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World Egg Organisation's
Global Leadership Conference 2025
7-10 September 2025 Cartagena | Colombia

Vaccination Strategies and Insights for the Control of HPAI in China

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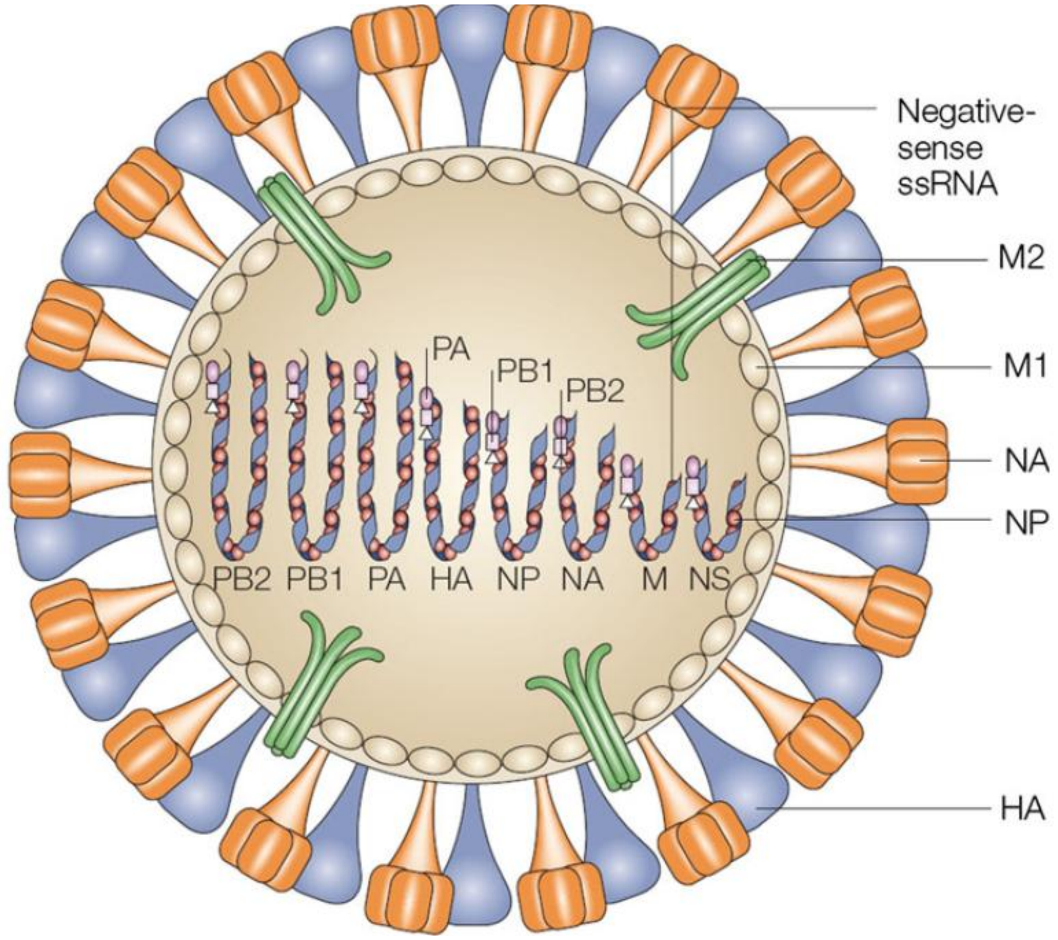
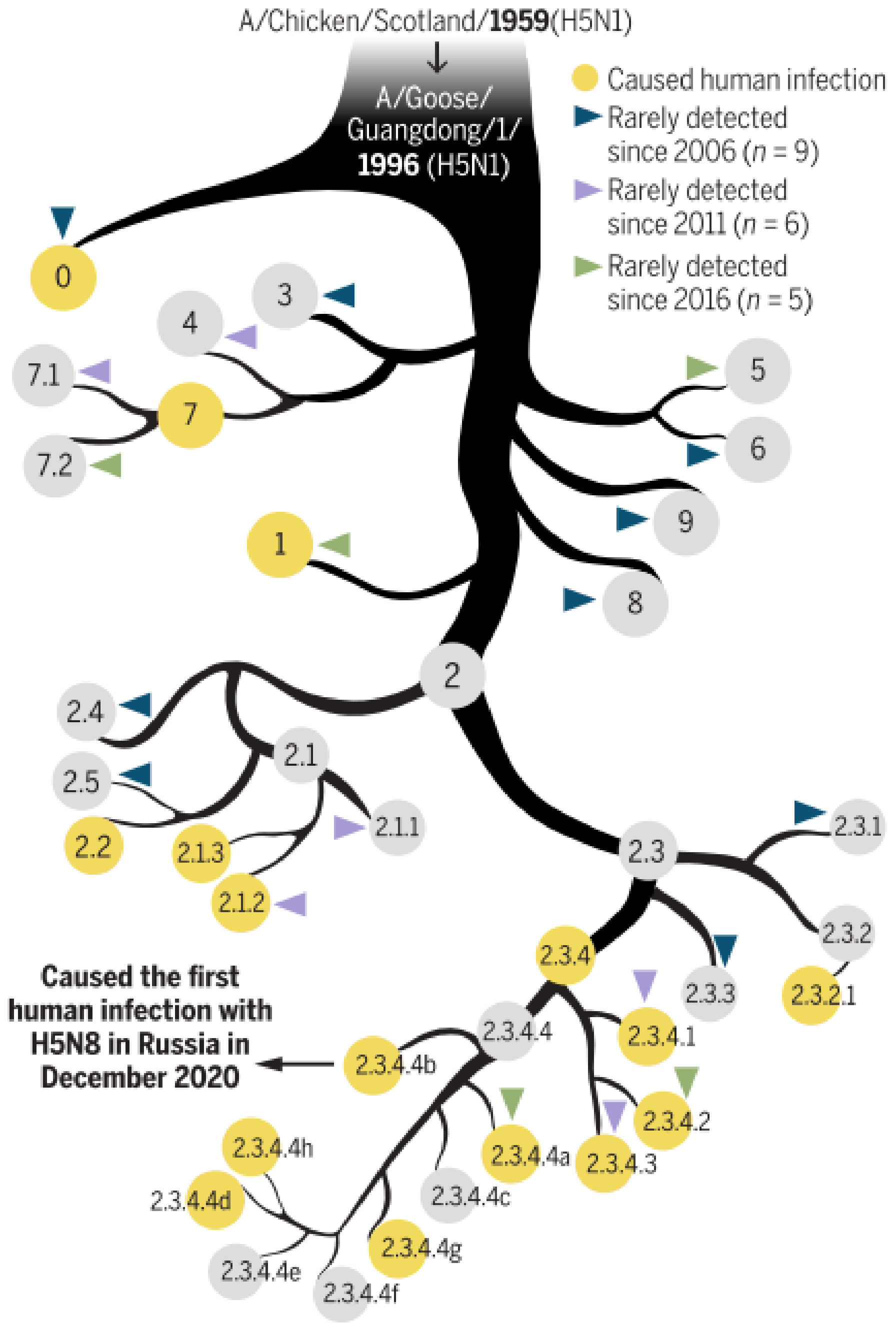
Influenza A virus

- Multiple subtypes：
  - 18 HA and 11 NA
  - Highly pathogenic avian influenza viruses (HPAIVs): H5 and H7 subty
- Mutation and reassortment
  - H5N1, H5N2, H5N6, H5N8, etc
  - H7N1, H7N3, H7N9, etc

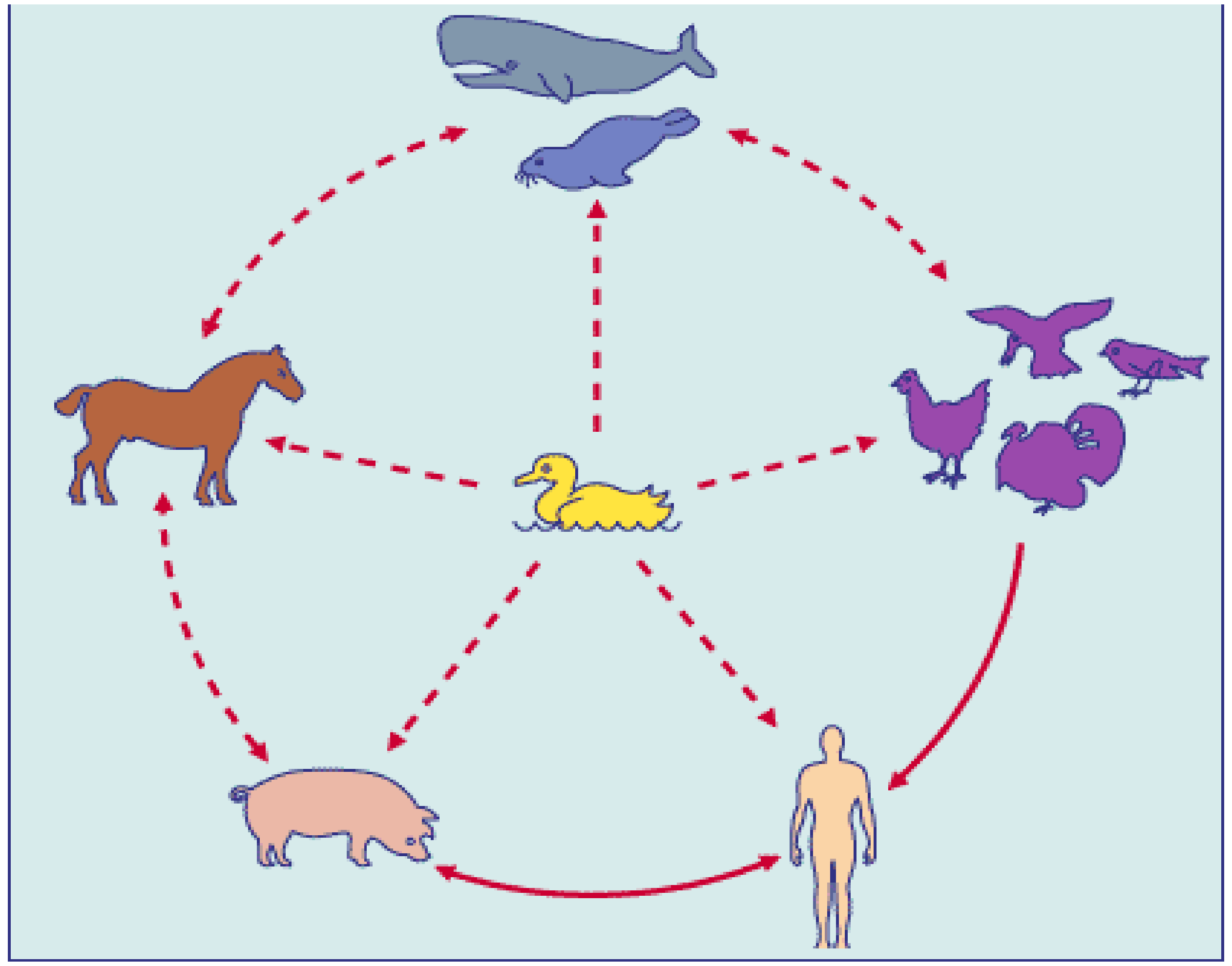


The structure of influenza A virus



Multiple HA clades of H5 AIVs

- Wide host range
  - –Waterfowl, poultry, mammals, human
  - –Over 350,000 wild and domesticated mammals have been lost due to H5N1 infection



The reservoir of influenza A viruses

Finland, Raccoon dog

Finland, Fox

Chile and Peru, Seal and Sea lion

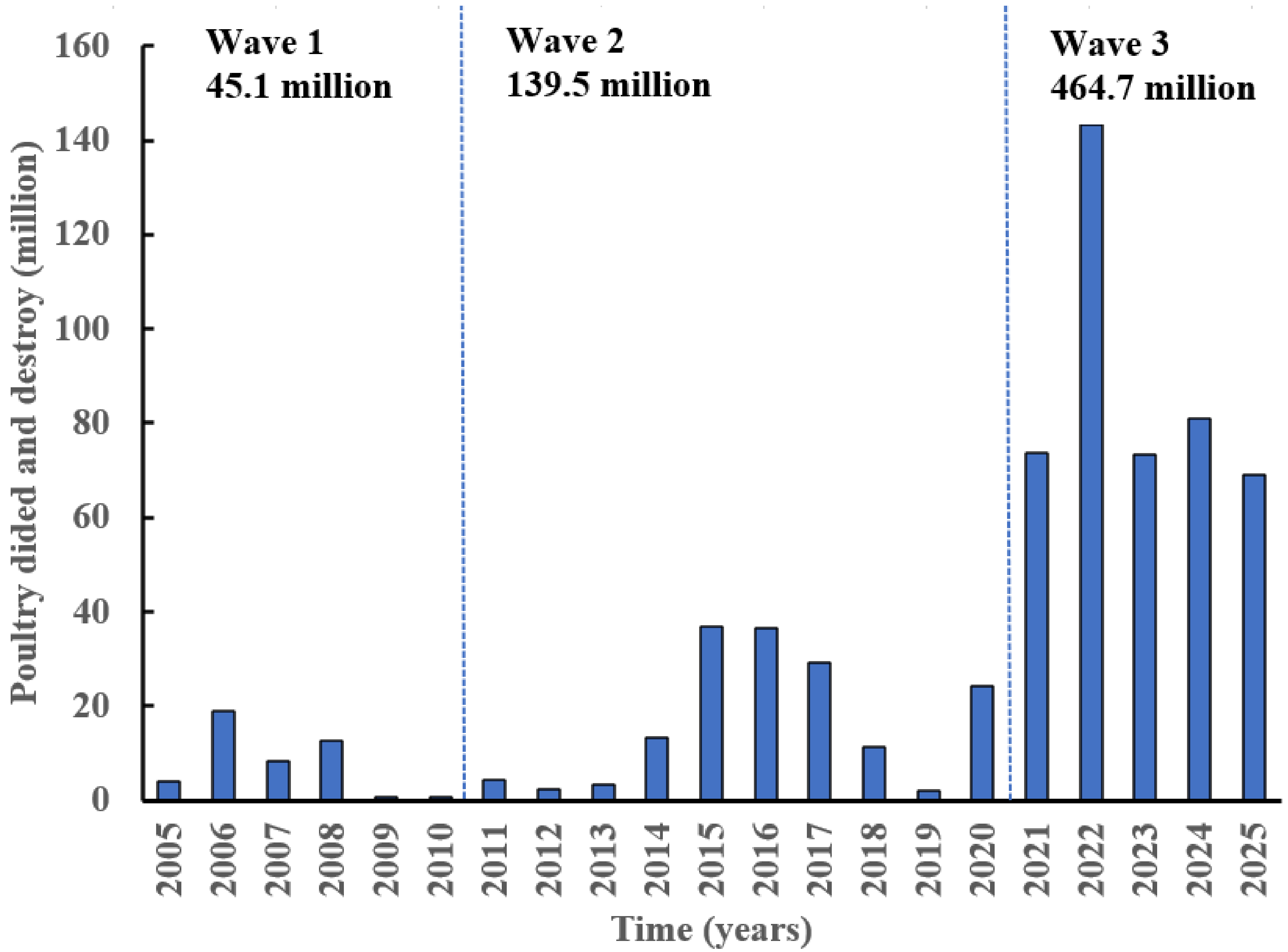
Finland and Spain, Mink

USA, Cattle

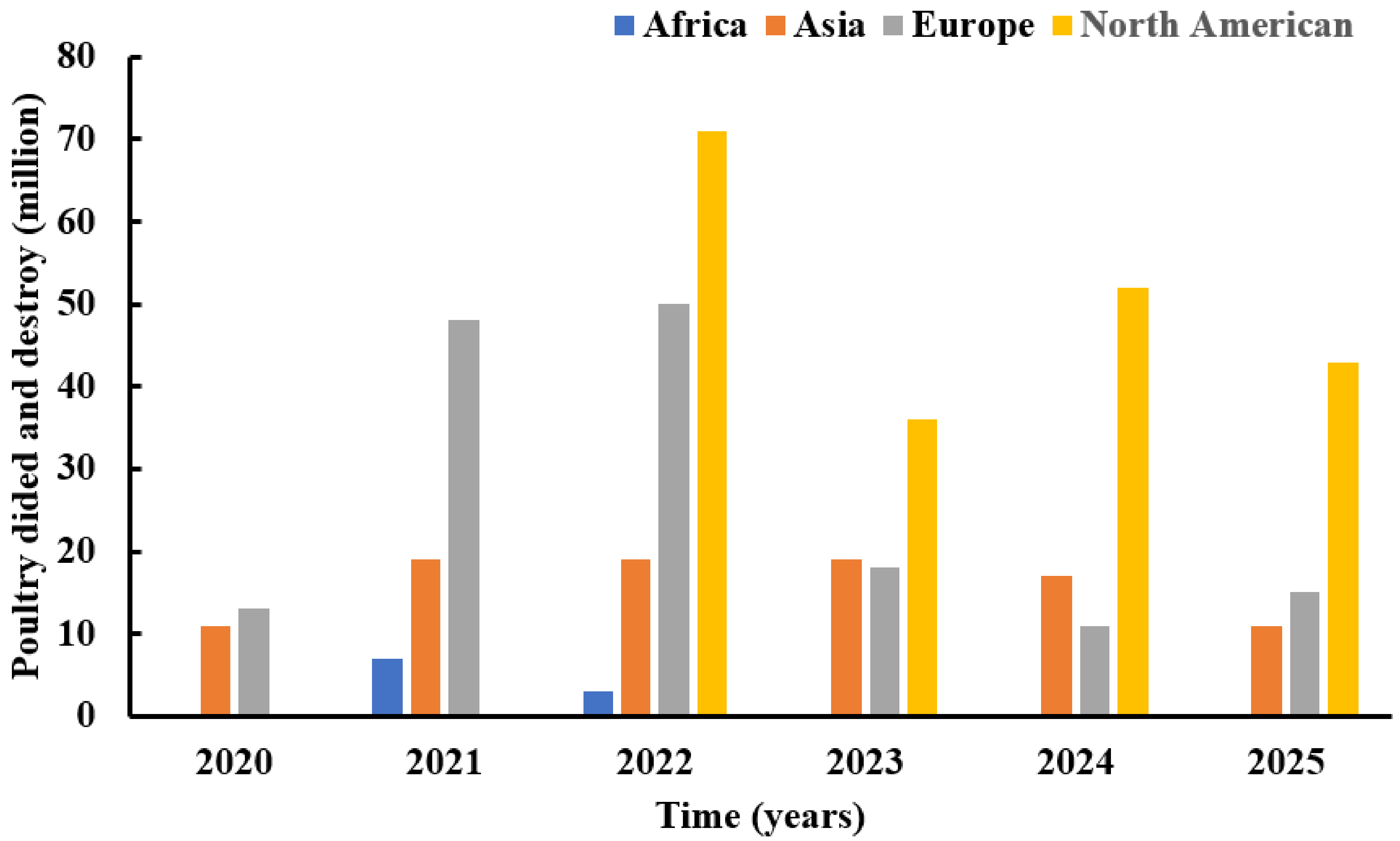
USA, Goat

The H5 influenza virus has caused the loss of over 649 million poultry worldwide since 2005

