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OPTIONS IX *for* THE CONTROL OF INFLUENZA

24–28 AUGUST 2016

10 YEARS

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The Market as an Influenza Risk Factor:

The Animal Human Interface

Yuelong Shu
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25 August 2016

Live poultry market in China

Guan Y, et al, J Infect Dev Ctries 2013

Live poultry market in China

Guan Y, et al, J Infect Dev Ctries 2013

Live poultry market in Cambodia

Horm SV et al, Emerging Microbes & Infections, 2016

Live poultry markets

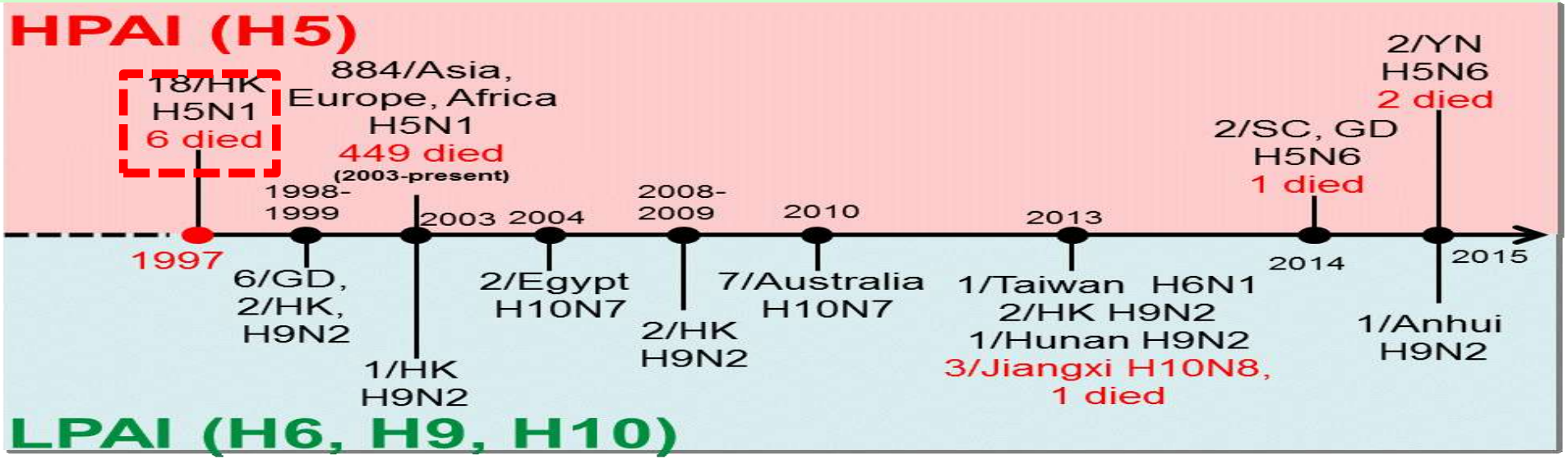
- Source of human infections

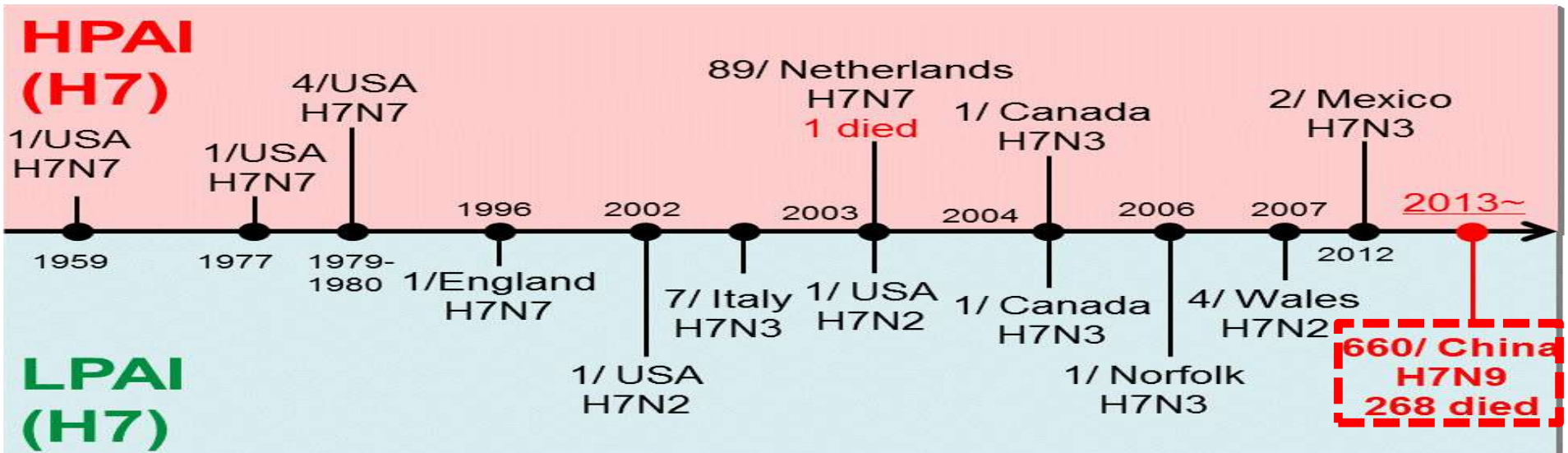
- Source of generation of novel avian influenza viruses

Live poultry markets & human infections with AIVs

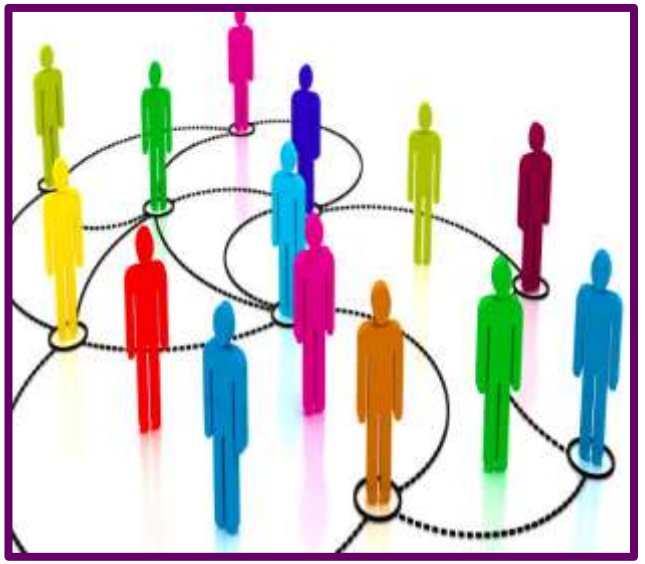
- Exposure history investigation
- Molecular epidemiology evidences
- Serological evidences
- Effects of LPMs closure

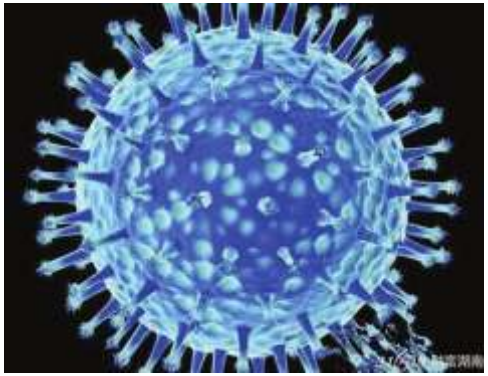
Human infections with avian influenza viruses



