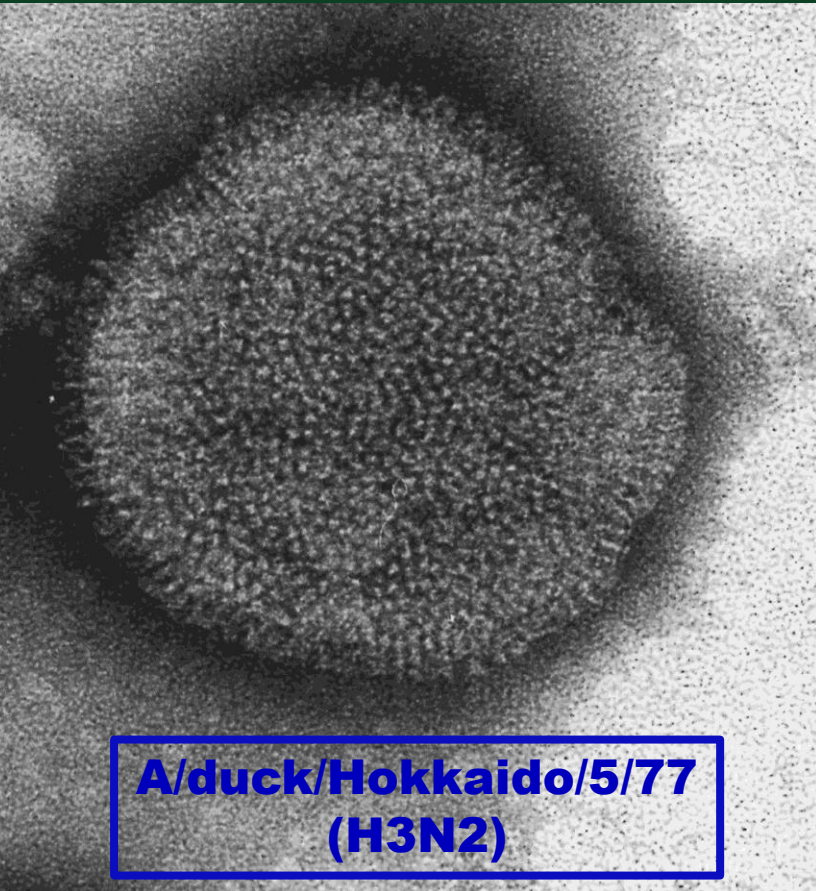
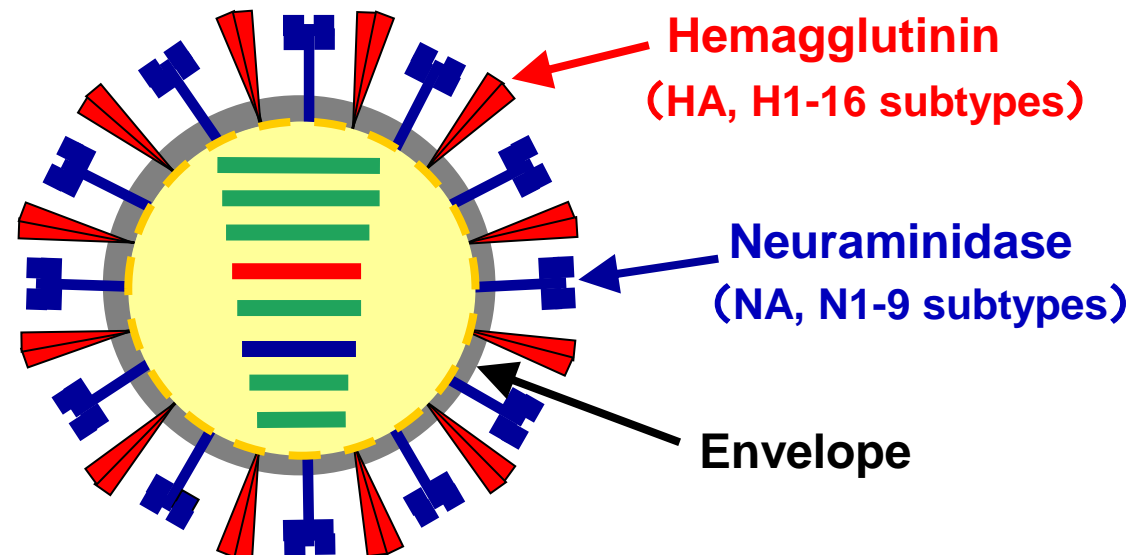