- Three waves of epidemics: 2005-2010; 2011-2019; 2020-
- The third wave: North American, Europe, Asia



Globe killed and disposed poultry since 2005 （*WAHIS, 2025*）



Continental Distribution of killed and disposed poultry since 2020

The H7 influenza virus has caused the loss of over 44 million poultry worldwide since 2005

- Most of the outbreaks were independent, with continuous occurrences in China and Mexico
- The domestic poultry included chickens and turkeys
- The subtypes included H7N2, H7N3, H7N7, H7N8, H7N9, etc

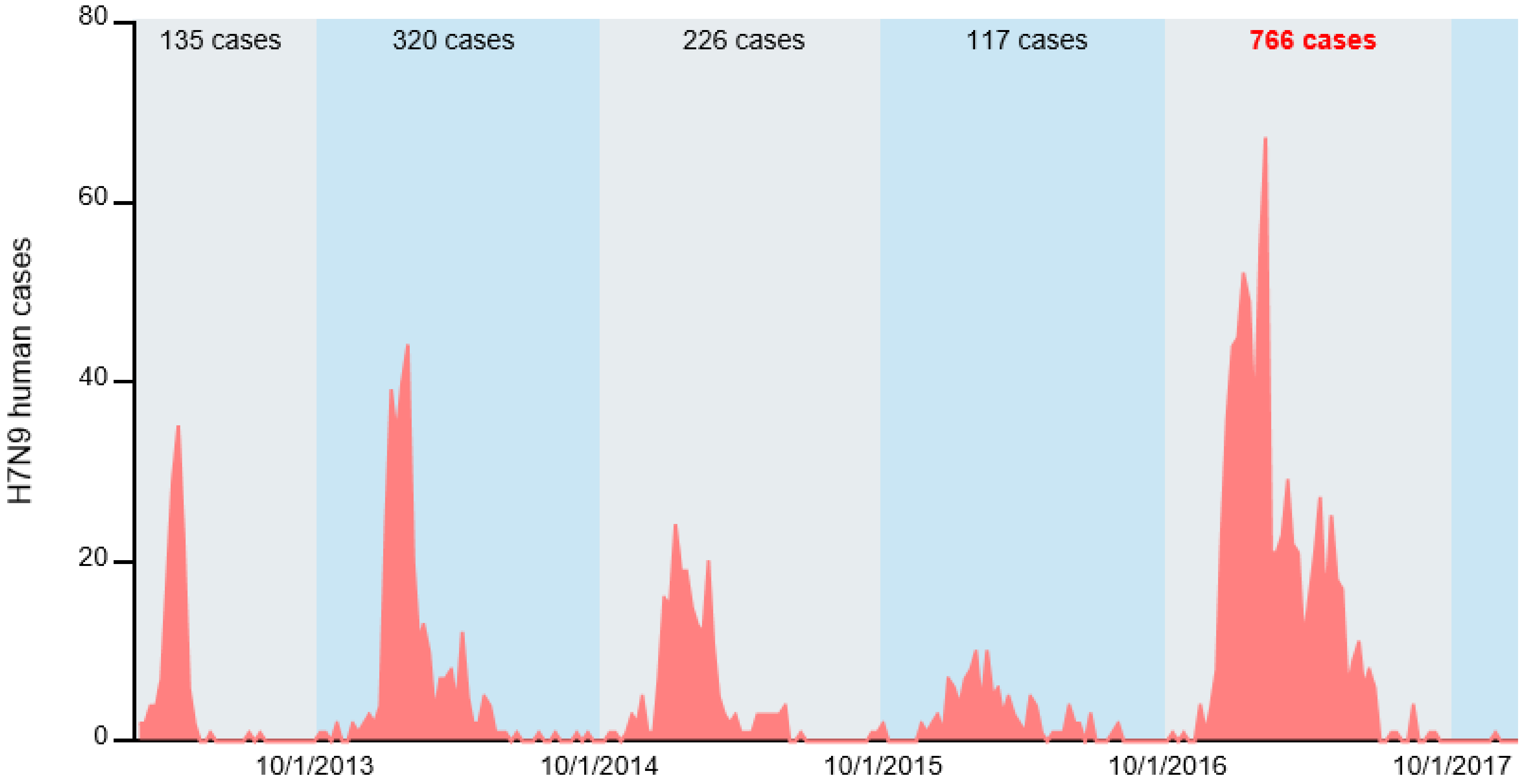
Year	Country	Subtype	Host	Killed
2005	North Korea	H7N7	Chicken	218788
2007	Canada	H7N3	Chicken	49100
2008	UK	H7N7	Chicken	25000
2009	Spain	H7N7	Chicken	208640
2012-	Mexico	H7N3	Poultry	31068754
2012, 2013, 2020, 2024, 2025	Australia	H7N2/N3/N7/ N8/N9	Chicken	3243172
2013, 2016	Italy	H7N7	Chicken	1245833
2015	England	H7N7	Chicken	179865
2015, 2024	Germany	H7N7/N5	Chicken	94983
2016, 2017, 2020, 2025	USA	H7N3/N8/N9	Turkey	197711
2016-2019	China	H7N9	Chicken	745665
2023, 2024	South African	H7N6	Chicken	7484040
2024	New Zealand	H7N6	Chicken	194500
Total				44956051

Human infection with avian influenza viruses

- ➢ A total of 1077 cases of human infection with H5 AIV, with mortality nearly 50%
- ➢ A total of 1568 cases of human infection with H7N9 AIV, with mortality nearly 40%

Human infections with H5 subtype avian influenza virus from 2003 to 2025 （WHO, 2025）

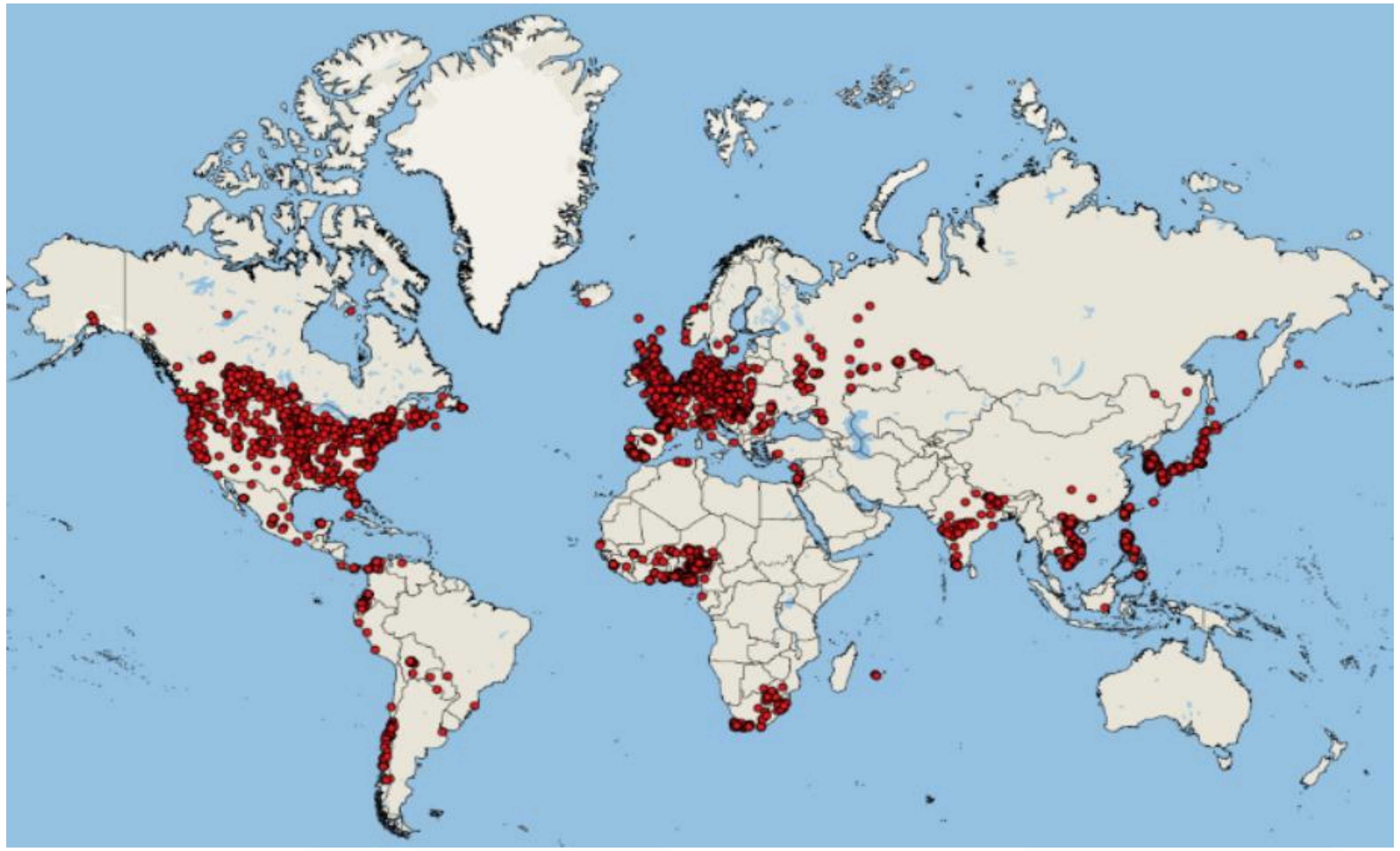
Viruses	Confirmed Cases	Deaths	Mortality (%)
H5N1	976	470	48
H5N2	1	1	100
H5N6	93	57	61
H5N8	7	0	0
Total	1077	508	49



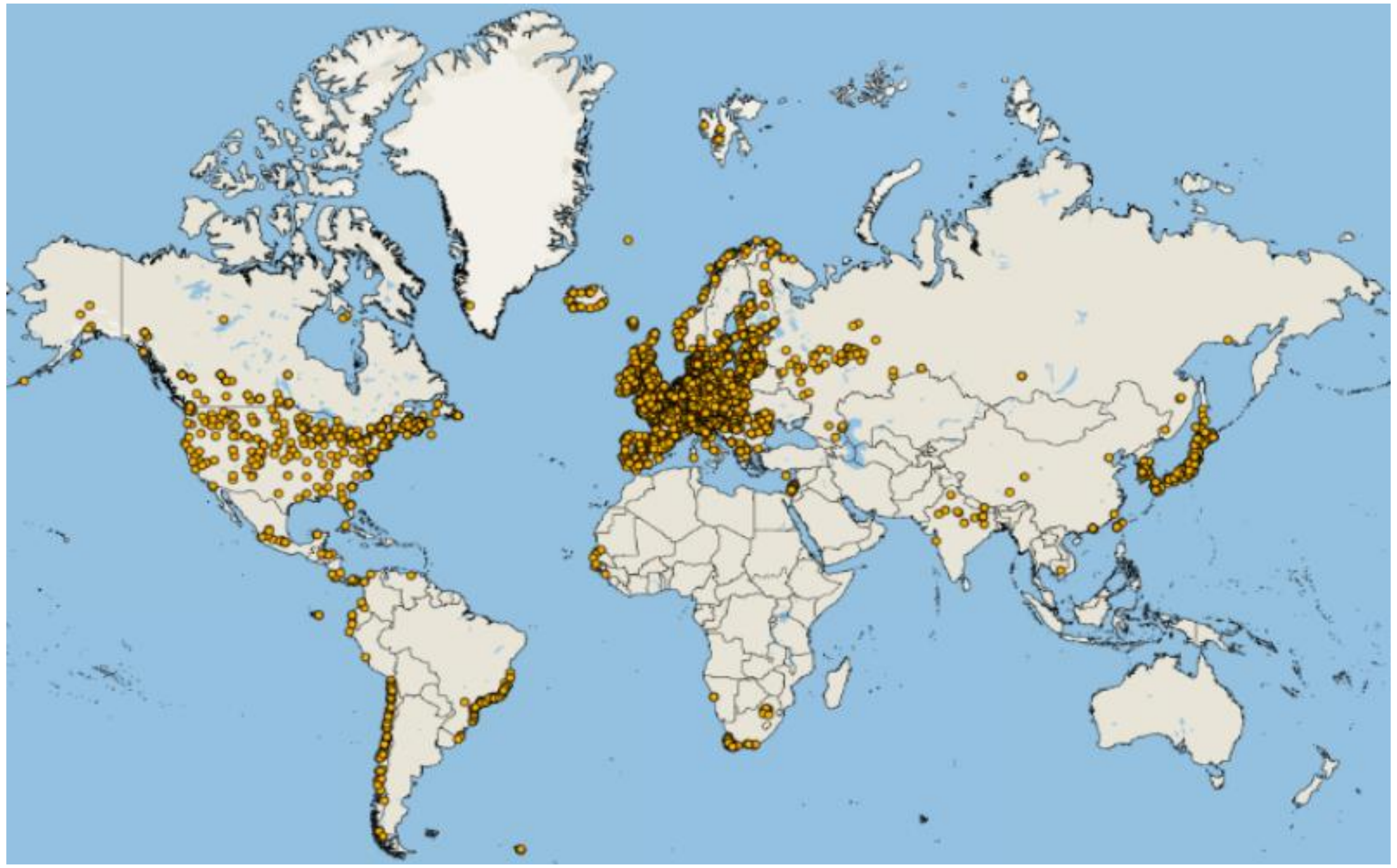
Temporal distribution of human infection with H7N9

