Control highly pathogenic avian influenza by vaccination

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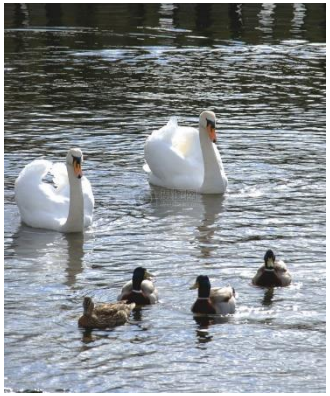
Topics

- H5 influenza control in China.
- H7N9 influenza control in China.

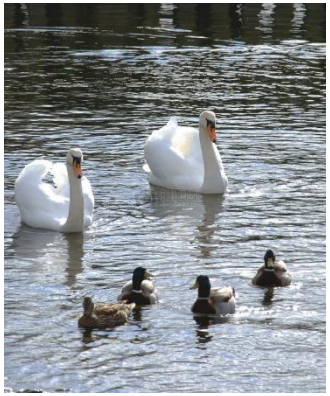
China is the largest poultry-producing country in the world

- Over 17 billion poultry, including 4 billion ducks, are reared annually in China.



China is the largest poultry-producing country in the world

- Over 17 billion poultry, including 4 billion ducks, are reared annually in China.
- Many birds, especially ducks and geese, are often reared in open fields with no biosecurity measures, which could be easily attacked by wild bird viruses.

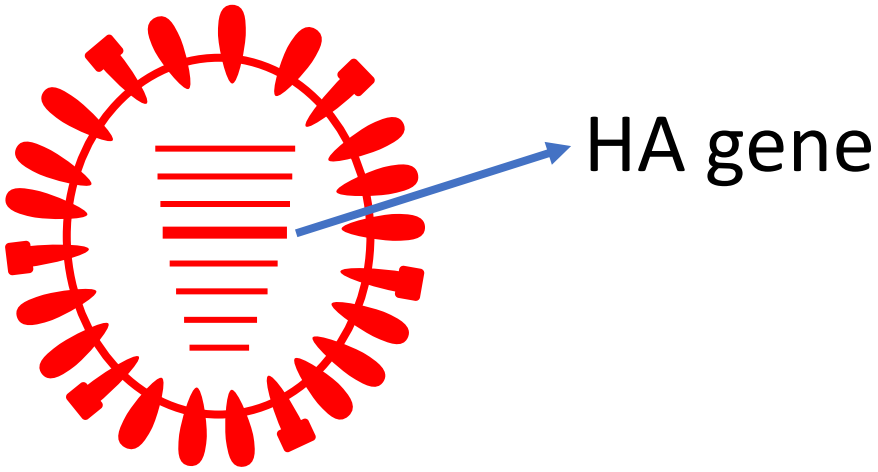

Avian influenza control strategies

- Many countries in Europe and North America used to control highly pathogenic influenza by culling infected and suspected poultry.

- China is a leading country to control highly pathogenic avian influenza by vaccination strategy.

Key issue for the vaccination strategy

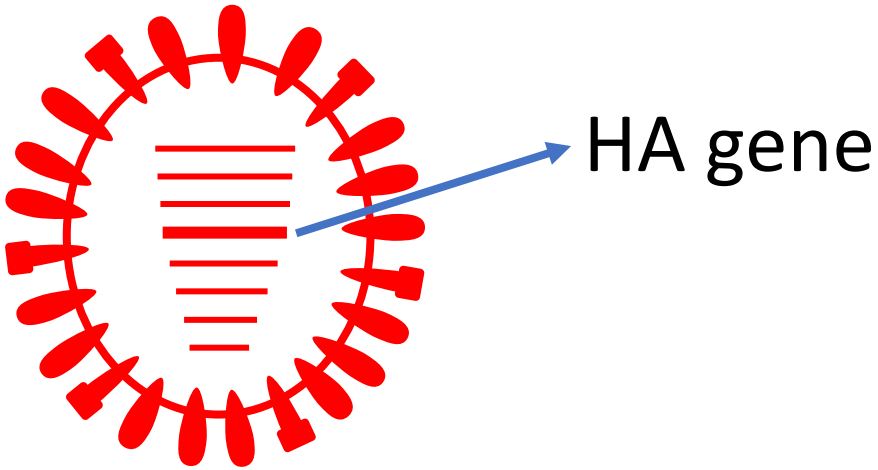
- Influenza virus mutates easily, and mutation of the HA gene often causes antigenic variation, which compromises the protective efficacy of vaccine.



Key issue for the vaccination strategy

- Influenza virus mutates easily, and mutation of the HA gene often causes antigenic variation, which compromises the protective efficacy of vaccine.

- So, it is important to make sure that the vaccine matches the circulating virus.



Surveillance and analysis the strains

- We continuously perform active surveillance in wild birds and domestic poultry to monitor the newly introduced viruses (about 40,000 samples per year collected by our lab).

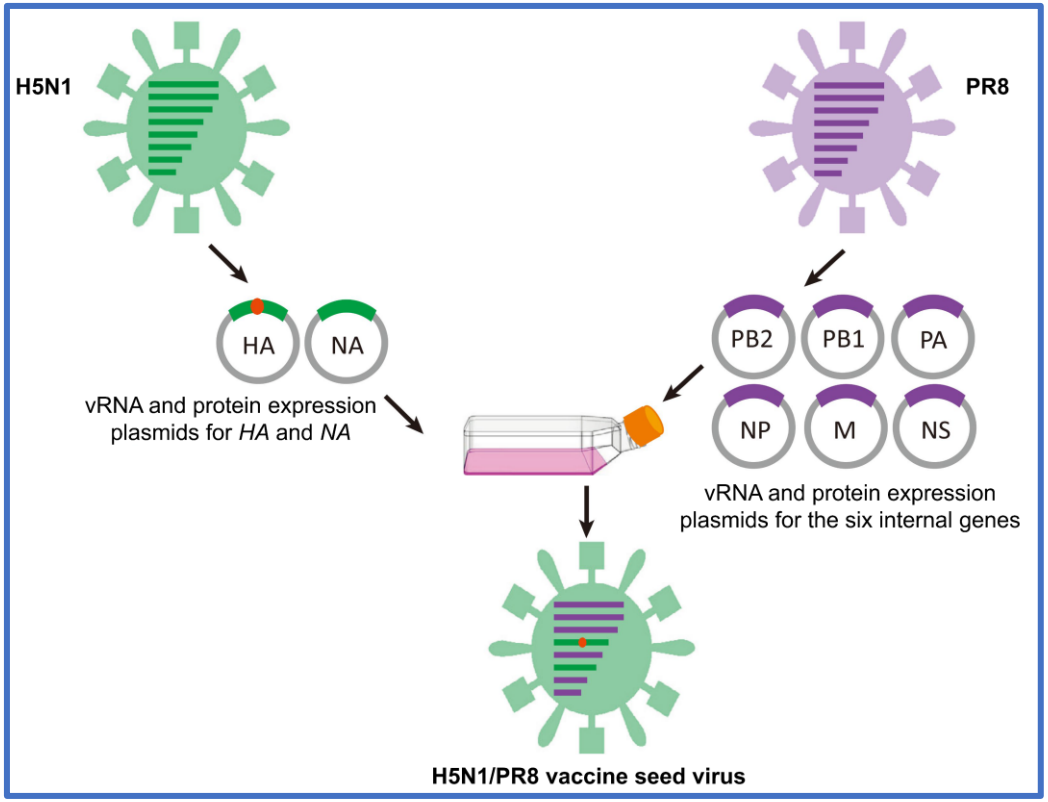
Surveillance and analysis the strains

- We continuously perform active surveillance in wild birds and domestic poultry to monitor the newly introduced viruses (about 40,000 samples per year collected by our lab).