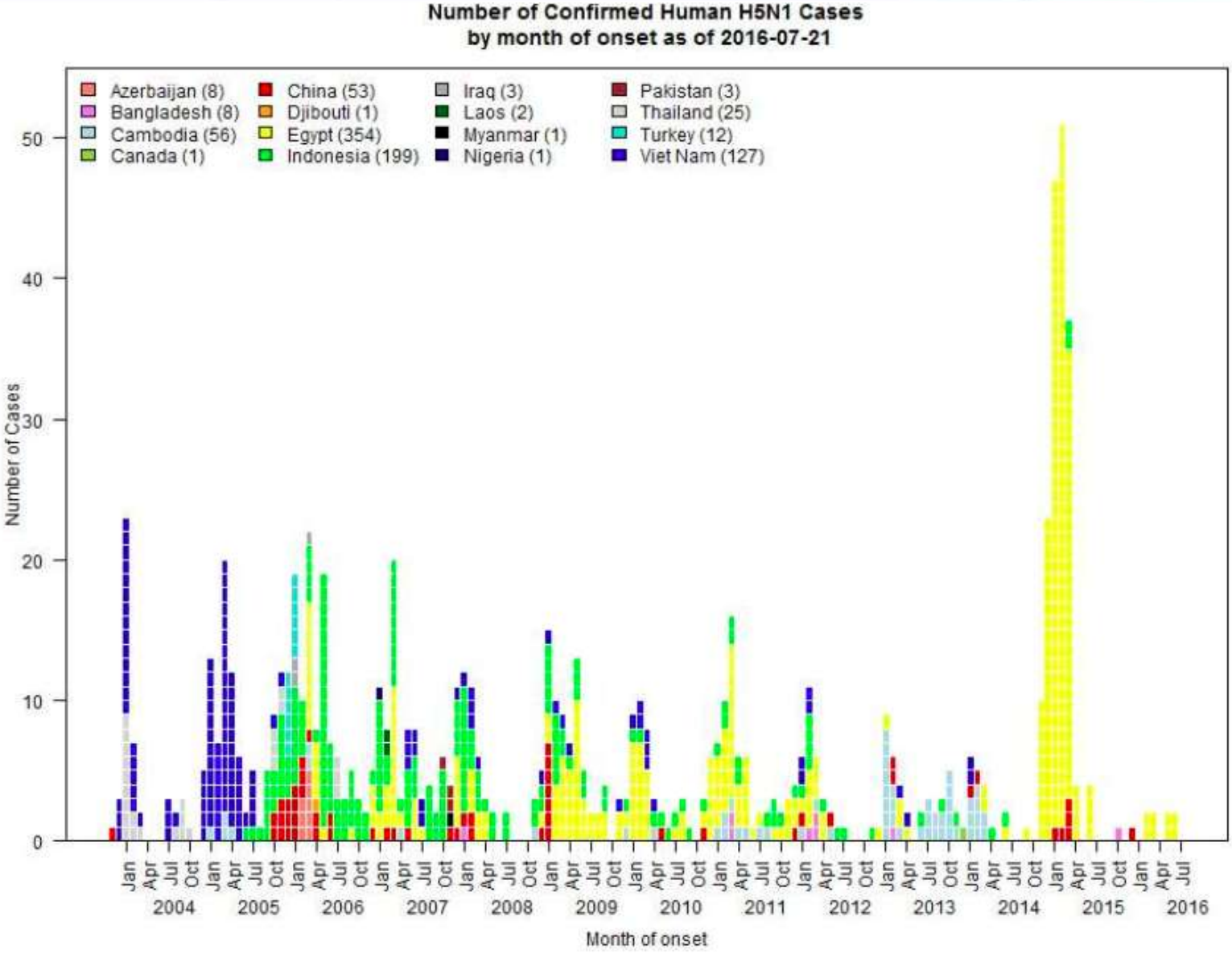


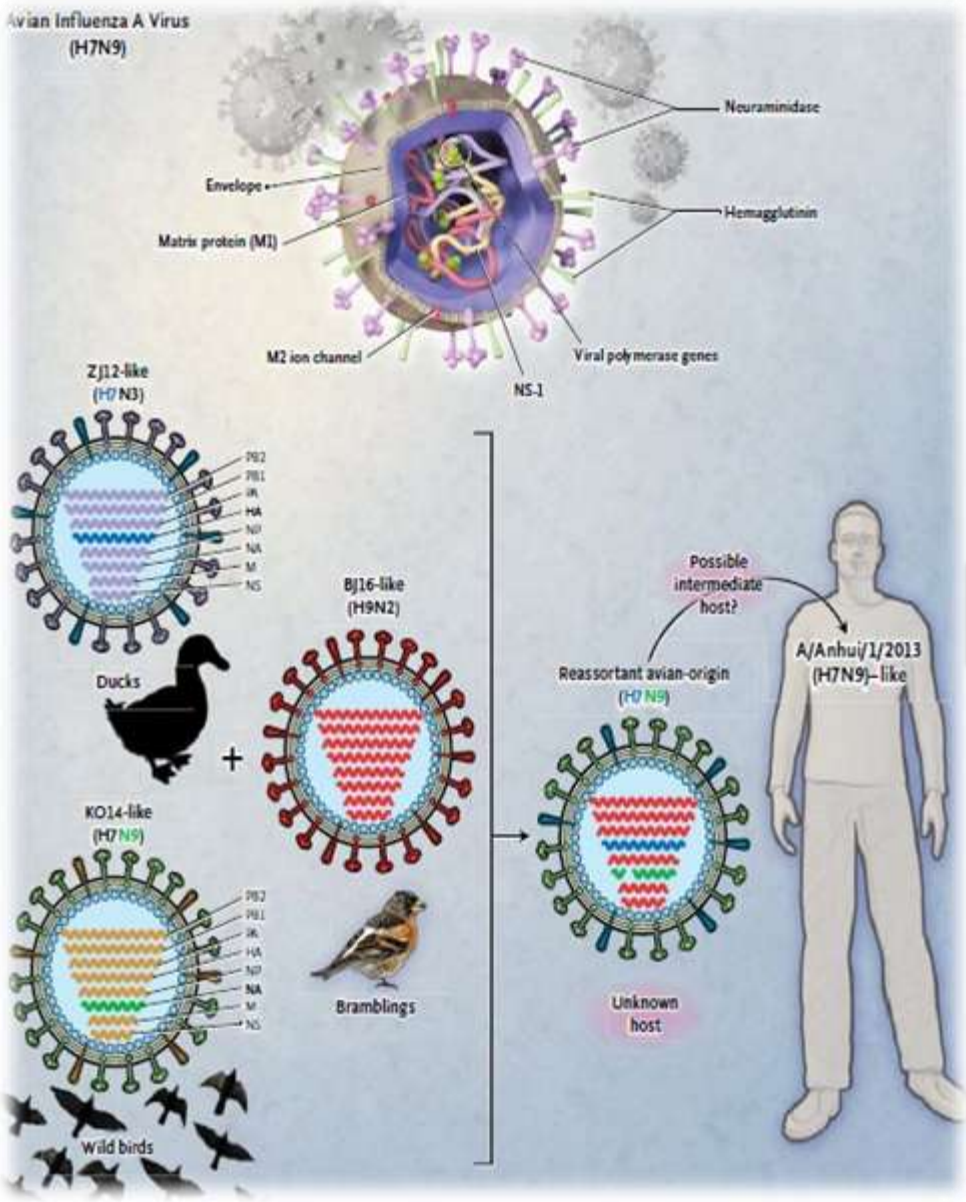
H5Nx
H7Nx
H6Nx
H10Nx
H9N2

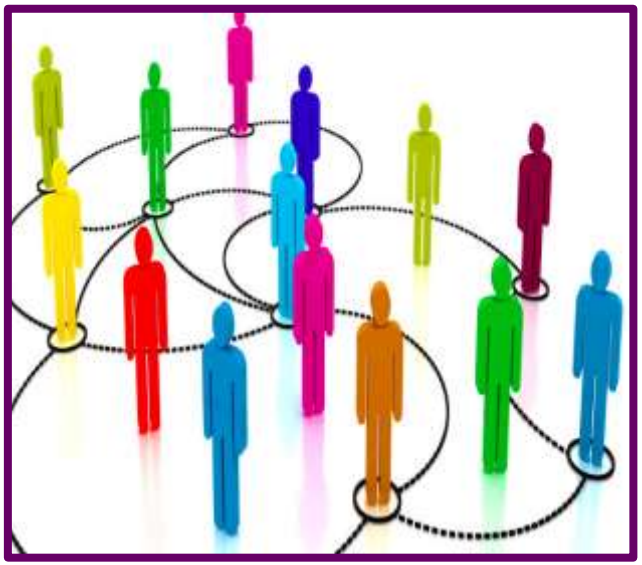




Subclinical
Mild
Severe
Death

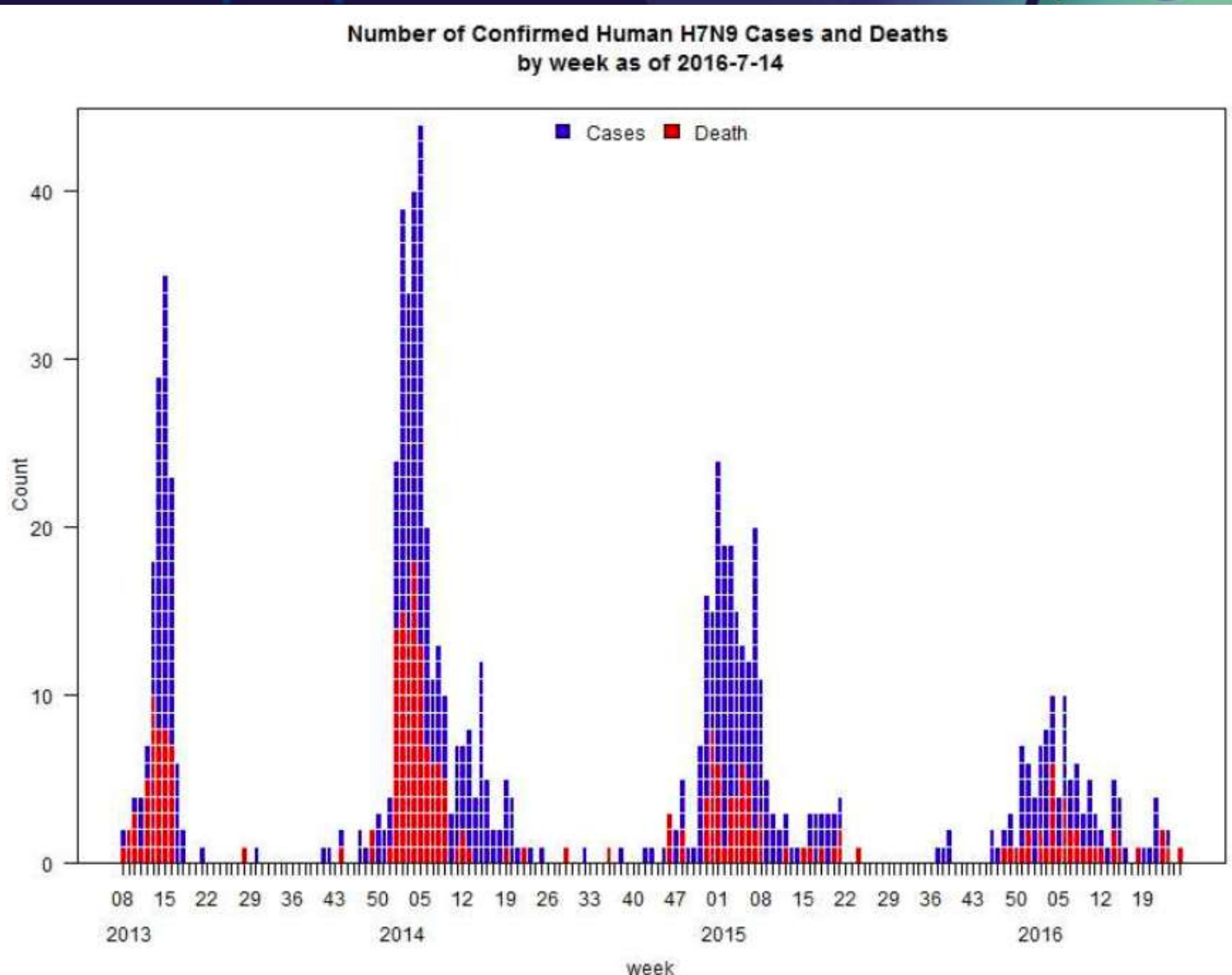

Number of Confirmed Human H5N1 Cases
by month of onset as of 2016-07-21
Azerbaijan (8)
Bangladesh (8)
Cambodia (56)
Canada (1)
China (53)
Djibouti (1)
Egypt (354)
Indonesia (199)
Iraq (3)
Laos (2)
Myanmar (1)
Nigeria (1)
Pakistan (3)
Thailand (25)
Turkey (12)
Viet Nam (127)
Number of Cases
0
10
20
30
40
50
Jan Apr Jul Oct
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
Month of onset





- ✓ *4 waves*
- ✓ *775 confirmed cases*
- ✓ *316 cases died*

Gao RB, et al, NEJM,2013


Number of Confirmed Human H7N9 Cases and Deaths
by week as of 2016-7-14
Cases
Death
Count
0
10
20
30
40
08 15 22 29 36 43 50 05 12 19 26 33 40 47 01 08 15 22 29 36 43 50 05 12 19
2013
2014
2015
2016
week

	Influenza A H7N9 (n=130)	Influenza A H5N1 (n=43)
Median age, years	62 (47–73)	26 (19–35)
Number of men	92 (71%)	22 (51%)
Presence of at least one underlying medical disorder*	50/111 (45%)	5/41 (12%)
Urban residence	93 (72%)	19 (44%)
Rural residence	37 (28%)	24 (56%)
Possible source of infection		
Any exposure to poultry	92/123 (75%)	29/41 (71%)
Occupational exposure to live poultry	6 (5%)	4 (9%)
Visited live poultry market	43/84 (51%)	23/41 (56%)
Exposure to sick or dead poultry	3/123 (2%)	16/41 (39%)
Exposure to backyard poultry	19/71 (27%)	21/41(51%)

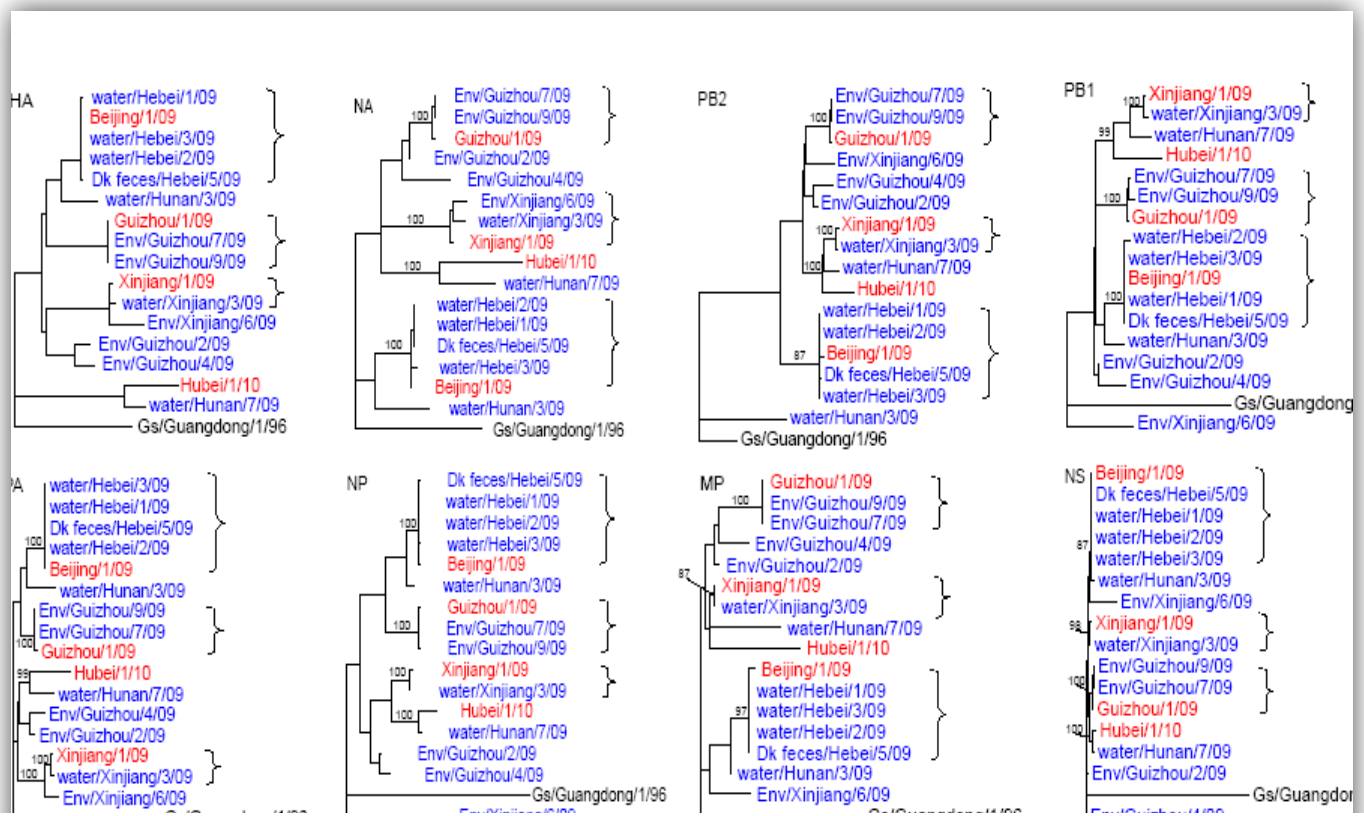
Data are median (IQR), n (%), or n/N (%). *Only underlying medical disorders associated with a high risk for influenza complications[10] were counted here, including chronic respiratory disease, asthma, chronic cardiovascular disease, diabetes, chronic liver disease, chronic kidney disease, immunosuppressed status, and neuromuscular disorders.

Table 1: **Characteristics of laboratory-confirmed cases of human infection with avian influenza A H7N9 and H5N1 viruses in mainland China**

More than 50% human infections with avian influenza viruses H5N1(56%) or H7N9 (51%) due to live poultry market visiting

Hongjie Yu, et al. Lancet, 2013

Investigation the source of Human infection with **H5N1 viruses**



FIRST MOLECULAR EVIDENCE LINKS LIVE POULTRY MARKETS TO HUMAN H5N1 INFECTION IN CHINA

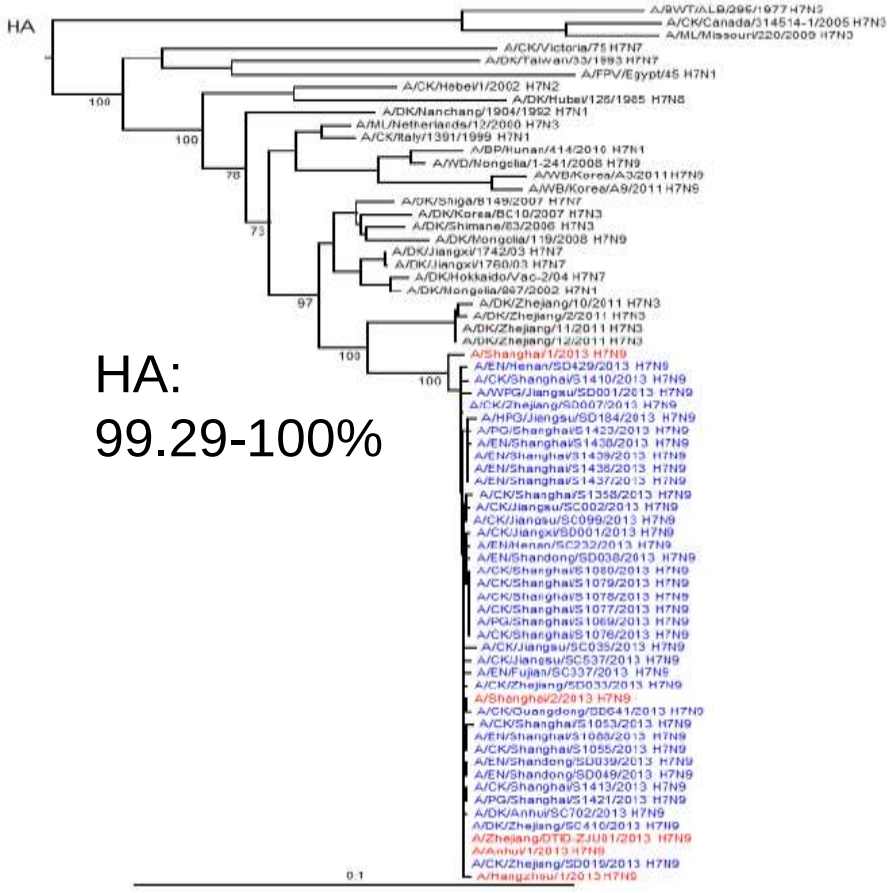
Investigation the source of Human infection with H7N9

Table S1. Details of samples collected for H7N9 influenza virus testing.