H5N1 virus caused over 13,200 outbreaks worldwide by the end of 2023

Poultry, 5,951 outbreaks

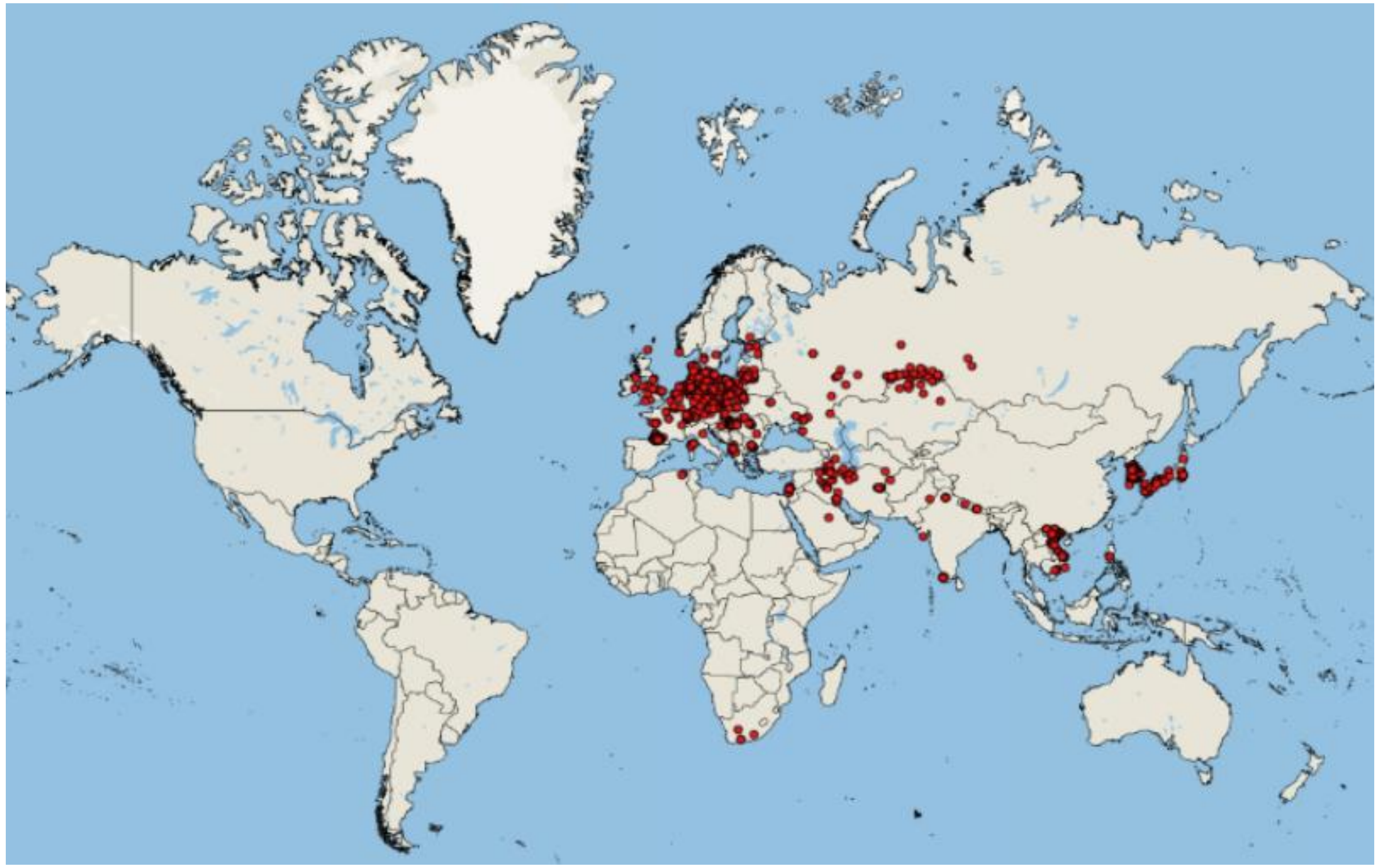


Wild birds, 7,252 outbreaks

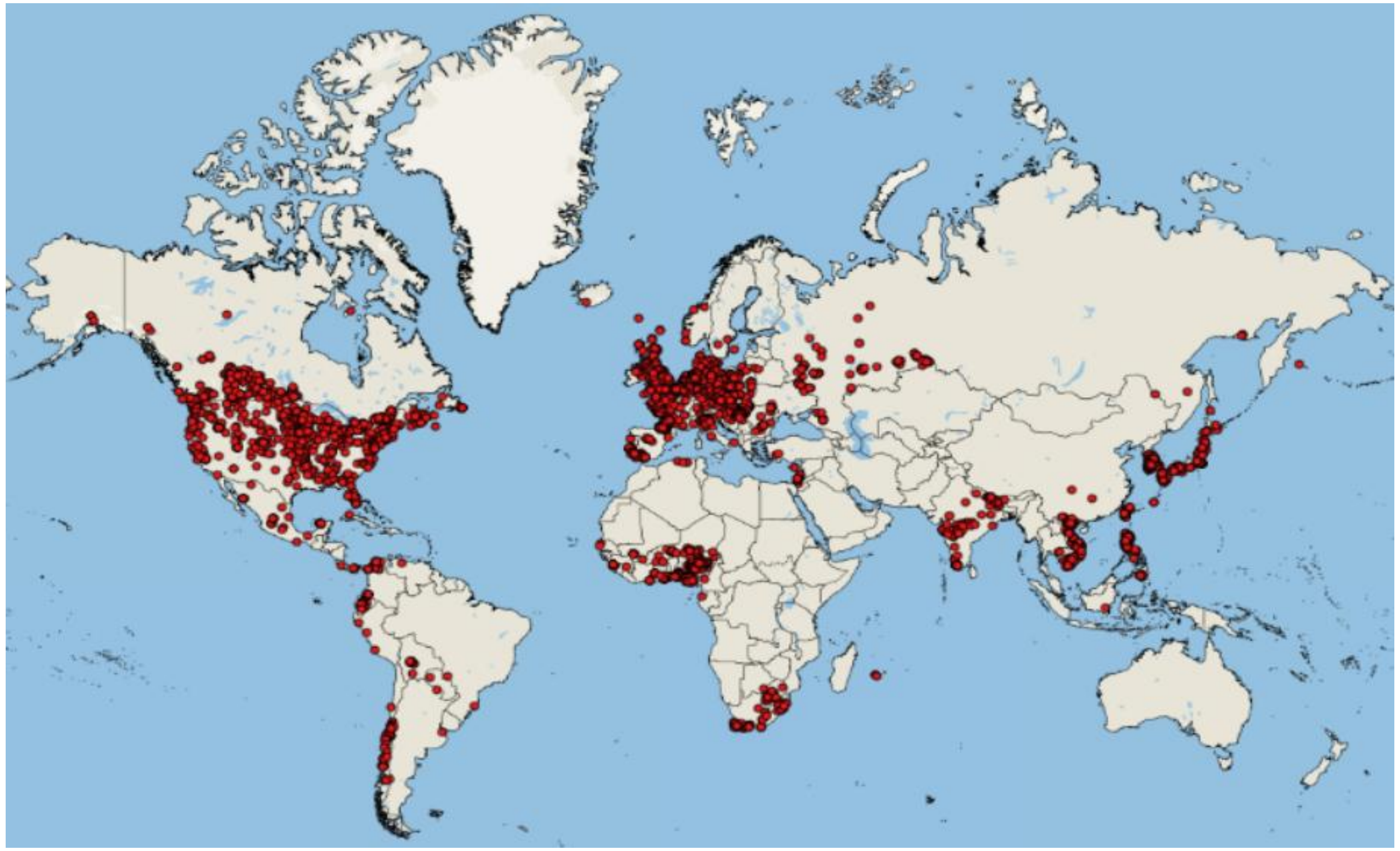


Why are there so few outbreaks in poultry in China?

H5N8 outbreaks in poultry



H5N1 outbreaks in poultry



Highly pathogenic avian influenza control strategies

Countries in Europe and North America

Biosecurity
+
Culling

China (since 2004)

Vaccination
+
Culling

Two examples

- H5 avian influenza control in China
- H7N9 influenza control in China

H5 influenza control in China

Top poultry number and multiple species

Laying chickens: 1.3 billion

Broiler chickens: 17.3billion

Laying duck: 0.2 billion

Meat ducks: 4.2 billion

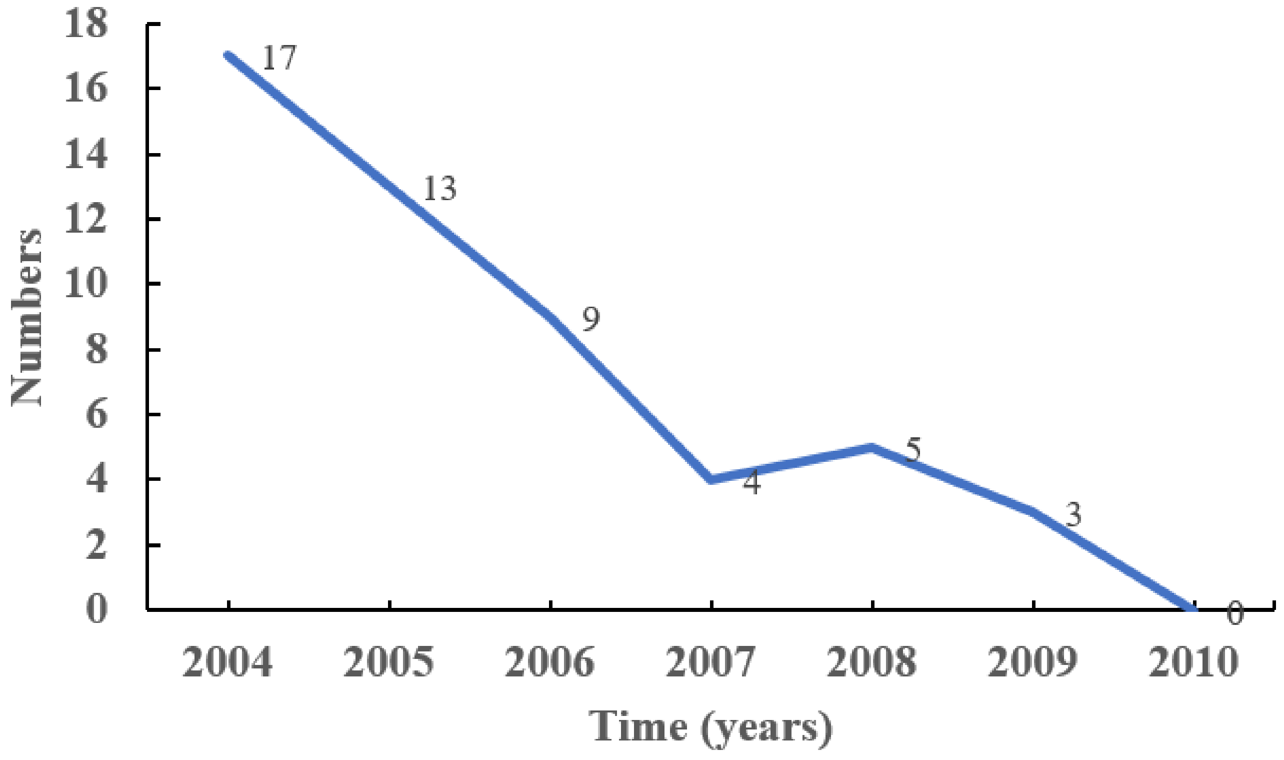
Geese: 0.6 billion

Pigeon

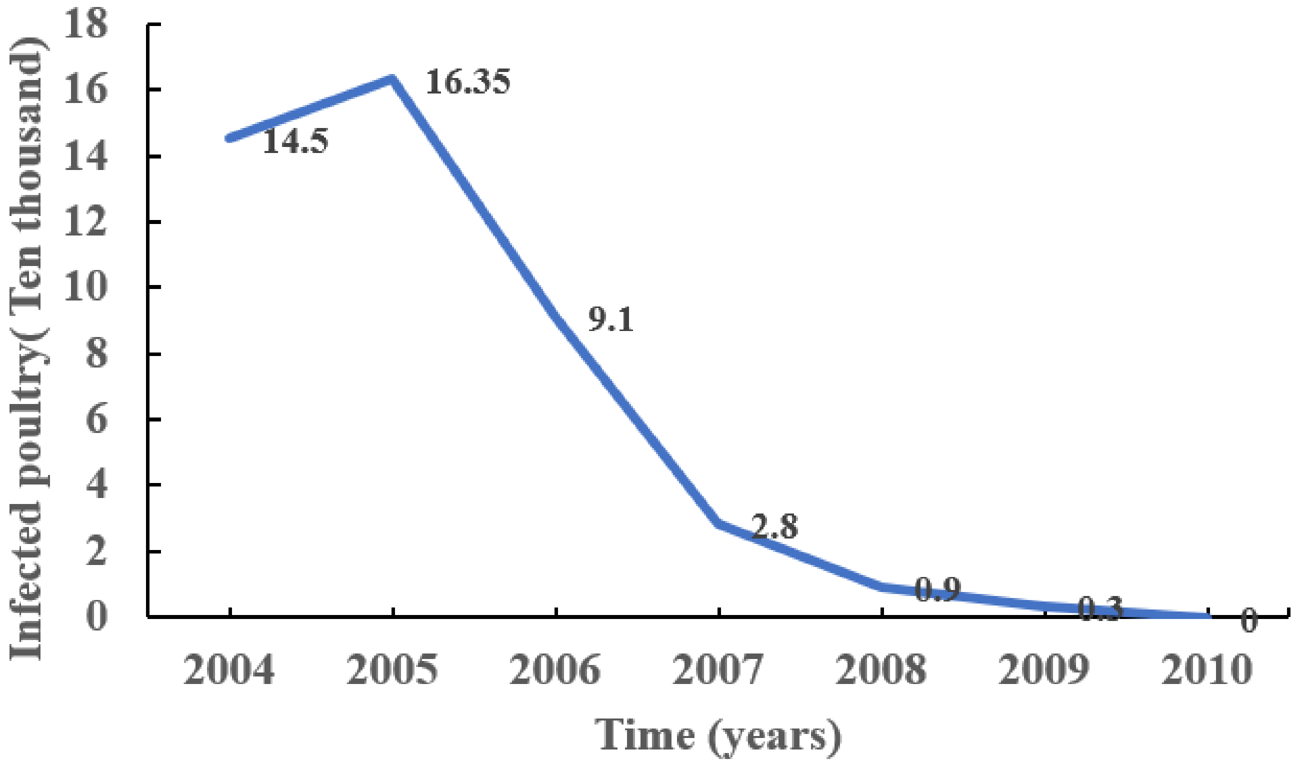
Quails

Outbreaks of H5N1 avian influenza in China, 2004-2010

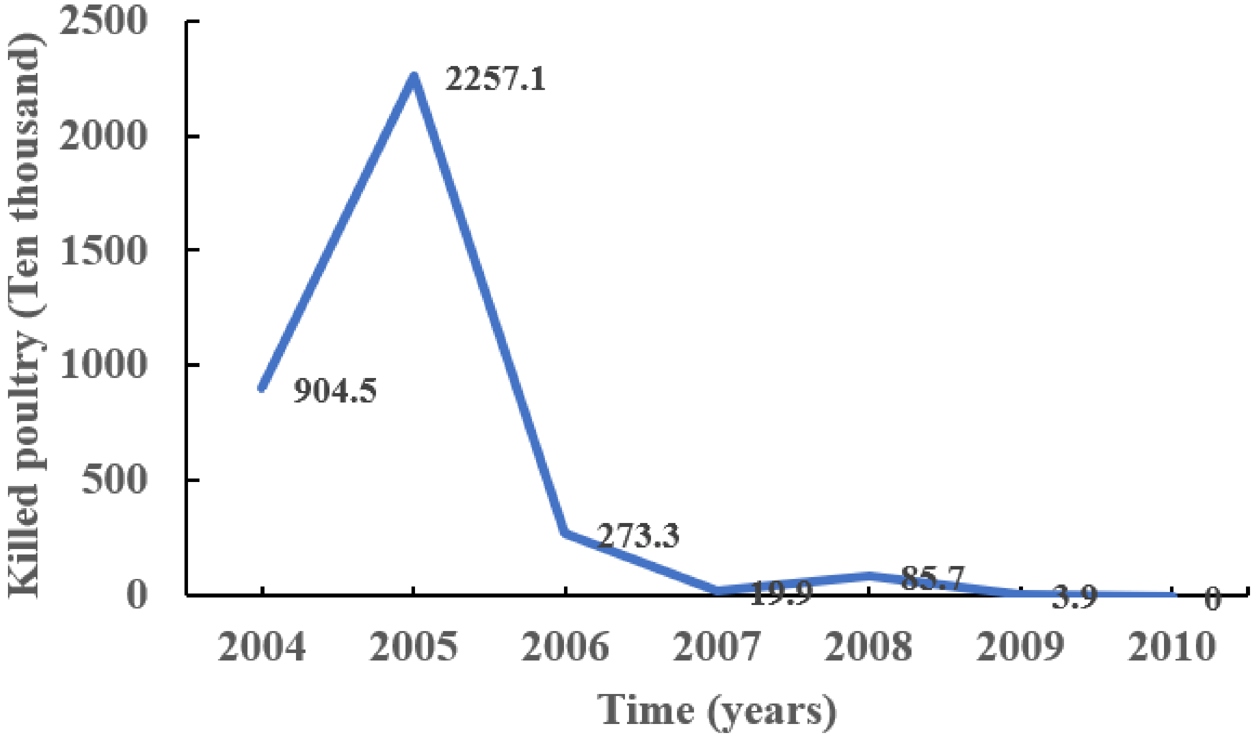
- ➢ H5N1 strain A/goose/Guangdong/1/96 was first isolated in China, Culling
- ➢ In 2004, 50 outbreaks, 17 provinces in China. Culling plus partial vaccination.
- ➢ In 2005, peak of the outbreaks. Culling plus mass vaccination.
- ➢ After 2006, both the number of outbreaks and the scale of depopulation began to decrease.