Role of academia in the control of zoonoses

- influenza as an example - 9-11 Apr 2019, Bangkok

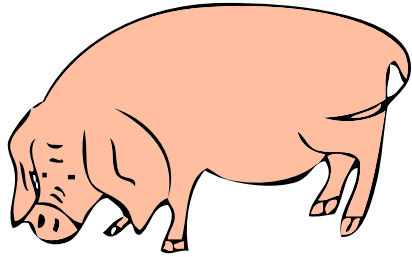


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*Kida & Yanagawa (1979) Zentralbl Bakteriolog Orig A 244
Isolation and characterization of influenza A viruses from
wild free-flying ducks in Hokkaido, Japan.*

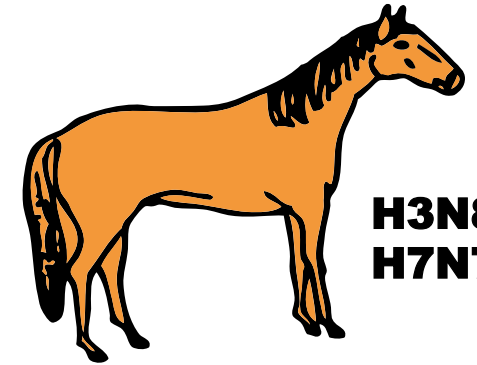
Host range, and HA and NA subtypes of influenza A virus



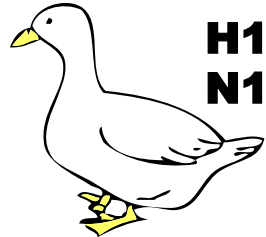
H1N1
H1N2
H3N2
H2N3, H3N1, H3N3,
H3N8, H4N6, H5N1,
H5N2, H9N2