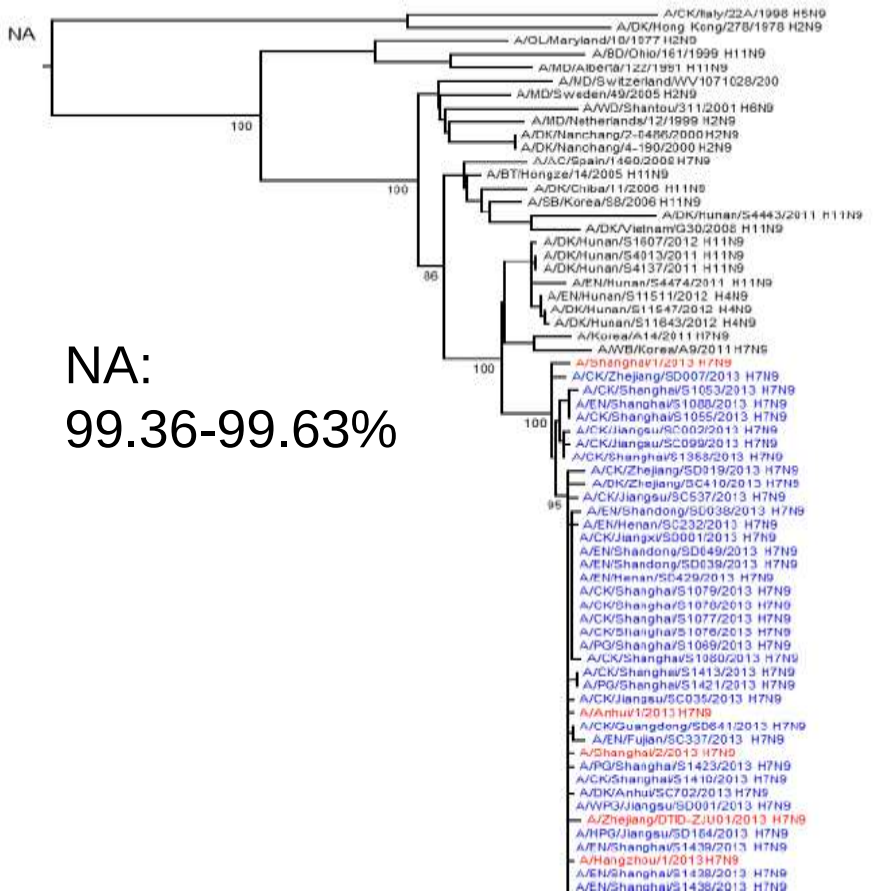
Province or city	Sampling site	Species	Total samples collected	Number of HA-positive samples	Newcastle disease virus-positive	Influenza virus-positive	
						Total	H7N9 virus (sequenced)
Shanghai	Poultry market	Chicken	269	21	2	19	10 (10)
		Duck	8	5	0	5	0
		Pigeon	50	3	0	3	3 (3)
		Environment	80	23	5	18	7 (5)
	Farm	Chicken	449	1	0	1	0
		Duck	350	0	0	0	0
		Pigeon	120	0	0	0	0
		Swine	150	0	0	0	0
	Wild bird habitat	Feces	219	0	0	0	0
	Slaughterhouse	Swine	300	0	0	0	0
Anhui	Poultry market	Chicken	255	4	0	4	0
		Duck	45	1	0	1	1 (1)
		Goose	75	1	0	1	0
		Pigeon	15	1	0	1	0
		Environment	10	2	1	1	0
	Farm	Chicken	450	1	1	0	0
		Duck	45	0	0	0	0
		Goose	114	0	0	0	0
		Pigeon	15	0	0	0	0
		Swine	96	0	0	0	0
	Wild bird habitat	Feces	65	0	0	0	0
	Slaughterhouse	Swine	216	0	0	0	0
Jiangsu	Poultry market	Chicken	319	92	39	53	11 (4)
		Duck	25	3	2	1	0
		Goose	15	0	0	0	0
		Pigeon	25	0	0	0	0
		Environment	29	9	9	0	0
	Farm	Chicken	79	3	2	1	0
		Duck	87	0	0	0	0
		Homing pigeon	50	1	0	1	1 (1)
		Swine	35	0	0	0	0
	Wild bird habitat	Wild Pigeon	1	1	0	1	1 (1)
		Feces	134	0	0	0	0
	Slaughterhouse	Swine	311	0	0	0	0

Q Zhang et al., Science, 2013

Investigation the source of Human infection with H7N9



HA:
99.29-100%



NA:
99.36-99.63%

Q Zhang et al., Science, 2013

Investigation the source of Human infection with H7N9

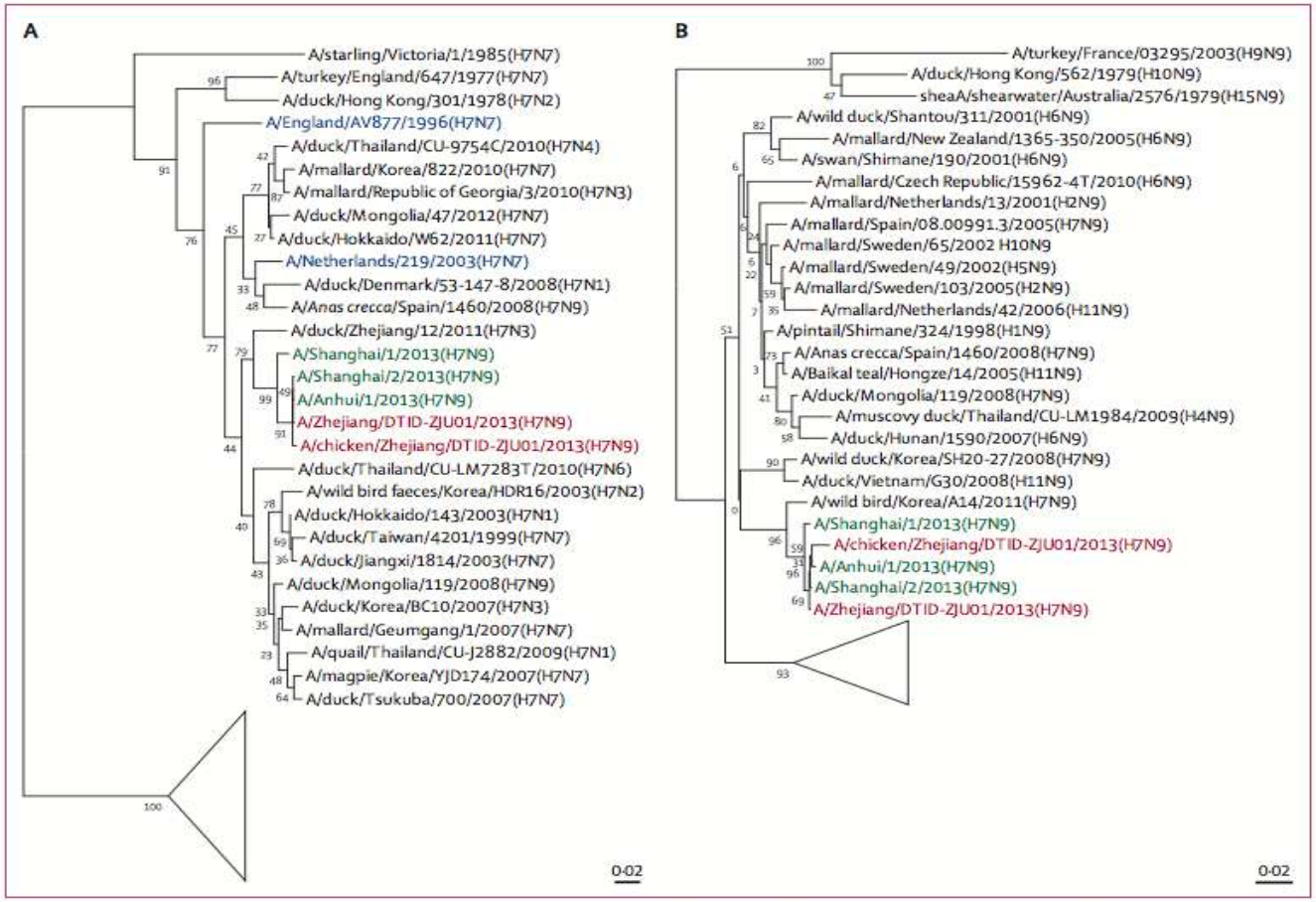
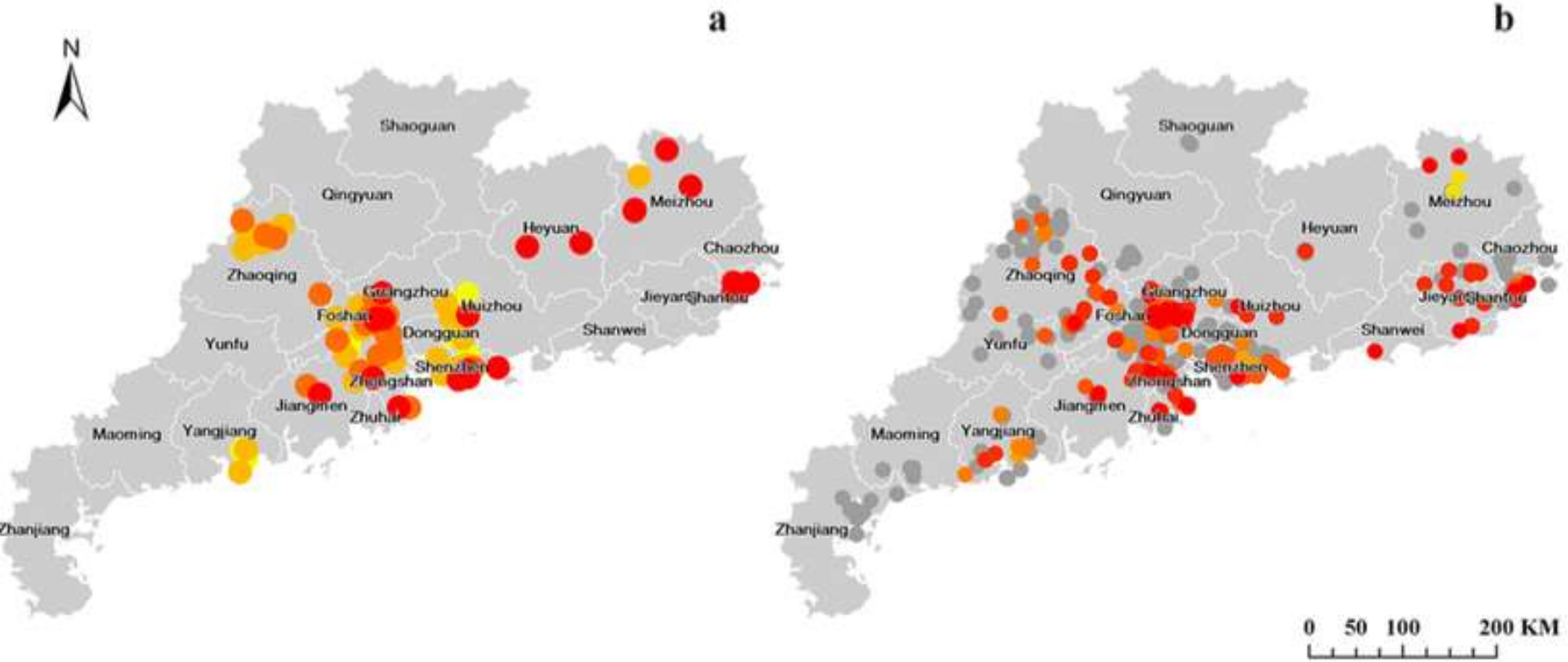


Figure 3: Phylogenetic trees for the haemagglutinin (HA1) (A) and neuraminidase (N) (B) genes of H7N9 viruses isolated from a patient and a chicken in Zhejiang, China