Distribution of provinces affected by the epidemic



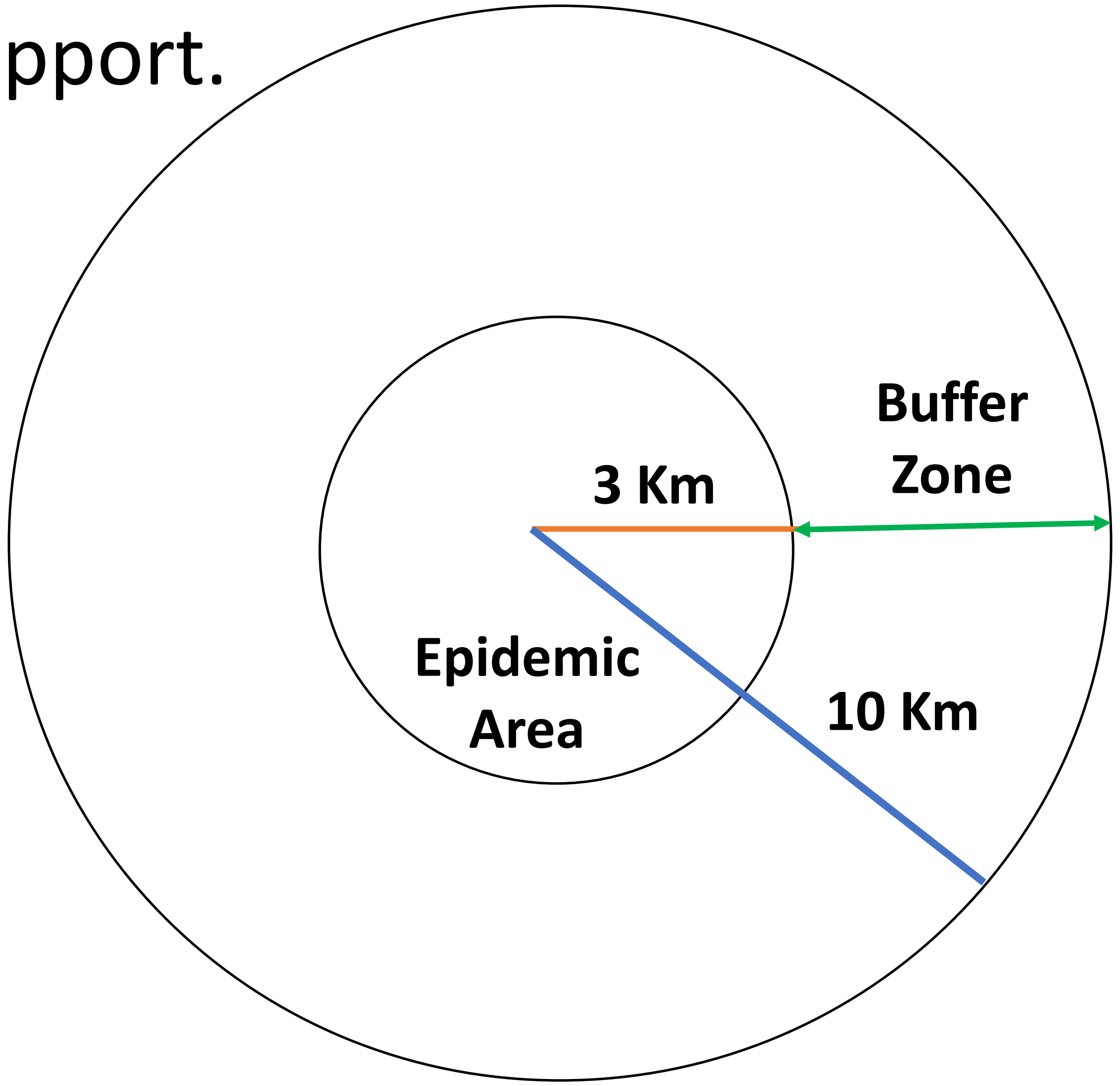
The number of infected poultry



The number of killed poultry

A culling plus vaccination mixed strategy

- Poultry within a 3 kilometer radius should be depopulated. Live bird market within a 10 kilometer radius will be shut down.
- Poultry in the buffer zone should be vaccinated, the government provided financial support.



Division of epidemic areas and buffer zones

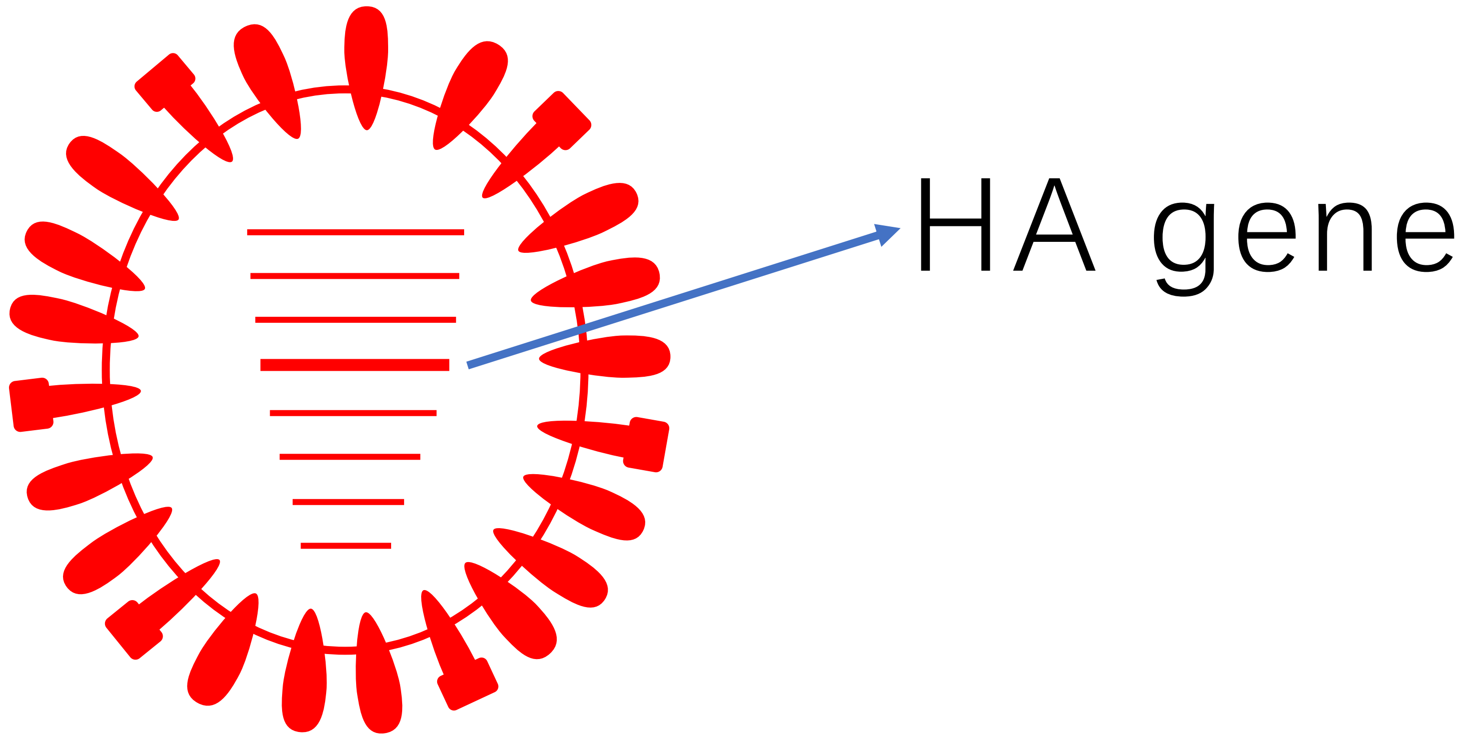
Isolation and quarantine in the epidemic areas

Poultry depopulation

Vaccination

Key issues for a successful vaccination strategy

- Influenza virus mutates easily, and mutation of the HA gene often causes antigenic variation, which compromises the protective efficacy of vaccine
- Therefore, it is important to make sure that the vaccine matches the circulating virus



Surveillance and analysis of circulating viruses

- Active surveillance in wild birds and domestic poultry to monitor the newly introduced viruses (More than 50,000 samples per year)
- Comparison of the antigenic properties between the newly detected target virus and the vaccine seed virus, if a clear difference is observed, the vaccine will be updated

WOAH/FAO/National Avian Influenza Reference Laboratory

中国农业科学院哈尔滨兽医研究所
HARBIN VETERINARY RESEARCH INSTITUTE , CAAS

National Avian Influenza Professional Laboratory

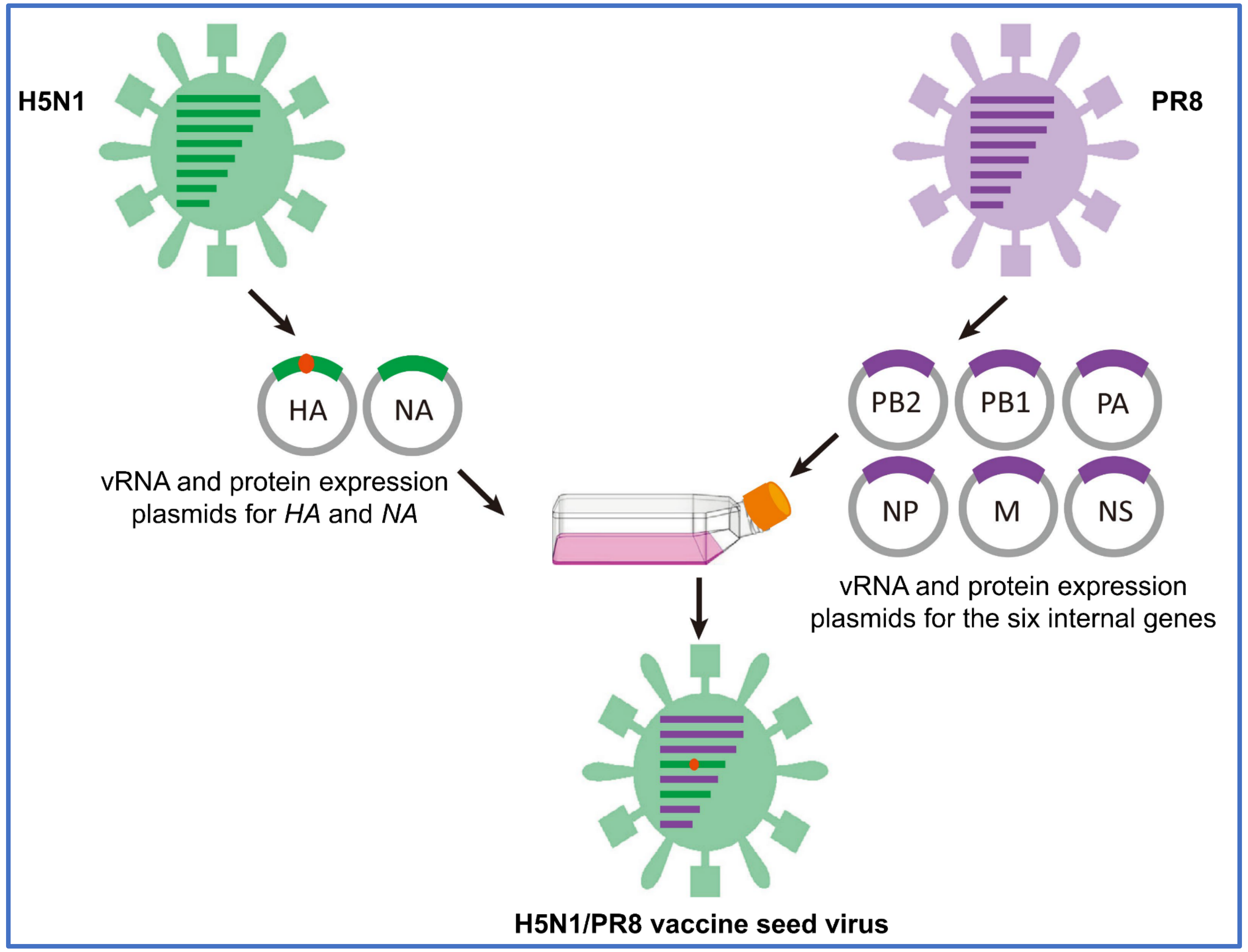
中国动物卫生与流行病学中心
China Animal Health And Epidemiology Center

揚州大學
YANGZHOU UNIVERSITY

華南農業大學
South China Agricultural University

Inactivated vaccine development platform

Vaccine seed virus generation by reverse genetics



Tian et al., Virology, 2005

An ideal vaccine seed virus can be generated within a week

A large number of migratory birds fly over China every year, and they introduced different H5 influenza viruses into China in the past years by close contact with waterfowls

Viruses carrying different clades or subclades of HA isolated in China in the past two decades

Year	Subtype/clade	Representative strain
2005	H5N1/clade 2.2	A/bar-headed goose/Qinghai/3/2005
2006	H5N1/clade 7.2	A/chicken/Shanxi/2/2006
2006	H5N1/clade 2.3.4	A/duck/Anhui/1/2006
2010	H5N1/clade 2.3.2	A/duck/goose/S1322/2010
2013	H5N1/clade 2.3.4.4g	A/chicken/Guizhou/4/2013
2017	H5N6/clade 2.3.4.4h	A/duck/Guizhou/S4184/2017
2017	H5N1/clade 2.3.2.1f	A/chicken/Liaoning/SD007/2017
2020	H5N8/clade 2.3.4.4b	A/whooper swan/SX/4-1/2020
2021	H5N1/clade2.3.4.4b	A/wild duck/Hebei/SD012/2021

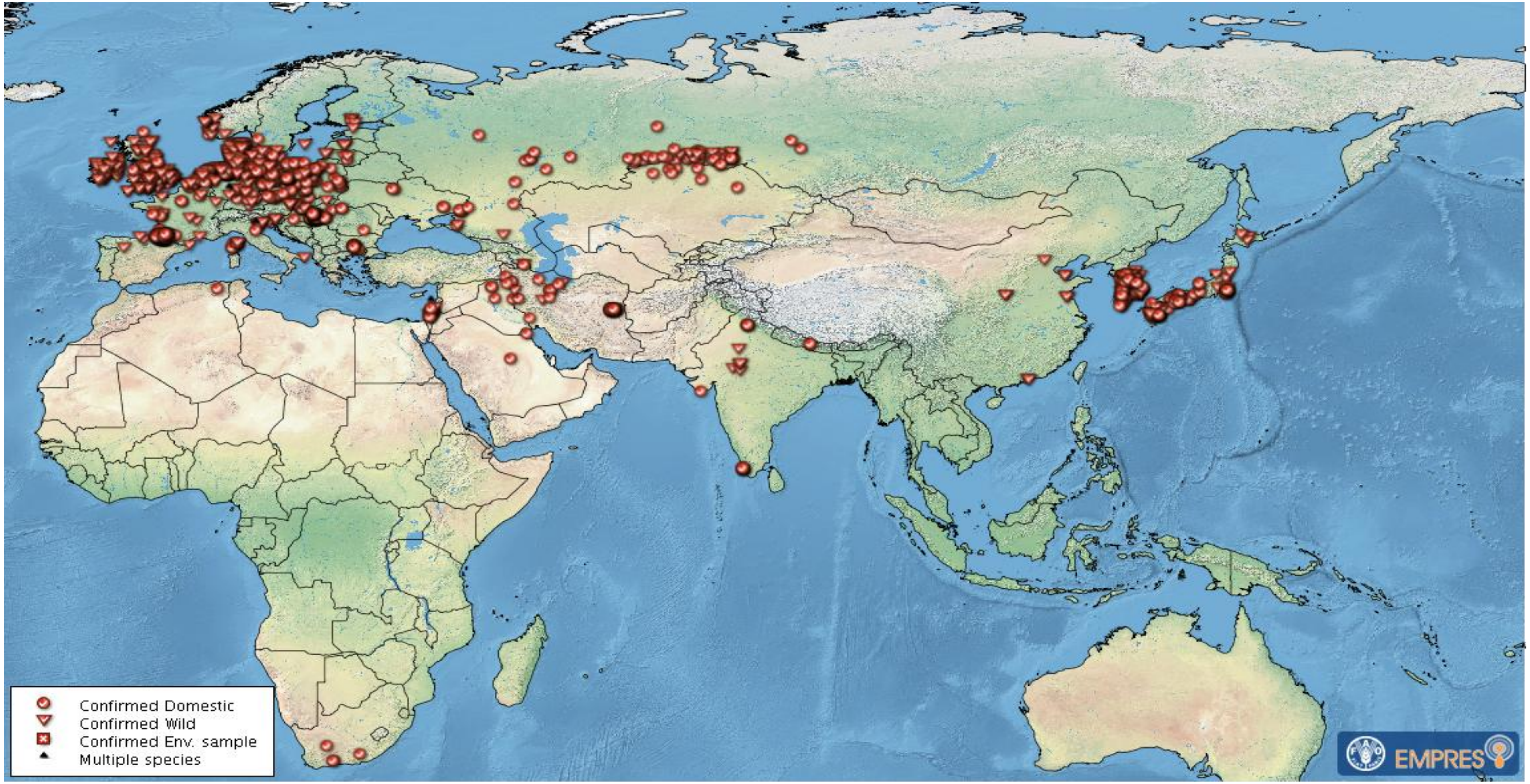
Ten H5 vaccine seed viruses have been used in China Since 2004

Seed virus	HA donor virus (clade)	Application period	Complete protection against the clade of
H5-Re1	GD/GD/1/1996(H5N1) (0)	03/2004–03/2008	0, 1, 2.2, 2.3.4
H5-Re4	CK/SX/2/2006(H5N1) (7.2)	07/2006–04/2014	7.2
H5-Re7	CK/LN/S4092/2011(H5N1) (7.2)	04/2014–09/2017	7.2
H5-Re6	DK/GD/S1322/2010(H5N1) (2.3.2)	06/2012–09/2017	2.3.2
H5-Re12	CK/LN/SD007/2017(H5N1) (2.3.2.1f)	12/2018–12/2021	2.3.2.1f
H5-Re5	DK/AH/1/2006(H5N1) (2.3.4)	03/2008–06/2012	2.3.4
H5-Re8	CK/GZ/4/2013(H5N1) (2.3.4.4g)	12/2015–12/2018	2.3.4.4g
H5-Re11	DK/GZ/S4184/2017(H5N6) (2.3.4.4h)	12/2018–12/2021	2.3.4.4h
H5-Re13	DK/FJ/S1424/2020	01/2022-	2.3.4.4h
H5-Re14	WH/SX/4-1/2020	01.2022-	2.3.4.4b

