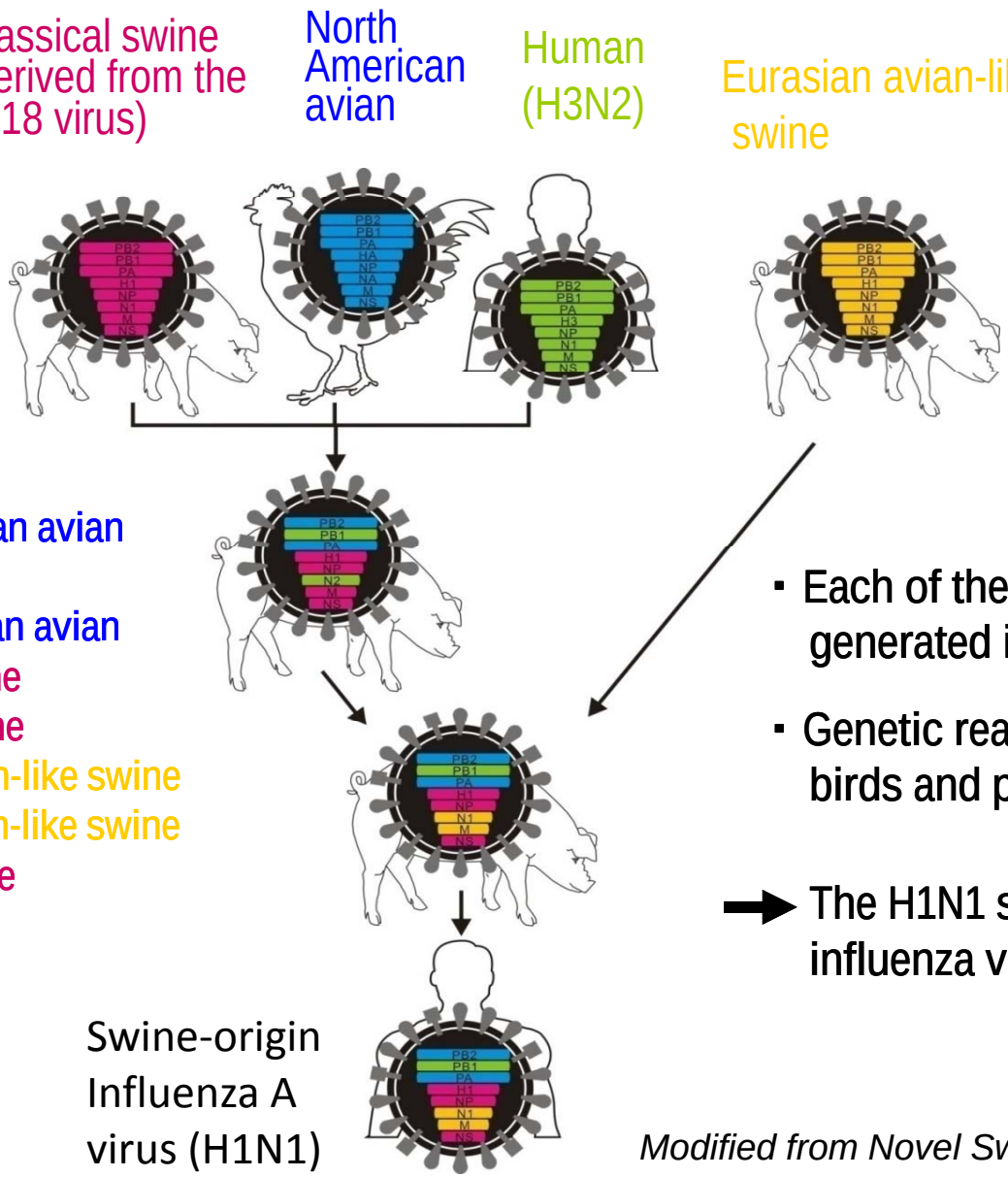
Timeline (22 July 2009 onwards)
Pandemic (H1N1) 2009 laboratory confirmed cases
And number of deaths as reported to WHO