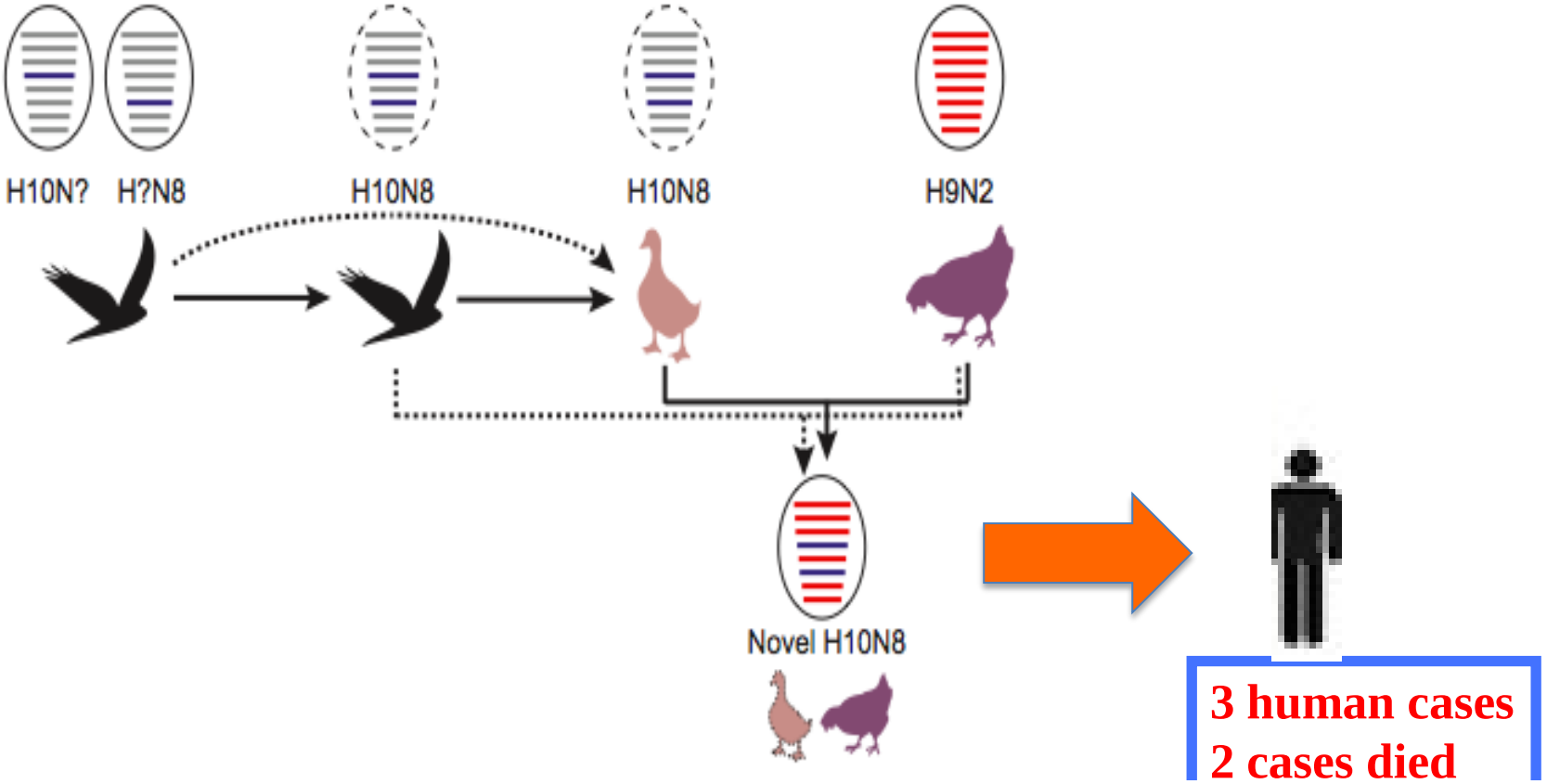
Yu Chen, et al. Lancet, 2013



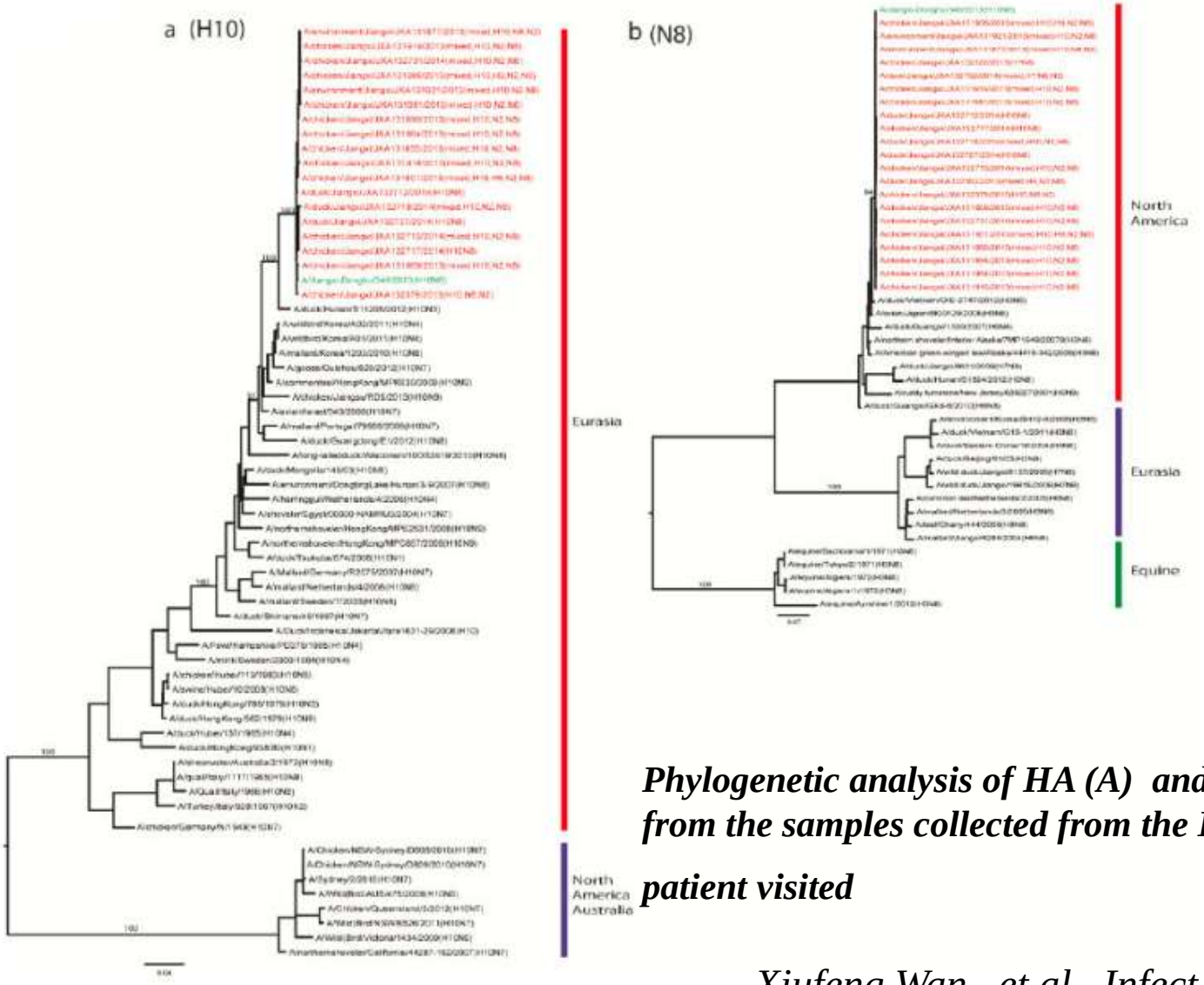
Geographic distribution of H7N9 human infection and H7N9-positive markets in Guangdong

(a) Human infection with H7N9 in Guangdong. (b) H7N9-positive markets in Guangdong.

Haojie Zhong., et al., Plos One. 2015

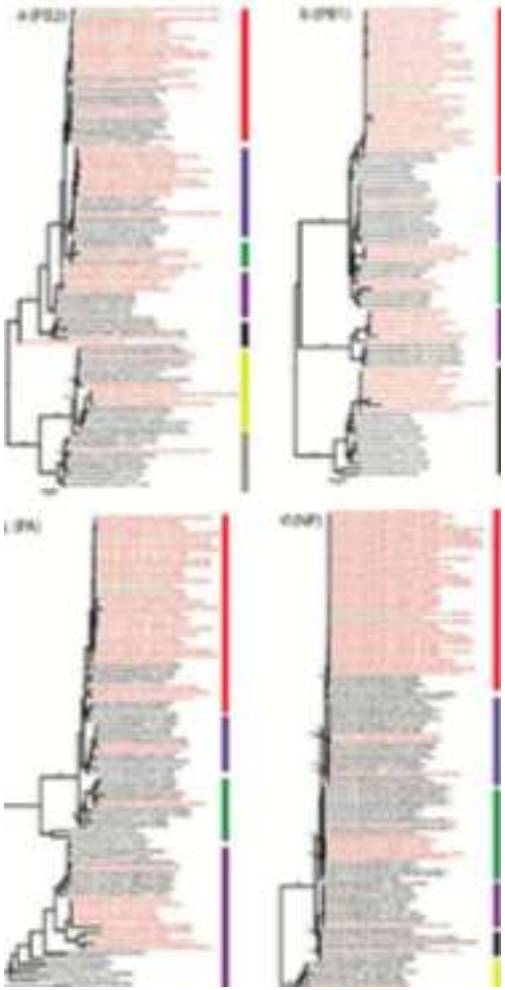


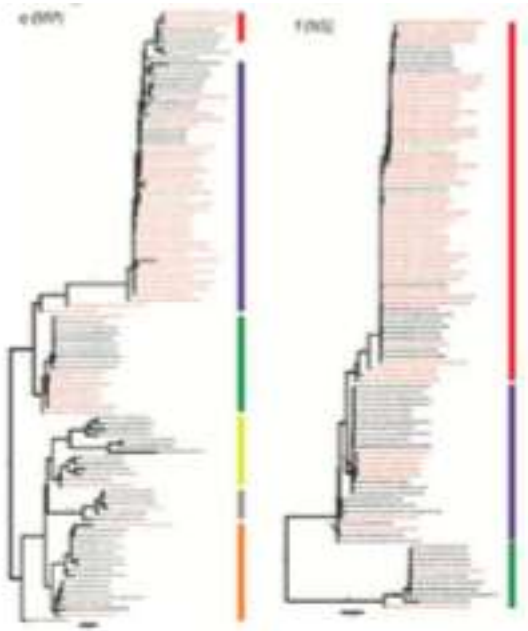
Clinical and epidemiological characteristics of a fatal case of avian influenza A H10N8 virus infection: a descriptive study



Phylogenetic analysis of HA (A) and NA genes recovered from the samples collected from the LPM which the index patient visited

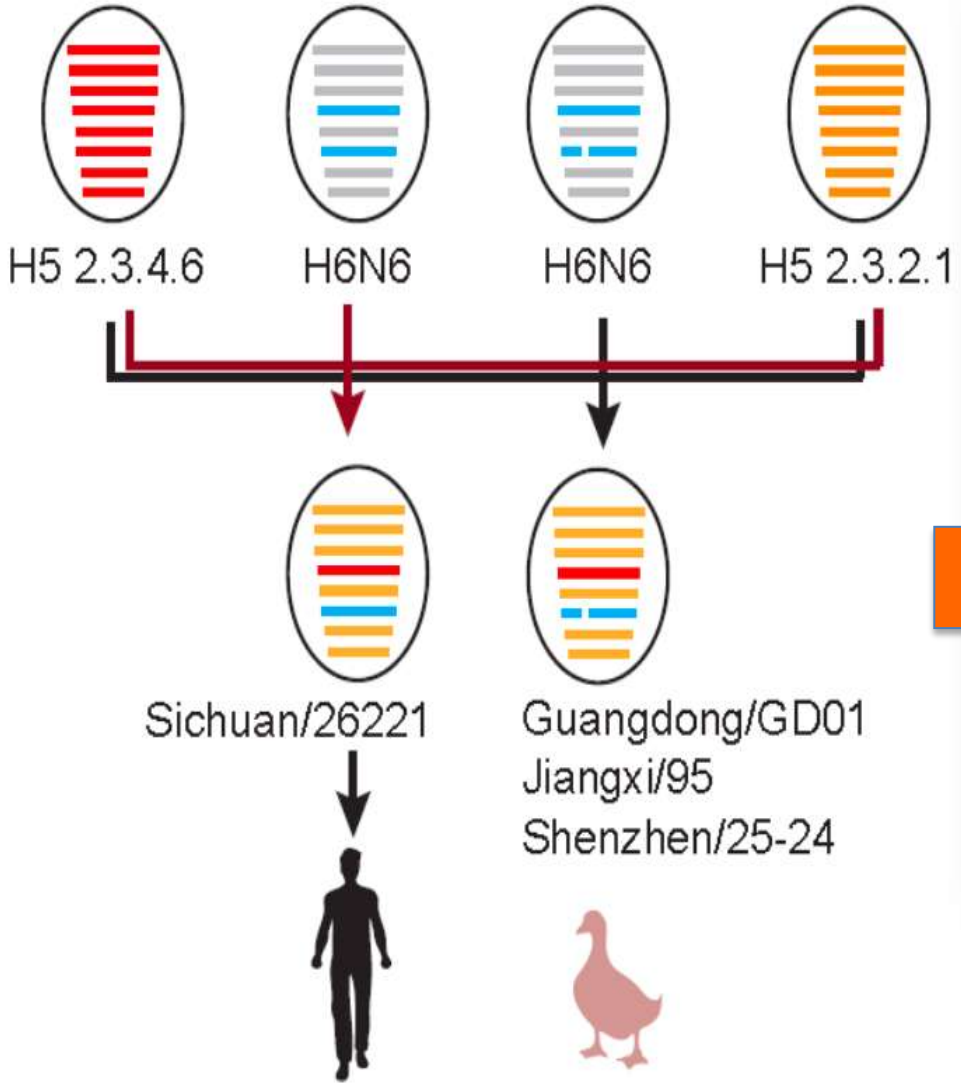
Xiufeng Wan., et al., Infect Genet Evol. 2015





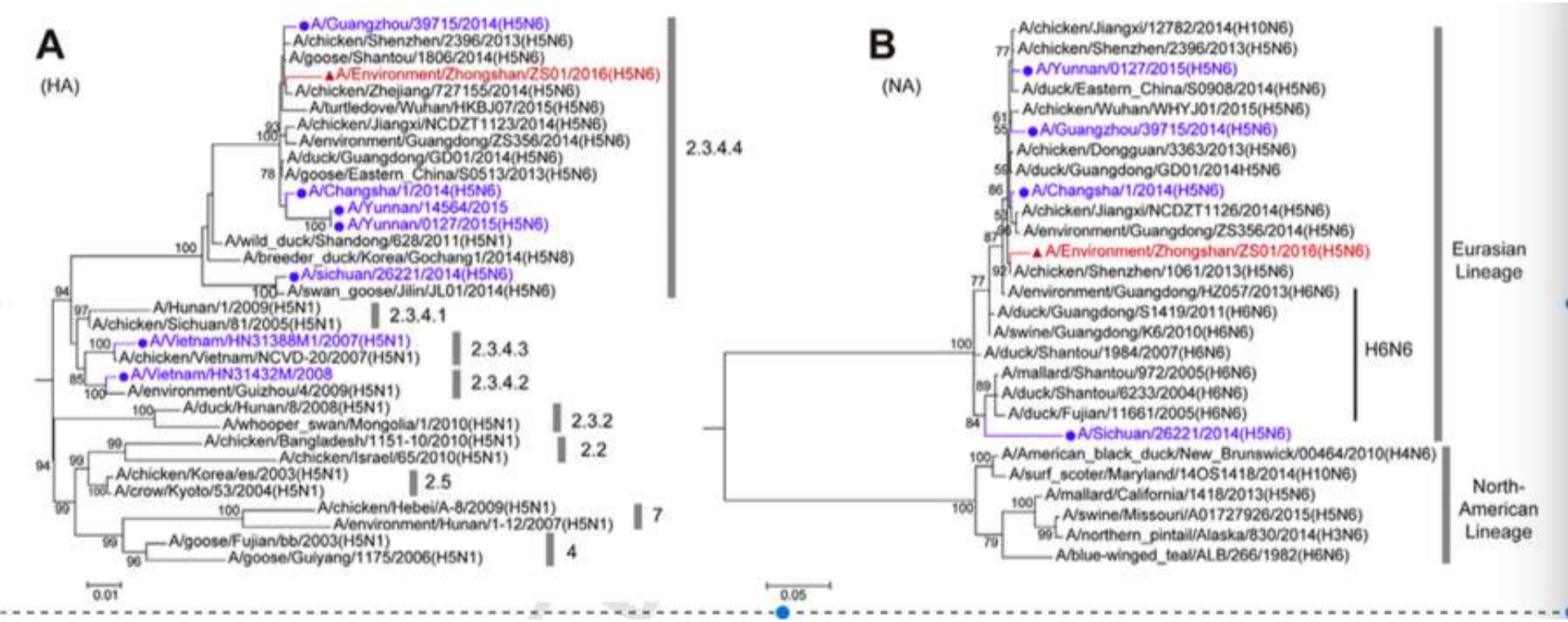
Phylogenetic analysis of PB2 (A), PB1 (B), PA (C), NP (D), MP (E), and NS (F) genes recovered from the samples collected from the LPM which the index patient visited