Several clades of H5 viruses have been eradicated in China through vaccination

Seed virus	HA donor virus (clade)	Application period	Complete protection against the clade of	Virus eliminated in China
H5-Re1	GD/GD/1/1996(H5N1) (0)	03/2004–03/2008	0, 1, 2.2, 2.3.4	Yes
H5-Re4	CK/SX/2/2006(H5N1) (7.2)	07/2006–04/2014	7.2	Yes
H5-Re7	CK/LN/S4092/2011(H5N1) (7.2)	04/2014–09/2017	7.2	
H5-Re6	DK/GD/S1322/2010(H5N1) (2.3.2)	06/2012–09/2017	2.3.2	Yes
H5-Re12	CK/LN/SD007/2017(H5N1) (2.3.2.1f)	12/2018–12/2021	2.3.2.1f	
H5-Re5	DK/AH/1/2006(H5N1) (2.3.4)	03/2008–06/2012	2.3.4	Yes
H5-Re8	CK/GZ/4/2013(H5N1) (2.3.4.4g)	12/2015–12/2018	2.3.4.4g	Yes

Clade 2.3.4.4b H5N8 viruses caused numerous outbreaks in other countries in 2020



Surveillance performed from Sept. 2020 to June 2021

Samples collected		H5N8 viruses isolated
Wild bird	317	22
Duck	13,908	8
Goose	1,552	6
Pigeon	189	0
Chicken	25,532	0
Total	41,172	36

The newly introduced H5N8 viruses shows clear antigenic difference with the previously used vaccines H5-Re11 and H5-Re12

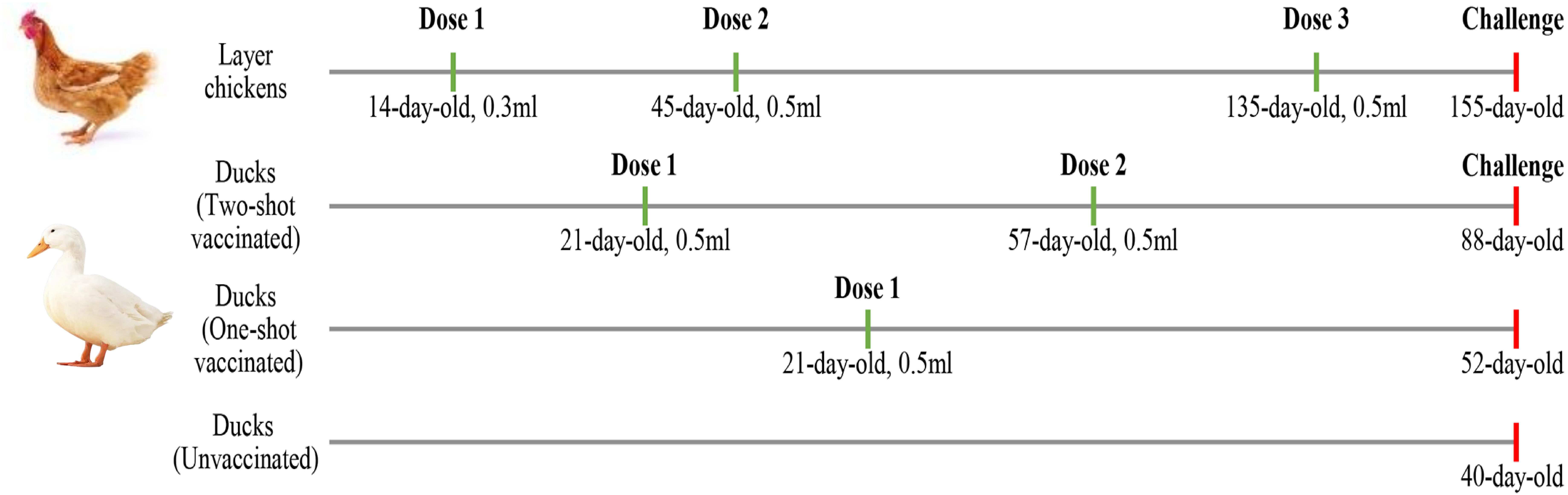
Virus	HA clade	HI antibody titer of antiserum	
		H5-Re11	H5-Re12
H5-Re11	2.3.4.4h	**512**	32
H5-Re12	2.3.2.1f	16	**512**
WS/SX/4-1/2020(G1)	2.3.4.4b	16	8
BS/BJ/1/2021(G1)	2.3.4.4b	16	8
GS/HuN/S11288/2021(G1)	2.3.4.4b	16	8
WS/SD/SC195/2021(G2)	2.3.4.4b	16	8

Cui et al., SCLS, 2022

The first H5N8 strain:
A/swan/Shanxi/4-1/2020 (H5N8)

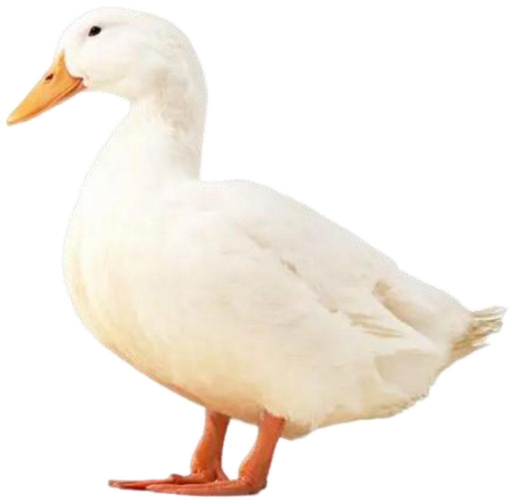
Could Re11+Re12 vaccinated poultry be well protected against this newly invasive virus?

Poultry from different farms (routinely vaccinated or unvaccinated) were challenged with H5N8 virus in the laboratory setting



Cui et al., SCLS, 2022

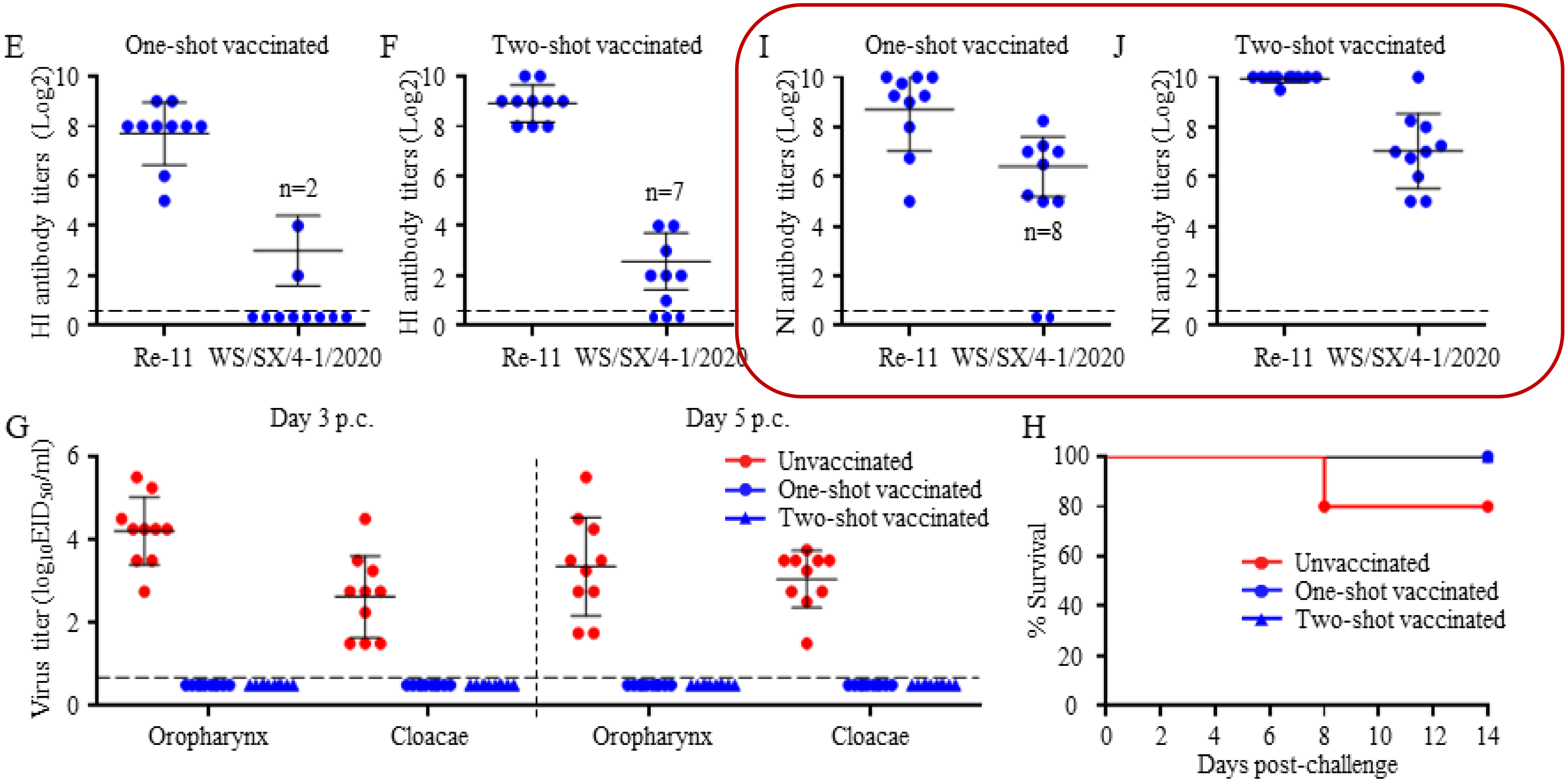
Vaccinated poultry were completely protected against the newly introduced H5N8 virus challenge



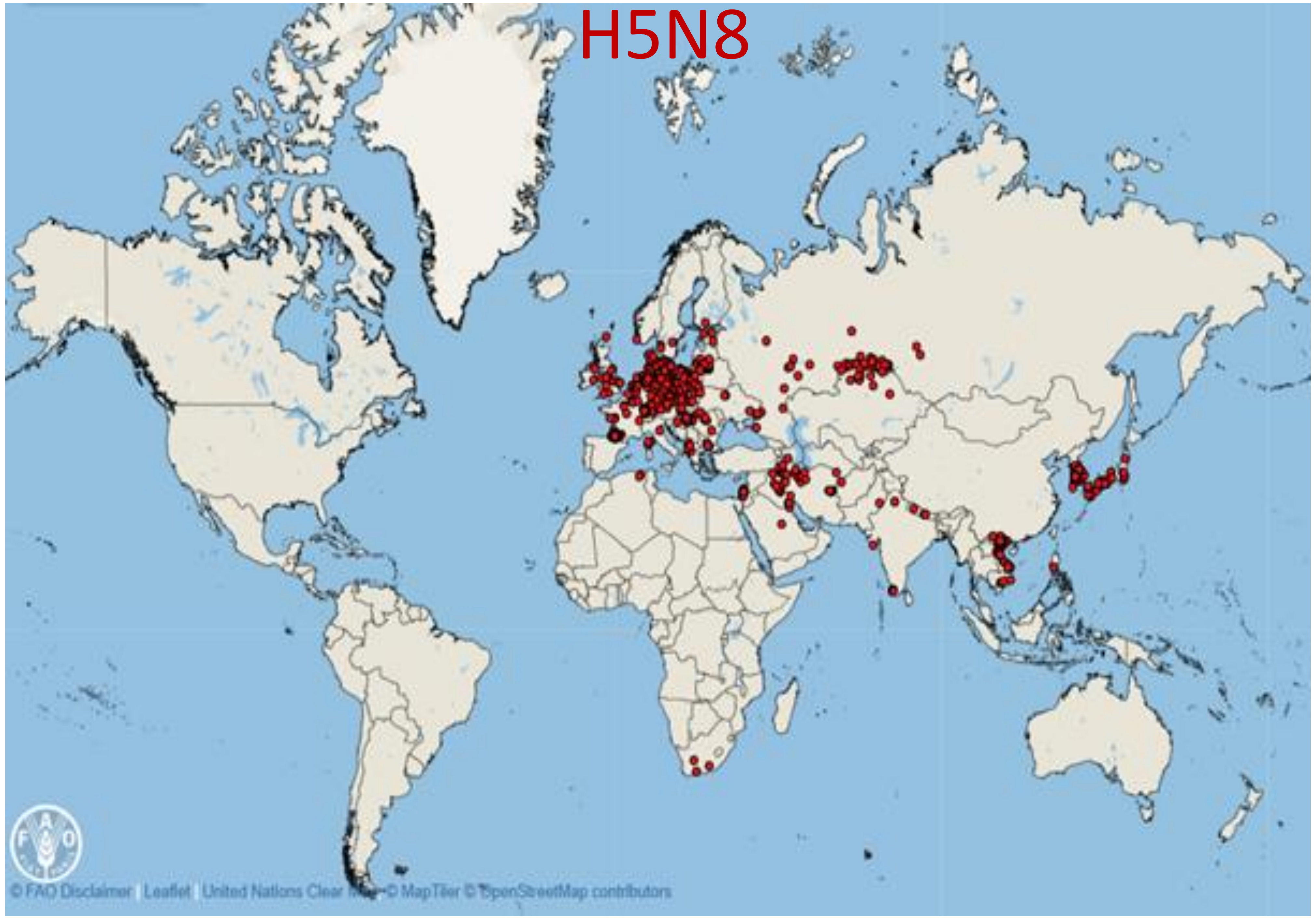
Group	Virus shedding (shedding/total)				Shedding/ Total	Survival /Total
	Day 3 post challenge		Day 5 post challenge			
	Oropharynx	Cloacae	Oropharynx	Cloacae		
Vaccinated layer chickens (three doses)	0/10	0/10	0/10	0/10	0/10	10/10
SPF chickens	10/10	10/10	/	/	10/10	0/10
Vaccinated ducks (one dose)	0/10	0/10	0/10	0/10	0/10	10/10
Vaccinated ducks (two doses)	0/10	0/10	0/10	0/10	0/10	10/10
Unvaccinated ducks	10/10	10/10	10/10	10/10	10/10	8/10

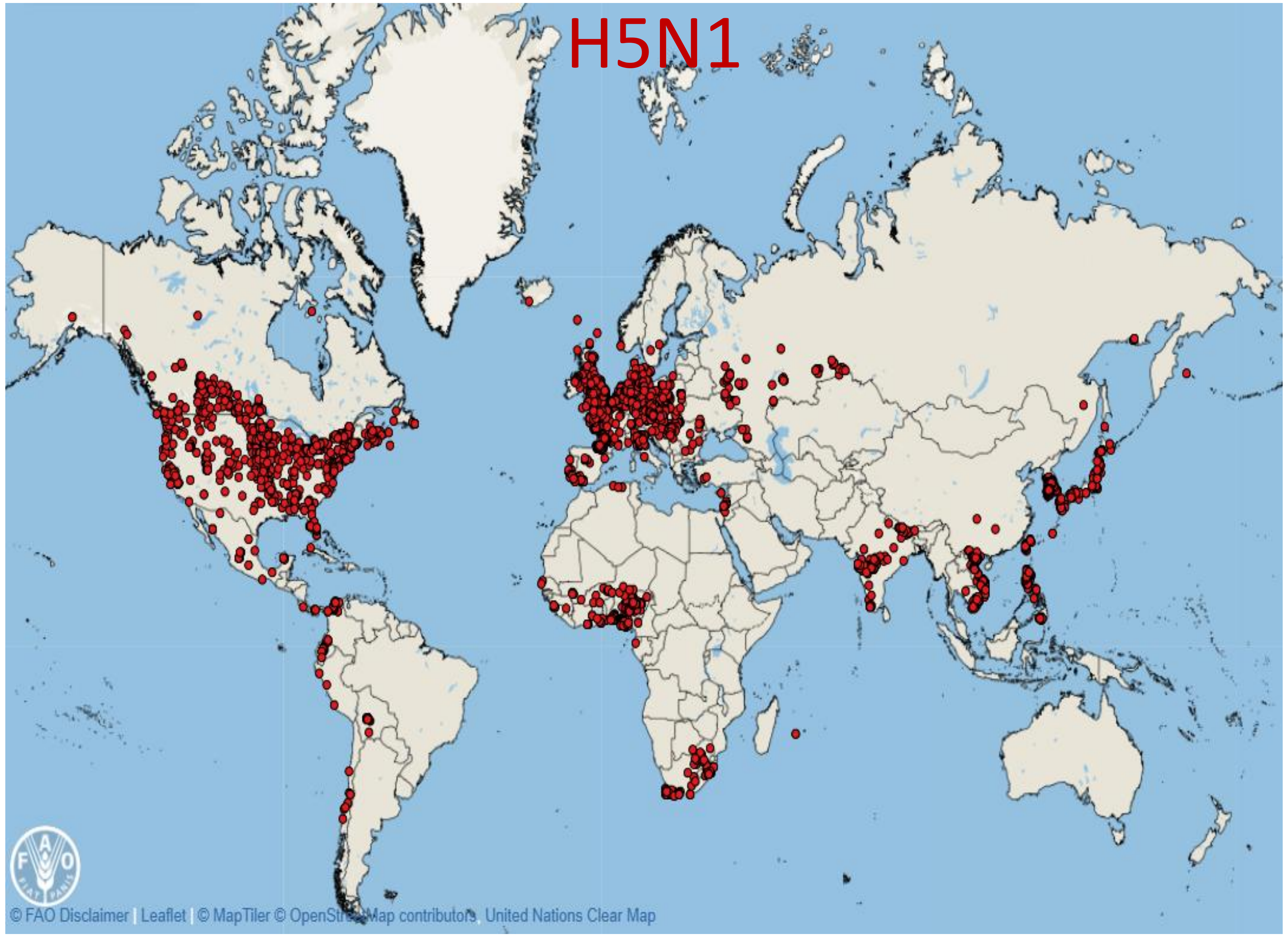
Cui et al., SCLS, 2022

Vaccinated ducks have low level of HI antibodies but high level of neutralization antibodies