- We compare the antigenic properties of the newly detected H5 virus with the vaccine seed virus, if a clear difference is observed, the vaccine will be updated

Inactivated vaccine development platform

Vaccine seed virus generation by reverse genetics

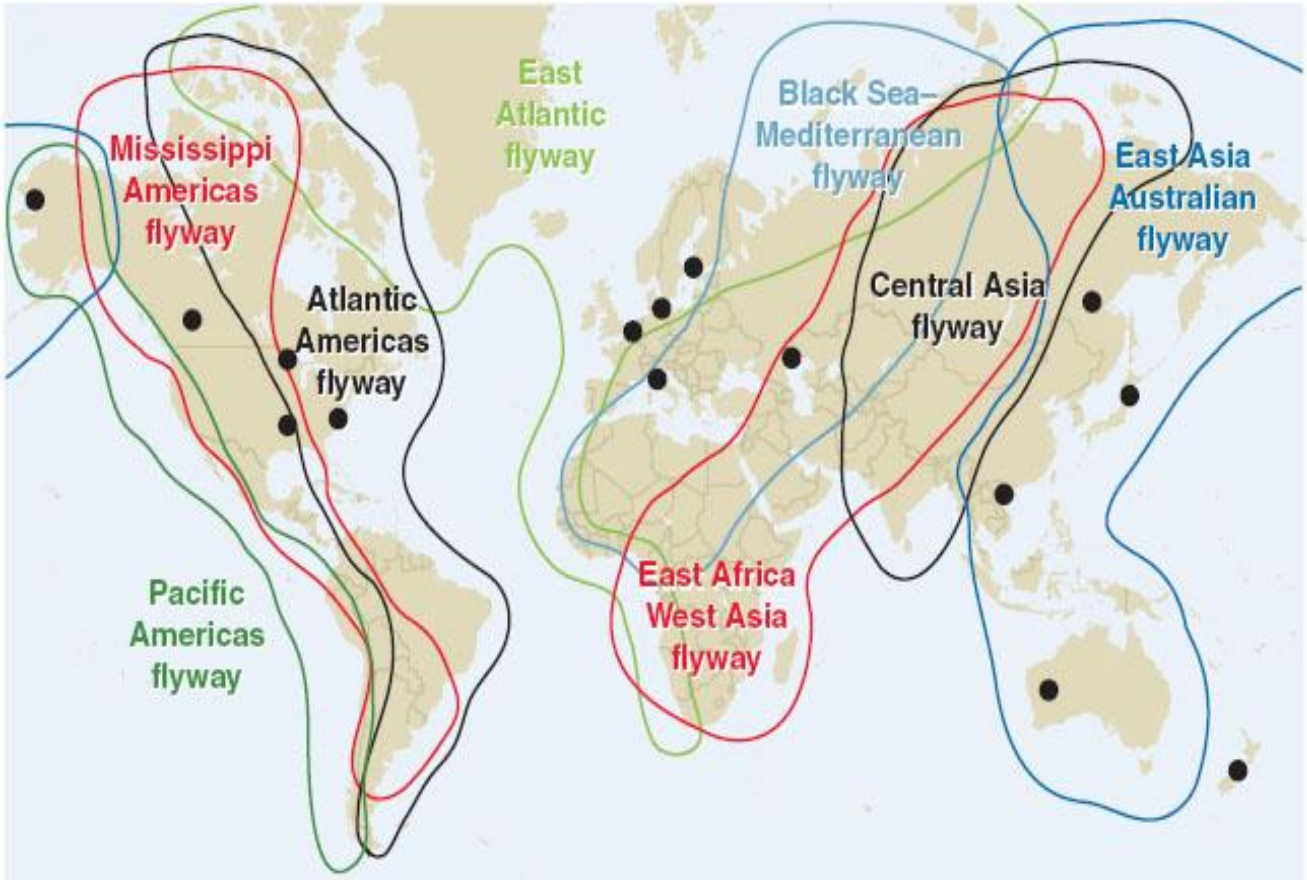


Tian et al., Virology, 2005

An ideal vaccine seed virus can be generated within a week

A large number of migratory birds fly over China, and they introduced different H5 influenza viruses into China in the past years.

Chen H., JVI, 2006;
Li Y., EID, 2010;
Cui Y., EMI, 2020;
Li Y., EID, 2020;
Cui P., SCLS, 2022;
Cui P., EMI, 2022



Viruses carrying different clades or subclades of HA that have been introduced into China before 2020

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

Eight H5 vaccine seed viruses had been used in China from 2004 to 2021

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

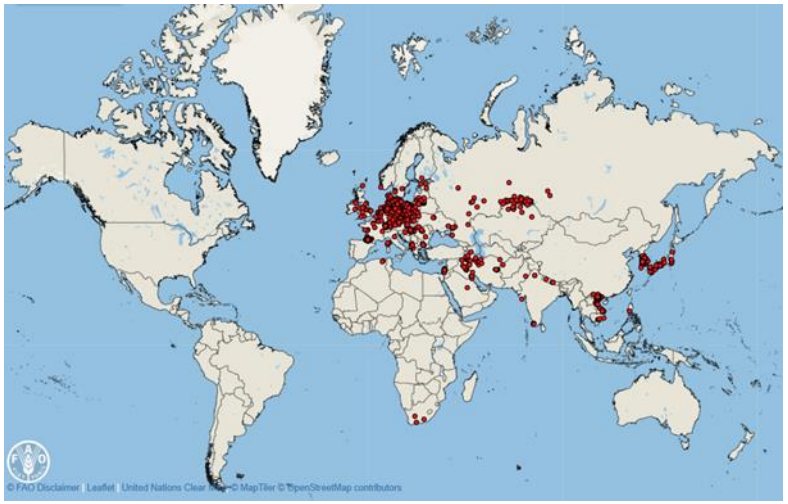
Viruses bearing the clades 2.2, 7.2, 2.3.4, 2.3.2, 2.3.2.1f, and 2.3.4.4g HA gene have been eliminated in China

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	**Yes**
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**
H5-Re11	DK/GZ/S4184/2017(H5N6) (2.3.4.4h)	12/2018–12/2021	2.3.4.4h	Not yet, but very soon

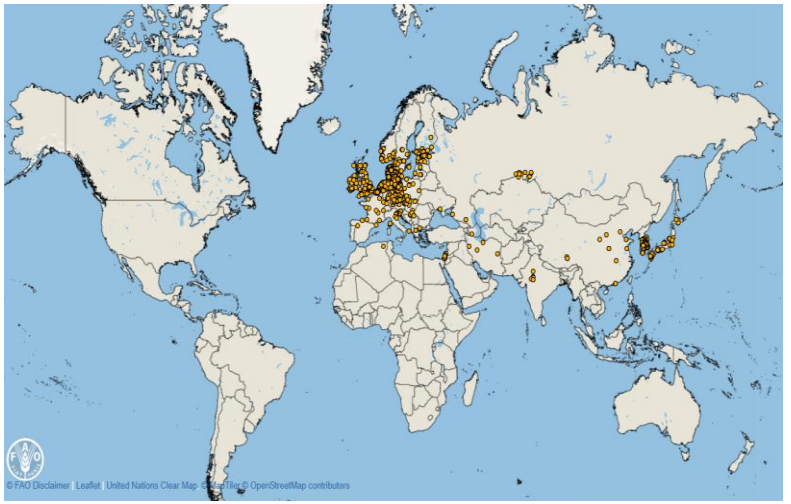
H5 viruses bearing the clade 2.3.4.4b HA gene have caused numerous outbreaks around the world since 2020