H1N1
H2N2
H3N2
(H2N8, H3N8)
H5N1, H7N7,
H7N9, H9N2

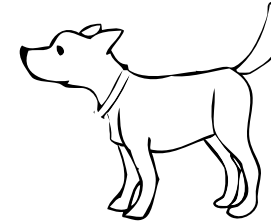


H3N8
H7N7

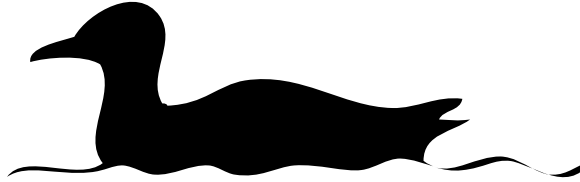


H1-H12
N1-9

Influenza is a zoonosis



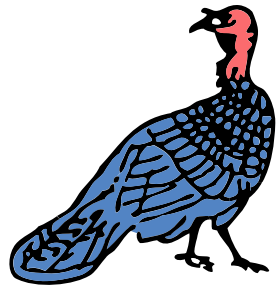
H3N8, H5N1



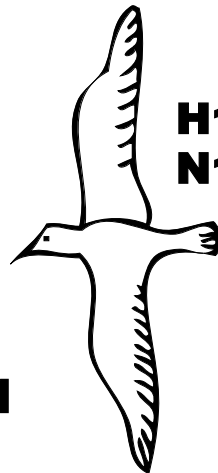
H1-16
N1-9



H5N1



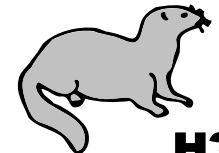
H1-10
N1-9



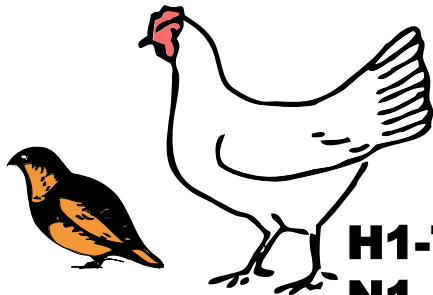
H1-7, H9-16
N1-9



H3N3
H4N5
H7N7



H3N2
H5N1
H10N4



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

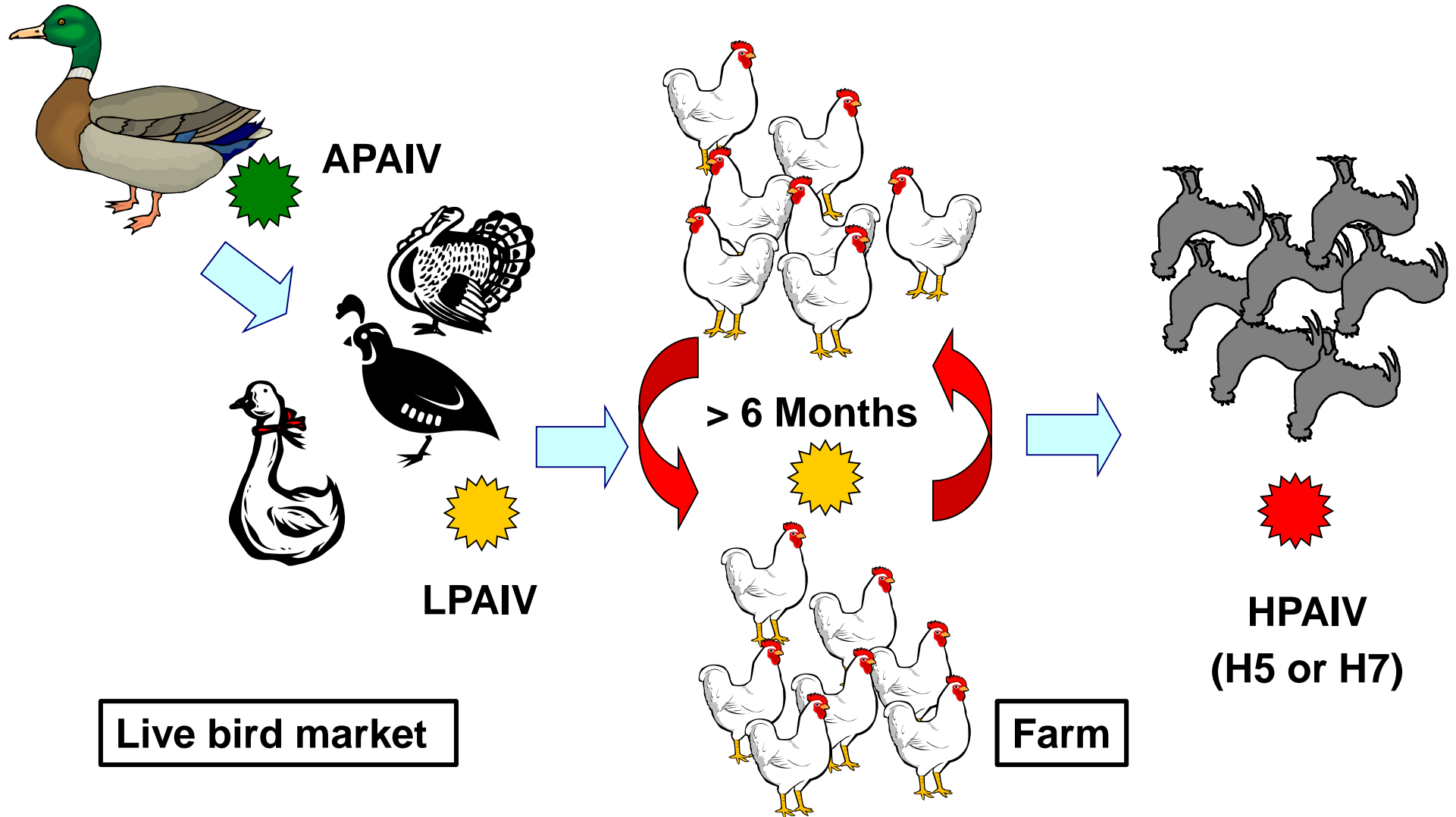


H1N3, H13N2, H13N9

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 for a week, and non-pathogenic.
 - ◆ Water-borne fecal-oral transmission of influenza viruses
 - ◆ **Viruses are preserved in frozen water of the lakes, where ducks nest in summer, in winter in Siberia, Alaska, and Canada etc.**
 - ◆ Ducks carry and provide viruses during migration and overwintering.
 - ◆ Influenza viruses circulating in ducks are extremely **stable** antigenically and genetically.
- **Migratory ducks are the natural host of influenza A viruses.**