Status as of: 13 September 2009

Previous



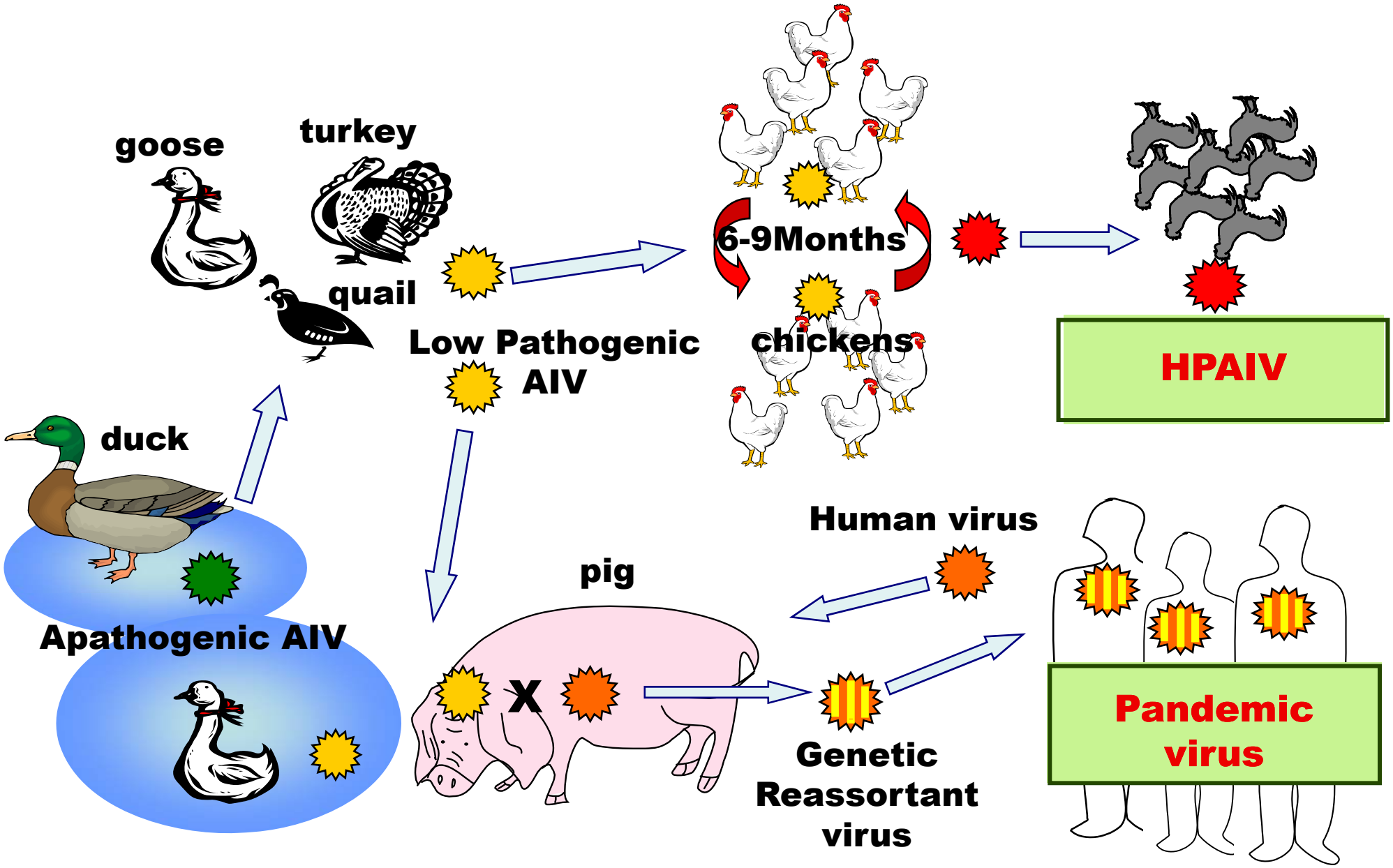
Gene derivation of the swine-origin influenza A (H1N1) virus



- Each of the pandemic strains have been generated in pigs.
- Genetic reassortment often occurs in birds and pigs.

