

Integration of animal influenza surveillance into influenza pandemic planning

Hui-Ling Yen

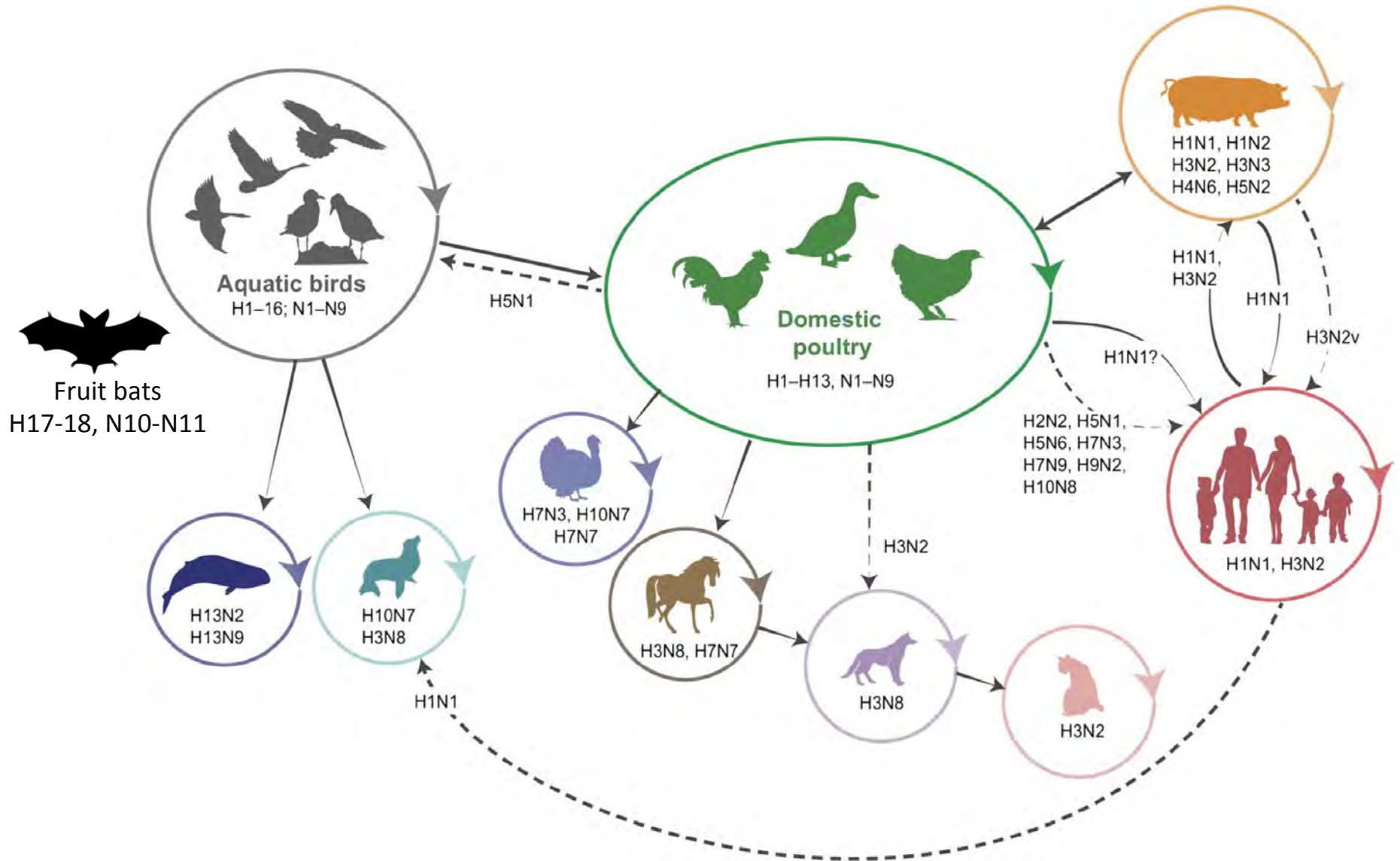
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2018 World Influenza Conference on Centenary of the 1918 influenza pandemic
7-10 September 2018, Beijing, China

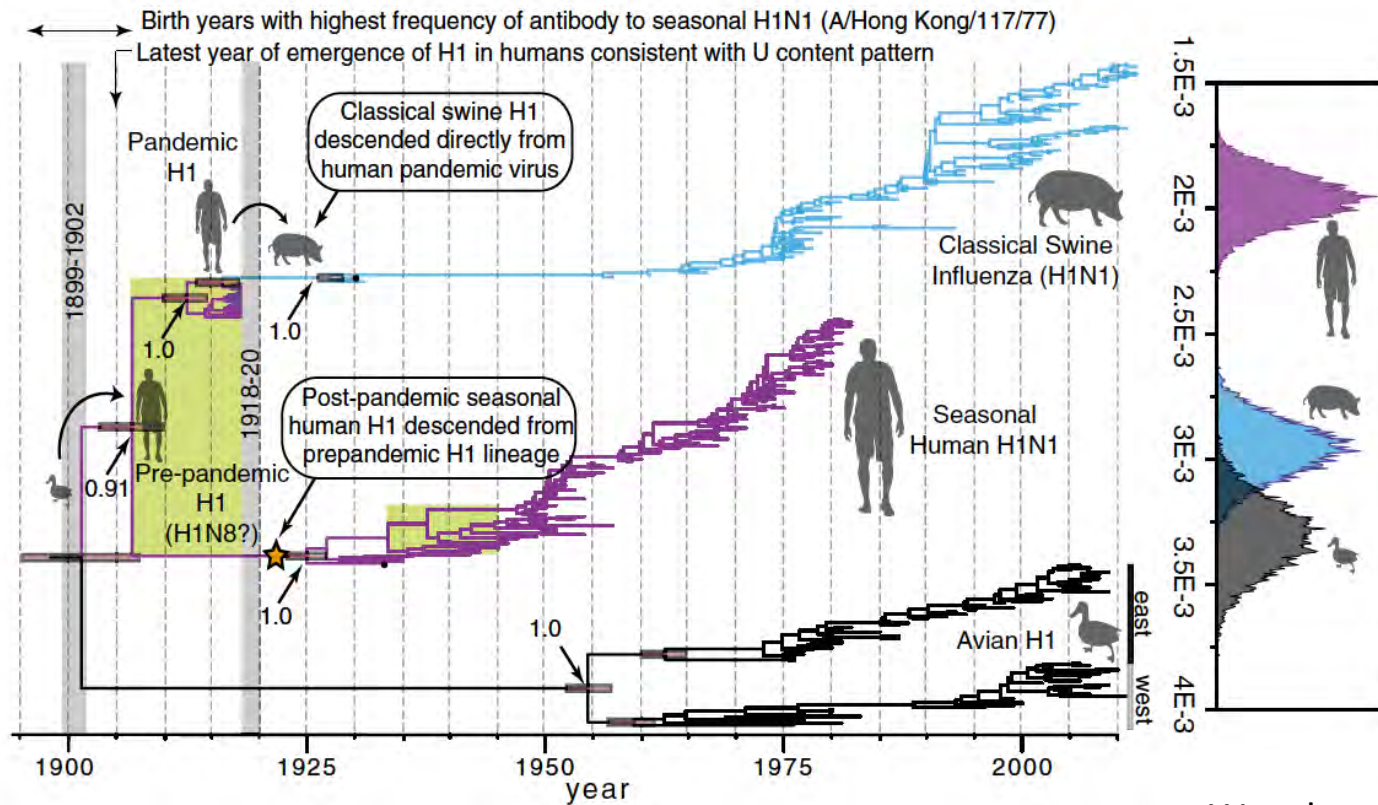
Influenza A viruses infect a wide range of hosts



Pandemic influenza virus emergence: reassortment & contain animal influenza gene segments

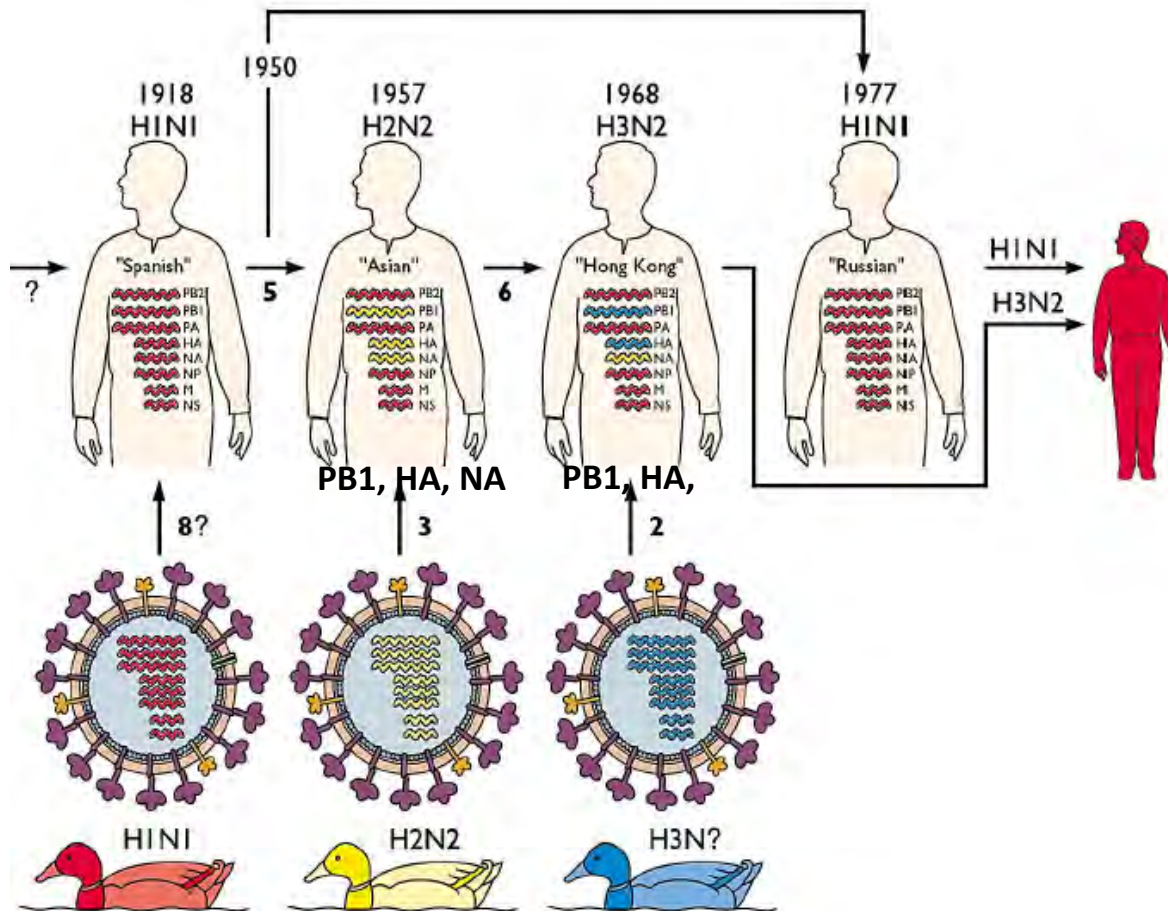
1918 pandemic H1N1 virus

HA derived from a human H1 virus emerged prior to 1907
NA and internal genes derived from avian influenza virus