H5N8

Poultry, 1799 outbreaks

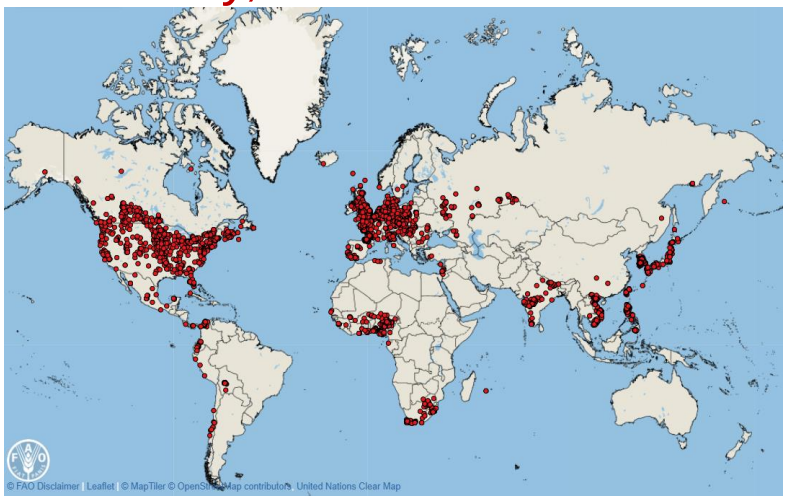


Wild birds, 1469 outbreaks

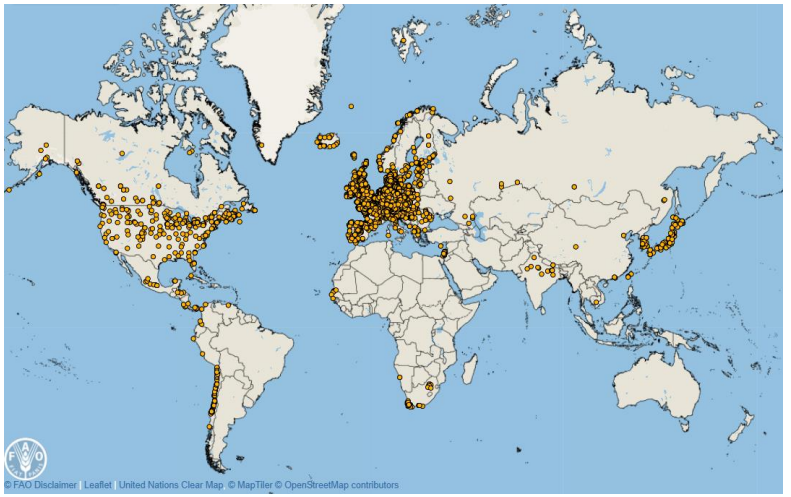


H5N1

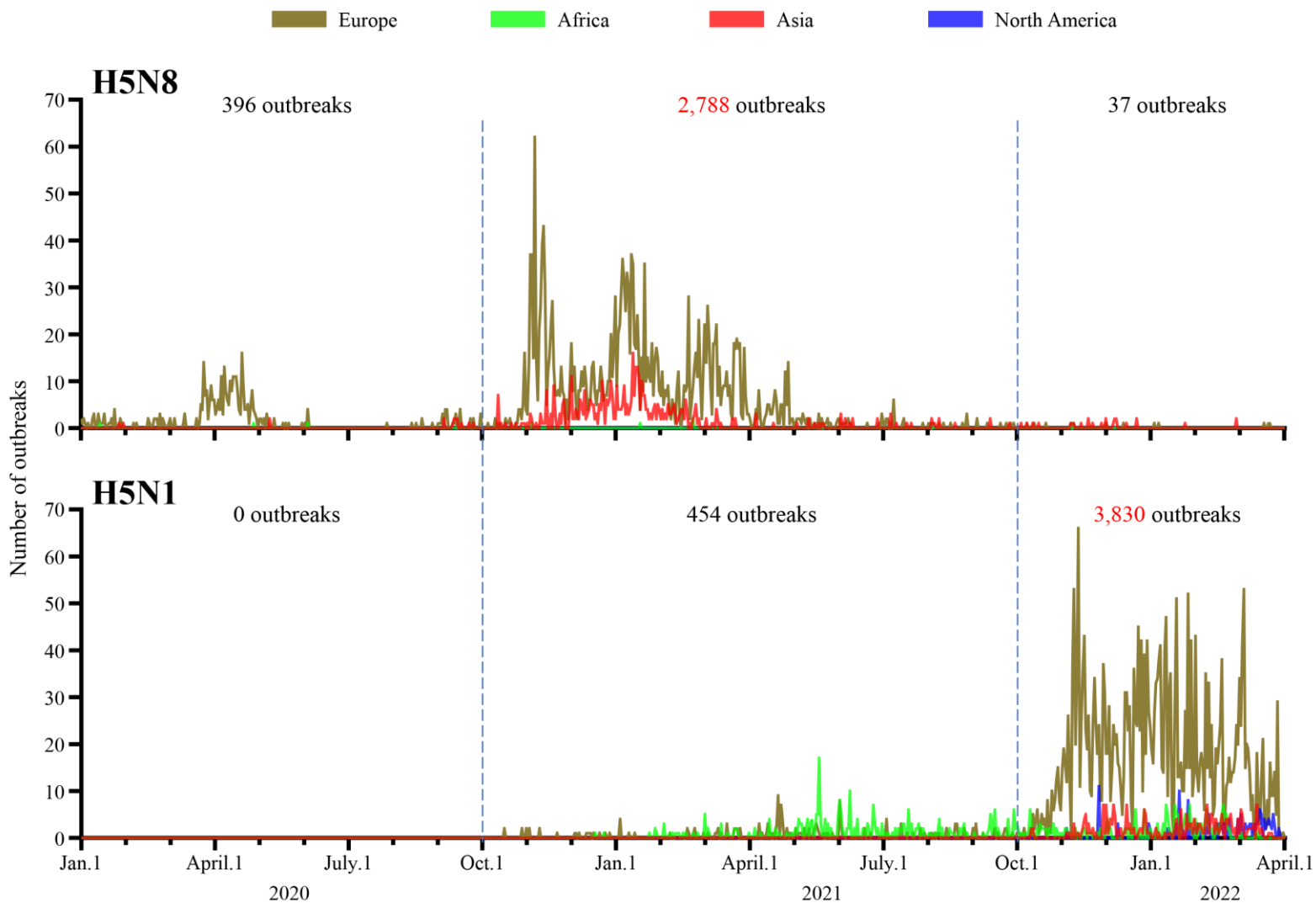
Poultry, 5215 outbreaks



Wild birds, 5441 outbreaks



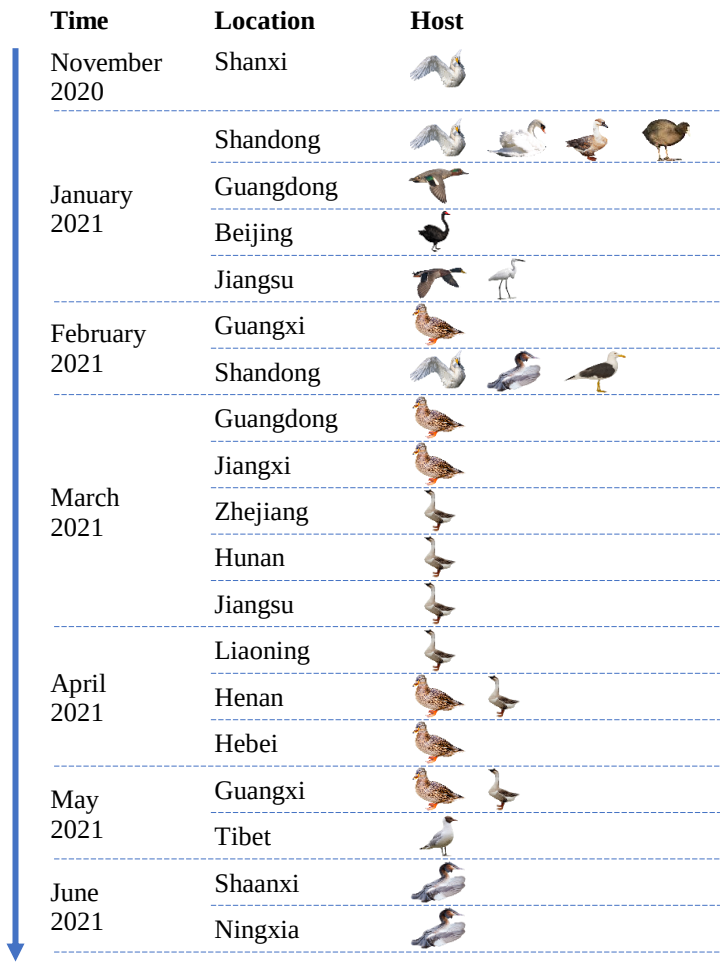
H5N1 replaced the H5N8 and caused huge disease outbreaks since October 2022



Introduction of H5N8 virus into China by wild birds

Surveillance performed from September 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