Xiufeng Wan., et al., Infect Genet Evol. 2015



- ✓ *14 confirmed cases*
- ✓ *10 cases died*

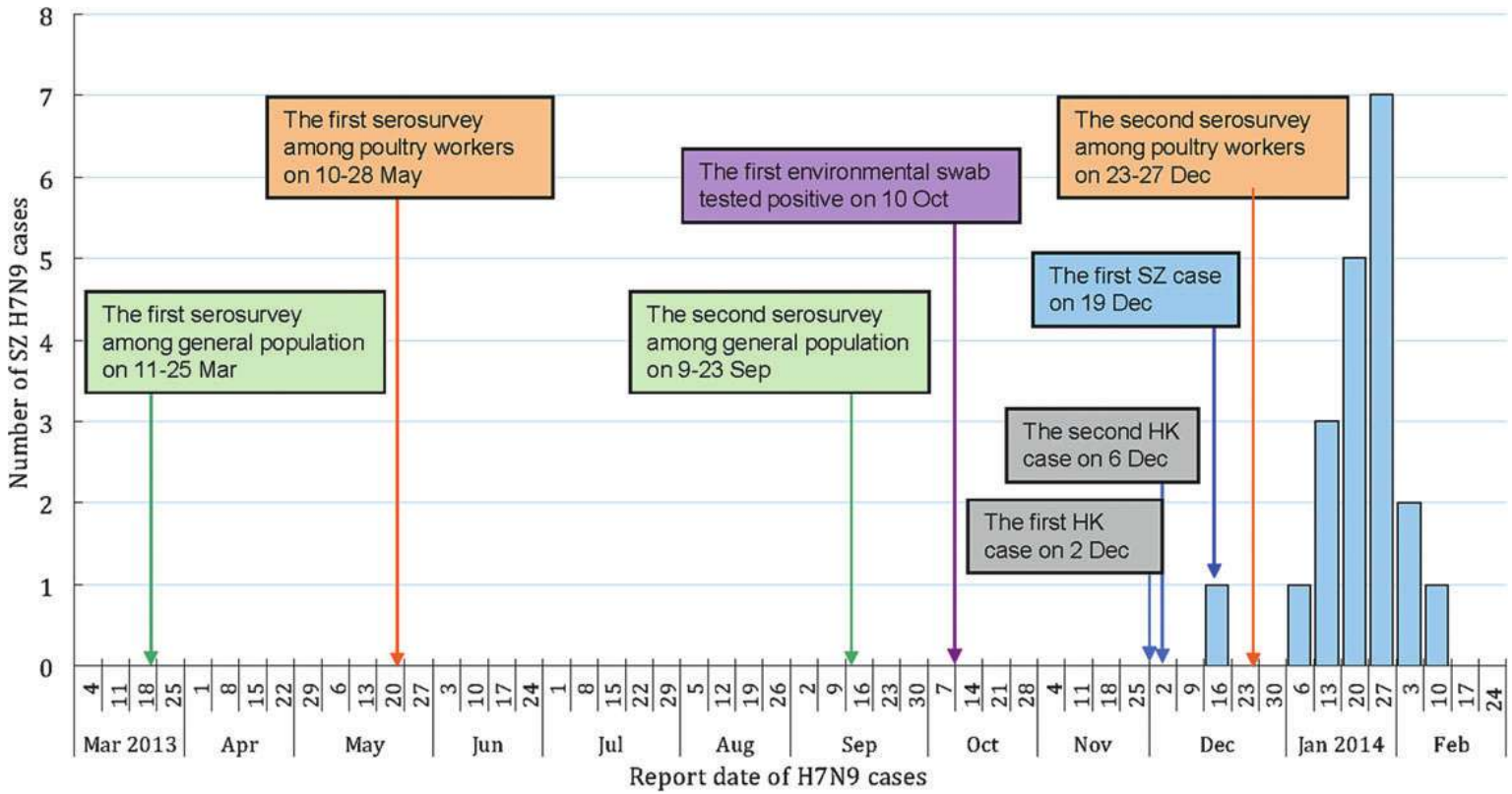
Aerosolized avian influenza A (H5N6) virus isolated from a live poultry market, China



Jiahai Lu., et al. J Infect2016

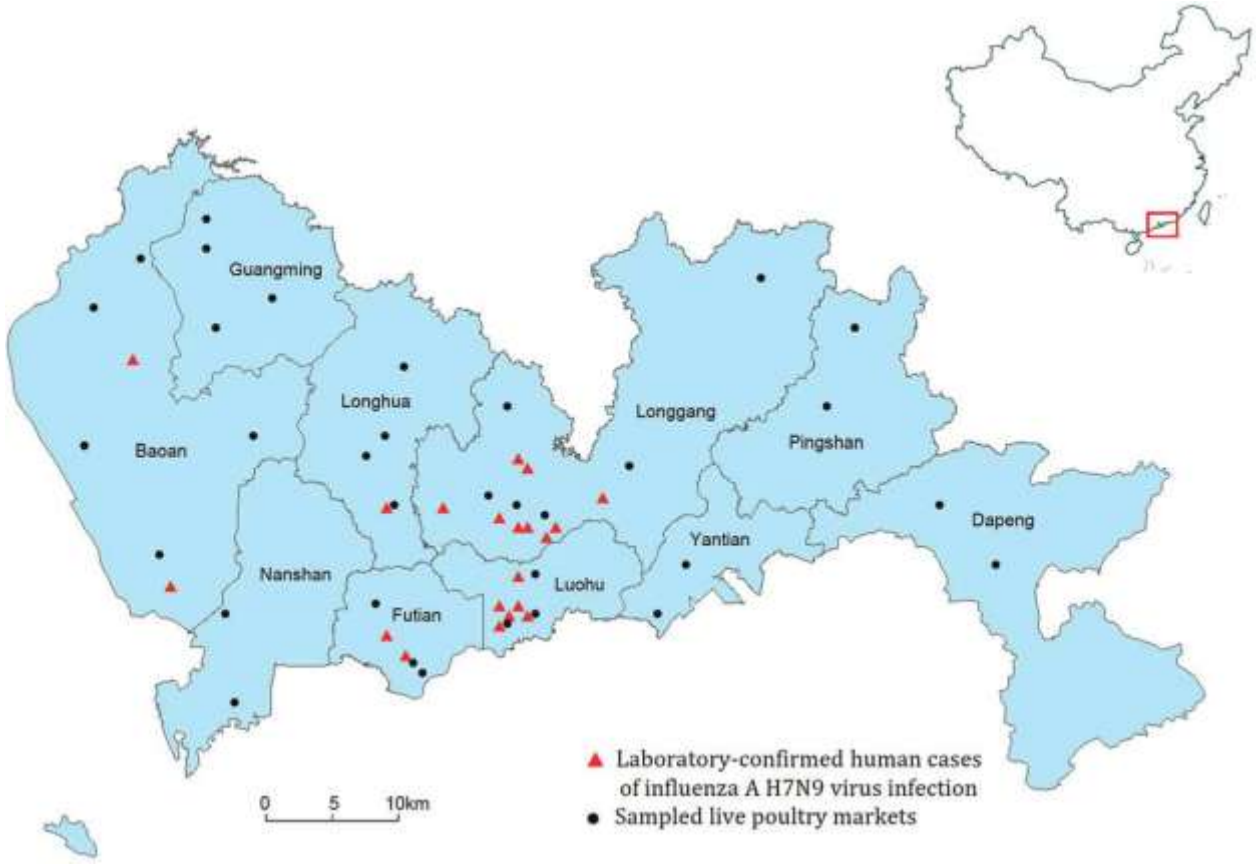
- ✓ The overall seroprevalence of H5N1 in Viet Nam was 4.% in 2001and 6.1% in 2011respectively
- ✓ the A(H5N1) seropositive rate among LPM workers increased from 0% in 2013 to 37.8% in 2014 ($P < 0.001$) and the A(H9N2) seropositive rate increased from 10% to 55.6% ($P < 0.001$) in Hong Kong
- ✓ the positive rate of anti-H9 antibody among market poultry workers (51/600, 8.5%) was significantly higher than that among the general population (11/600, 1.8%)
- ✓ The positive rate of anti-H6 antibody among market poultry workers was 0.4% (63/15689) in China
- ✓ The positive rate of anti-H7 antibody among market poultry workers was3.2% in Italy

Schultsz C et al ., Plos One 2005 Tham C et al ., WPSAR 2014
Li S et al ., J Med Virol 2016 To KK et al., J infection 2016
Xin L et al., EID 2015 Di TL , et al. Avian Dis. 2012



Serological studies suggested a substantial risk of mild H7N9 infections in live poultry markets

Jinquan Cheng., et CID 2014



Serological studies suggested a substantial risk of mild H7N9 infections in live poultry markets

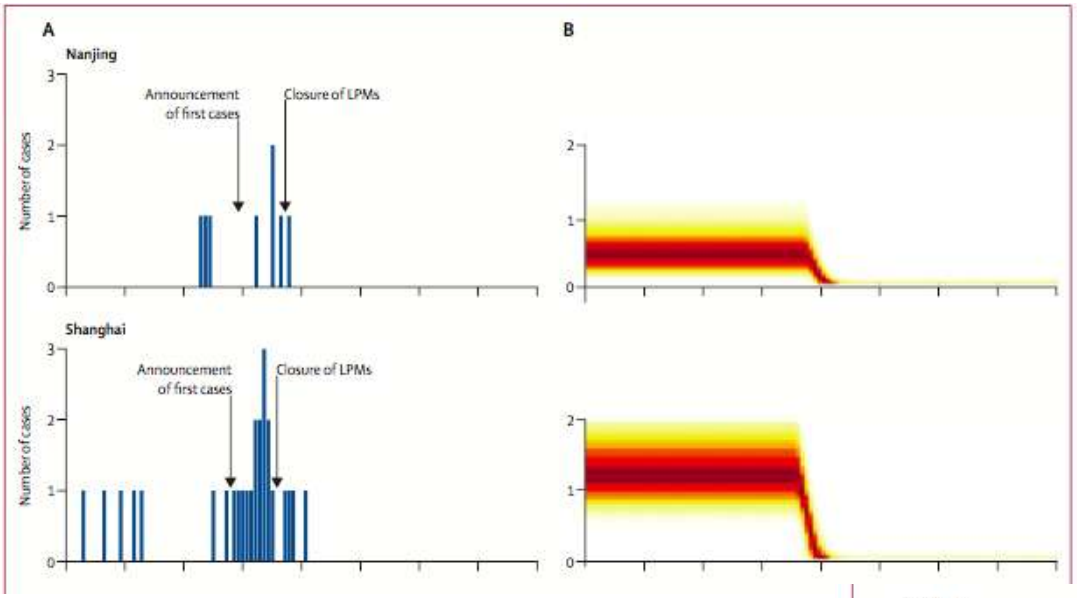
Jinquan Cheng., et CID 2014

- ✓ First survey: poultry workers (36/501=7.2%)

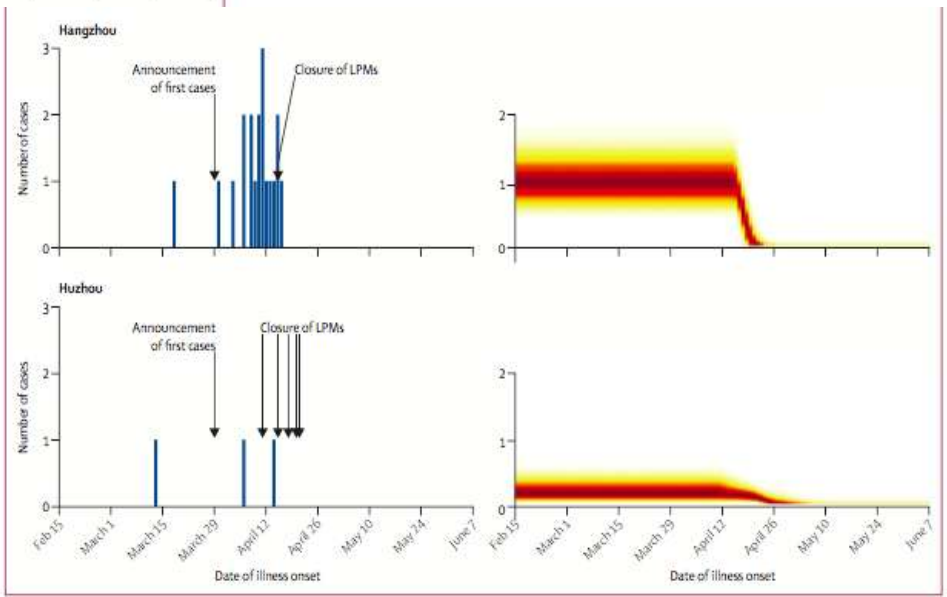
  general population(0/417)
- ✓ Second survey: poultry workers(56/375=14.9%),

  general population(0/408)
- ✓ Of 96 individuals who participated in both surveys, 52 (54.2%) workers had a ≥4-fold rise in H7N9 antibody
- ✓ In a multivariable analysis, female sex and ≥10 years of occupational exposure were identified as risk factors for infection.
- ✓ Serological studies suggested a substantial risk of mild H7N9 infections in live poultry markets

Jinquan Cheng., et CID 2014



The closure of LPMs reduced the mean daily number of infections by 99% in Shanghai, 99% in Hangzhou, 97% in Huzhou, and 97% in Nanjing