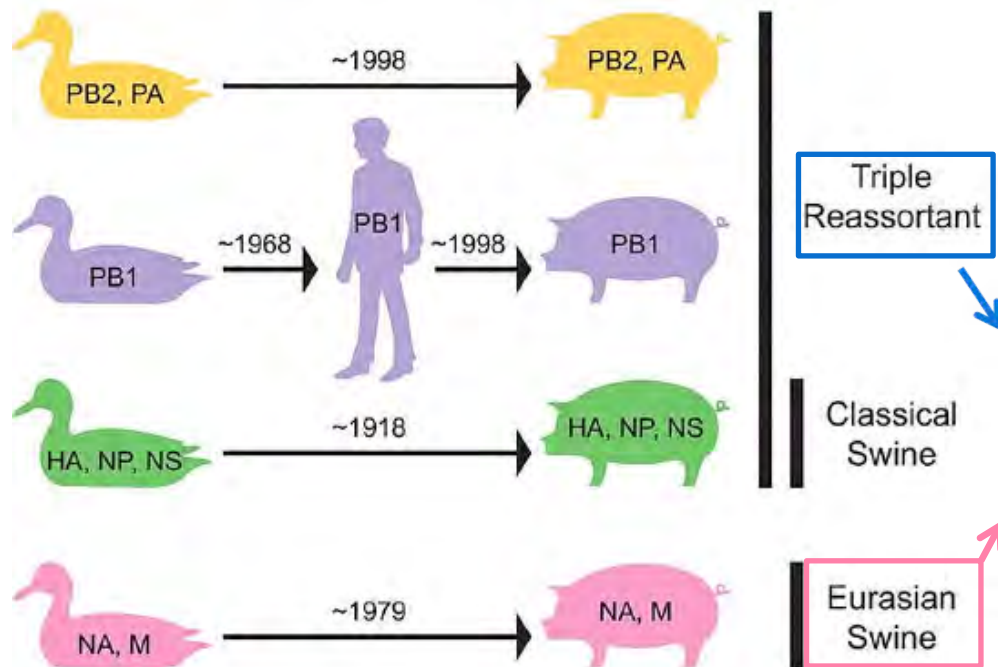
Pandemic influenza virus emergence: reassortment & contain animal influenza gene segments

1957 (H2N2) and 1968 (H3N2) pandemic viruses



Pandemic influenza virus emergence: reassortment & contain animal influenza gene segments

2009 pandemic H1N1 virus



Reverse zoonosis: A(H1N1)pdm09 and reassortants has been frequently detected in swine since 2009



TRENDS in Microbiology

Nelson and Vincent. Trends in Microbiology. 2015

After 2009: genotypic diversity of swine influenza in China

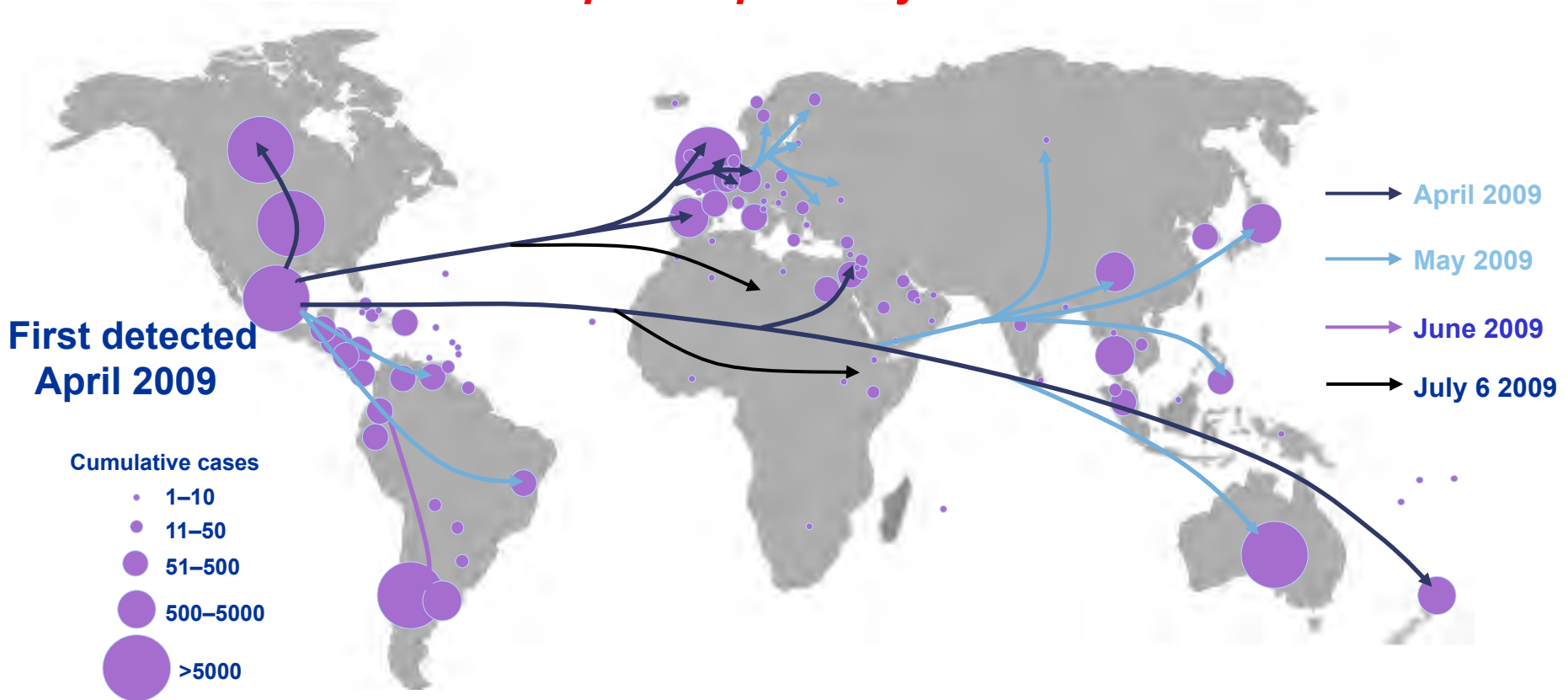
- Swine influenza viruses (N=387) isolated from 2009-2012 identified 29 genotypes.
- 17 genotypes contains pdm09 gene(s)*, pdm09 internal genes became predominant.
- Most reassortants contained HA and NA from EA swine lineage or human H3N2 lineage.
- But humans have cross-reacting immunity vs H1 and H3 in swine → low pandemic risk.



Nominative strains	PB2	PB1	PA	HA	NP	NA	M	NS	Isolates
<u>Sw/GX/NS2783/10</u>	red	red	red	purple	red	purple	red	red	* 74
<u>Sw/HK/2433/09</u>	green	green	green	green	green	green	green	green	66
<u>Sw/HK/NS1054/09</u>	green	green	green	green	green	green	green	yellow	43
<u>Sw/HK/NS1583/09</u>	red	red	red	red	red	red	red	red	42
<u>Sw/GD/1361/10</u>	red	red	red	green	red	green	red	red	* 29
Sw/HK/NS3954/11	red	red	red	red	red	yellow	red	red	* 24
<u>Sw/HK/3048/10</u>	yellow	yellow	yellow	green	yellow	yellow	green	yellow	15
Sw/GX/3202/11	red	red	red	red	yellow	yellow	red	red	* 12
<u>Sw/GX/NS1402/12</u>	red	red	red	purple	red	purple	red	yellow	* 12
Sw/GX/2887/11	yellow	yellow	red	yellow	red	yellow	red	red	* 10
<u>Sw/HK/2569/10</u>	yellow	yellow	yellow	yellow	yellow	yellow	yellow	yellow	8
<u>Sw/HK/NS1630/10</u>	yellow	yellow	yellow	yellow	yellow	yellow	green	yellow	8
<u>Sw/HK/3125/11</u>	red	red	red	blue	red	yellow	red	yellow	* 7
Sw/GD/553/10	green	green	green	blue	green	darkblue	green	green	5
<u>Sw/GX/2803/11</u>	red	yellow	red	purple	red	purple	red	red	* 5
Sw/GD/3542/11	red	red	red	blue	red	yellow	red	red	* 4
Sw/HK/NS2378/12	green	green	green	green	green	green	red	green	* 4
Sw/HK/NS1889/09	yellow	yellow	yellow	blue	yellow	yellow	yellow	yellow	3
<u>Sw/HK/2857/11</u>	red	red	red	purple	yellow	purple	red	red	* 3
Sw/HK/3904/11	yellow	yellow	yellow	green	yellow	green	green	yellow	2
Sw/HK/201/10	yellow	yellow	yellow	green	yellow	red	yellow	yellow	* 1
Sw/HK/2314/09	yellow	yellow	yellow	yellow	yellow	yellow	blue	yellow	1
Sw/GD/3196/11	red	red	red	green	red	yellow	red	red	* 1
Sw/GX/NS3248/11	green	green	red	green	green	green	green	green	* 1
Sw/HK/NS26/12	red	red	red	red	red	darkblue	red	red	* 1
Sw/HK/268/12	yellow	yellow	yellow	green	yellow	green	yellow	yellow	1
Sw/HK/NS584/12	red	red	red	green	yellow	yellow	green	red	* 1
Sw/HK/NS2761/10	yellow	yellow	yellow	blue	yellow	green	yellow	yellow	1
Sw/GD/NS2897/12	red	green	red	green	red	green	red	green	* 1

The need to “get ahead of the curve”