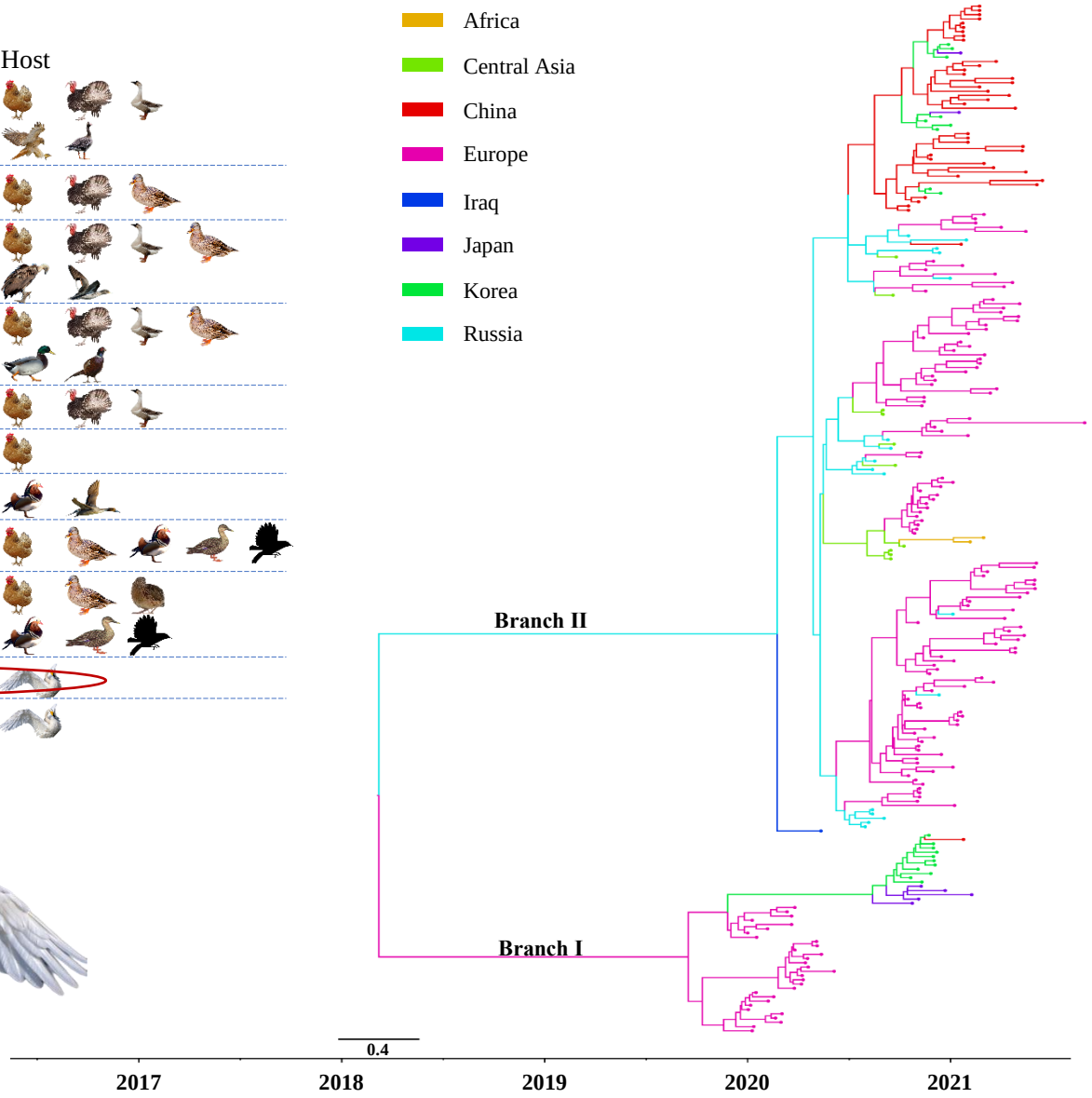


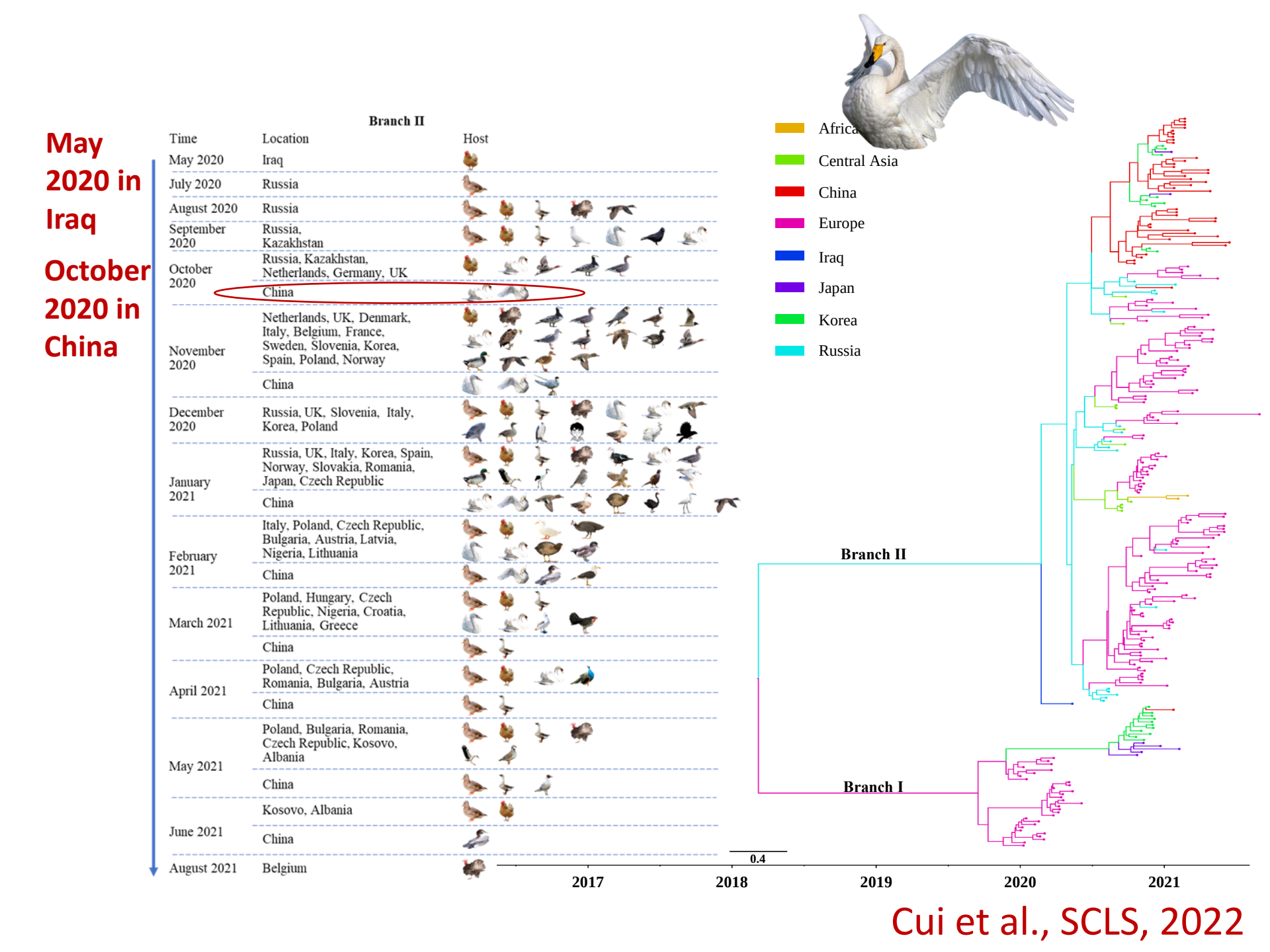
Jan. 2020 in Europe

Jan. 2021 in China

Branch I

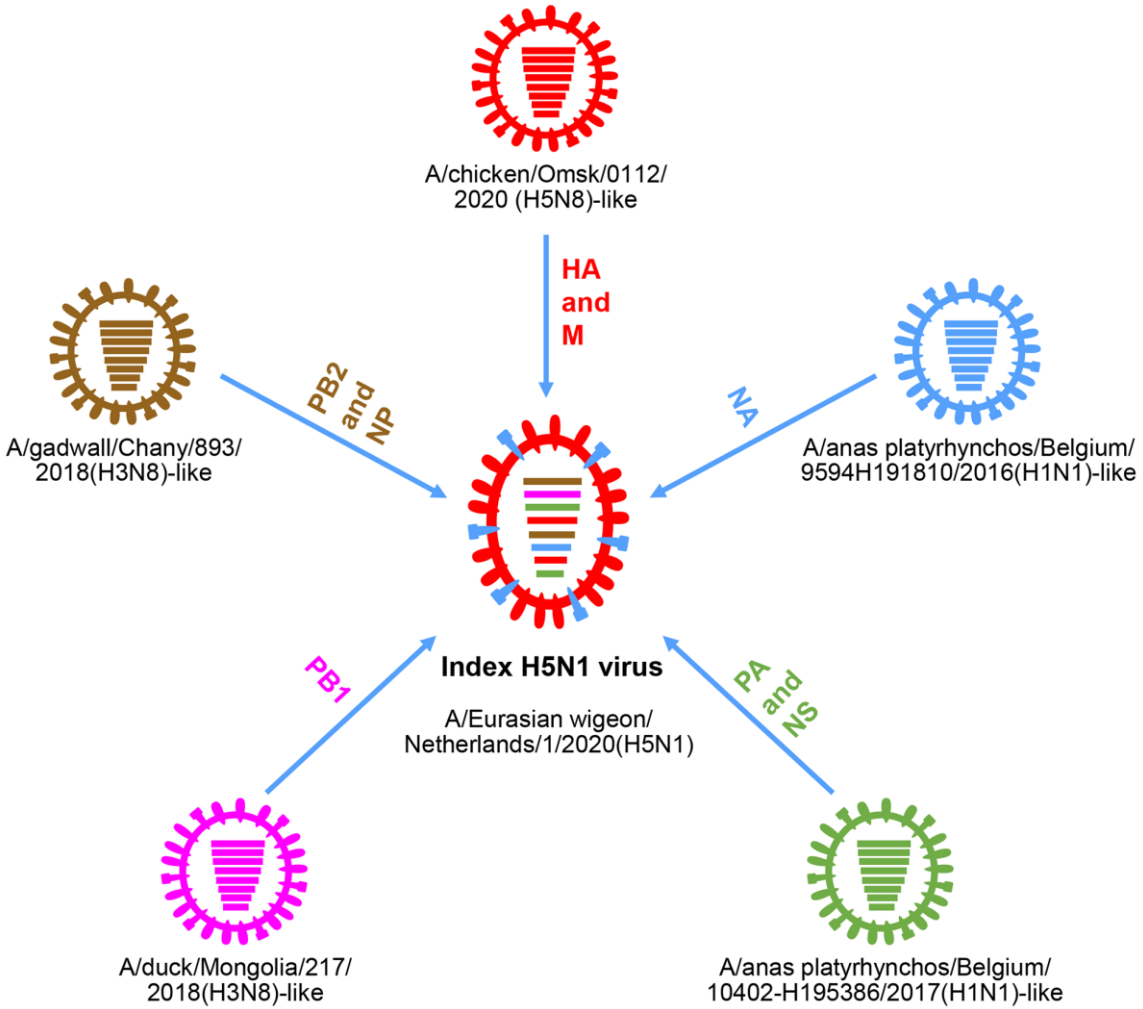
Time	Location	Host
January 2020	Poland, Hungary, Germany, Czech Republic	
February 2020	Germany, Poland, Czech Republic	
March 2020	Poland, Germany, Hungary	
April 2020	Hungary	
May 2020	Hungary	
June 2020	Hungary	
October 2020	Korea, Japan	
November 2020	Korea, Japan	
December 2020	Korea, Japan	
January 2021	China	
February 2021	Japan	