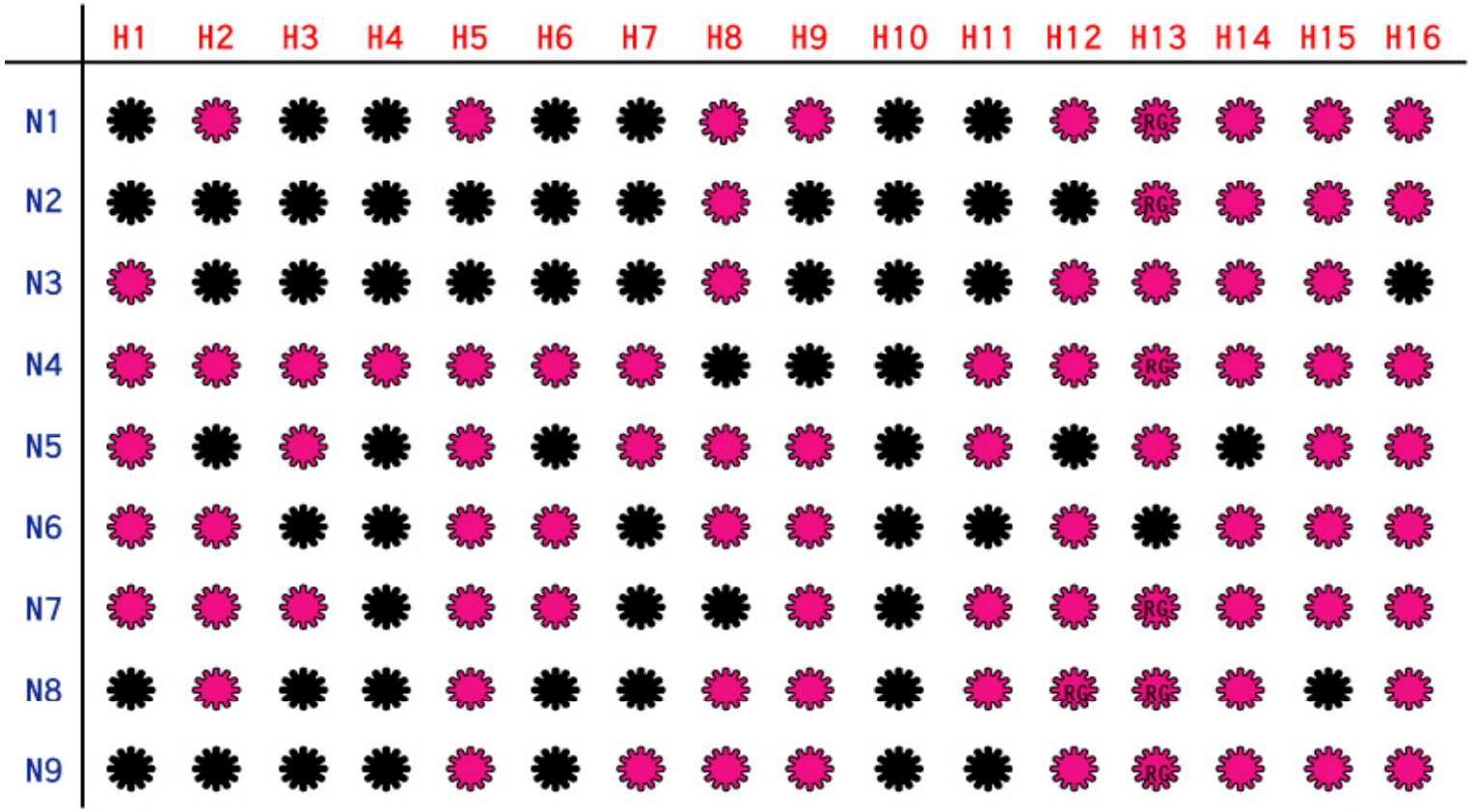
→ The H1N1 strain is a genuine swine influenza virus.

Modified from Novel Swine-Origin Influenza A (H1N1) Virus investigation Team, N Engl J Med, 2009



HPAI virus and human pandemic virus strains

Library of vaccine strain candidates



Influenza viruses of 61 combinations of the HA and NA subtypes have been isolated from fecal samples of ducks in Alaska, Siberia, Mongolia, Taiwan, China, and Japan (**black**).

83other combinatations have been generated by genetic reassortment procedure in the lab (**red**)..

Thus, 246 avian influenza viruses of 144 combinations of HA and NA subtypes have been stocked as vaccine strain candidates. Their pathogenicity, antigenicity, genetic information and yield in chicken embryo have been analyzed, databased, and opened for Web site (http://virusdb.czc.hokudai.ac.jp/vdbportal/view/index.jsp).

Are we prepared for pandemic flu?