** Reports up to July 2009*

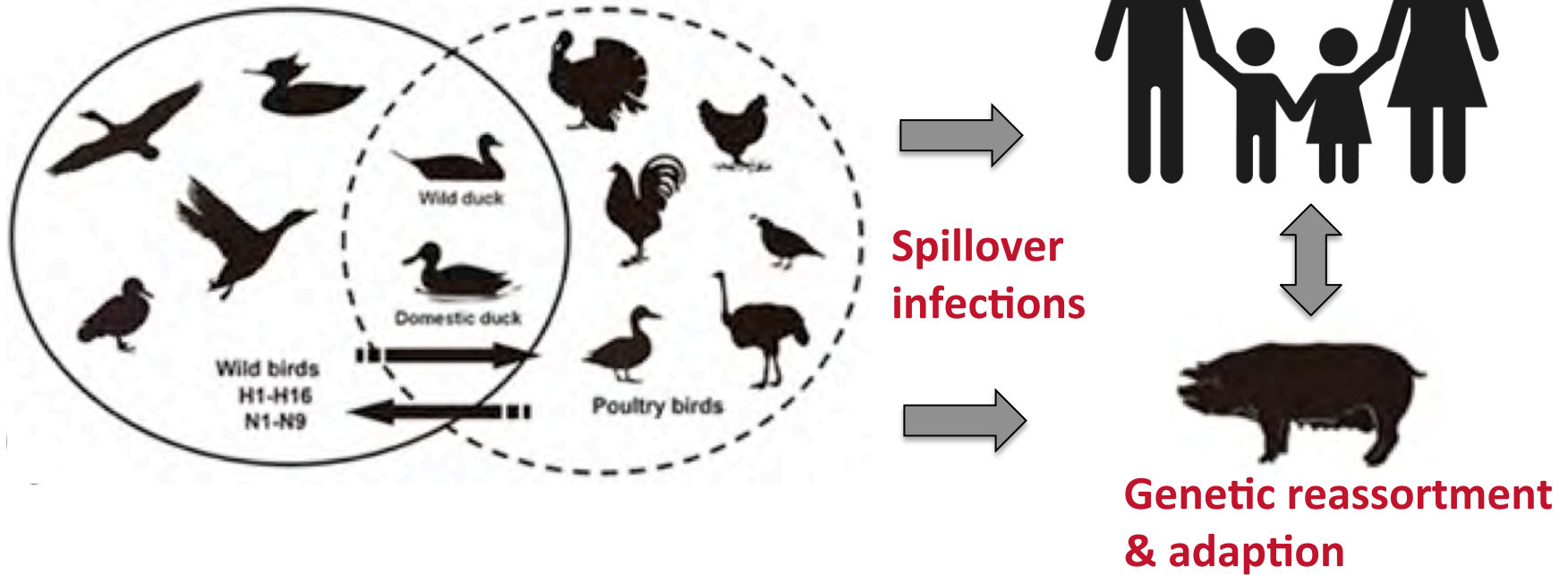


In a few weeks, the 2009 H1N1 pandemic spread around the world affecting all countries

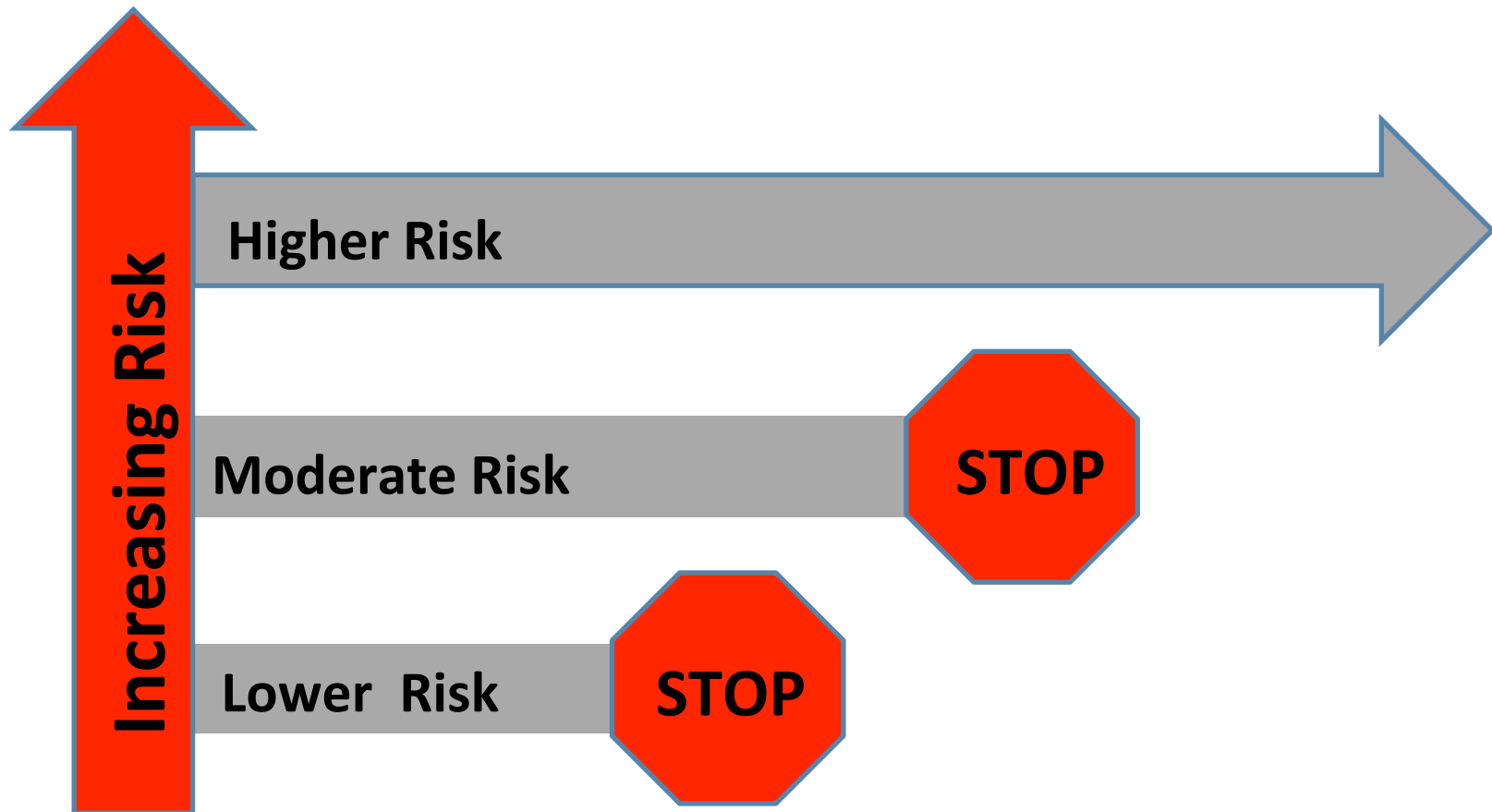
WHO, 2009. Pandemic (H1N1) 2009, situation update, available at: http://www.who.int/csr/don/2009_07_06/en/index.html (accessed 6 July 2009)

Animal influenza surveillance

Global dissemination



Many influenza viruses with pandemic potential, but limited resources...



Public health resources dedicated for preparedness and response

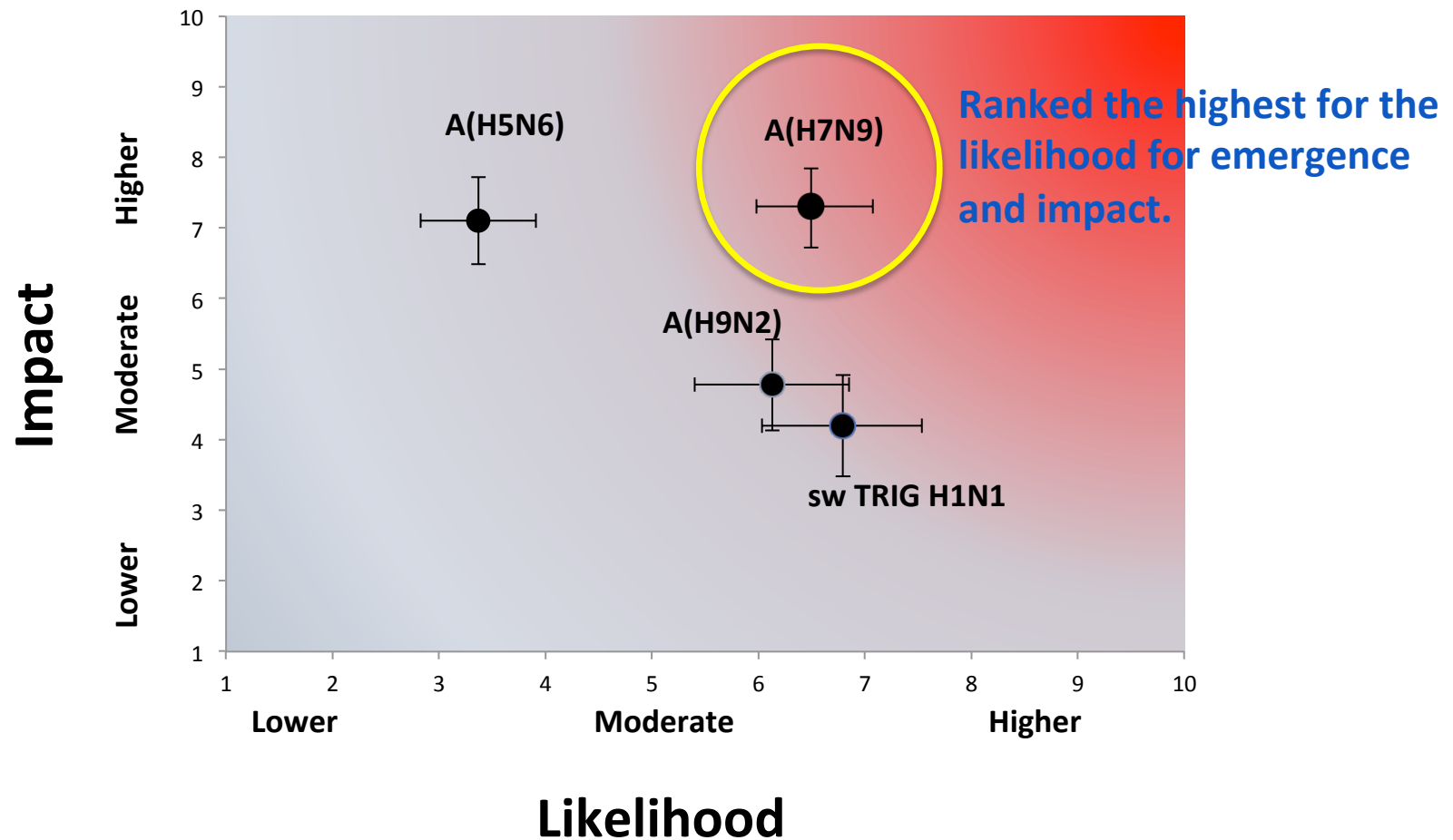
Acknowledge: US CDC for slide concept

Tool for Influenza Pandemic Risk Assessment (TIPRA), WHO



- Properties of the virus:
 - receptor binding properties
 - genomic characteristics
 - transmission in animal models
 - susceptibility to antiviral treatment
- Attributes in the human population:
 - human infection
 - disease severity
 - population immunity
- Virus ecology and epidemiology in non-human hosts:
 - geographic distribution in animals
 - infections in animals