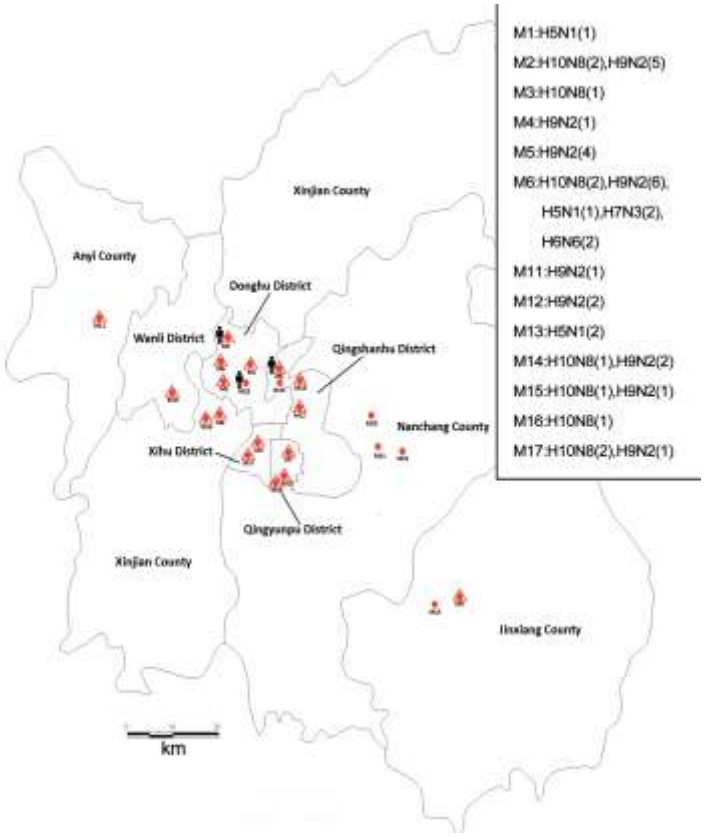


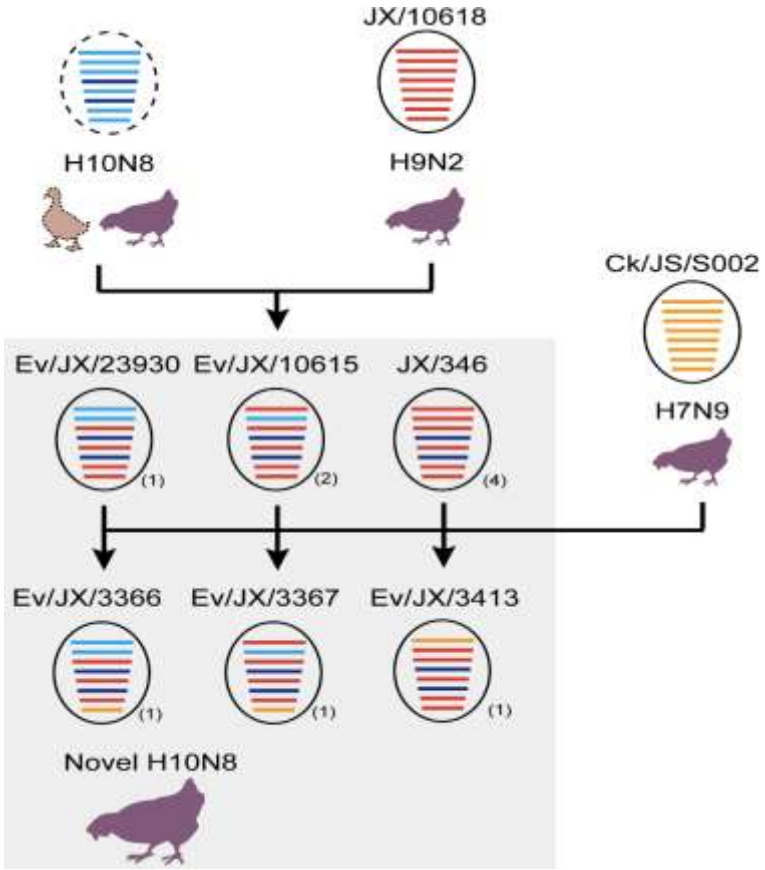
Live poultry markets

- Source of human infections

- Source of generation of novel influenza viruses

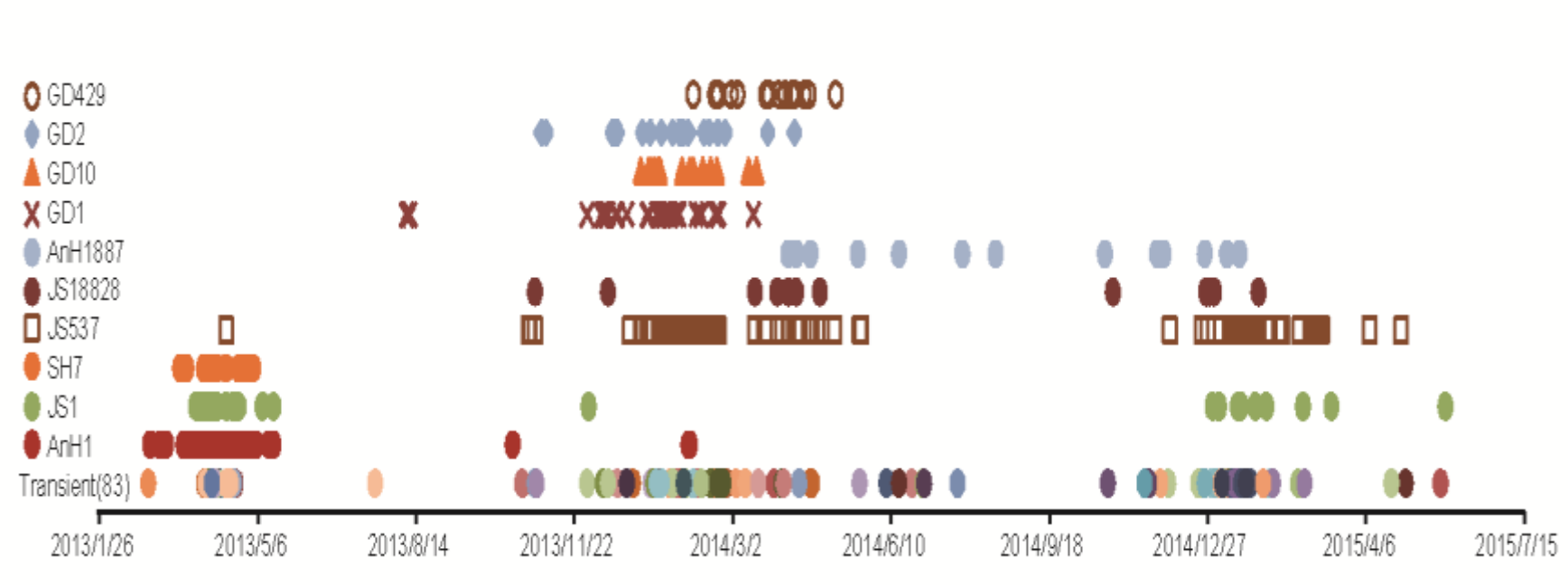
The genesis of H10N8 avian influenza viruses in poultry markets