Acquisition of pathogenicity of avian influenza viruses in chickens

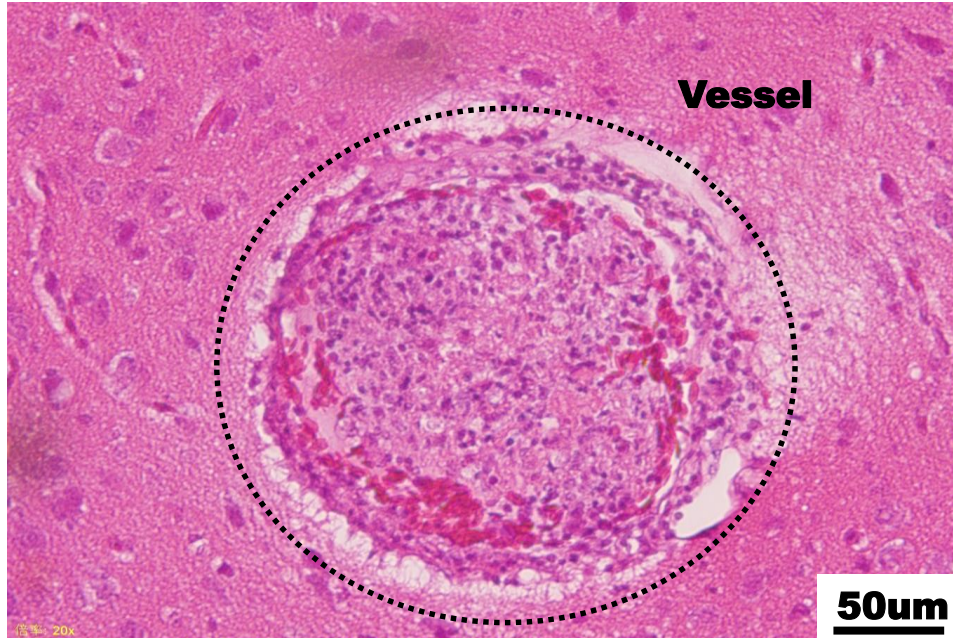


Amino acid sequences at the cleavage site of influenza A virus HAs

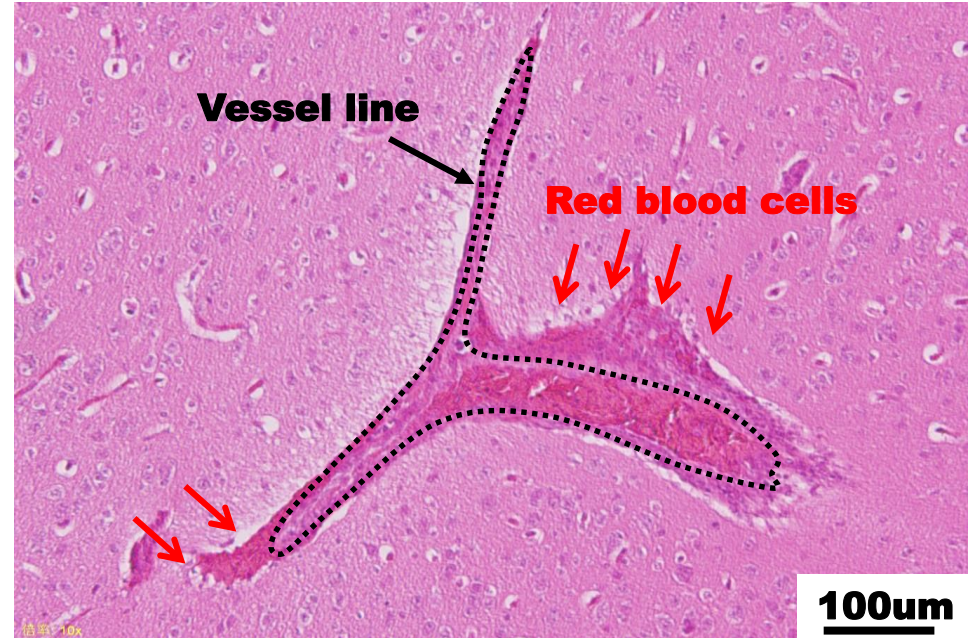
HA Subtype	Strain	AA sequence at CS of HA
H1	Dk/Alberta/35/76(H1N1) ^b	IQSR GLF
H2	Mal/MT/Y61(H2N2) ^b	IESR GLF
H3	Dk/Memphis/928/74(H3N8) ^b	KQTR GLF
H4	Dk/Czechoslovakia/56(H4N6) ^b	KASR GLF
H5	Ck/Scotland/59(H5N1)^b	RKKR GLF
H5	Ty/MN/3/92(H5N2) ^a	RETR GLF
H6	Shw/Australia/1/72(H6N5) ^b	IETR GLF
H7	FPV/Rostock/34(H7N1)^b	KKRKKR GLF
H7	Mal/Alberta/195/89(H7N3) ^a	KKTR GLF
H8	Ty/Ontario/6118/68(H8N4) ^b	VEPR GLF
H9	Ty/Wisconsin/66(H9N2) ^b	RSSR GLF
H10	Ck/Germany/N/49(H10N7) ^b	VQGR GLF
H11	Dk/England/56(H11N6) ^b	IASR GLF
H12	Dk/Alberta/60/76(H12N5) ^b	VQDR GLF
H13	GI/Maryland/704/77(H13N6) ^b	ISNR GLF
H14	Mal/Gurjev/263/82(H14N5) ^b	KQAK GLF
H15	Shw/Australia/2576/79(H15N9) ^b	IRTR GLF