Re-assessing the risk of Triple Reassortant-like swine influenza viruses



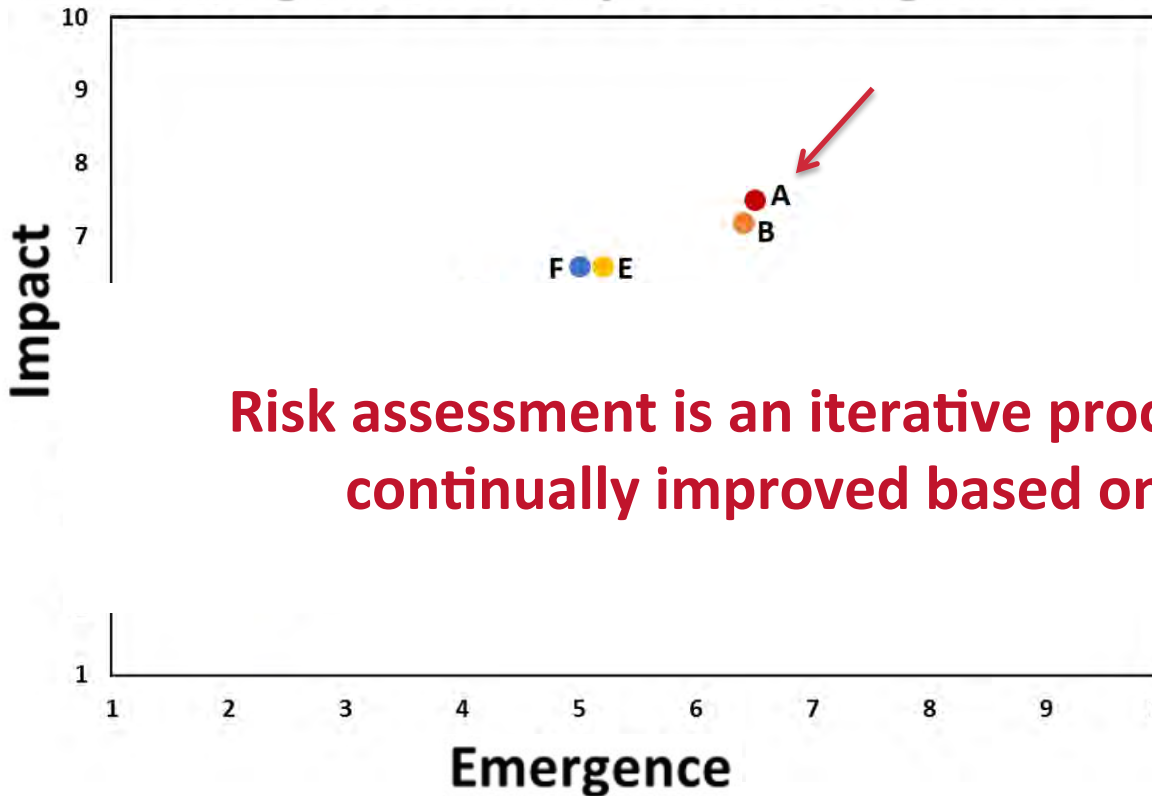
Acknowledgement of the slide: WHO GISRS

Influenza Risk Assessment Tool (IRAT), CDC

Each criteria is scored for the likelihood of “Emergence” & potential “Impact”.

- The “Properties of the Virus”:
 - Genomic variation
 - Receptor binding
 - Transmission in lab animals
 - Antiviral treatment susceptibility/resistance
- The “Attributes of the Population”:
 - Existing population immunity
 - Disease severity and pathogenesis
 - Antigenic relationship to vaccine candidates
- The “Ecology and Epidemiology”:
 - Global distribution (animals)
 - Infection in animal species
 - Human Infections

IRAT Emergence and Impact - Average Risk Scores

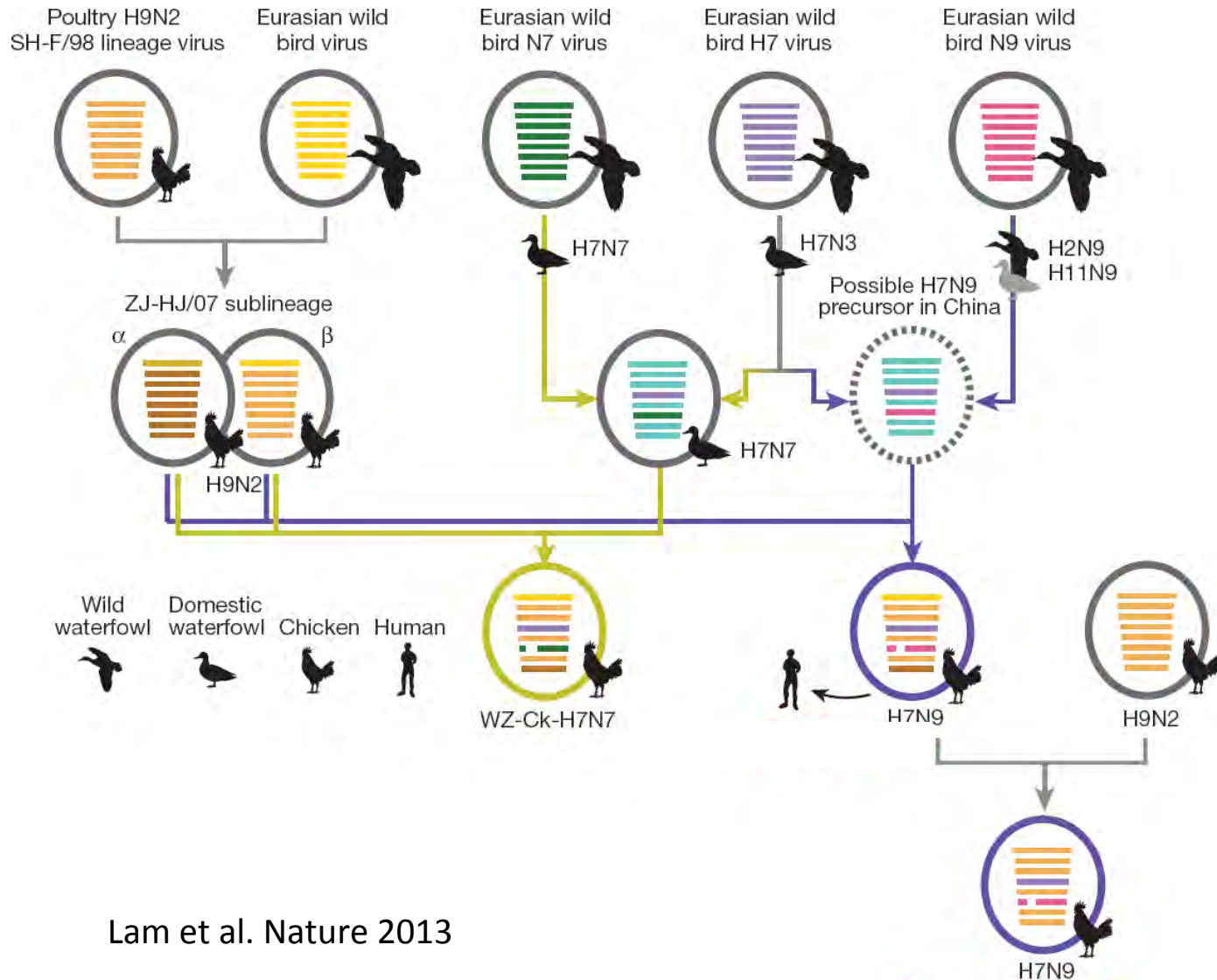


	Virus
● A	H7N9 [A/Hong Kong/125/2017]
● B	H7N9 [A/Shanghai/02/2013]
● C	H3N2 variant [A/Indiana/08/2011]
● D	H9N2 G1 lineage [A/Bangladesh/0994/2011]
● E	H5N1 [A/Indonesia/05/05]

Risk assessment is an iterative process that needs to be continually improved based on viral evolution.

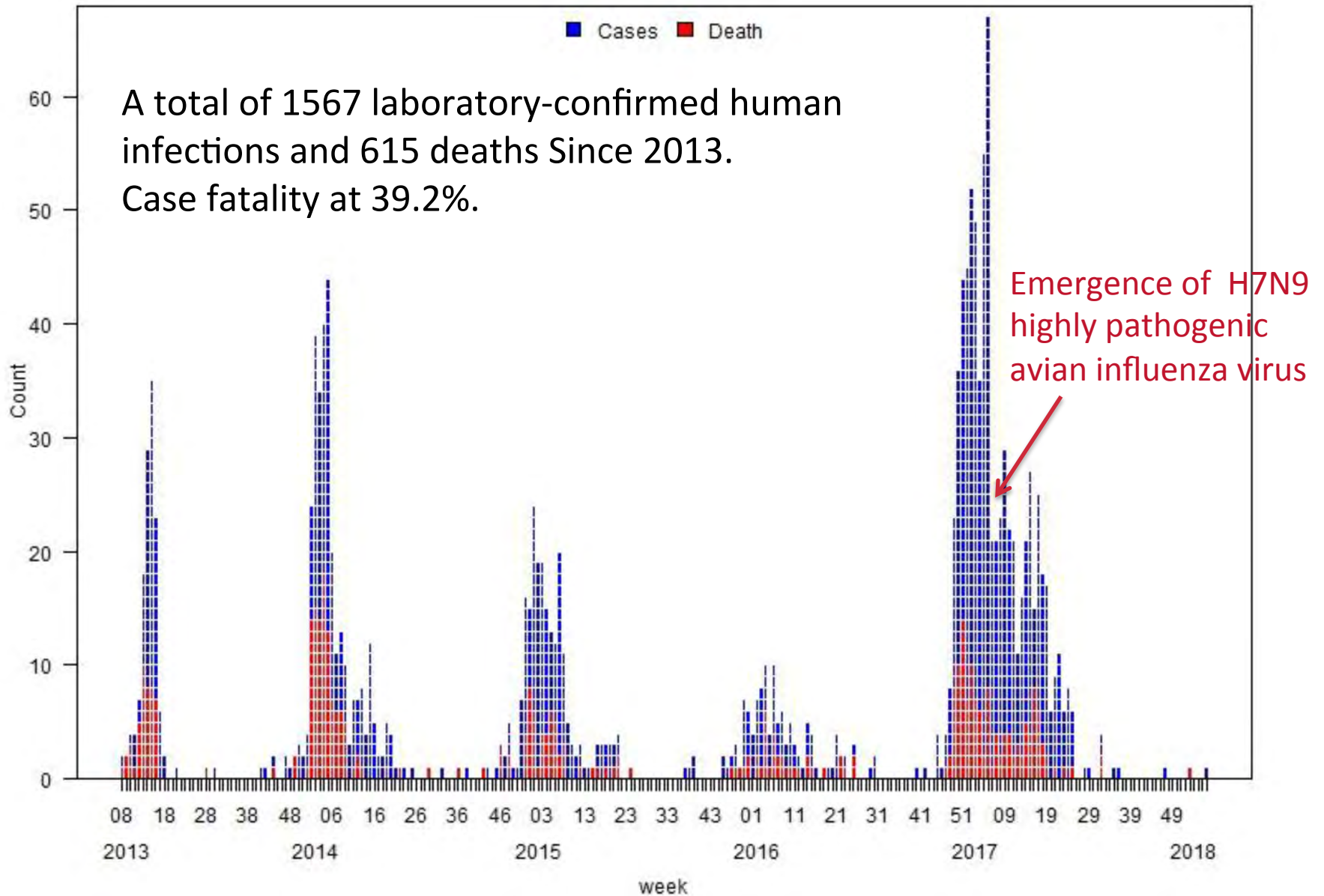
● L	H5N1 [A/American green-winged teal/Washington/1957050/2014]
● M	H7N8 [A/turkey/Indiana/1573-2/2016]
● N	H1N1 [A/duck/New York/1996]