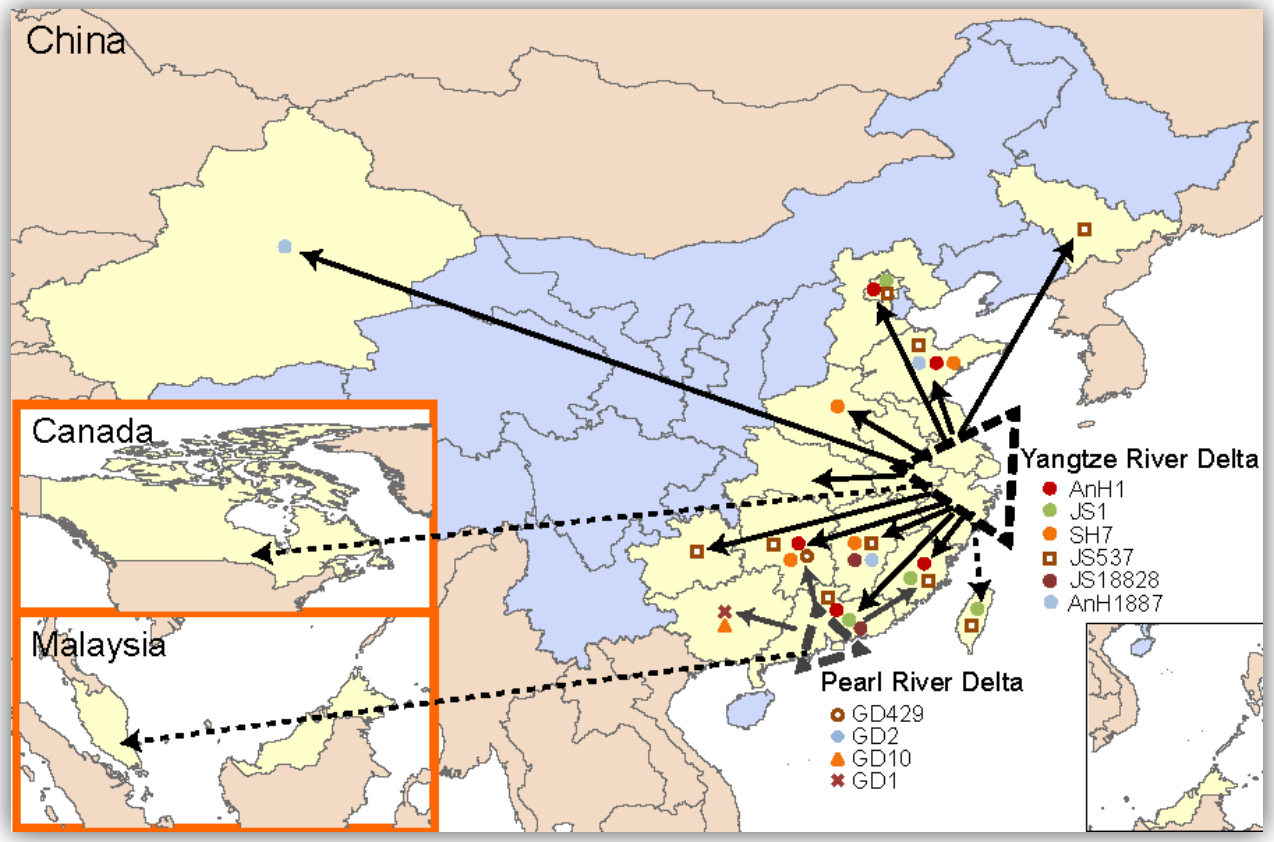
Shu et al, Scientific Report, 2015

Frequent reassortment events of H7N9 AIVs

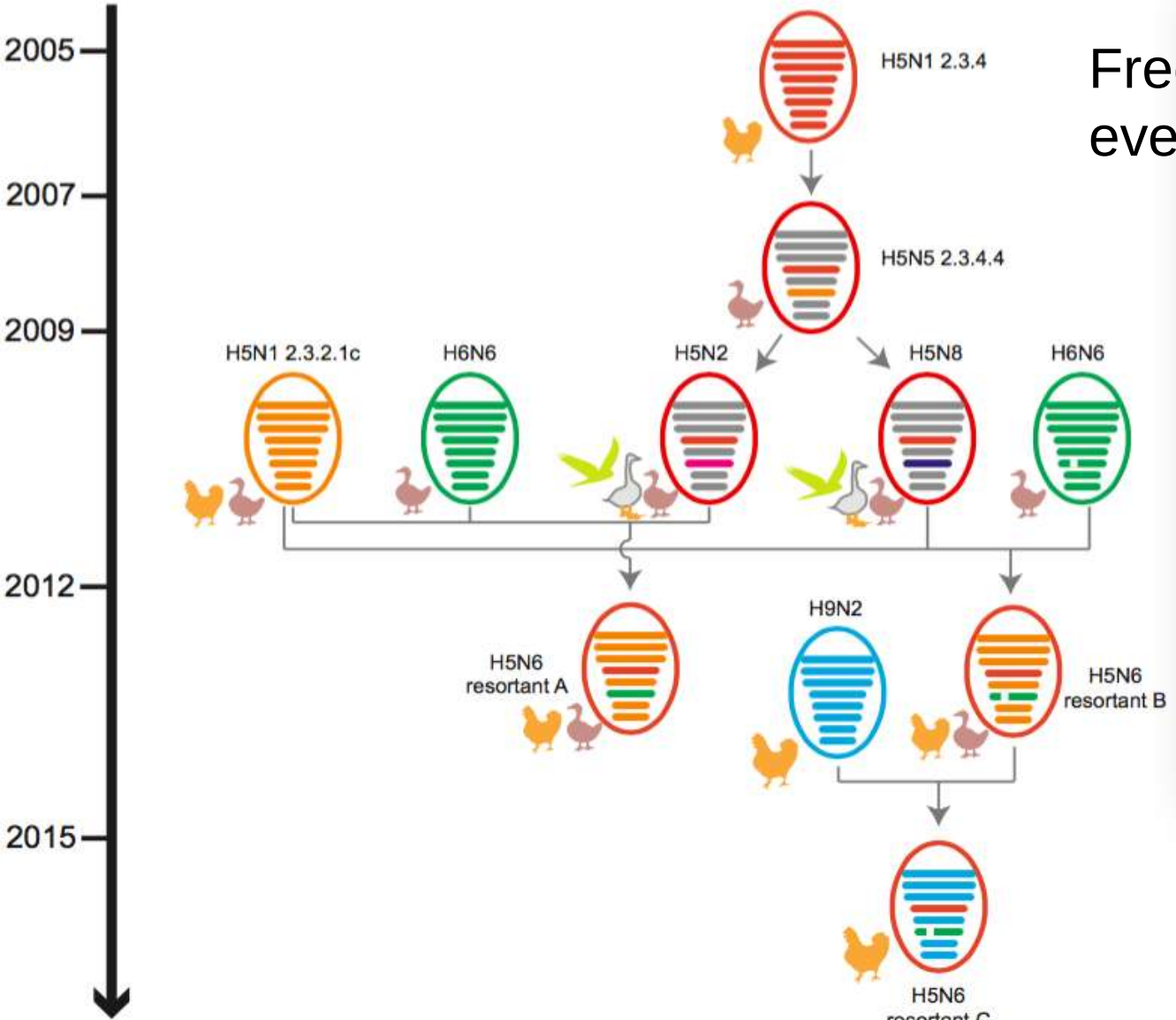


Shu et al, J Virol, 2016

Dissemination of H7N9 AIVs

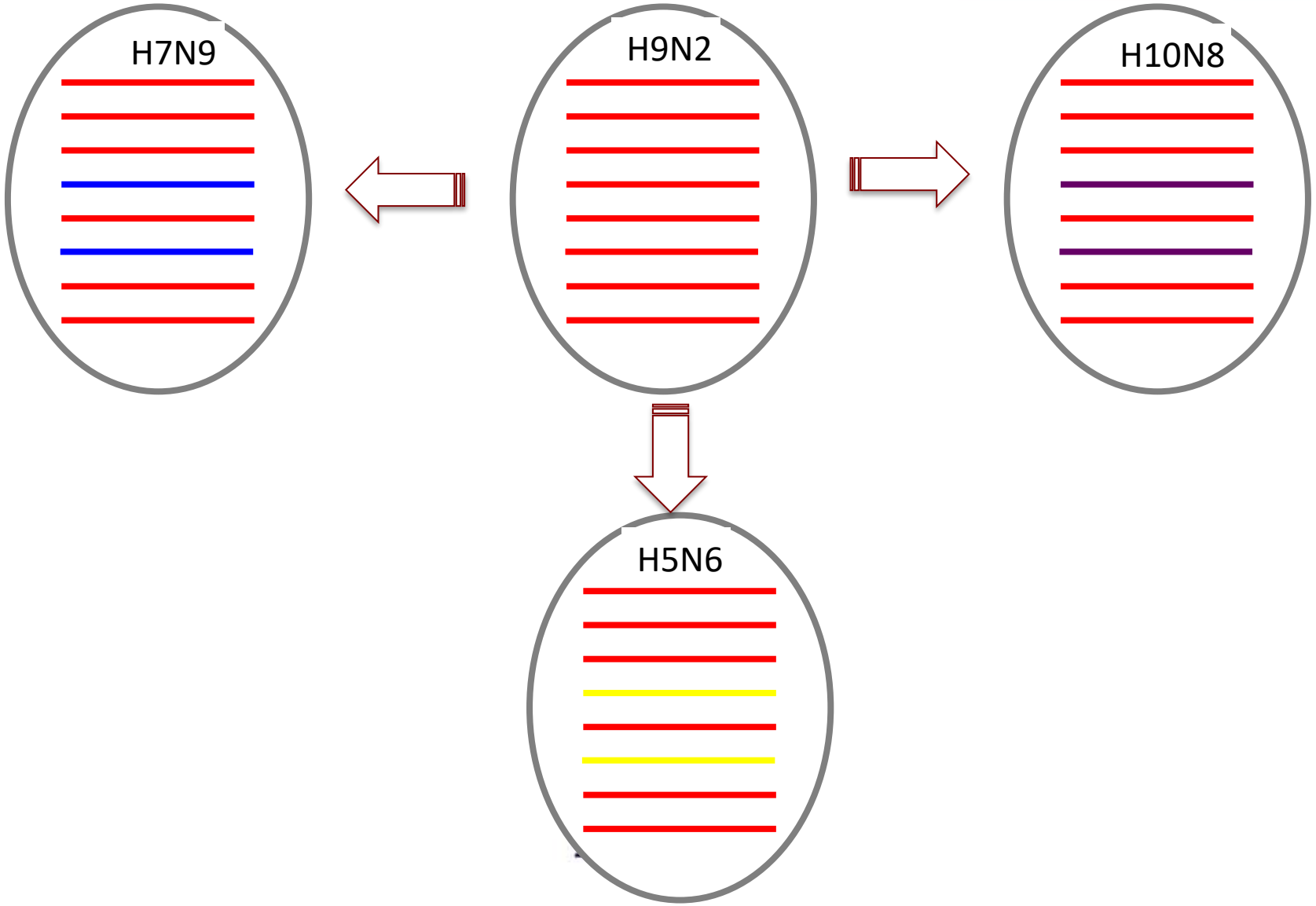


Shu et al, J Virol, 2016



Frequent reassortment events of H5N6 AIVs

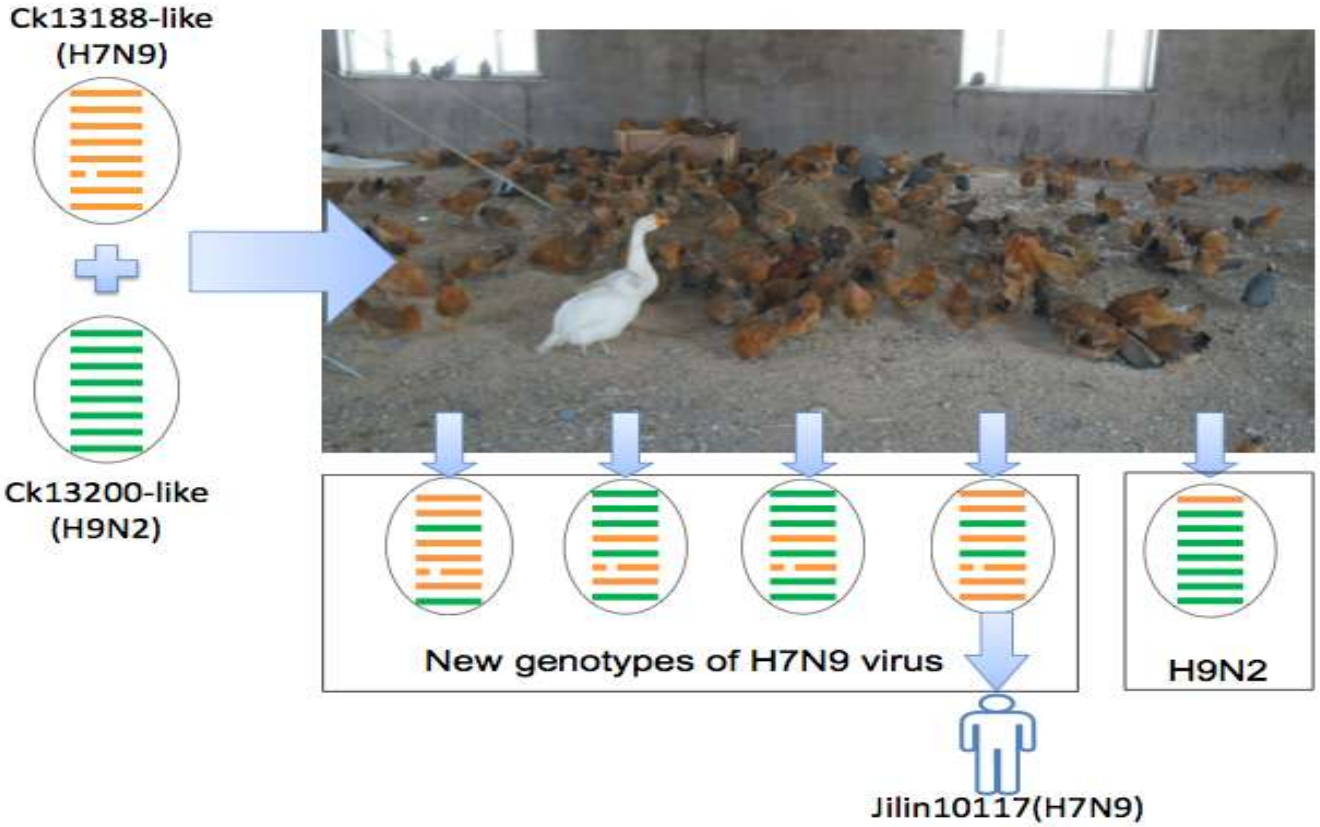
Shu et al, submitted


H7N9
H9N2
H10N8
H5N6

Poultry farm

emergence of novel viruses

Poultry farm --- emergence of novel viruses



Poultry farm --- emergence of novel viruses

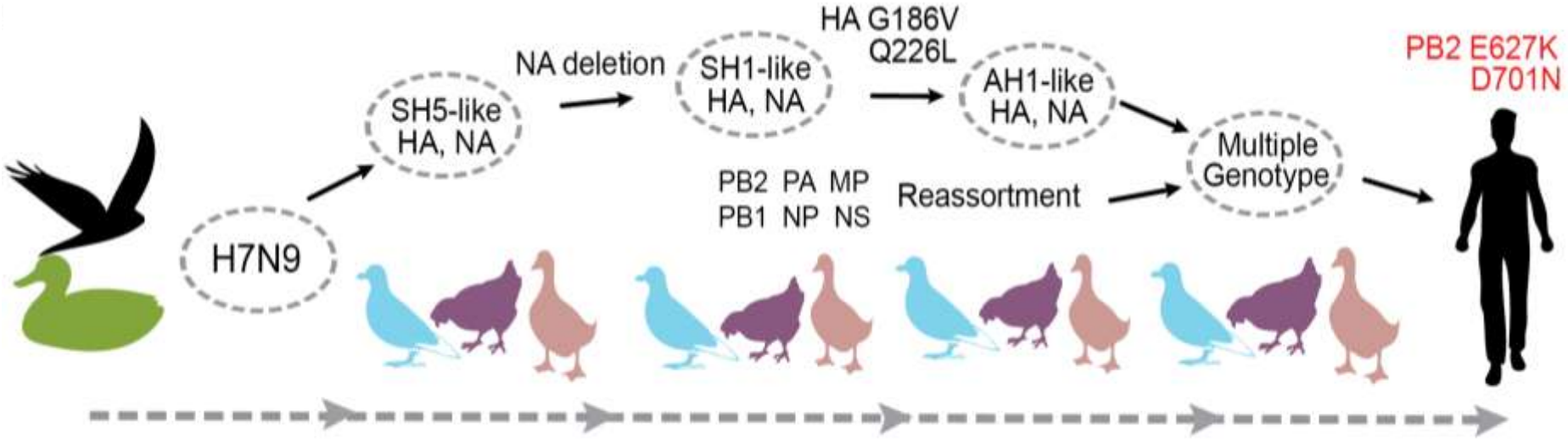
Table. Homology among influenza viruses closely related to avian influenza virus A/chicken/Jilin/SD020/2014(H7N2) from Jilin, China, 2014*

Gene	Virus	Homology, %
HA	A/chicken/Zhejiang/S4135/2013(H7N9)	99.6
NA	A/chicken/Jilin/SD001/2014(H9N2)	99.1
PB2	A/chicken/Zhejiang/S4135/2013(H7N9)	99.9
PB1	A/chicken/Zhejiang/S4135/2013(H7N9)	99.5
PA	A/chicken/Hunan/SD015/2014(H7N9)	99.7
NP	A/Shanghai/02/2013(H7N9)	99.8
M	A/Shanghai/5190T/2013(H7N9)	99.7
NS	A/chicken/Jilin/SD001/2014(H9N2)	100

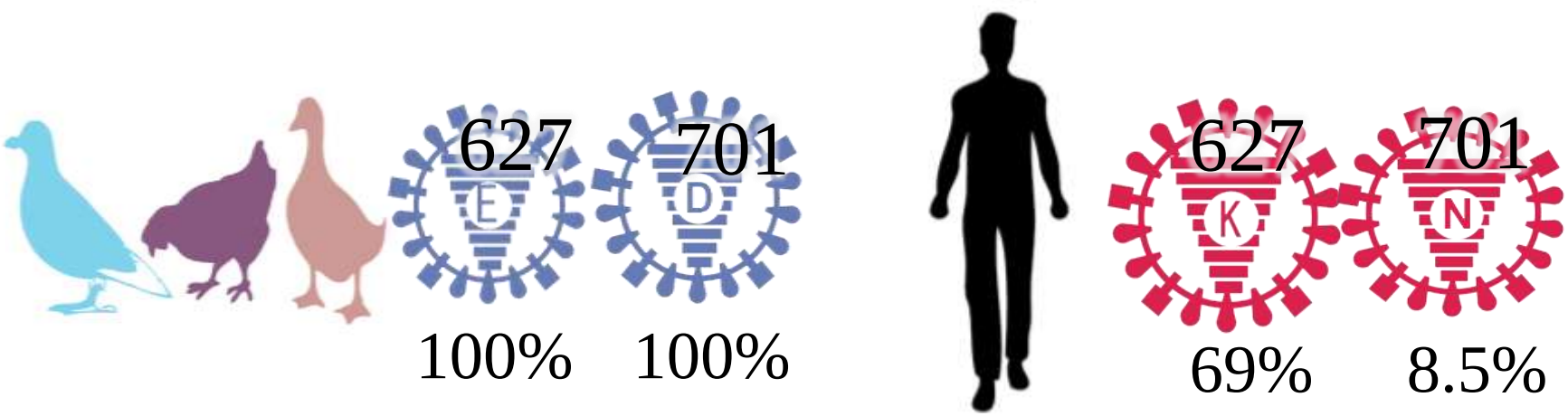
*HA, hemagglutinin; NA, neuraminidase; NP, nucleoprotein; M, matrix; NS, nonstructural; PA, polymerase basic; PB, polymerase basic.

Shi et al, EID, 2014

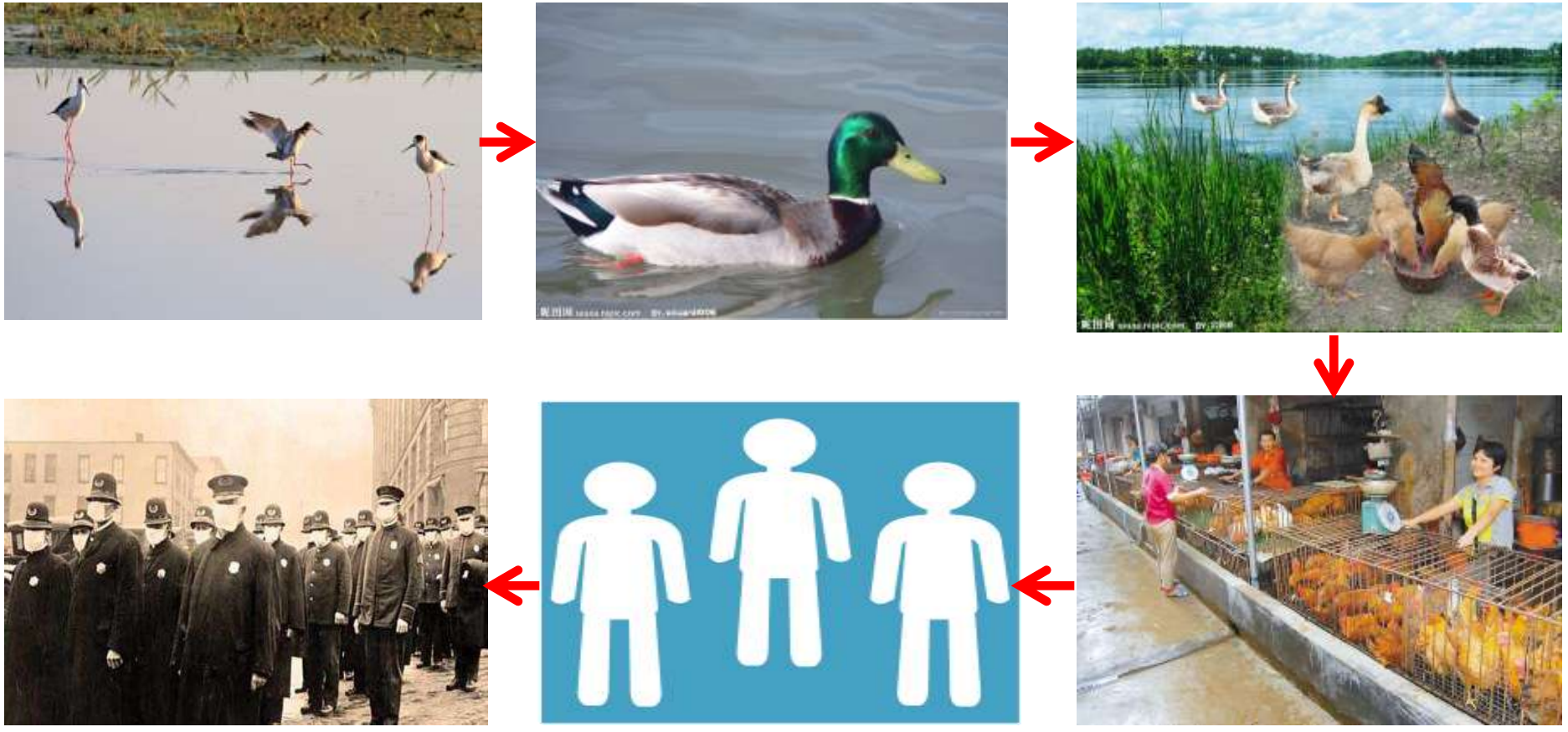
Genetic tuning promote the interspecies transmission



Wang D et al, Eurosurveillance, 2014



Interspecies transmission of influenza A viruses



What we could do?