Cui et al., SCLS, 2022

Emerging of the H5N1 virus in Northern Europe



Shi et al., EMI, 2022

Evolution and spread of H5N1 virus bearing the clade 2.3.4.4b HA since October 2020

October 2020 in The Netherlands

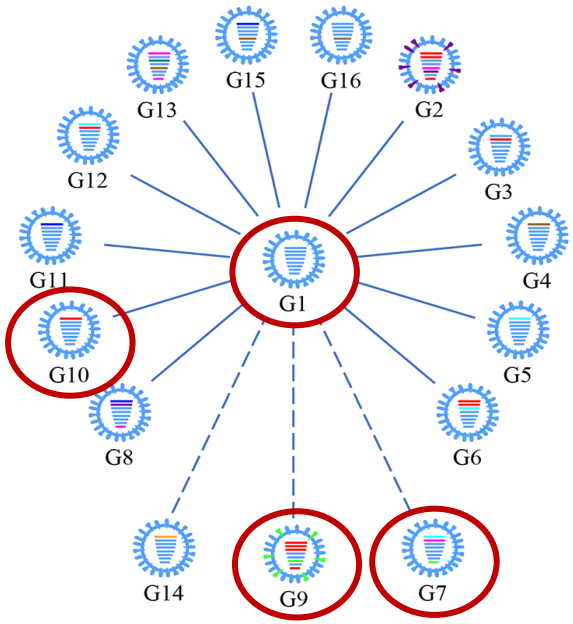
November 2021 in China

a

Time	Location: Europe	Africa	Asia -Others	Asia -China	North America
Oct. 2020	G1				
Nov. 2020	G1, G2				
Dec. 2020	G1	G1			
Jan. 2021	G1	G1			
Feb. 2021	G1	G1			
March 2021	G1	G1			
April 2021	G1				
May 2021	G1				
June 2021	G1				
July 2021	G1				
Aug. 2021	G1				
Sept. 2021	G1, G3, G4				
Oct. 2021	G1, G4, G5, G6, G8, G10		G7		
Nov. 2021	G1, G4, G8, G11, G12, G13,		G7	G1, G9	
Dec. 2021	G1, G4, G5, G8, G12, G15		G14	G7, G9	G1
Jan. 2022	G1, G4, G8, G16	G1		G7, G9, G10	G1
Feb. 2022	G1, G4			G7	G1
March 2022				G9	

16 genotypes formed

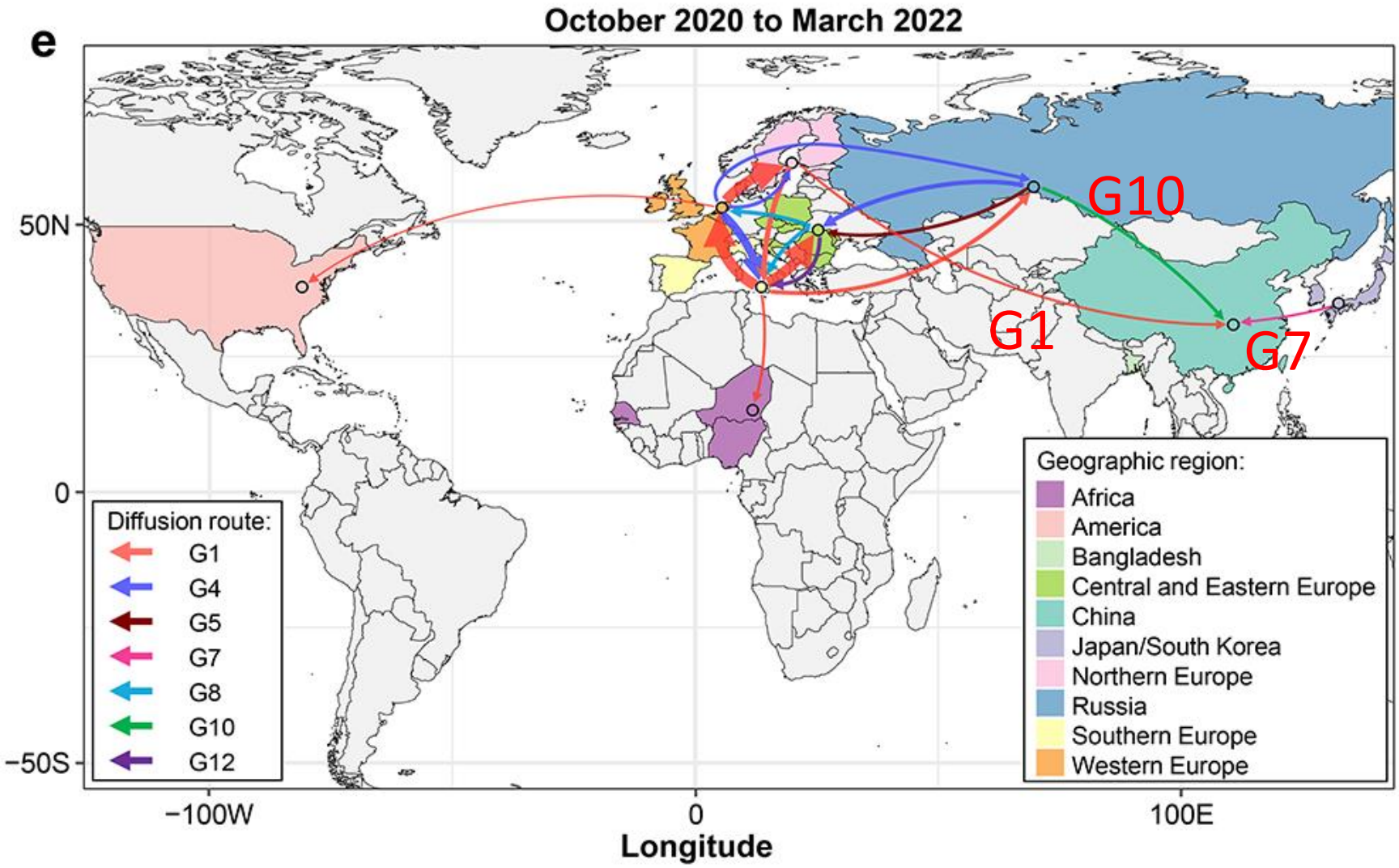
b



Gene donor:

- A/anas platyrhynchos/Belgium/10402-H195386/2017 (H1N1)-like
- A/wild duck/South Korea/KNU2020-58/2020(H1N1) -like
- A/mallard/Novosibirsk region/1894k/2019(H4N6)-like
- A/anas platyrhynchos/Belgium/827/2020(H3N8)-like
- A/duck/Moscow/5586/2018|(H1N2)-like
- A/common Teal/Amur region/31b/2019(H3N6)-like
- A/anas platyrhynchos/Belgium/204-0003/2020(H4N6) -like
- A/green sandpiper/Kurgan/1050/2018(H3N8)-like
- A/mallard/Denmark/12947-12/2020(H7N5)-like
- Wild bird H5N8

Three different H5N1 viruses were respectively spread to China from Northern Europe, Russia, and Japan/Korea