H7N9 emerged through multiple genetic reassortment events

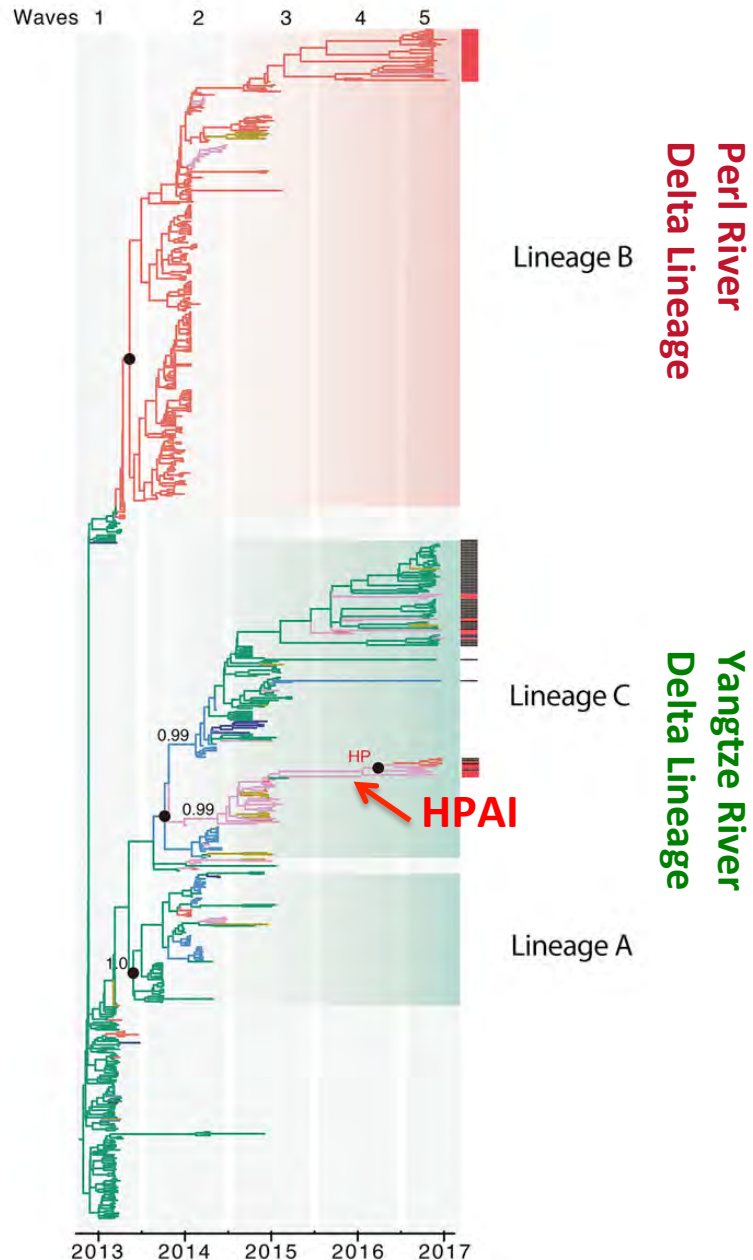


Lam et al. Nature 2013

Spillover infection by avian influenza A(H7N9)



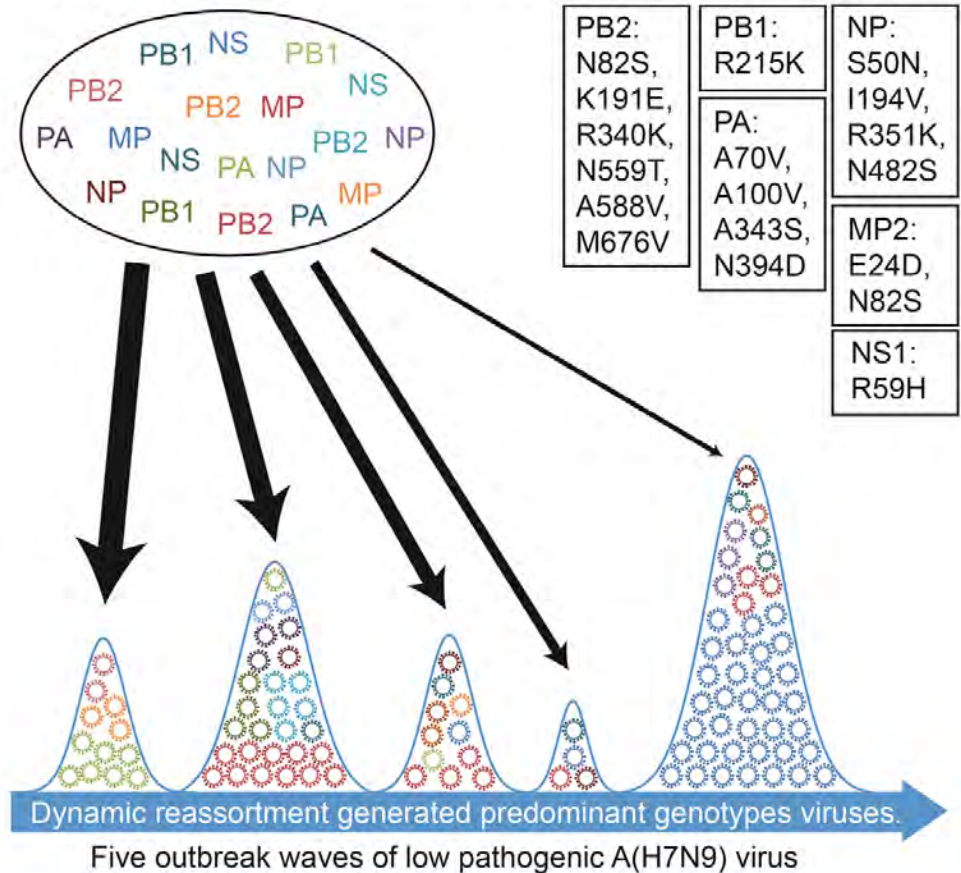
Genomic characteristics: A(H7N9) evolution



The ZJ11 genotype caused the majority of human infections in wave V.

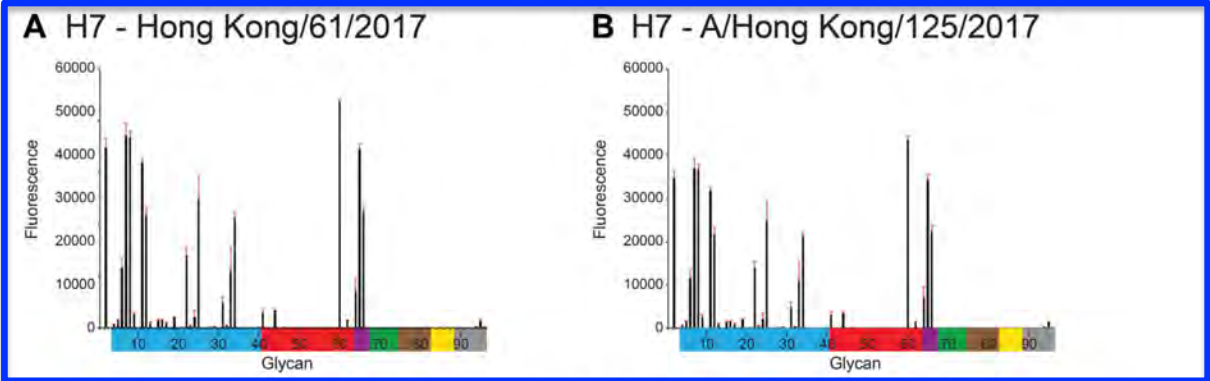
Poultry H9N2 gene pool in China

List of accumulated substitutions

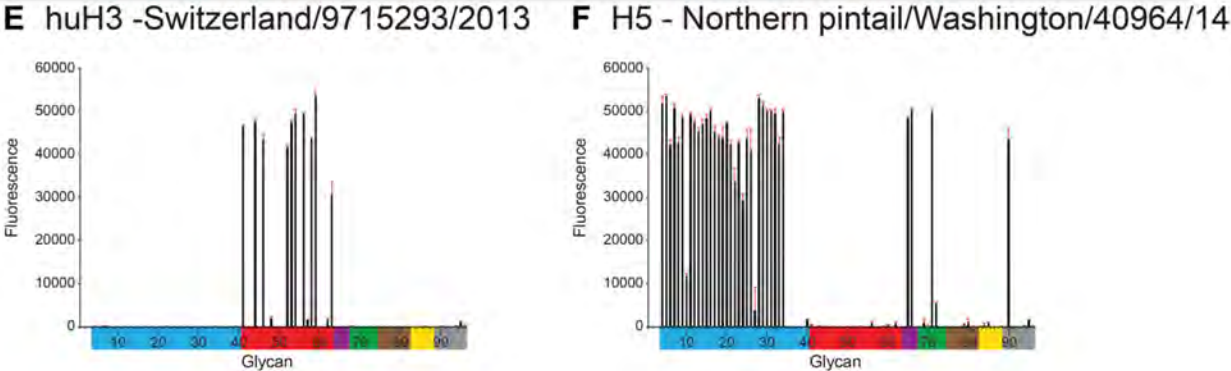
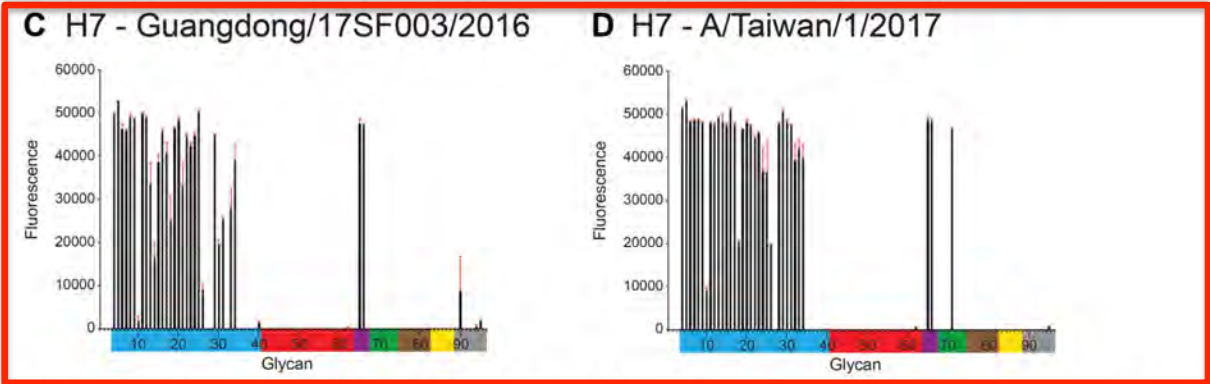