Modified: ^a Senne et al (1996), ^b Kovacova et al (2002)

Findings of abnormal coagulation in the brain of the chickens infected with Ty/Italy/99



thrombus



hemorrhage

Systemic breakdown of capillaries

➔ Multiple organ disorder

Avian influenza vaccine

- prevent manifestation of disease signs and decrease the amount of virus shed, but does not confer immunity to completely protect from infection.
- “Stamping-out policy” is recommended for the control of avian influenza.
- Vaccination was not primarily recommended, and later approved as one of the **options** applied when the control of avian influenza is difficult.
- Country where vaccine is used is not designated as HPAI-free.
→ **leads silent spread of virus.**

RECOMMENDATION FOR THE CONTROL OF AVIAN INFLUENZA

It is considered that;

- Highly pathogenic avian influenza H5N1 virus strains have persisted in domestic poultry for 24 years and antigenic variants have been selected due to **misuse of vaccine**.
- HPAI has been put under control in several countries.
- **Stamping-out** is the most effective measures for the control HPAI.
- Vaccine is used in 4 countries where HPAI has not been controlled.
- Vaccine is used **instead of stamping out** in 2 countries and in the other 2 countries, basically **in addition to stamping out**.
- Sentinel birds are put in the vaccinated poultry population in Viet Nam and not in the other 3 countries where vaccine is used.
- **Compensation** for livestock owners is done in most countries in case of stamping out.

It is recommended that;

- Since stamping out is the best and ultimate measure for the control of HPAI, **vaccine, if used, should be applied in addition to, not instead of stamping out**.
- The OIE should continue and develop standards on animal influenza surveillance, prevention and control.
- Surveillance of swine flu is crucial in the countries where avian flu has not been controlled.

Cases of H5 and H7 virus infections in Japan

2004	Poultry	<u>H5</u> N1 (clade 2.5)	HPAIV
2005	Poultry	<u>H5</u> N2	LPAIV
2007	Poultry	<u>H5</u> N1 (clade 2.2)	HPAIV
2008	Wild birds	<u>H5</u> N1 (clade 2.3.2)	HPAIV
2009	Poultry	<u>H7</u> N6	LPAIV
2010-2011	Wild birds Poultry	<u>H5</u> N1 (clade 2.3.2.1)	HPAIV
2014 (Apr)	Poultry	<u>H5</u> N8 (clade 2.3.4.4A)	HPAIV
2014 - 2015	Wild birds Poultry	<u>H5</u> N8 (clade 2.3.4.4A)	HPAIV
2016 – 2017	Wild birds Poultry	<u>H5</u> N6 (clade 2.3.4.4C)	HPAIV
2017 (Nov) - 2018 (Mar)	Wild birds Poultry	<u>H5</u> N6 (clade 2.3.4.4B)	HPAIV