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

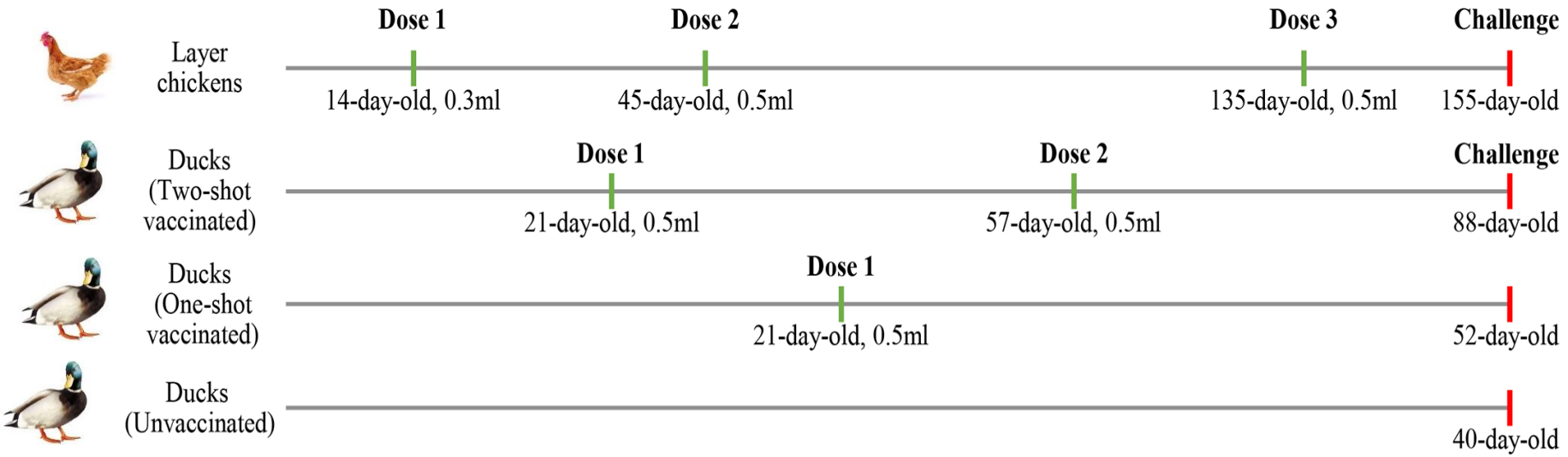
Virus	HA clade	HI antibody titer of antiserum	
		H5-Re11	H5-Re12
H5-Re11	2.3.4.4h	**512**	32
H5-Re12	2.3.2.1f	16	**512**
WS/SX/4-1/2020(G1)	2.3.4.4b	16	8
BS/BJ/1/2021(G1)	2.3.4.4b	16	8
GS/HuN/S11288/2021(G1)	2.3.4.4b	16	8
WS/SD/SC195/2021(G2)	2.3.4.4b	16	8

Cui et al., SCLS, 2022

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

Could our vaccinated poultry be well protected against this newly invasive virus?

Chickens and ducks from different poultry farms that were routinely vaccinated or unvaccinated were challenged with H5N8 virus in the laboratory setting



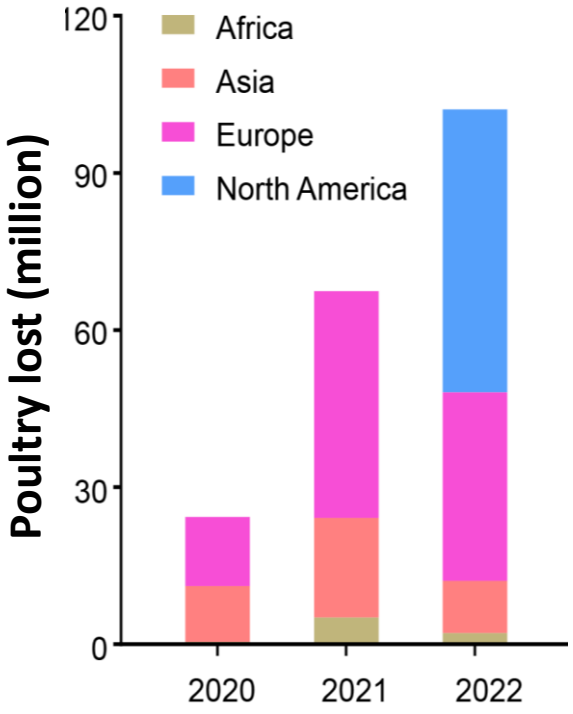
Cui et al., SCLS, 2022

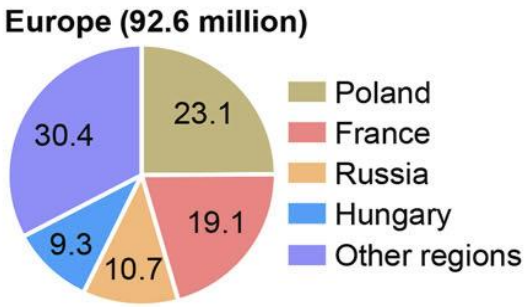
Vaccinated poultry were completely protected against the newly introduced H5N8 virus challenge

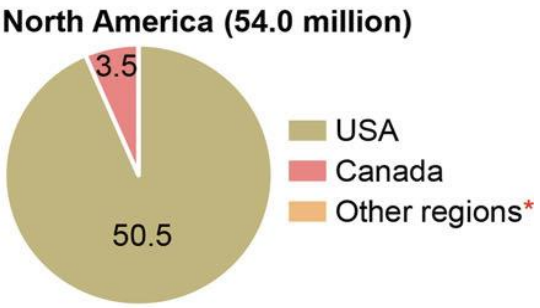
Group	Virus shedding (shedding/total)				Shedding/ Total	Survival /Total
	Day 3 post challenge		Day 5 post challenge			
	Oropharynx	Cloacae	Oropharynx	Cloacae		
Vaccinated layer chickens (three doses)	0/10	0/10	0/10	0/10	0/10	10/10
SPF chickens	10/10	10/10	/	/	10/10	0/10
Vaccinated ducks (one dose)	0/10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

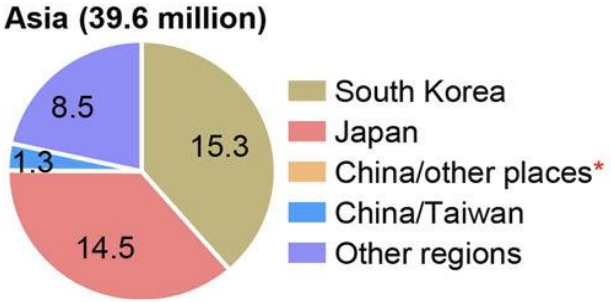
Cui et al., SCLS, 2022

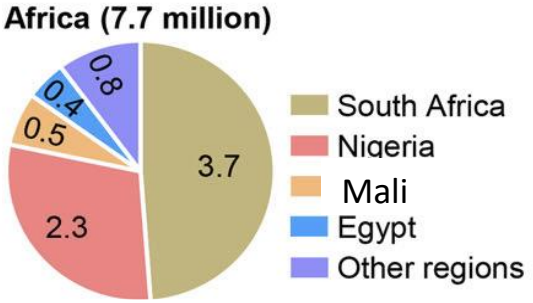
Over 194 million poultry died or were destroyed due to H5 virus infection from January 2020 to March 2022; of note, Mainland China lost <10, 000 birds during this period