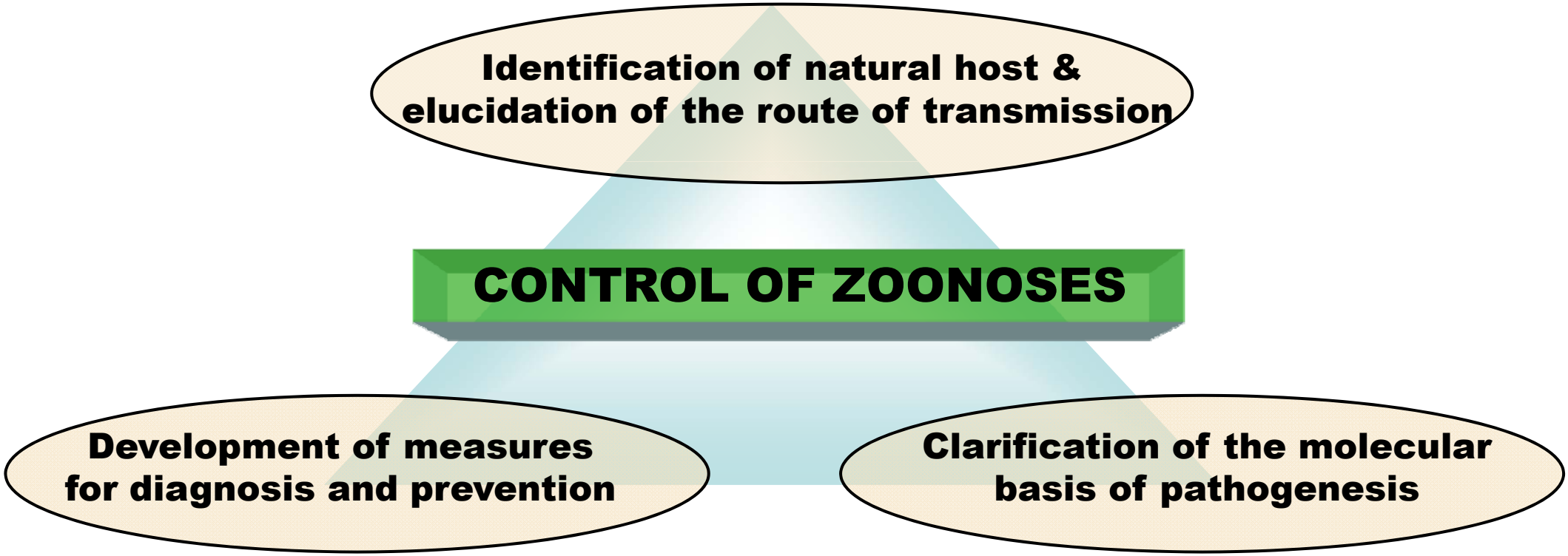
1. H1 to H16 and N1 to N9 subtypes of influenza A viruses perpetuate in the lakes where ducks nest in nature.
2. Viruses maintained by natural reservoir are antigenically and genetically stasis.
3. 1957 H2N2 and 1968 H3N2 viruses are reassortants between avian influenza virus and the preceding human strains.
4. Pigs are susceptible to both of avian and mammalian viruses and generate reassortants.
5. Avian viruses of any subtype can contribute genes for reassortants: None of the 16 HA and 9 NA subtypes can be ruled out as potential candidates for future pandemics.
6. Surveillance of swine flu is crucial in the countries where avian flu has not been controlled.
7. Preparedness for pandemic flu should be based on the measures for the control of seasonal flu.
8. Does the swine-origin new H1N1 virus cause seasonal influenza? Then, what should be done for the seasonal flu vaccine?

How should influenza be controlled?

* **Why do the H5N1 HPAIVs have persisted in poultry for 12 years ?**
* **Why do these strains show antigenic variation ?** Misuse of Vaccine
* **Will the HPAIVs that returned to migratory birds persist in nature ?**
* **How should avian influenza be controlled in poultry ?**
  Stamping-out without misuse of vaccine is only way, so far.
* **What are the advantage and disadvantage of the use of vaccines ?**
* **Are the measures for the control of seasonal flu satisfactory ?**
  The measures how to control pandemic influenza should be based on the measures for the control of seasonal influenza.
* **The swine-origin new H1N1 virus should cause seasonal influenza.**
  Vaccine for seasonal influenza should contain the new H1N1 virus antigen.

★ Global surveillance and seasonal flu control measure-based strategy

For the control of zoonoses



Zoonoses should be controlled when the novel field of science is established by the collaboration with and fusion of Veterinary Medicine, Medicine, Public Health, Ecology, Epidemiology, and Computer Science.

Research Center for the Control of Zoonoses

Veterinary Medicine

Ministry of Agriculture, Forestry and Fisheries

Prevention and therapeutics of diseases in livestock

OIE

Medicine

Ministry of Health, Labour and Welfare

Maintenance and improvement of human and public health

WHO

Ministry of Education, Culture, Sports, Science and Technology

Transmission of Pathogens

Ecology of zoonotic pathogens
Prevention and control of zoonoses

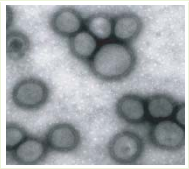
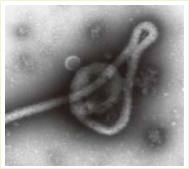
Ministry of the Environment

Species conservation of wild animals

Hokkaido University Research Center for Zoonosis Control

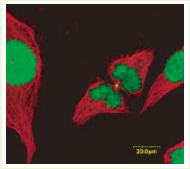
Department of Global Epidemiology

Identification of natural host animals of zoonotic pathogens

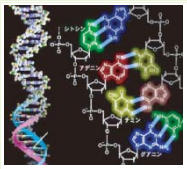
Dept of Molecular Pathobiology

Diagnosis of zoonotic infections and development of detection methods




Dept of Bioresources

Preservation and supply of pathogens, cells, genes and animal strains




Dept of Collaboration and Education

Coordination of collaboration programs with international and domestic organizations


Hokudai Center for Zns Control in Zambia

Identification of natural host animals and transmission routes of zoonotic pathogens