Receptor binding profile of wave V viruses

LPAI from PRD or YRD

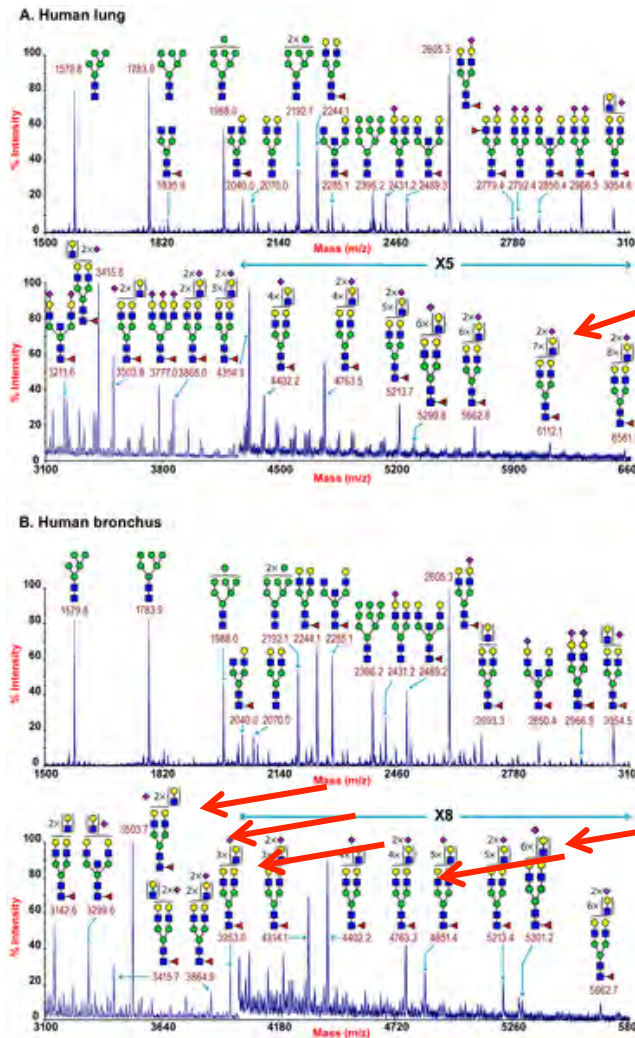


HPAI



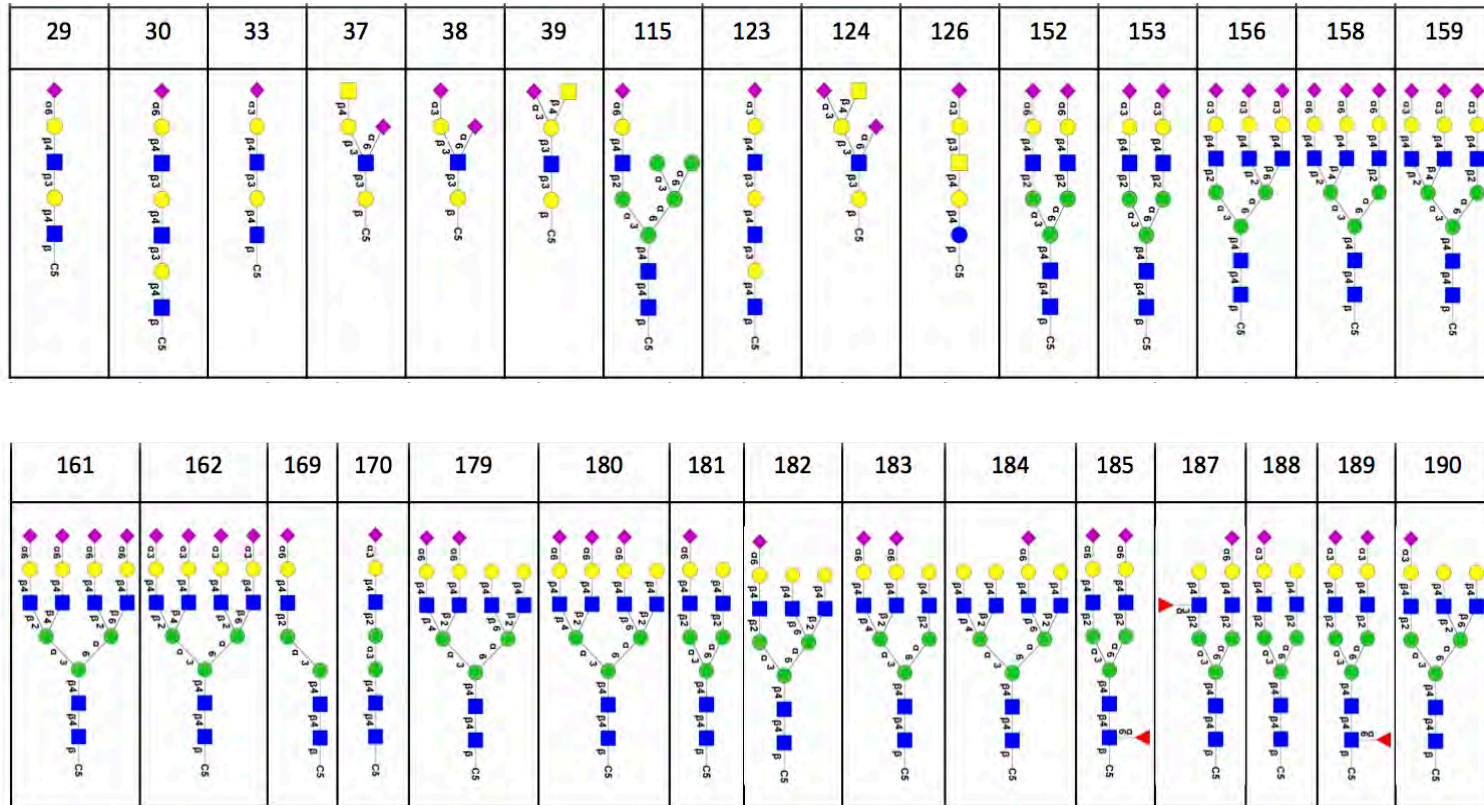
Which glycans are found at the human respiratory tract?

Many of the longer glycans with the extended LacNac disaccharide found in human airway were **not** included in the existing glycan arrays used for risk assessment.



Walther T et al. (2013) Glycomic Analysis of Human Respiratory Tract Tissues and Correlation with Influenza Virus Infection. PLOS Pathogens 9(3): e1003223. <https://doi.org/10.1371/journal.ppat.1003223>

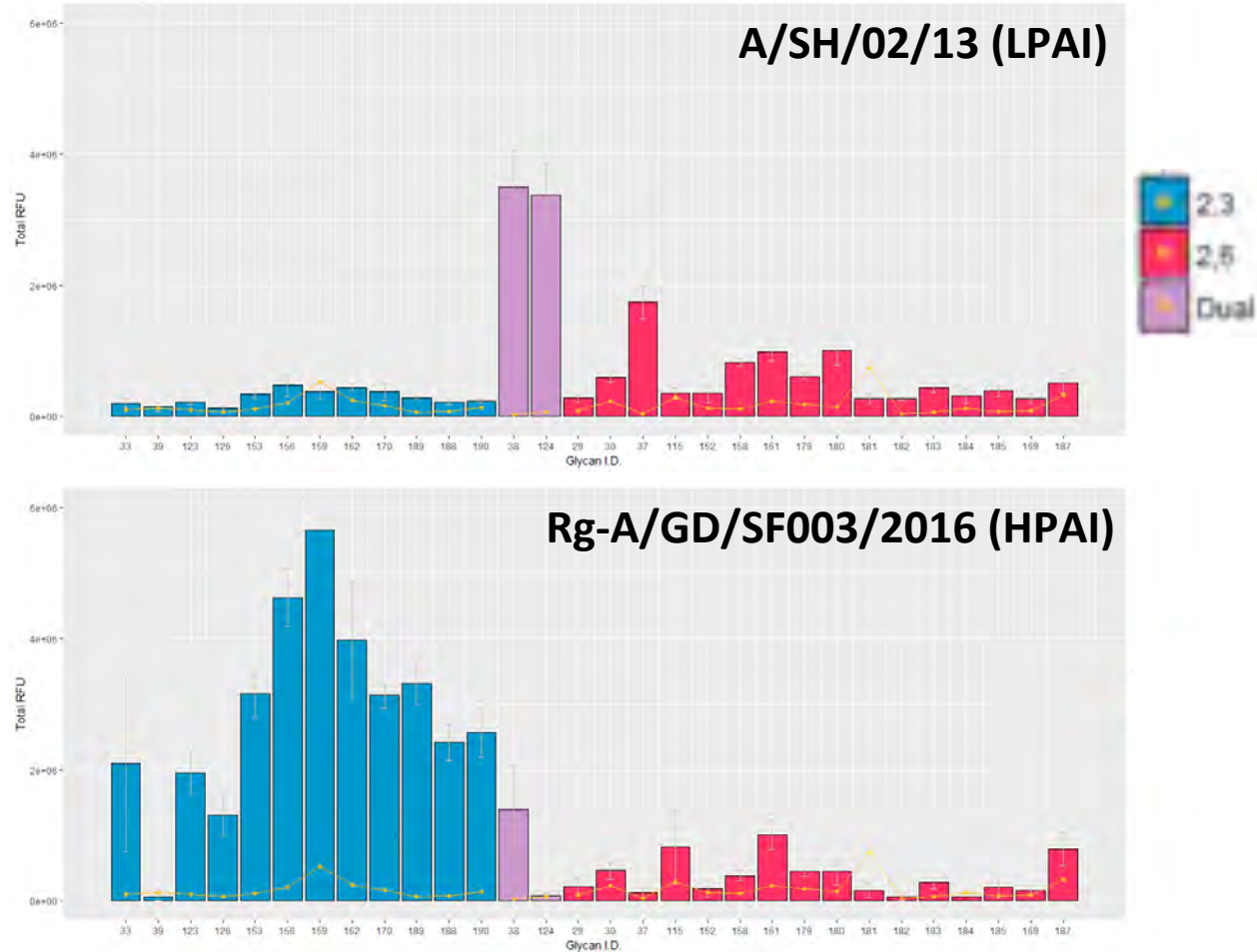
A focused glycan array representing glycans commonly found in human respiratory tract



α 2-6 linked (n=16), α 2-3 link (n=12), and α 2-6 & 2-3 dual linked terminal sialic acids (n=2).