Over 311 million poultry died or were destroyed due to H5 virus infection from 2020 to 2023, but Mainland China lost <10, 000 poultry during this period

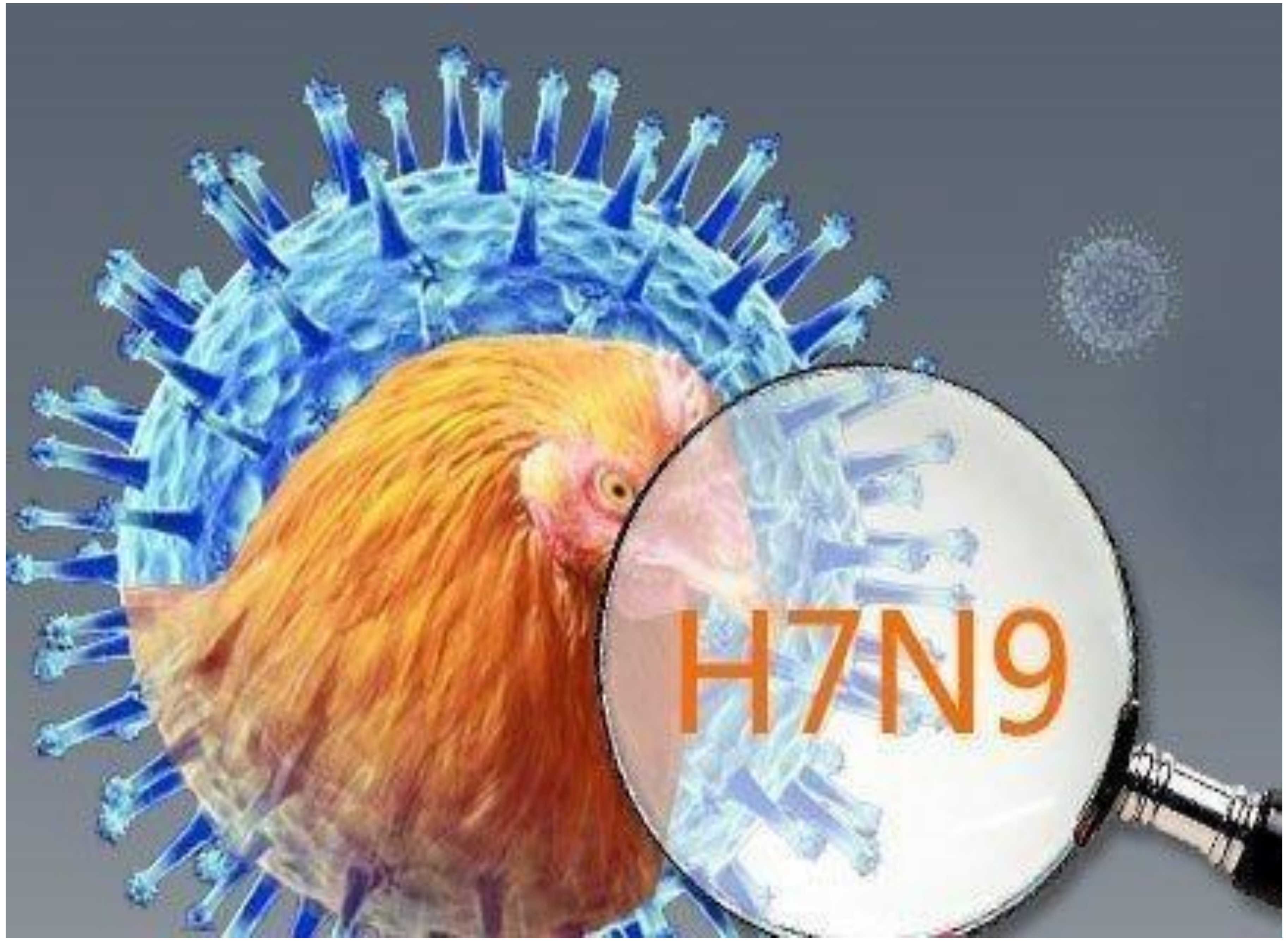




The H5 vaccine seed viruses have been updated in 2022, even though the previous vaccine could still provide complete protection against the emerging H5N8 virus

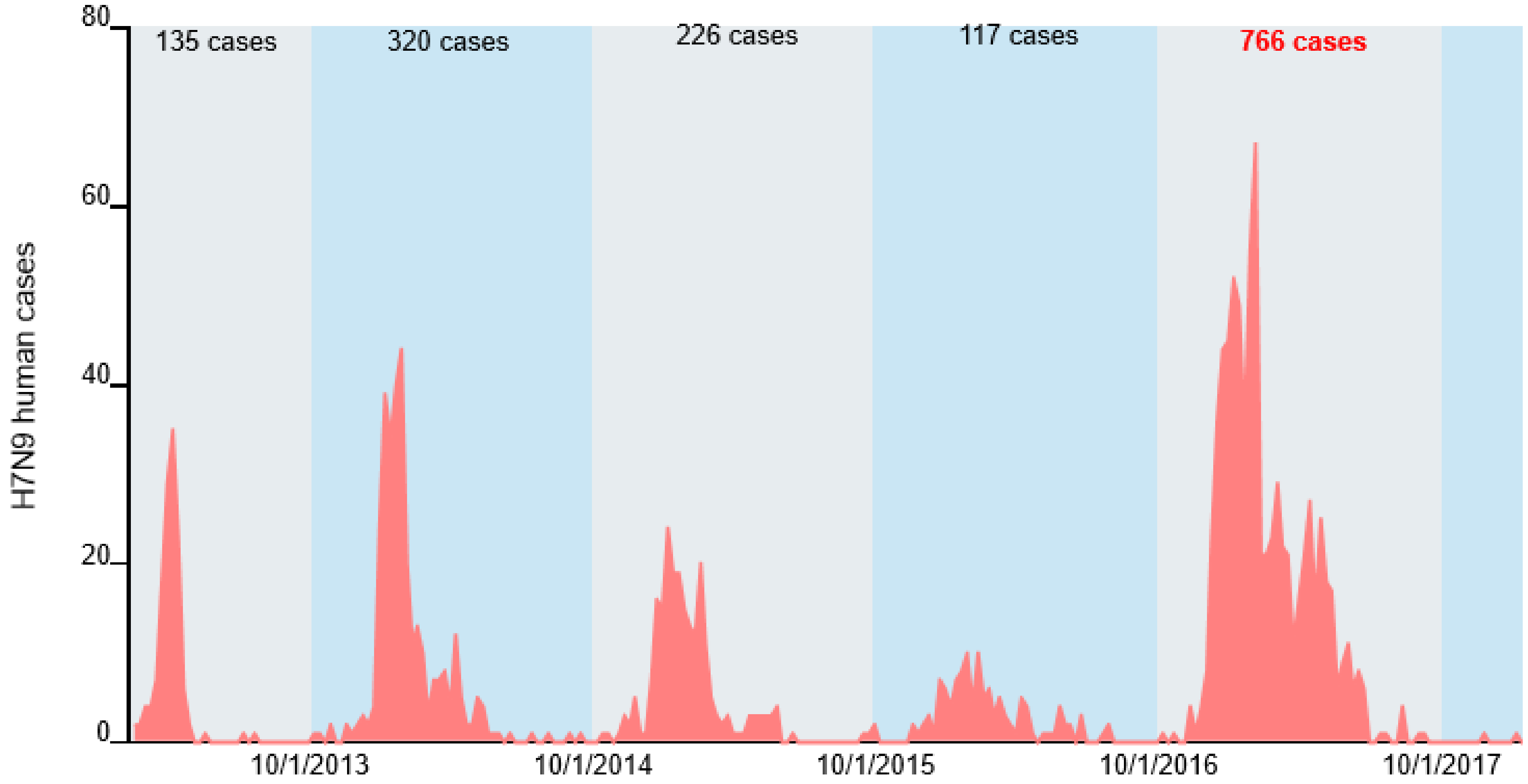
Seed virus	HA donor virus (clade)	Application period	Complete protection against the clade of
H5-Re13	DK/FJ/S1424/2020(H5N6) (2.3.4.4h)	01/2022–	2.3.4.4h
H5-Re14	WH/SX/4-1/2020(H5N8) (2.3.4.4b)	01/2022–	2.3.4.4b

Control of H7N9 virus in China



Damage to humans caused by H7N9 viruses in China

- In March 2013, three cases of human infection with H7N9 virus were reported.
- The virus caused over 1,560 human infections in five waves from March 2013 to September 2017, with a mortality rate of nearly 40%.



Li C and Chen H, Cold Spring Harb Perspect Med, 2021

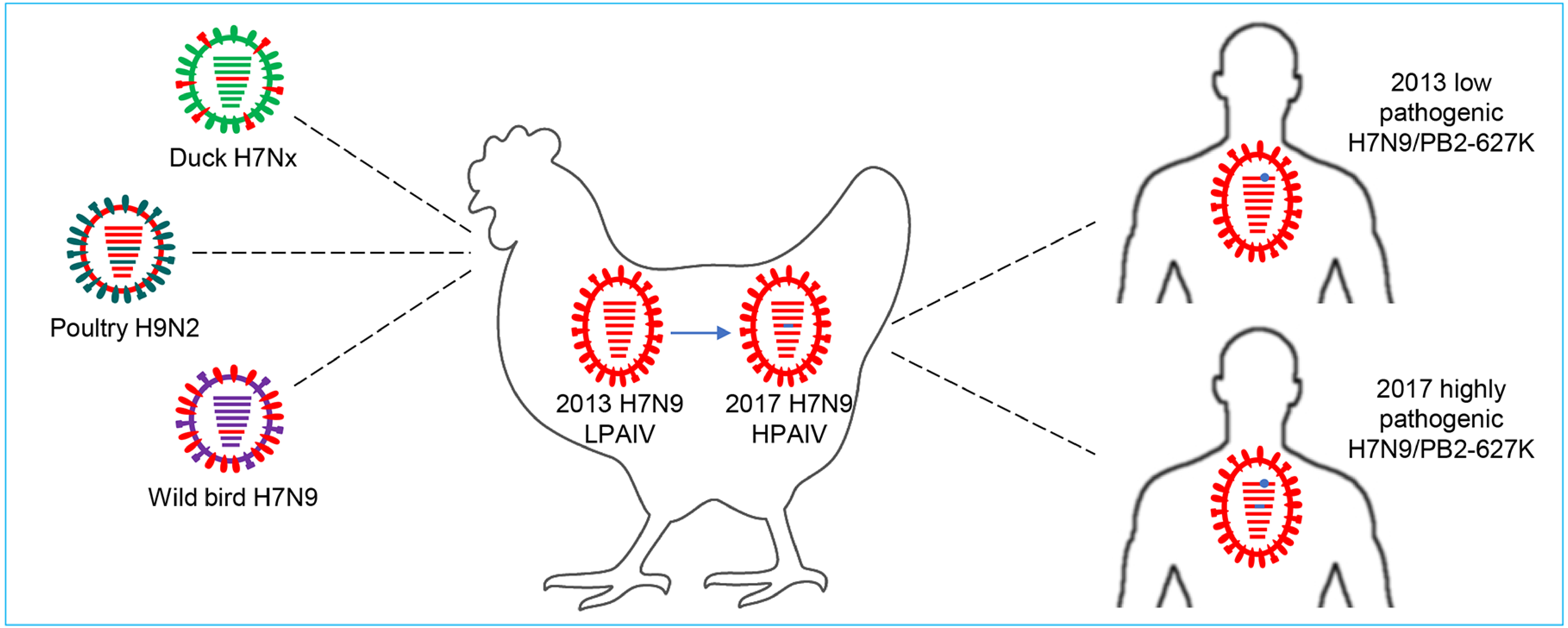
Damage to poultry industry caused by H7N9 viruses in China

- Live birds markets (LBM) have played pivotal roles in the genesis of novel AIVs
- Tons of uninfected poultry and poultry products were destroyed.
- Periodic closure of the LBMs resulted in a 79% and 92% decrease in detection and isolation rates

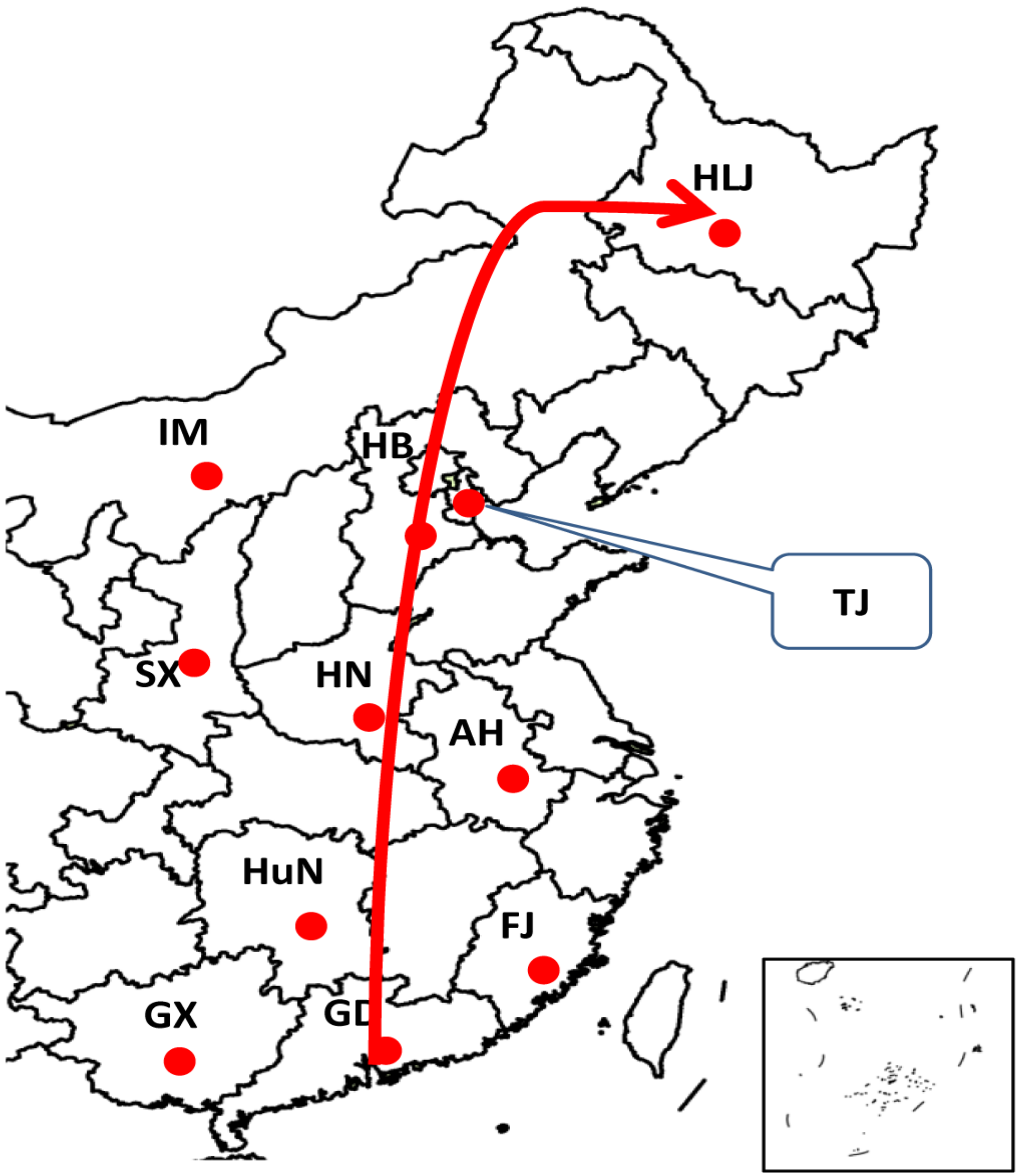
Live bird markets with multiple poultry species

Evolution, biological properties, and pathogenicity of H7N9 avian influenza viruses

- ➢H7N9 LPAIV is a reassortment virus originating from duck, poultry and wild bird viruses
- ➢After adaption in chicken, the H7N9 LPAIV acquired the mutation in HA to form H7N9 HPAIV. Both human viruses have the PB2 E627K mutation



The H7N9 highly pathogenic viruses caused severe disease outbreaks in layer chickens from March to August in 2017 in eight provinces, and several millions of the birds were destroyed to control the outbreaks