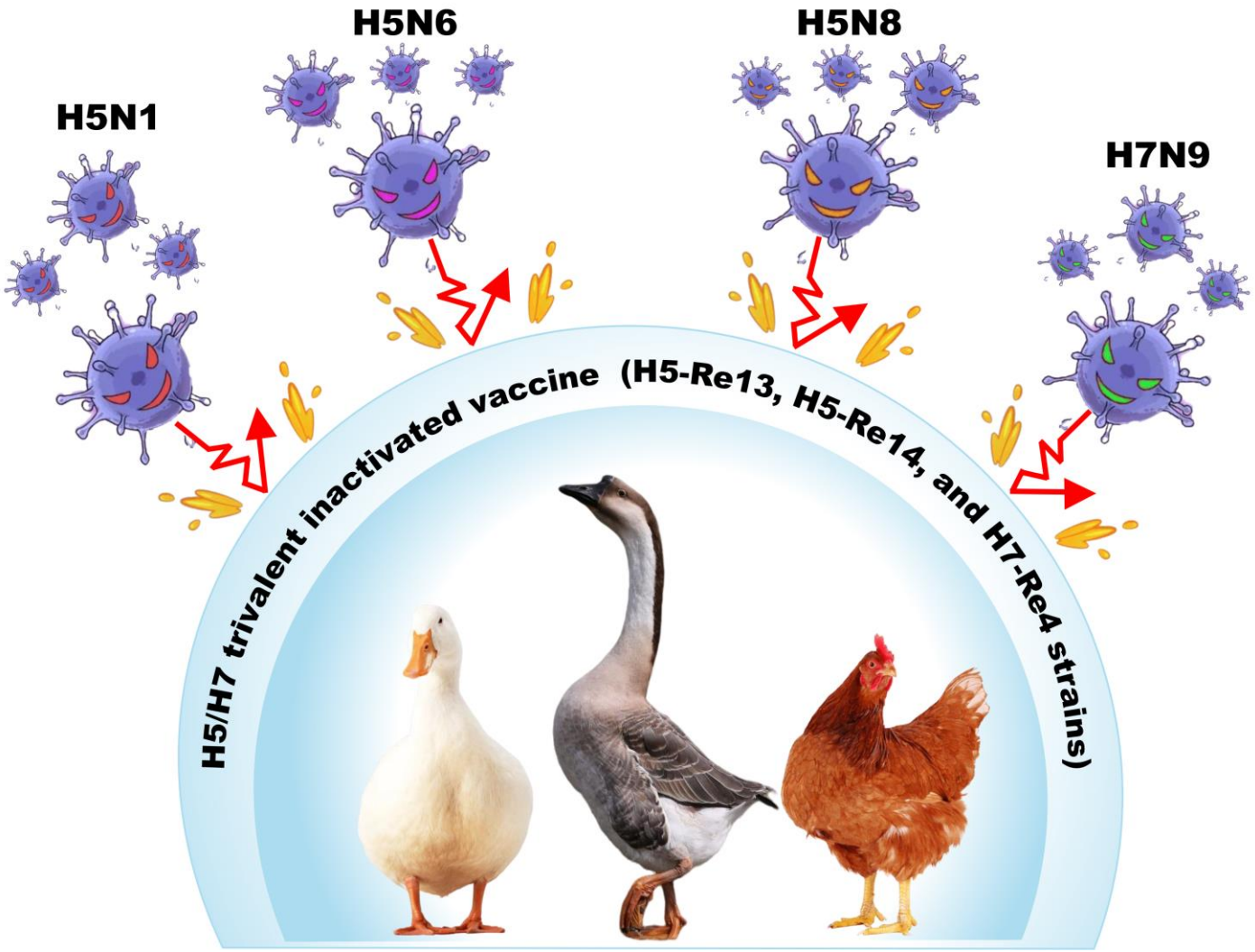
Shi et al., EMI, 2022

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.

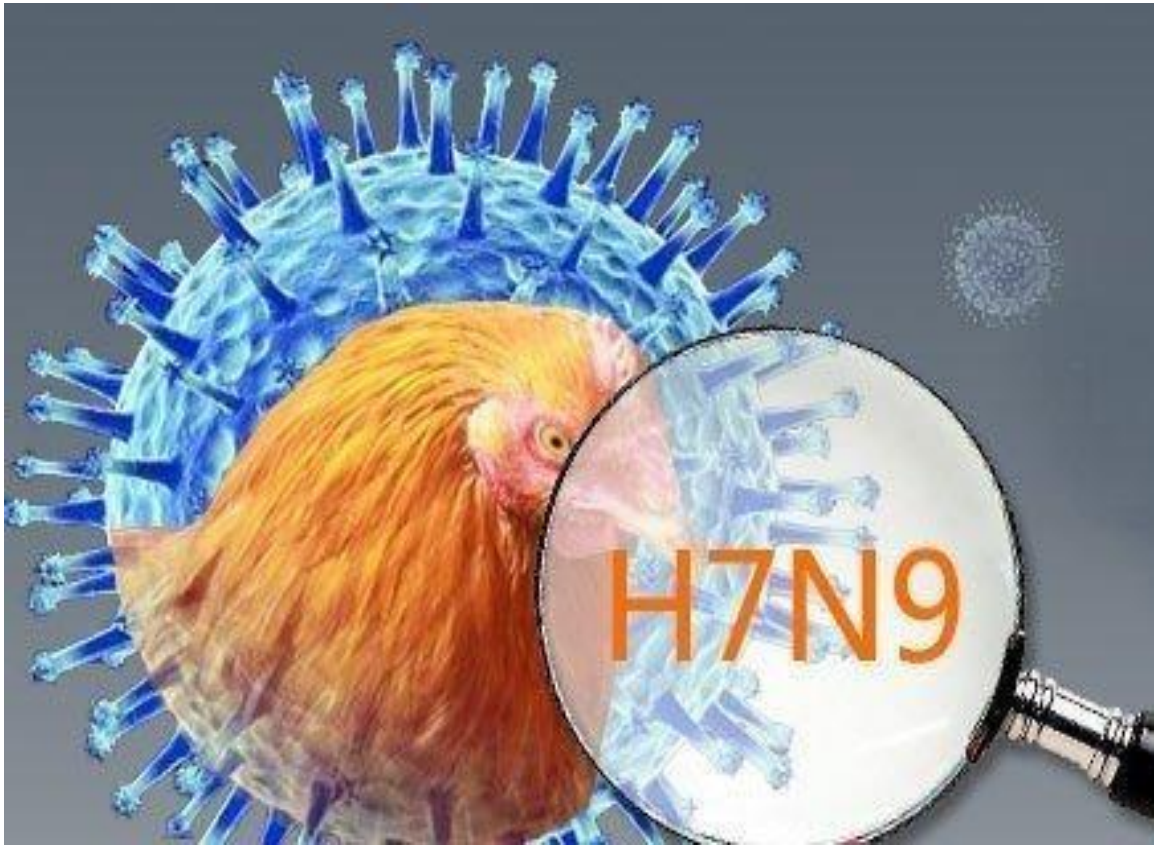
Seed virus	HA donor virus (clade)	Application period	Complete protection against the clade of
H5-Re13	DK/FJ/S1424/2020(H5N6) (2.3.4.4h)	01/2022–	2.3.4.4h
H5-Re14	WH/SX/4-1/2020(H5N8) (2.3.4.4b)	01/2022–	2.3.4.4b

Zeng et al., Protective efficacy of an H5/H7 trivalent inactivated vaccine (H5-Re13, H5-Re14, and H7-Re4 strains) in chickens, ducks, and geese against newly detected H5N1, H5N6, H5N8, and H7N9 viruses.

Journal of Integrative Agriculture, 2022, 21(7): 2086–2094

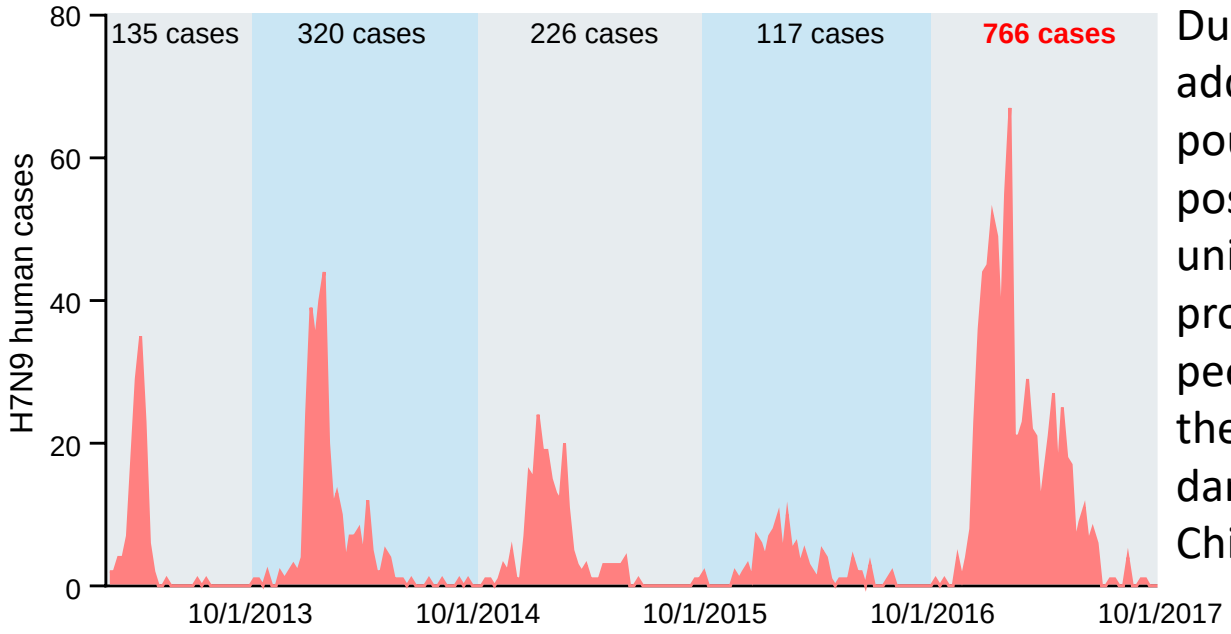


Control of H7N9 virus in China



Damage to humans and poultry industry caused by H7N9 viruses in China

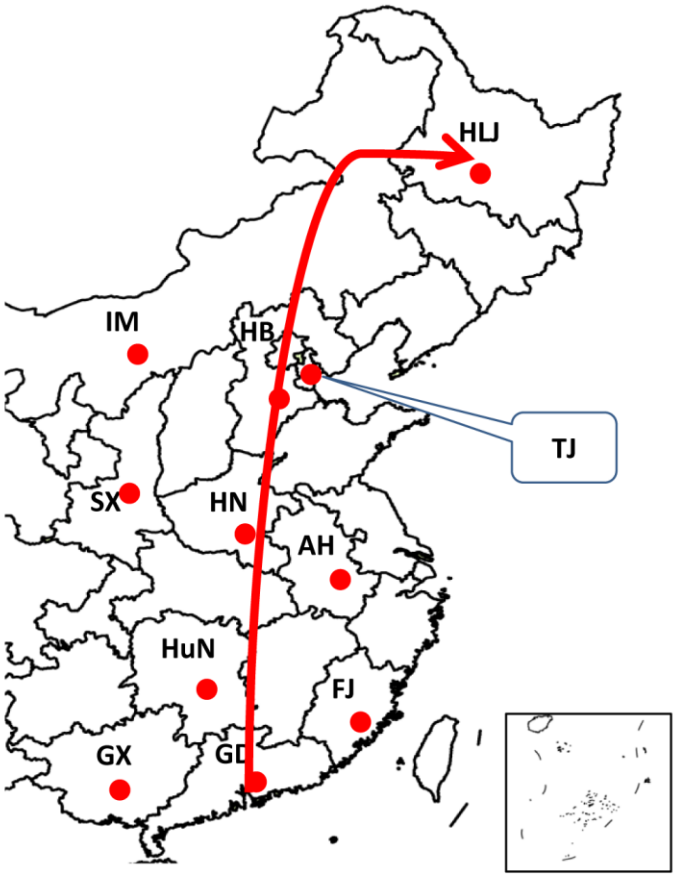
The virus caused over 1,560 human infections in five waves from February 2013 to September 2017, with a mortality rate of nearly 40%.