Control measures of HPAI in Japan

- Bio-security in the farms
- Continued intensive surveillance

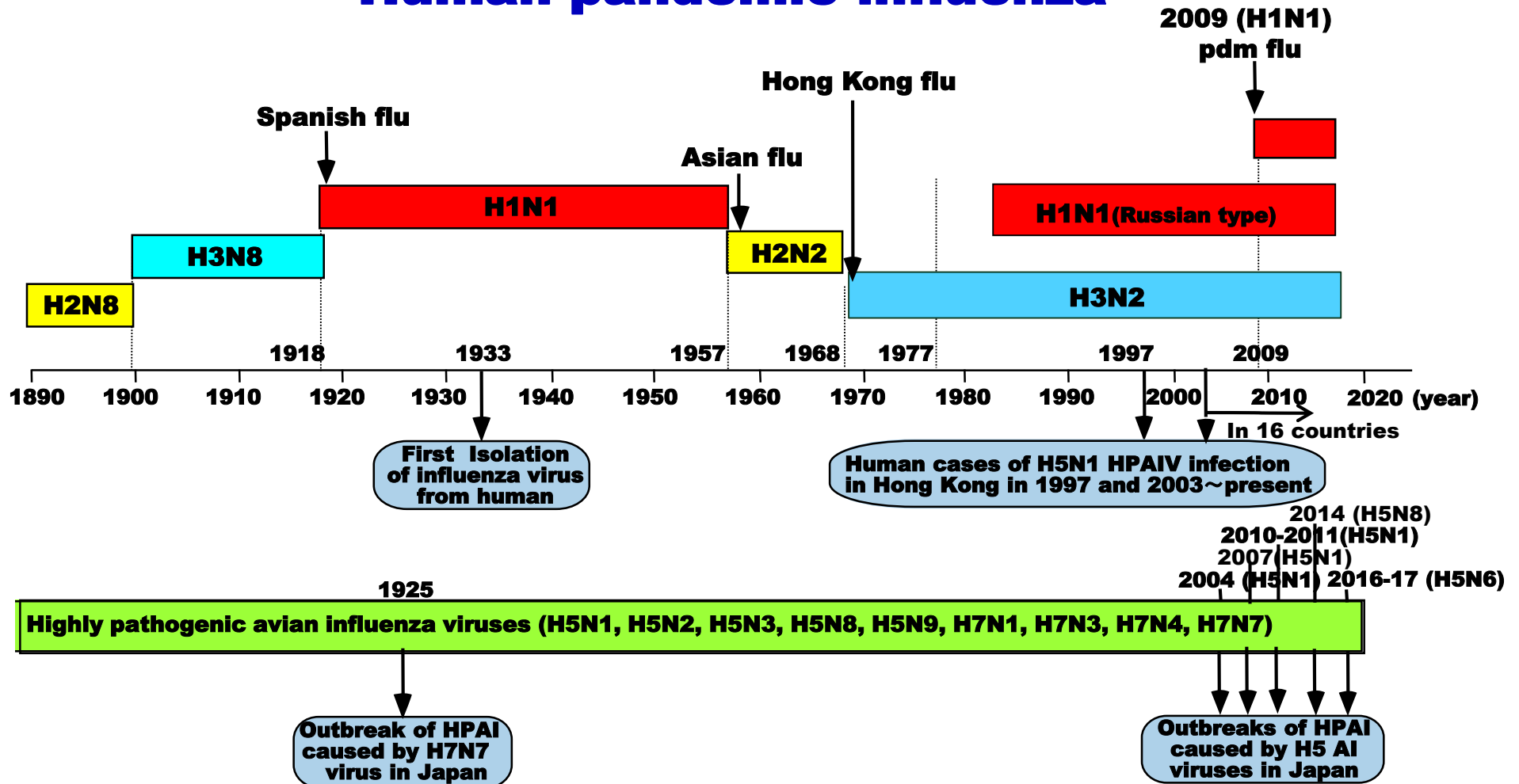


- Early detection and diagnosis

Stamping out policy

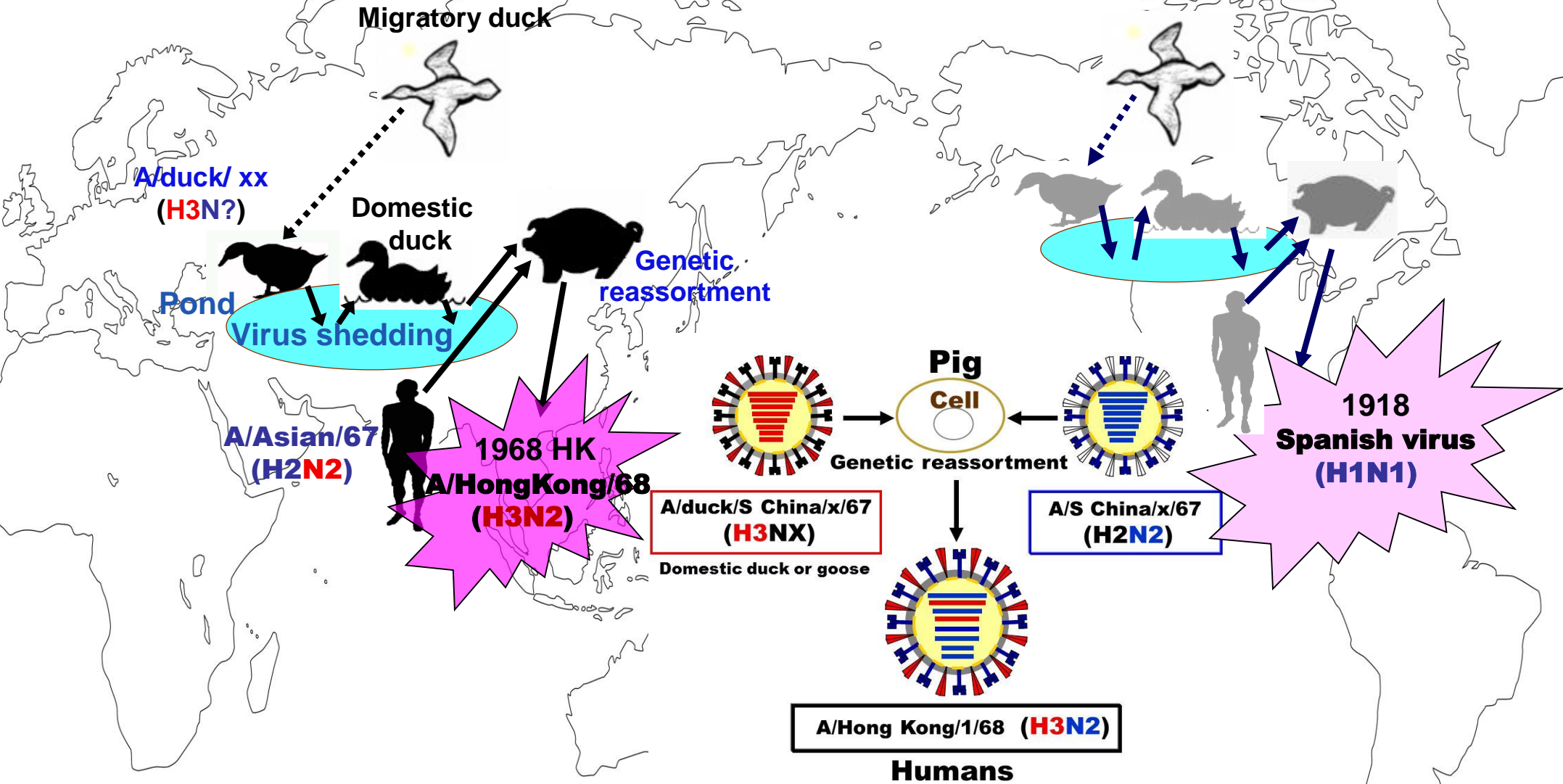
1. Culling the flock infected
 2. Movement restriction
 3. Disinfection
 4. Monitoring
 5. Compensation
- * No vaccination