Shi et al, Cell Research, 2017

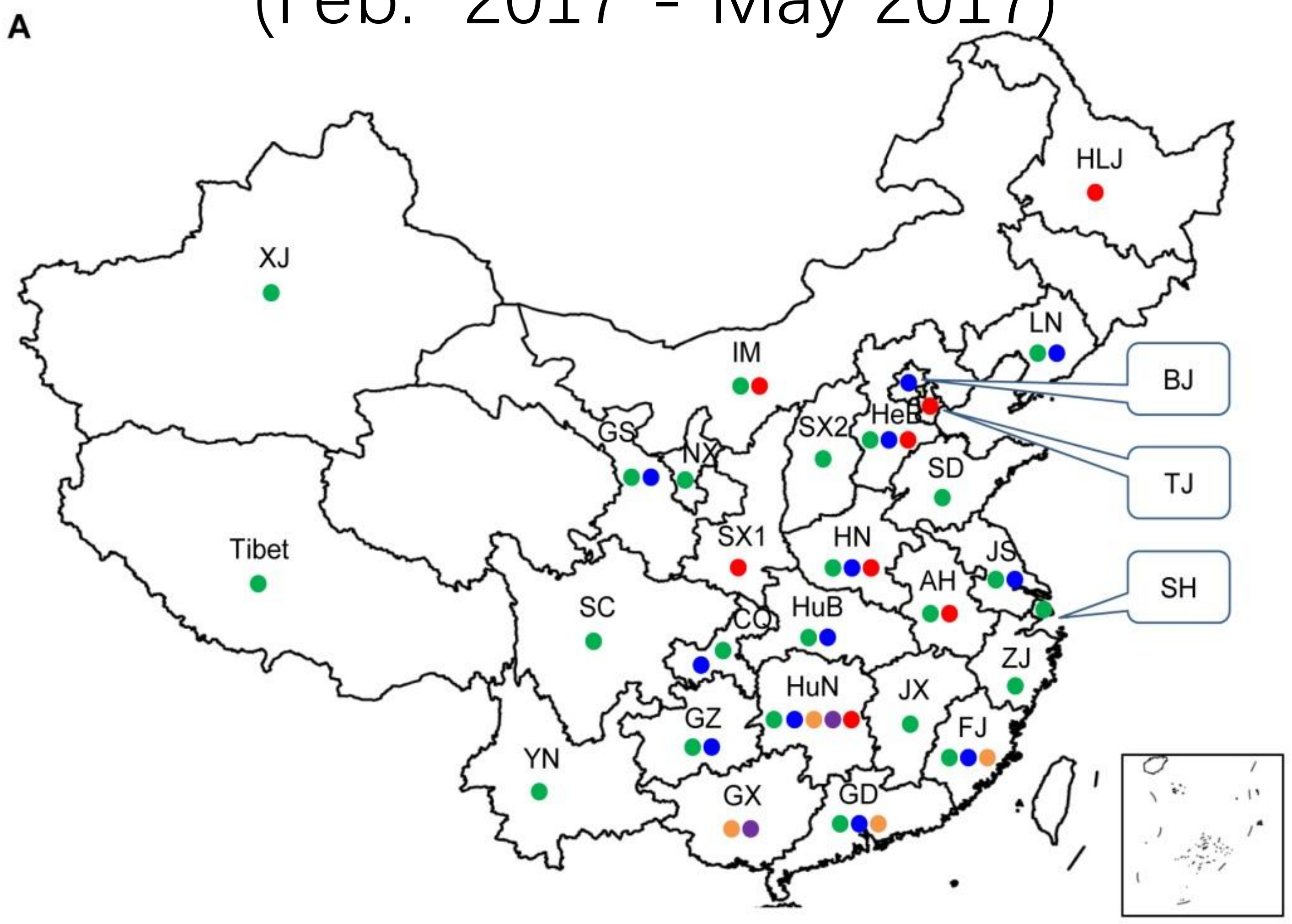
- In September 2017, the control strategy of H7N9 influenza was changed from “stamping-out” to “massive vaccination”, and an H5+H7 bivalent vaccine was started to be used to control both H5 and H7 avian influenza in China

Shi et al, Cell Host & Microbe, 2018

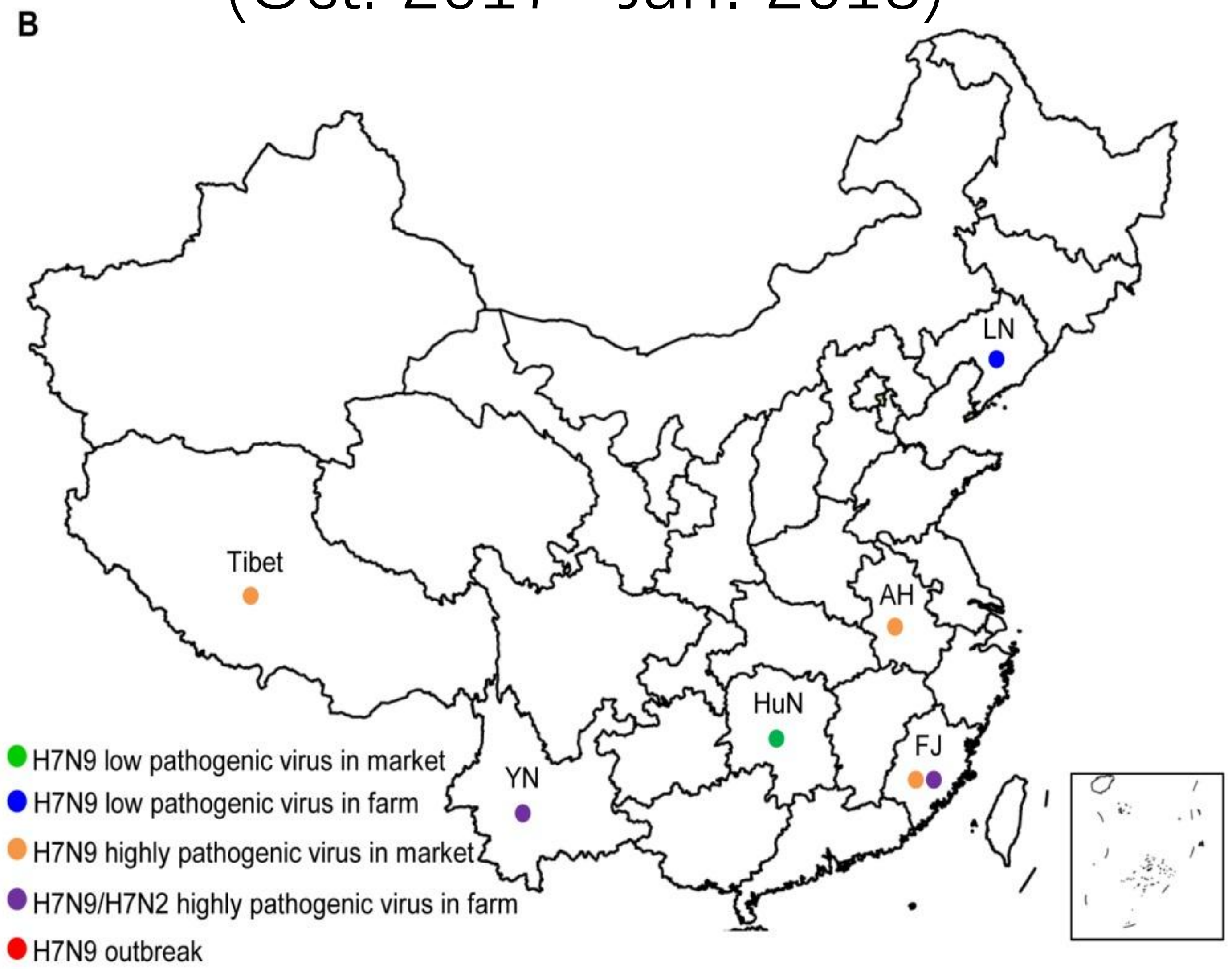
Vaccination dramatically prevented the prevalence of H7N9 virus in poultry

- The isolation rate of H7N9 virus in poultry was immediately reduced by 93.3% after birds were inoculated with the H5/H7 vaccine

Pre-vaccination
(Feb. 2017 - May 2017)

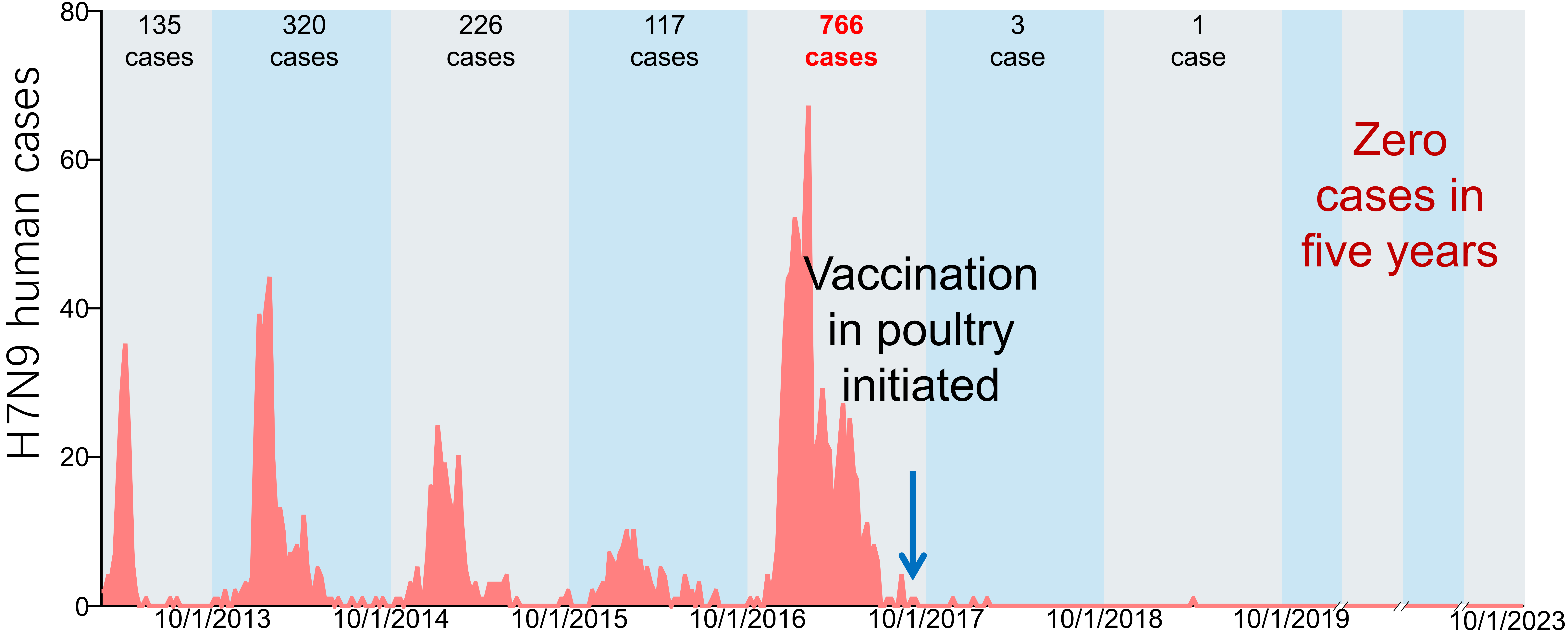


Post-vaccination
(Oct. 2017- Jan. 2018)



Shi et al, Cell Host & Microbe, 2018

Vaccination of poultry successfully eliminated human infection with H7N9 virus



Challenge and solutions

1. A large number of wild birds come into contact with domestic birds

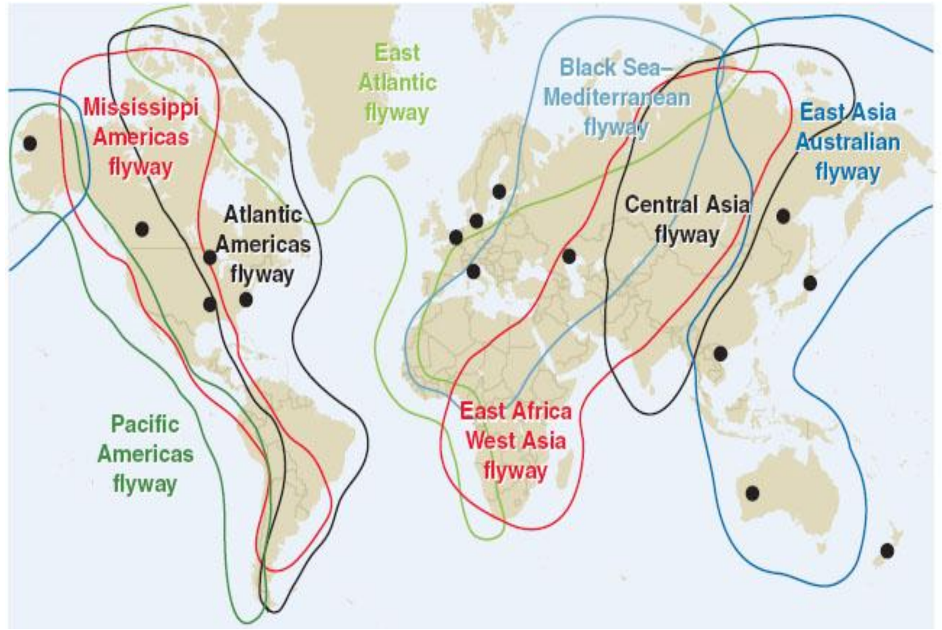
–Active surveillance, Enhanced biosecurity measures

2. Small poultry farms with limited biosecurity and high poultry densities

– Raise the requirements for breeding condition (Facility, environment, etc)

3. Live bird Markets and long distance transportation

–Period closure and disinfection, enhanced quarantine measures



Migratory routes of wild birds

Large-scale layer chicken farm

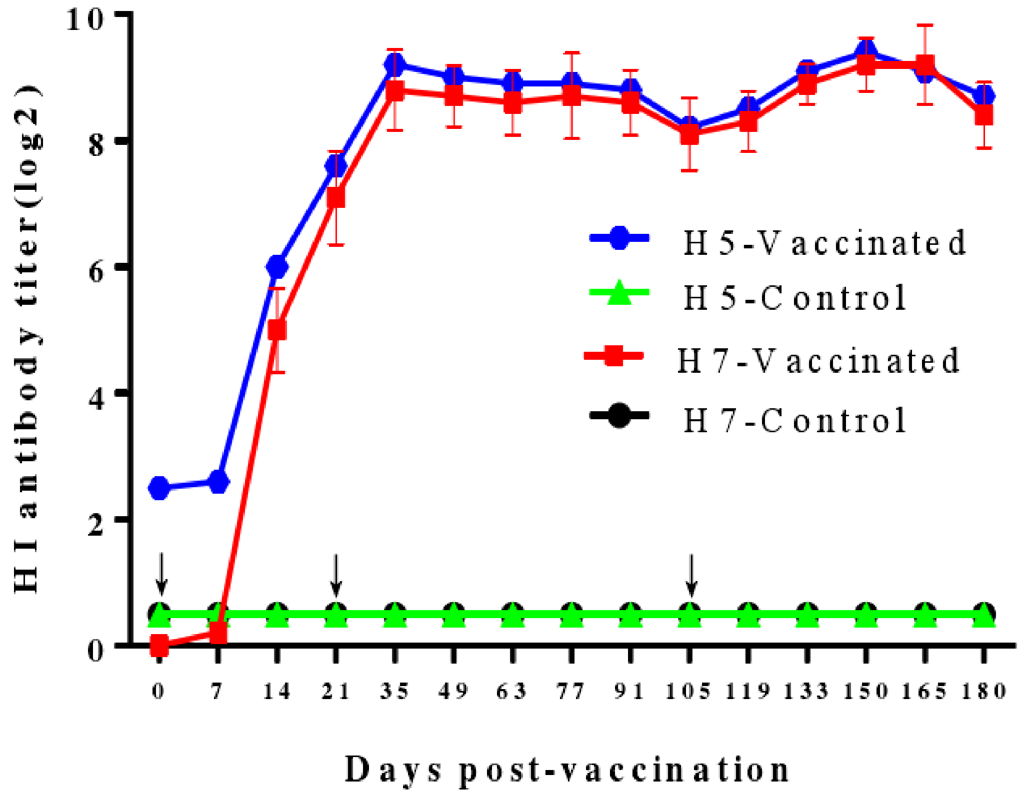
Well-regulated Live bird markets

4. Low vaccination coverage rates (30-50%) in waterfowl

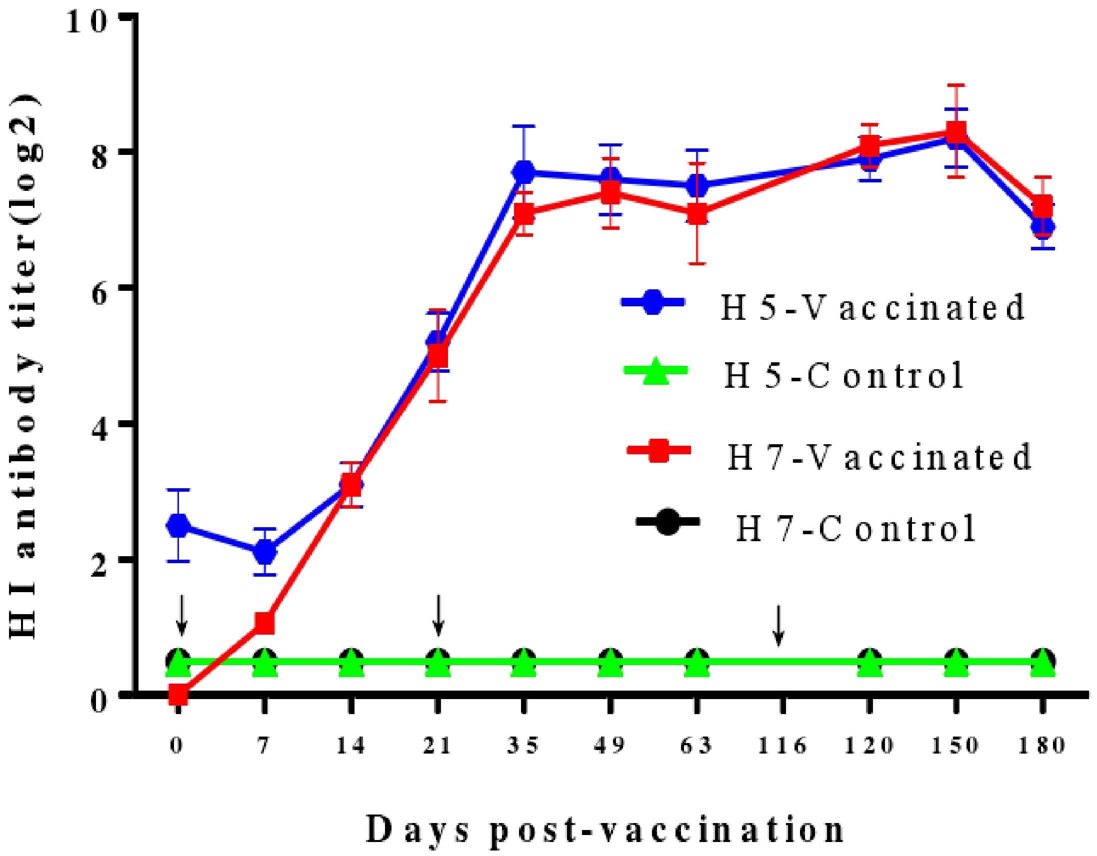
– Increased detection coverage of HI antibody in waterfowl