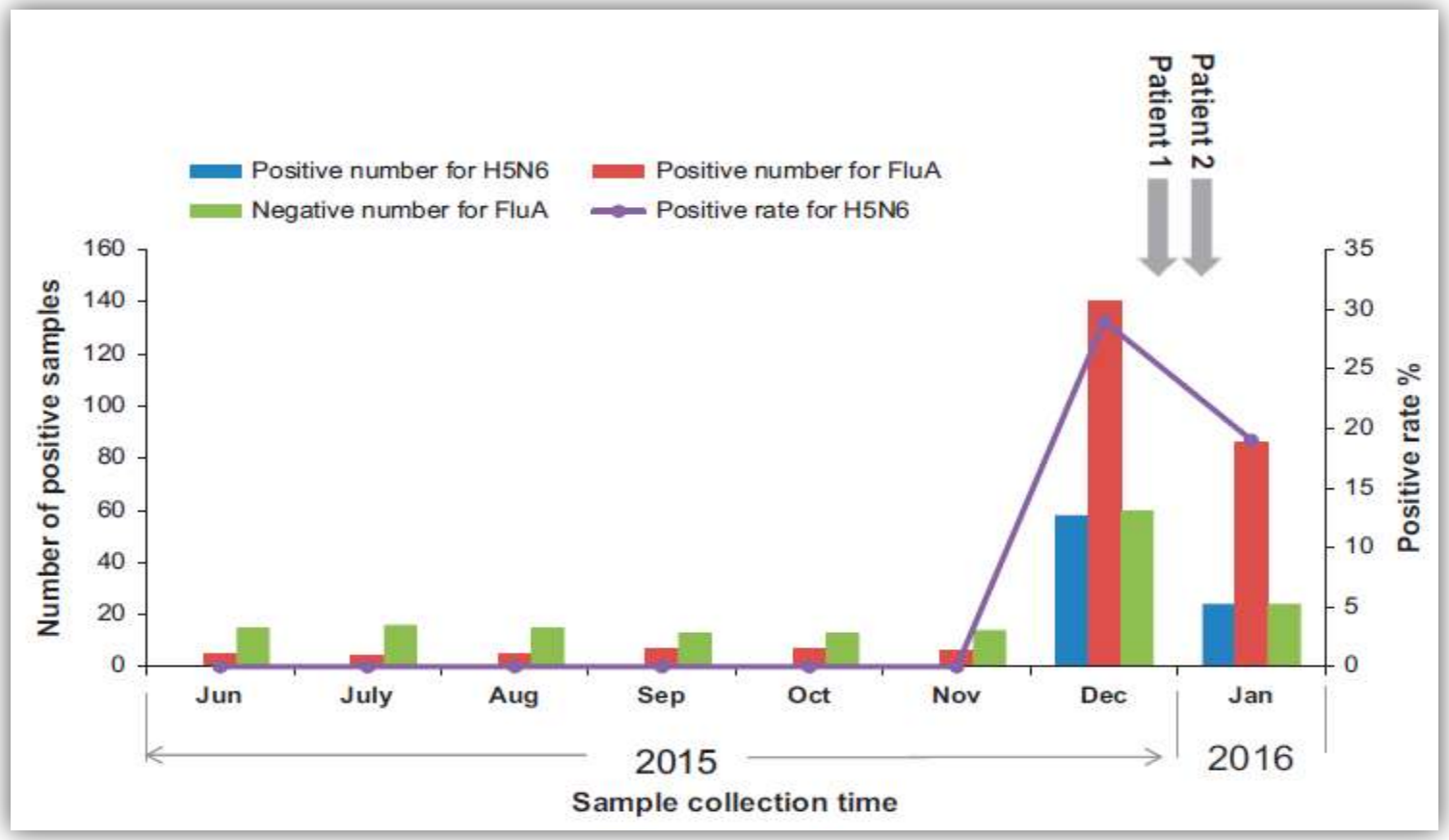
LPM surveillance

Sustained LPM surveillance in China

	N1	N2	N3	N5	N6	N7	N8	N9
H1								
H2								
H3								
H4								
H5								
H6								
H7								
H9								
H10								
H11								
H12								

- **250,000 were collected from live poultry markets and farms**
- **More than 40,000 viruses isolated**
- **1000 whole genome sequenced**

Sustained LPM surveillance contributes to early warnings for human infection with AIVs

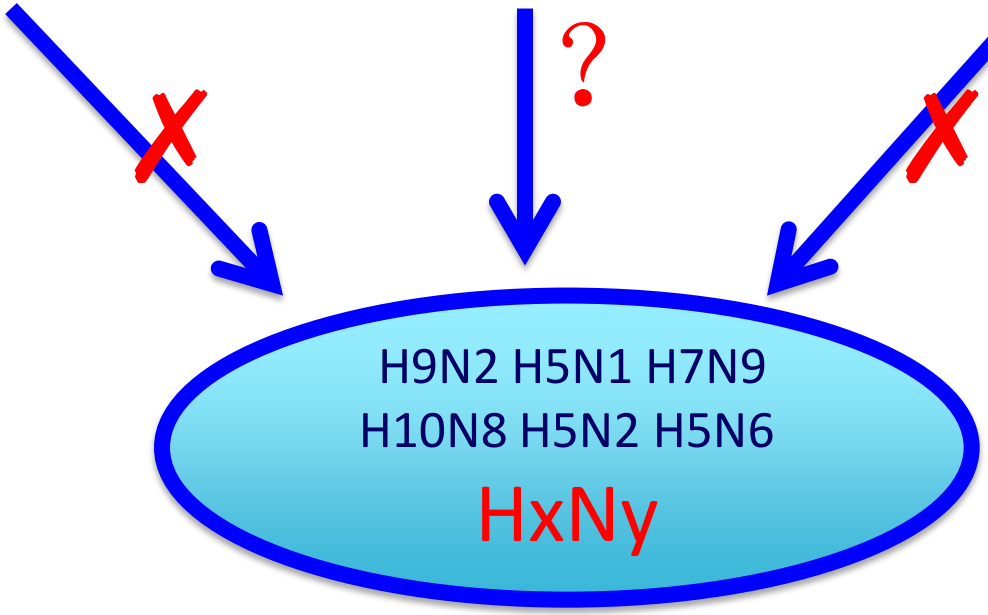


Shu YL et al, Emerging Microbes & Infections, 2016

Production system

Vaccination

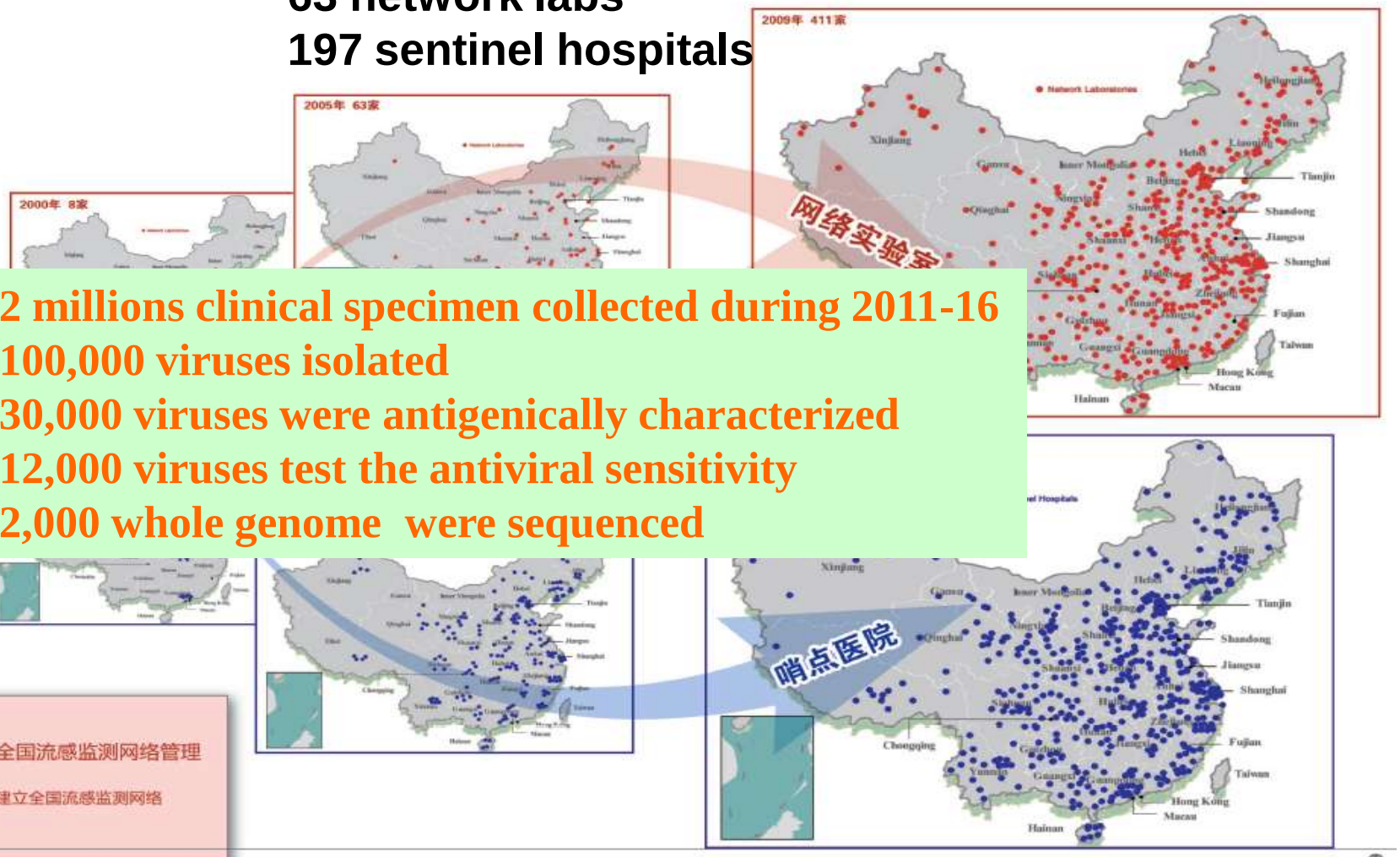
live poultry mareket



Surveillance, always surveillance

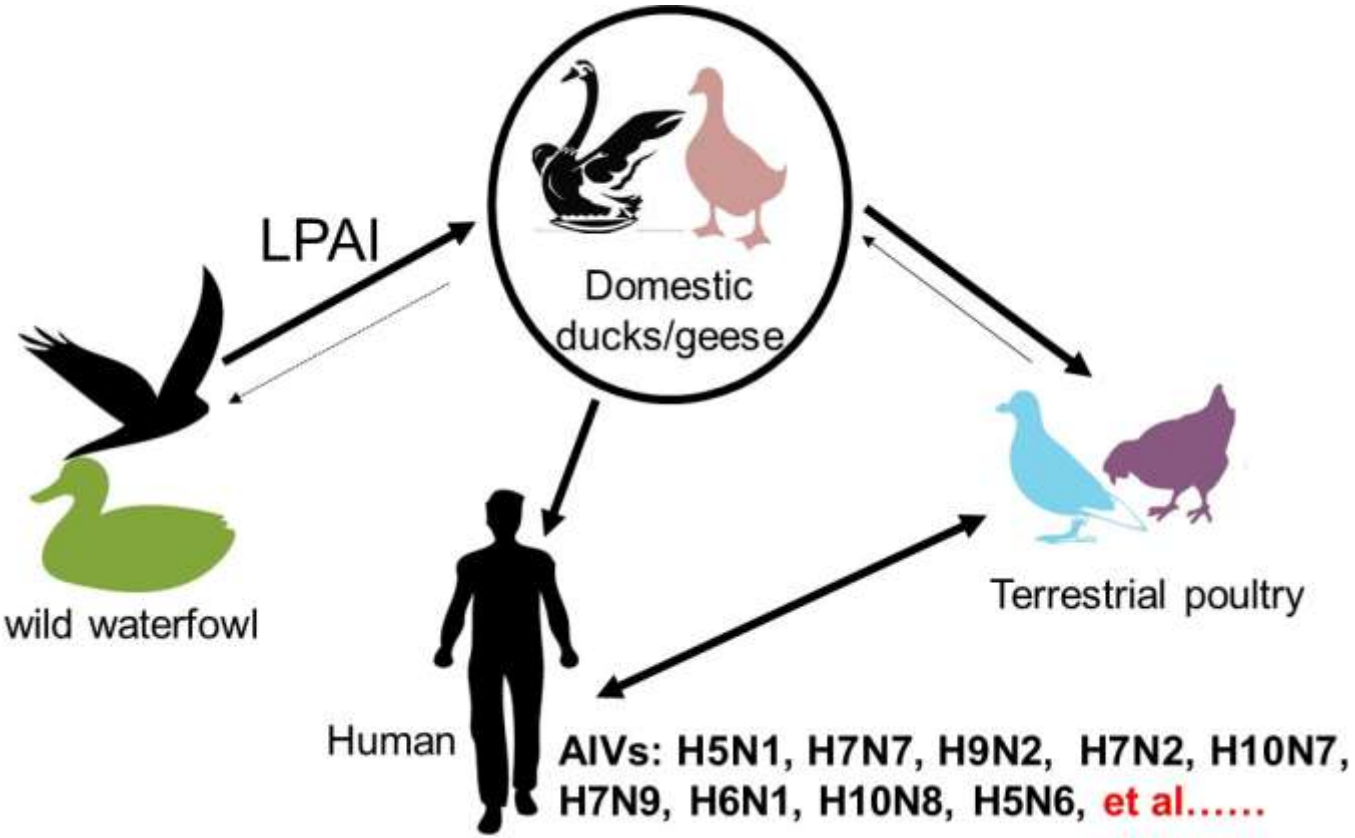
411 network labs
556 sentinel hospitals

63 network labs
197 sentinel hospitals



- 2 millions clinical specimen collected during 2011-16
- 100,000 viruses isolated
- 30,000 viruses were antigenically characterized
- 12,000 viruses test the antiviral sensitivity
- 2,000 whole genome were sequenced

Summary


LPAI
Domestic ducks/geese
wild waterfowl
Terrestrial poultry
Human
AIVs: H5N1, H7N7, H9N2, H7N2, H10N7, H7N9, H6N1, H10N8, H5N6, et al……

SAVE THE DATE: 14-16 June 2017

The 5th isirv-AVG Conference

Prevention and Treatment of Respiratory Virus Infections: Antivirals, Traditional Therapies, Probiotics and Host-Directed Interventions

Regal East Asia Hotel, Shanghai, China, **14-16 June 2017**

This Conference will be of interest to research investigators, clinicians and Public Health experts. It will focus on the progress in combatting respiratory virus infections (RVIs) with vaccines and therapeutics, including novel antiviral approaches, and will address regional issues, like the impact of RVIs in Asia and the use/effectiveness of traditional Chinese medicines. A special symposium on novel coronaviruses (SARS/MERS) will be featured.

Thank you for your attention!