Human pandemic influenza



Highly pathogenic avian influenza

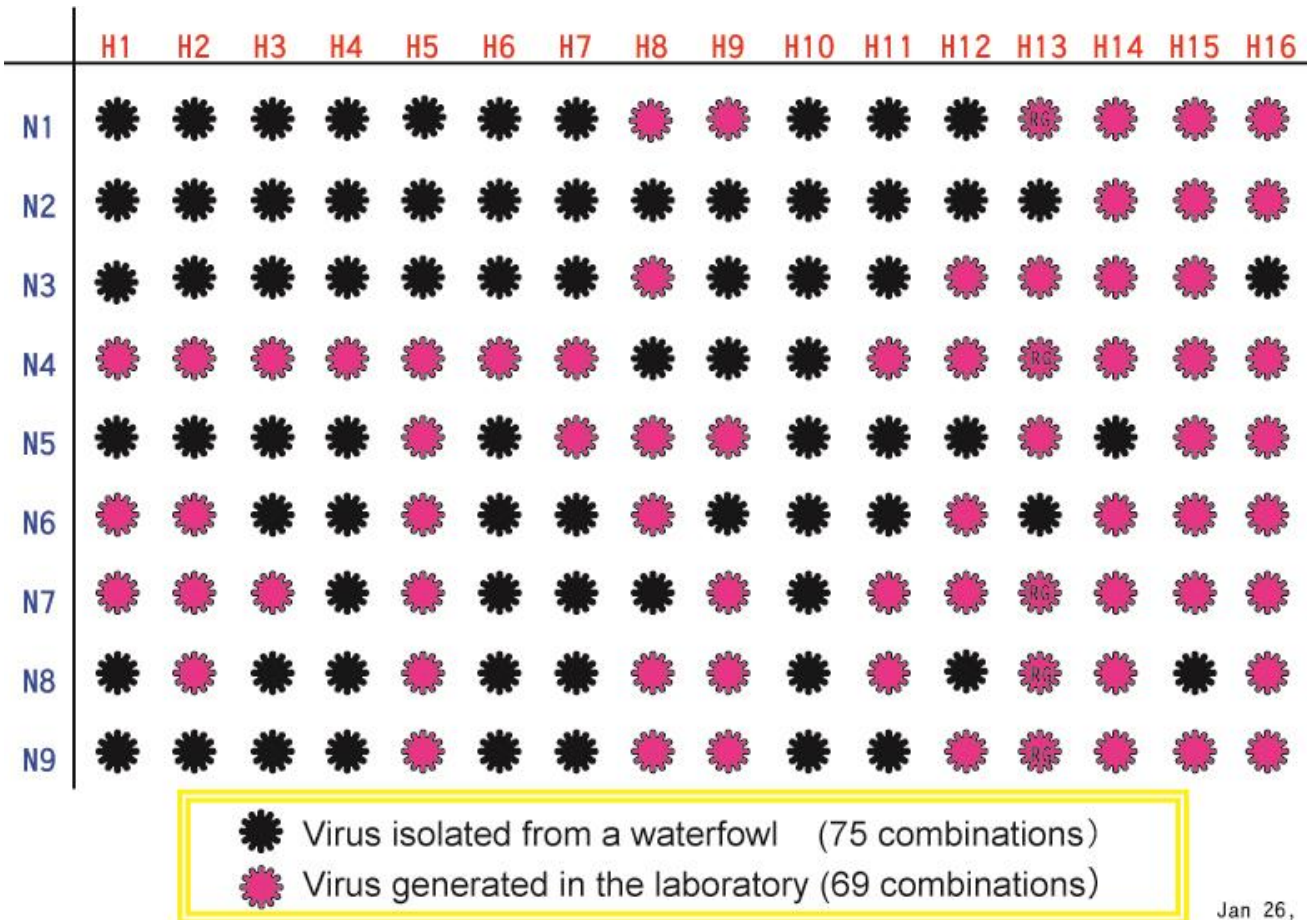
Route of transmission of the HA genes of pandemic strains