5. Waterfowl exhibit a lower immune response compared to chickens

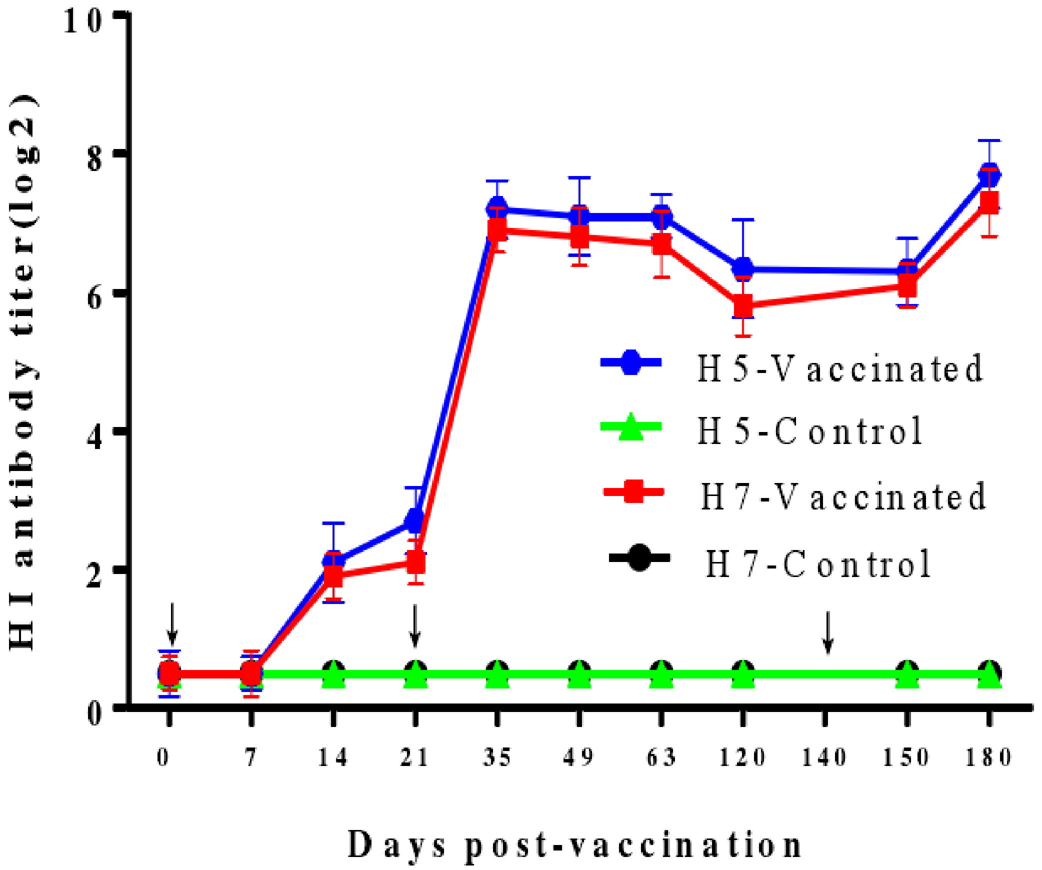
– Development of new vaccine: recombinant duck enteritis virus vector vaccine



HI antibody levels in vaccinated layer chickens



HI antibody levels in vaccinated layer ducks



HI antibody levels in vaccinated gooses

6. Rapid viral evolution under vaccination pressure

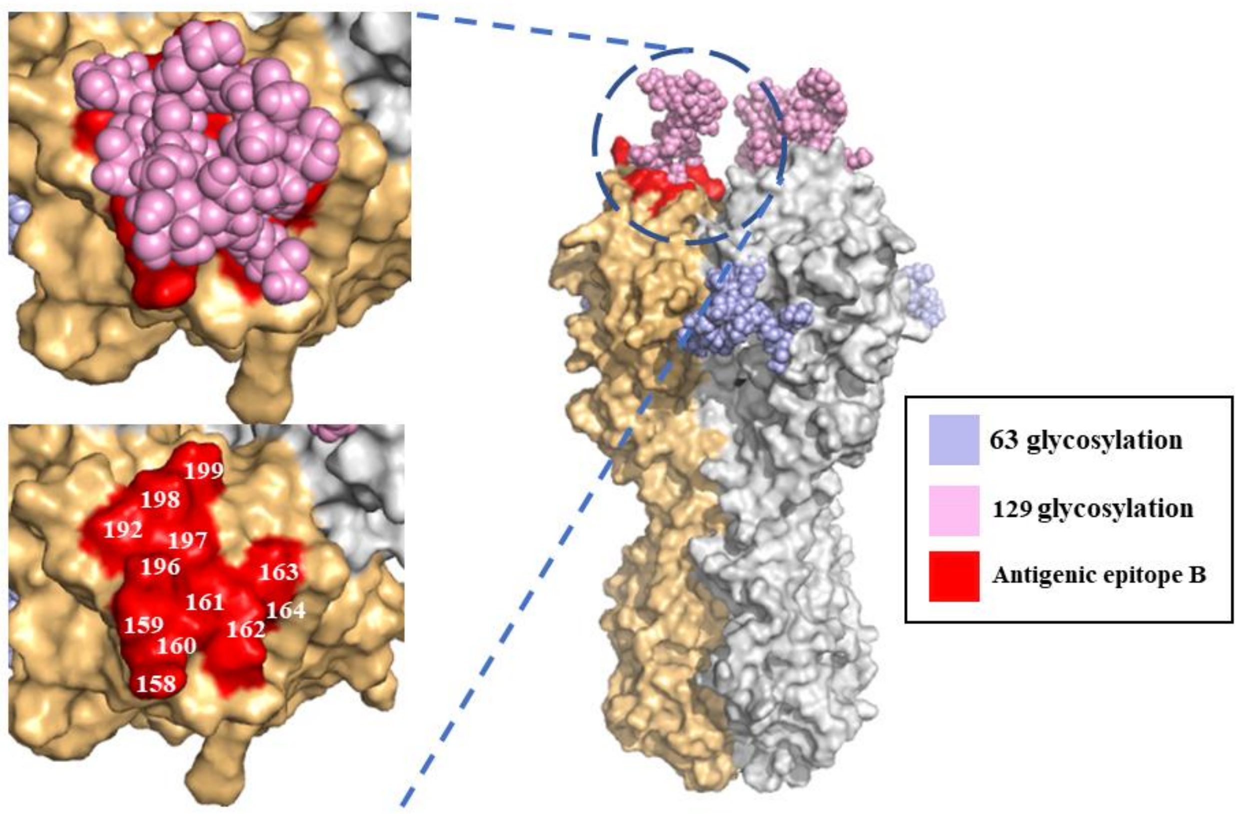
The virus evolution multiple clade and subclade, glycosylation modification of HA protein

- Dynamic surveillance of vaccine-escape mutants
- Simplified the official inspection procedures and vaccine strains were updated in a timely manner in 2019 (H5, Re1-Re-16; H7, Re1-Re-6)

Percentage of HA clades of H5 HPAIVs

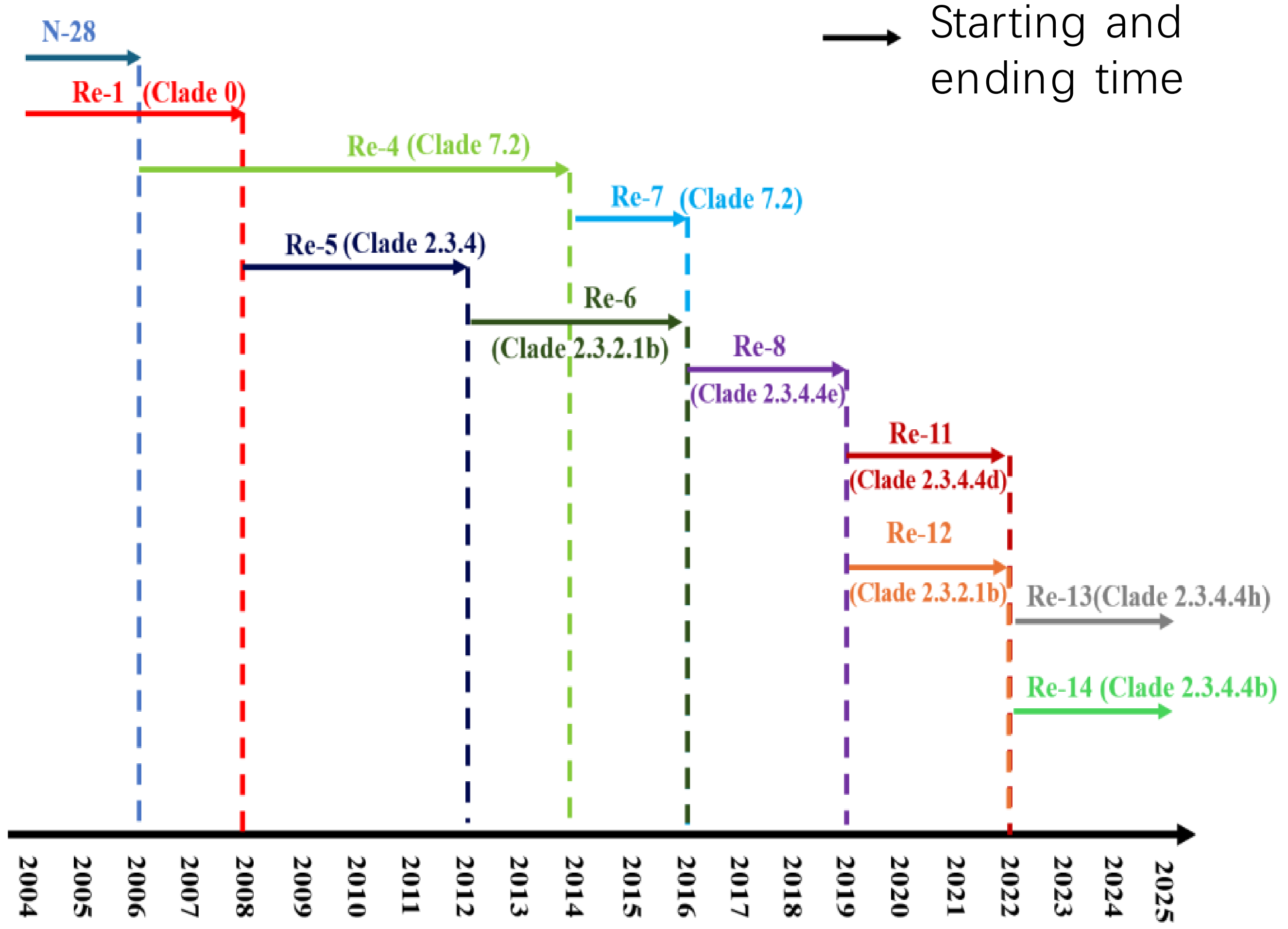
Year	Clades		
	2.3.2(%)	2.3.4(%)	7.2(%)
2007	0.0	100.0	0.0
2008	51.8	25.0	23.2
2009	92.3	3.4	4.2
2010	58.5	28.3	13.2
2011	80.9	4.6	14.5
2012	81.4	9.8	8.8
2013	62.6	34.3	3.0
2014	7.1	92.7	0.2
2015	7.6	92.4	0
2016	5.4	94.6	0
2017	2.3	97.7	0
2018	0.8	99.2	0

Liu et al, Transboundary Emerg Dis, 2020

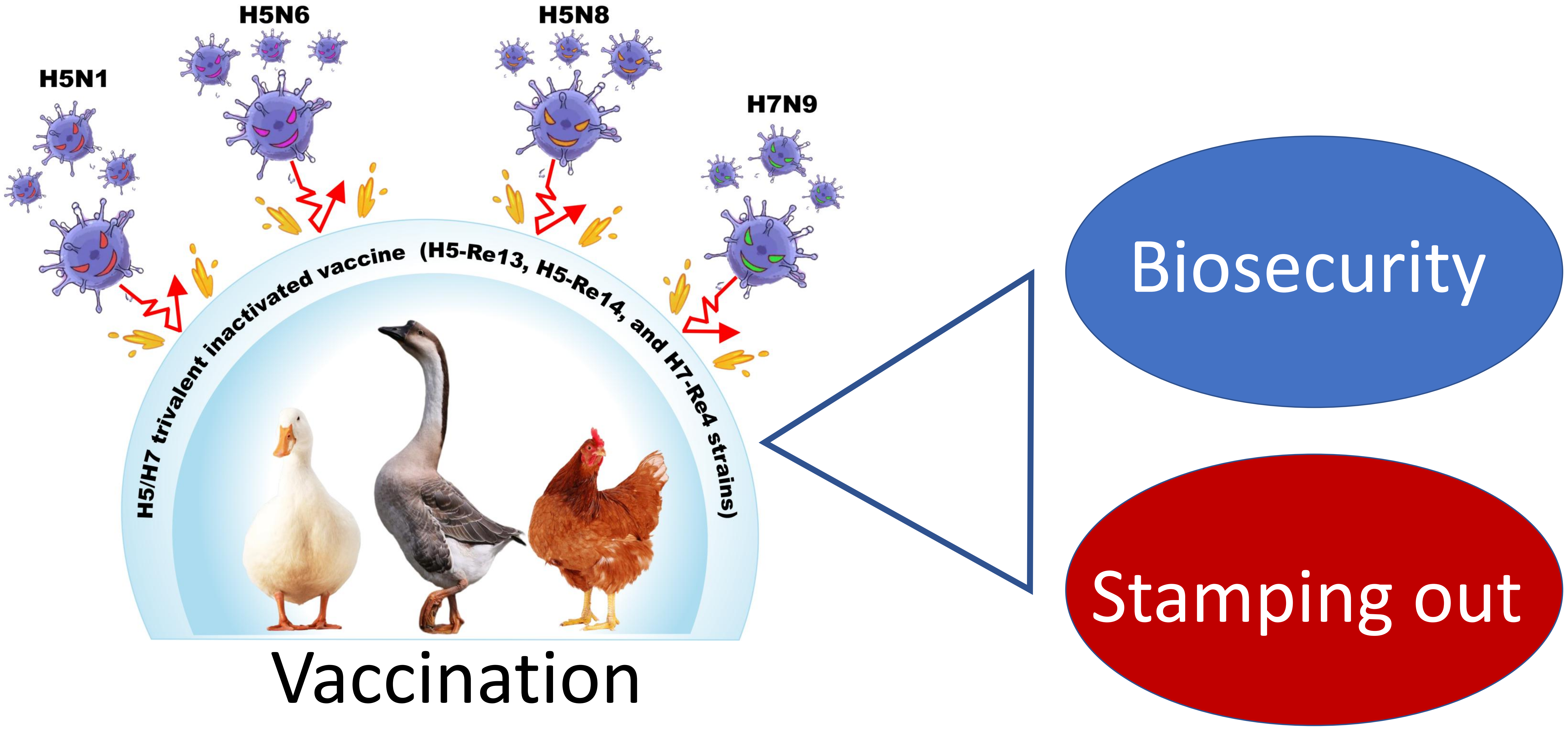


H5N6 AIV (129+) escapes protection of Re-8 vaccination

Xu et al, Microbiol Spectr, 2022



Update of H5 vaccine



Integration of multiple strategies

Conclusion and suggestions

- Vaccination strategy is very successful in China, as evidenced by the facts that several clades of H5 viruses have been eradicated and the H7N9 viruses have been nearly eliminated in China.
- Given that the H5 viruses are widely circulating in wild birds and causing problems in domestic poultry around the world, vaccination should be seriously considered as a control strategy globally.

Acknowledgements

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National Key R&D Program of China
(2021YFD1800202)

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Thank you very much for your attention!