During the human H7N9 waves, in addition to culling poultry from poultry markets that were positive for the virus, tons of uninfected poultry and poultry products were destroyed because people were afraid to consume them, which caused considerable damage to poultry industries in China from 2013-2017.

H7N9 virus mutated to highly pathogenic form in early 2017 in Guangdong province in China

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 J., et al, Cell Research, 2017

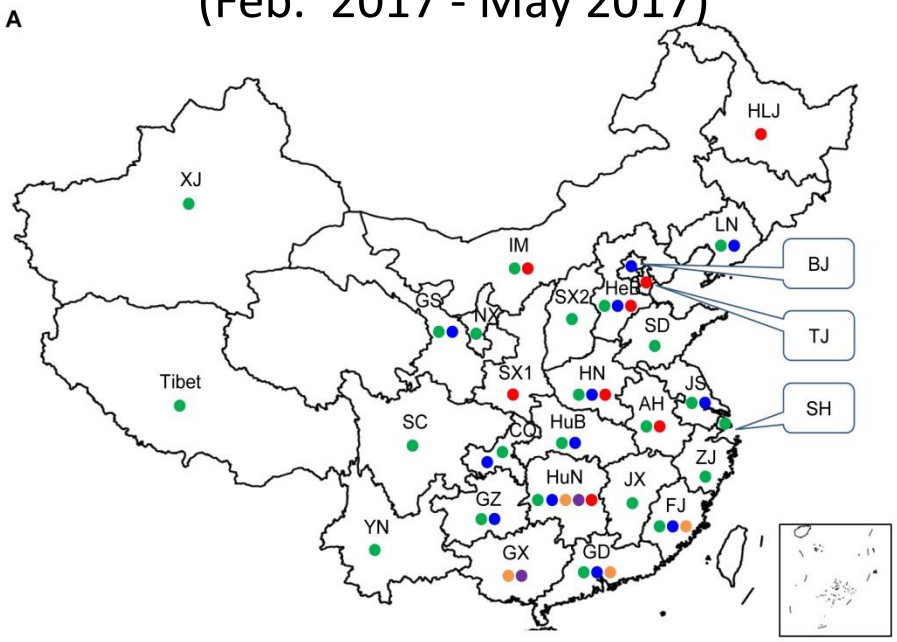
In September 2017, the control strategy of H7N9 influenza was changed from “stamping-out” to “massive vaccination”, and an H5+H7 bivalent vaccine was started to be used to control both H5 and H7 avian influenza in China.

Shi J., et al, Cell Host & Microbe, 2018

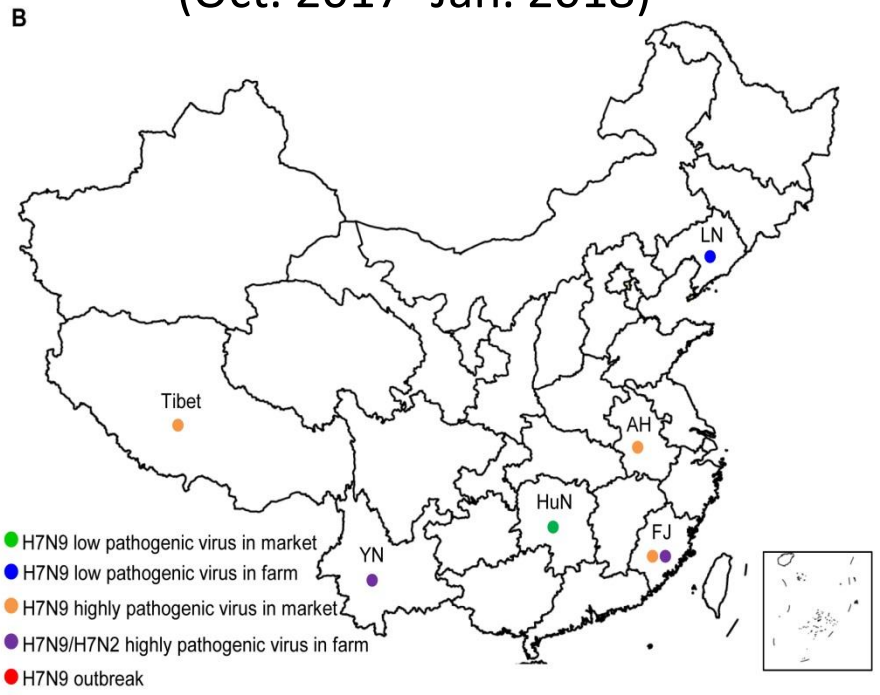
Vaccination dramatically prevented the prevalence of H7N9 virus in poultry

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)



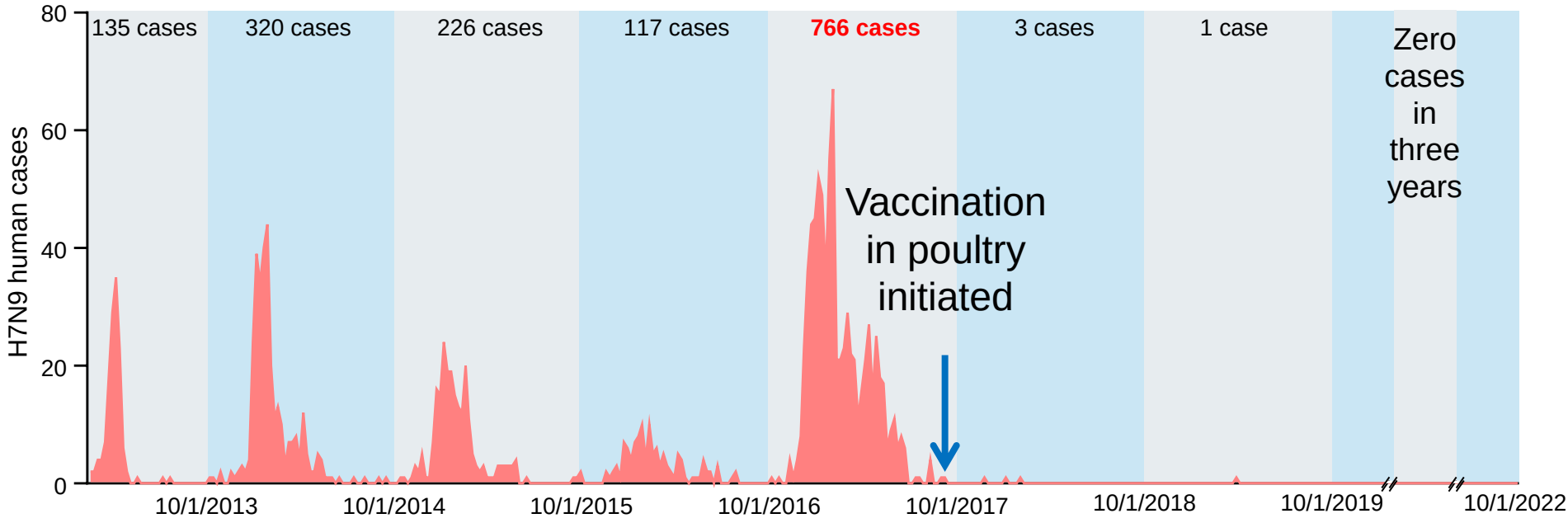
Post-vaccination
(Oct. 2017- Jan. 2018)



Shi J., et al, Cell Host & Microbe, 2018

Vaccination of poultry successfully eliminated human infection with H7N9 virus

Only three human cases and one human case were reported during the sixth and seventh waves, respectively, and no human case has been detected since April 2019



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 pervasive 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 immediately and seriously considered as a control strategy globally.

Thank you very much for your attention!