Kida et al: Virology (1987, 1988), J Gen Virol (1994); Yasuda et al: J Gen Virol (1991)

1957 Asian virus (H2N2), 1918 Spanish flu virus (H1N1) and 2009 H1N1 pdm virus must have appeared similarly.

Library of pandemic influenza vaccine strain candidates



Influenza viruses of 75 combinations of the HA and NA subtypes have been isolated from fecal samples of ducks in Alaska, Siberia, Mongolia, Taiwan, China and Japan (black).

69 other combinations have been generated by genetic reassortment procedure in the lab (red).

Test vaccines prepared from H1N1, H5N1, H6N2, H7N7, H7N9 and H9N2 viruses in the library induced sufficient immune response to protect chickens, mice and monkeys from the challenge with virus isolates from birds and humans.

Thus we have vaccine strains for pandemic influenza.

More than 3,000 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, data-based, and opened for Web site

(<http://virusdb.czc.hokudai.ac.jp/vdbportal/view/index.jsp>).

Jan 26, 2015

Points for the control of avian influenza and the preparedness for future pandemics

1. **Why have the H5 HPAIVs persisted in poultry for 24 years and been antigenic variants selected ?** Misuse of Vaccine

2. **Will the HPAIVs returned to migratory birds persist in nature ?**

Contamination of HPAIVs in the nesting lakes of migratory ducks must have occurred. Prompt eradication of the H5 HPAIVs from poultry in Asia is urgently needed.

3. **How should avian influenza be controlled ?**

For the containment and eradication of avian influenza viruses in the poultry infected, enhanced surveillance, early detection, culling the flock, movement restriction, and strengthening hygiene without misuse of vaccine should be done. Vaccine, if used, should be carefully applied **in addition to, not instead of stamping out.**

4. **Will H5 HPAIV and H7N9 AIV cause pandemic influenza?**

It is unlikely to occur; direct transmission of AIV from birds only to specific humans who have receptor for avian strains, and thus human-human transmission may not occur, but may occur via pigs. H5N1 or H7N9 are not only candidates of pandemic strains.

5. **Are the measures for the control of seasonal flu satisfactory ?**

How to control pandemic influenza should be based on the measures for the control of seasonal influenza. Especially seasonal flu vaccines should be drastically improved since current split vaccines prepared by ether- or detergent-disruption are poorly immunogenic. Inactivated WVP vaccines are now under pre- and clinical studies.

★ **Global surveillance of avian, swine and human influenza, and drastic improvement of seasonal influenza vaccines of global standard are of crucial importance.**

For the control of zoonoses

We must accept the fact that **zoonoses are not eradicable infectious diseases** since the causative pathogens are introduced from wildlife in nature. Such zoonotic infections, therefore, can be controlled only by taking preemptive measures to predict and prevent the outbreaks.

For the establishment of preemptive measures against zoonoses, a prerequisite is to identify **natural host** animals carrying potential pathogens, and to elucidate the **transmission routes** and **factors involved in the spread and pathogenesis of infections**. In addition to promoting basic research on zoonotic diseases, there is a pressing need to develop effective measures for **diagnosis, prophylaxis and therapy**, to widely disseminate information and technology, and **to train experts for the control of zoonoses**.

Hokkaido University Research Center for Zoonosis Control, thus, carries out coherent scientific and educational activities for the control of zoonoses under the umbrella of One World, One Health concept.



Hokkaido University Research Center for Zoonosis Control

**Thank you
for your kind attention.**

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