John Nicholls, Hui-Ling Yen, Malik Peiris, Chung-Yi Wu, unpublished data

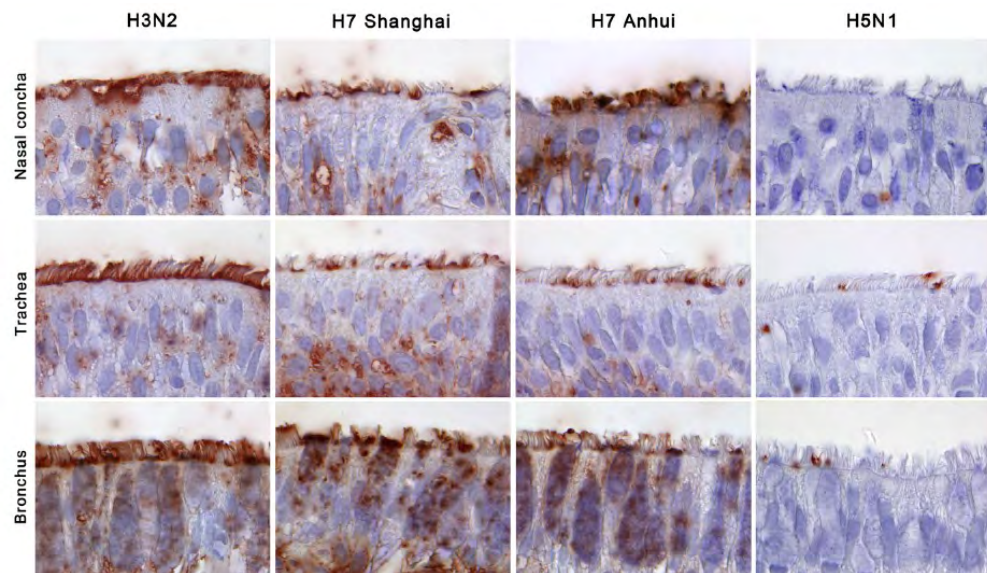
HPAI H7N9 virus showed preferred binding for α 2,3-linked sialyl receptors than LPAI



John Nicholls, Hui-Ling Yen, Malik Peiris, Chung-Yi Wu, unpublished data

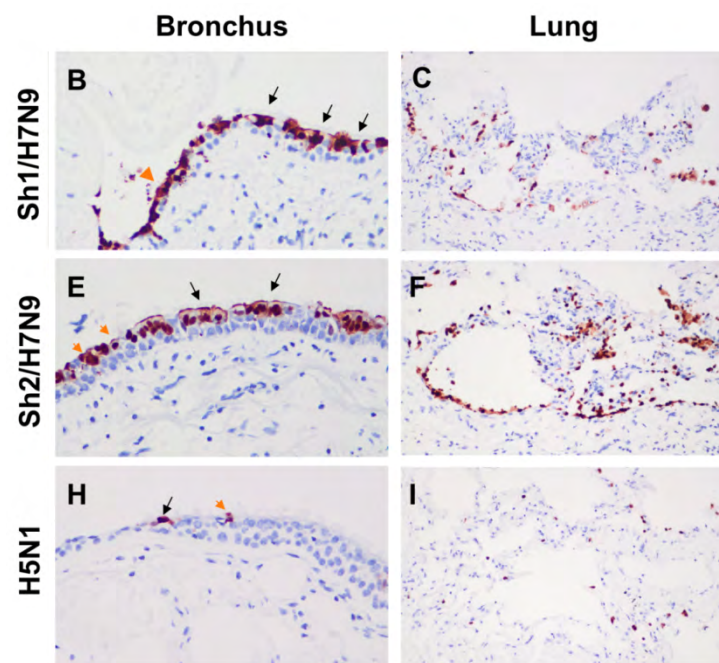
Assessing viral tissue tropism

Binding of labelled virus to human respiratory tract



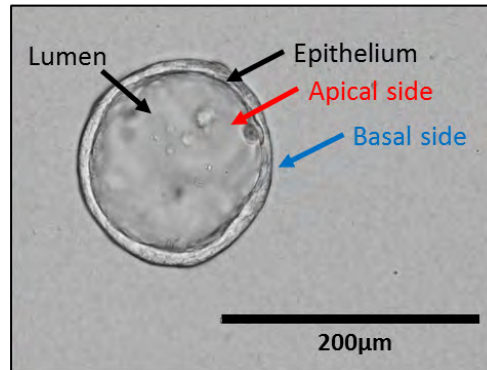
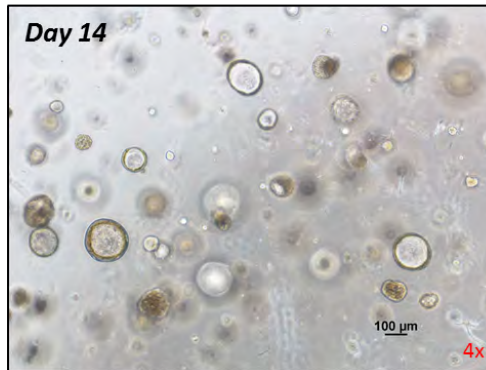
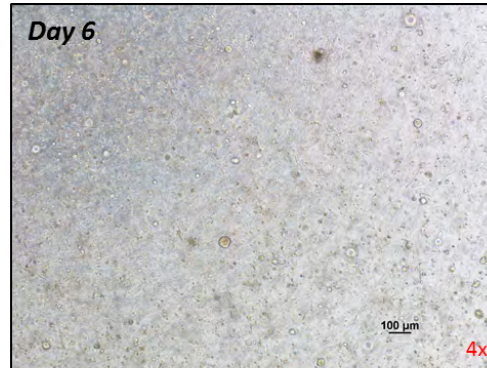
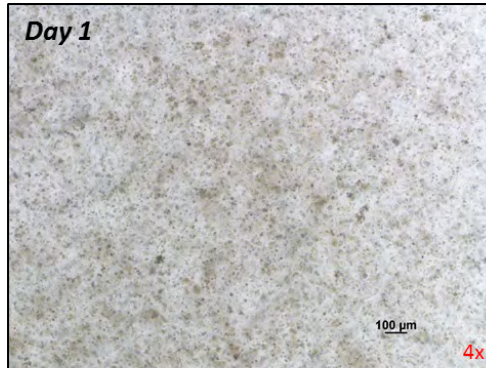
Van Riel et al Am J Pathol 2013

Infection of ex vivo cultures of the human respiratory tract



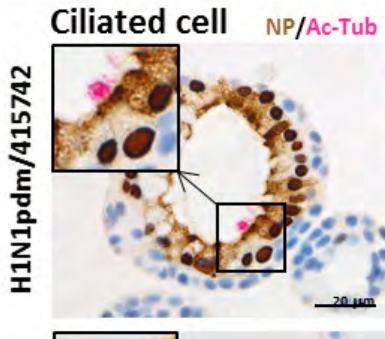
Chan et al Lancet Respir Dis 2013

Airway organoid isolated from human tissue



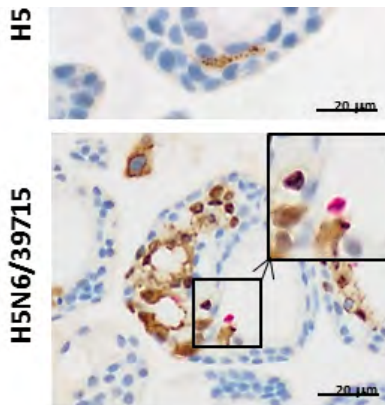
- **Human Airway Organoids** isolated from
 - *Human lung/bronchus tissue*
- **Single lung epithelial stem cells** can form organoids in 7-10 days
 - *Cystic organoids (round shape with lumen) containing ciliated, secretory, and basal cells*

Cellular tropism of influenza virus in airway organoids



Ciliated cells +:
H1N1, H7N9,
H5N6.
Not H5N1

Human airway organoids showed comparable results as the human ex vivo culture can be applied to assess tissue tropism and human infection risk of zoonotic respiratory viruses.



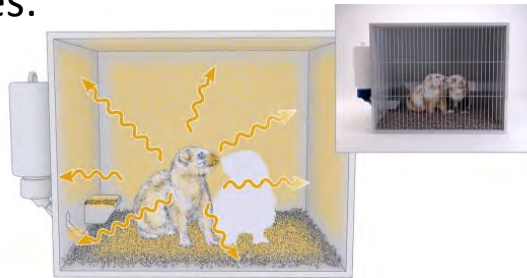
Basal cells:
Not infected

Transmissibility in animal models

Direct contact model/ co-housed model

Potential transmission modes:

- Direct contact
- Fomite
- Droplets
- Droplet nuclei



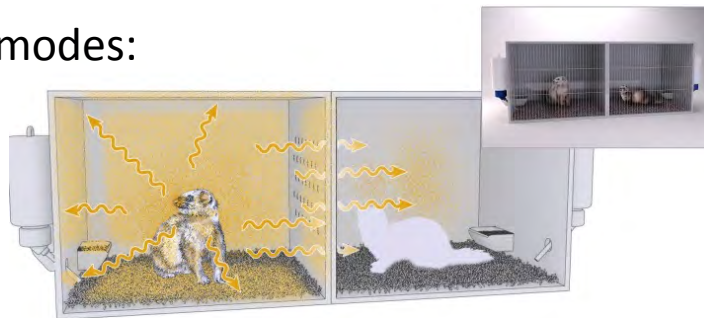
Transmissibility:

- H5N1: - to +
- **H7N9: + to ++**
- Swine influenza viruses: +++
- Human influenza viruses: +++

Respiratory droplet mode

Potential transmission modes:

- Droplets
- Droplet nuclei



Transmissibility:

- H5N1: -
- **H7N9: - to +**
- Swine influenza viruses: - to +
- Human influenza viruses: +++

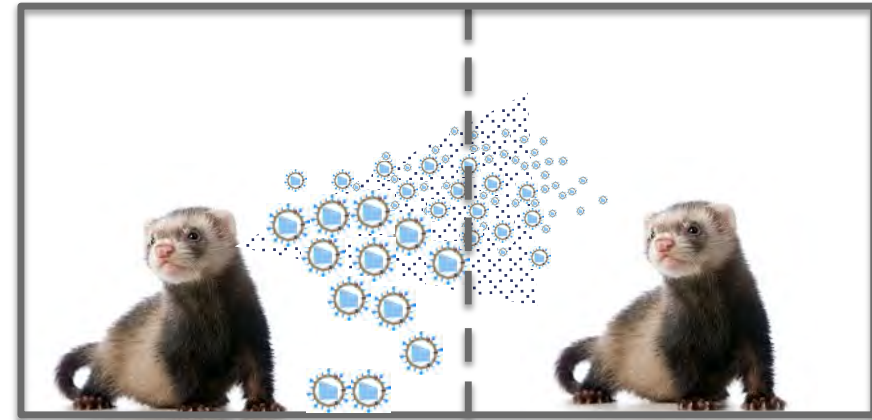
“Respiratory droplet” transmissibility between ferrets correlates with the transmission phenotypes of influenza viruses seen in humans.

Refinement of the transmission experiment designs

Effect of the heterogeneity in experimental designs between labs?

Table 1. Examples of heterogeneity in experimental designs among published risk-assessment studies using ferrets as models for influenza virus transmission studies and pandemic risk assessments*

Parameter	Examples of variability
Virus (before ferret introduction)	Seed stock passage history, stock growth matrix, stock titer, wild-type vs. reverse genetics, plaque-purified vs. quasispecies, storage and propagation conditions
Ferret (before virus introduction)	Source/genetic lineage, serostatus, age, sex, weight, neutered or intact status, hormonal treatment (females), anesthetic used, housing conditions
Virus inoculation	Inoculation route, method, dose, and volume; buffer for dilution
Transmission experimental designs	Donor:recipient ratio, number of replicates per containment, caging size and setup, perforation size and exposure area between cages, distance between cages, directional airflow, air changes per hour, temperature and humidity, timing and duration of exposure, frequency and sites for sample collection

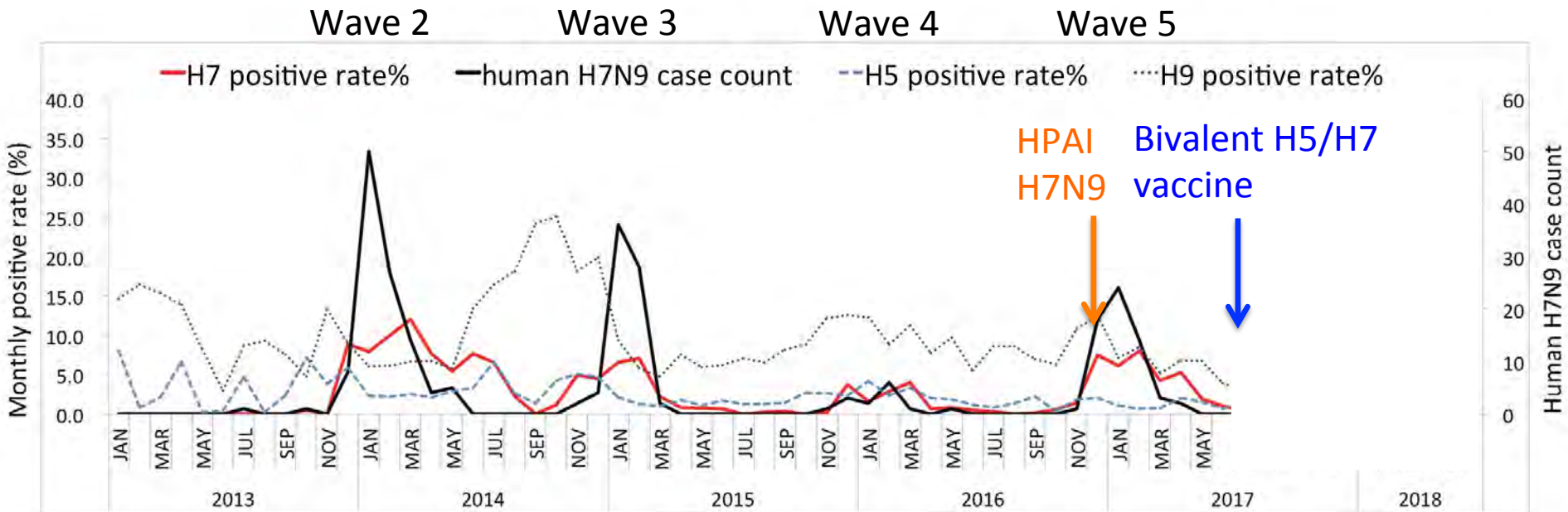


1. Quantity of influenza virus released in the airborne particles from the exhaled breath?
2. Exposure time required to mediate transmission?
3. Airborne particle size that mediate transmission?
4. Host factors?

Belser et al. Emerg Infect Dis 2018

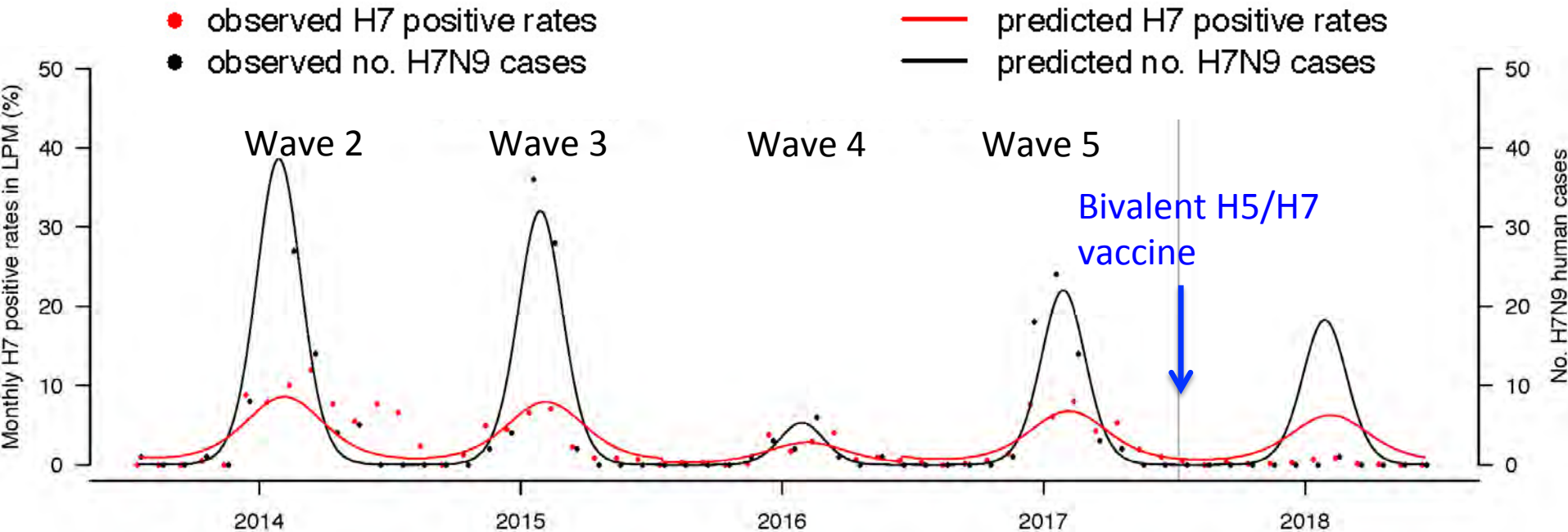
Zhou et al. PNAS 2018

Monthly H5, H7, and H9 positive rates at LPMs and human H7N9 cases in Guangdong, January 2013 – June 2018



- Environmental samples were collected monthly from **345 retail LPMs** and **24 wholesale LPMs** distributed in 21 cities in Guangdong Province, 2013-2018.
- A total of 81,984 environmental samples.

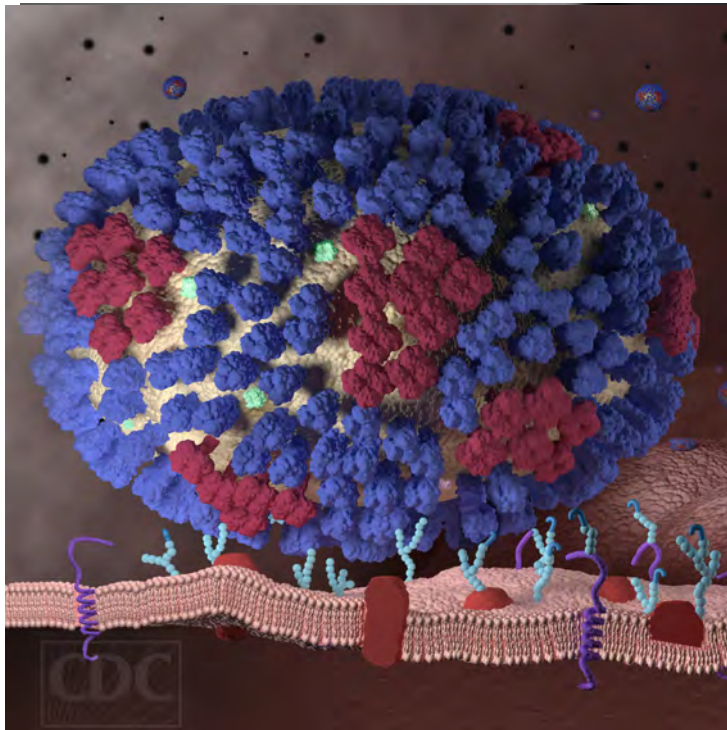
Reduced human infection risk in 2017-2018 was correlated with reduced detection of A(H7N9) virus at live poultry markets



Introduction of the bivalent H5/H7 vaccine was associated with 92% and 98% reduction in H7 positive rates in poultry and human H7N9 cases, respectively.

Looking forward...

What would be the next pandemic influenza virus?



- **Longitudinal animal surveillance is an essential element for the risk assessment process.**
- Risk assessment is not a prediction for the future.
- **An iterative process that needs to be continually improved and re-assessed based on viral evolution.**
- Refinement of risk assessment tools will help to better inform the pandemic risk.
- Seamless integration of global surveillance data from human and animal health sectors using the **“One Health” approach is essential for pandemic planning.**
- **Need to prepare for the unexpected.**

Acknowledgements

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Jie Wu, Chengwen Ke

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