
# Influenza nell'uomo


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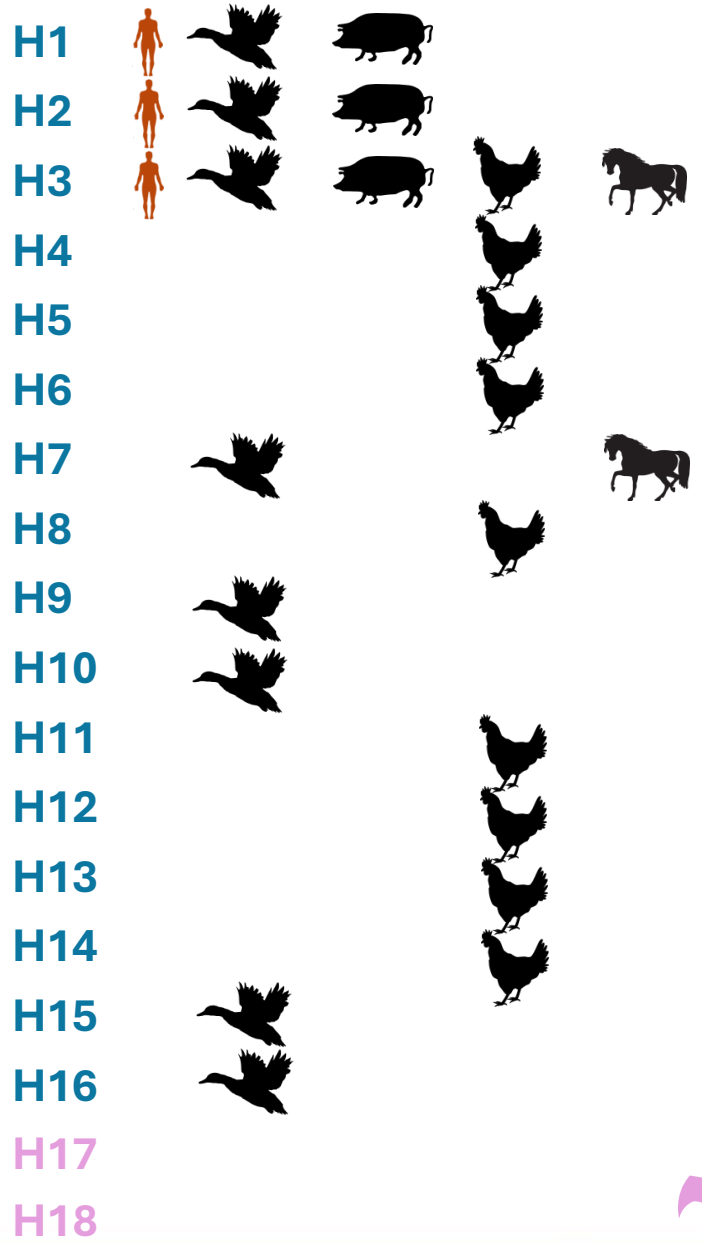
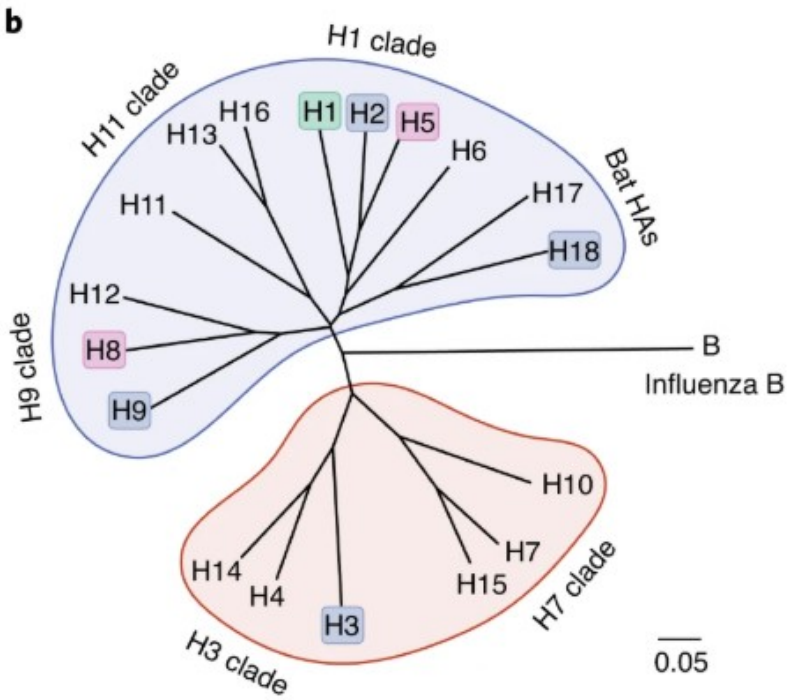
*SC Microbiologia e Virologia*
*Fondazione IRCCS Policlinico San Matteo (Pavia)*

# Influenza A : H1-H16 and N1-N9



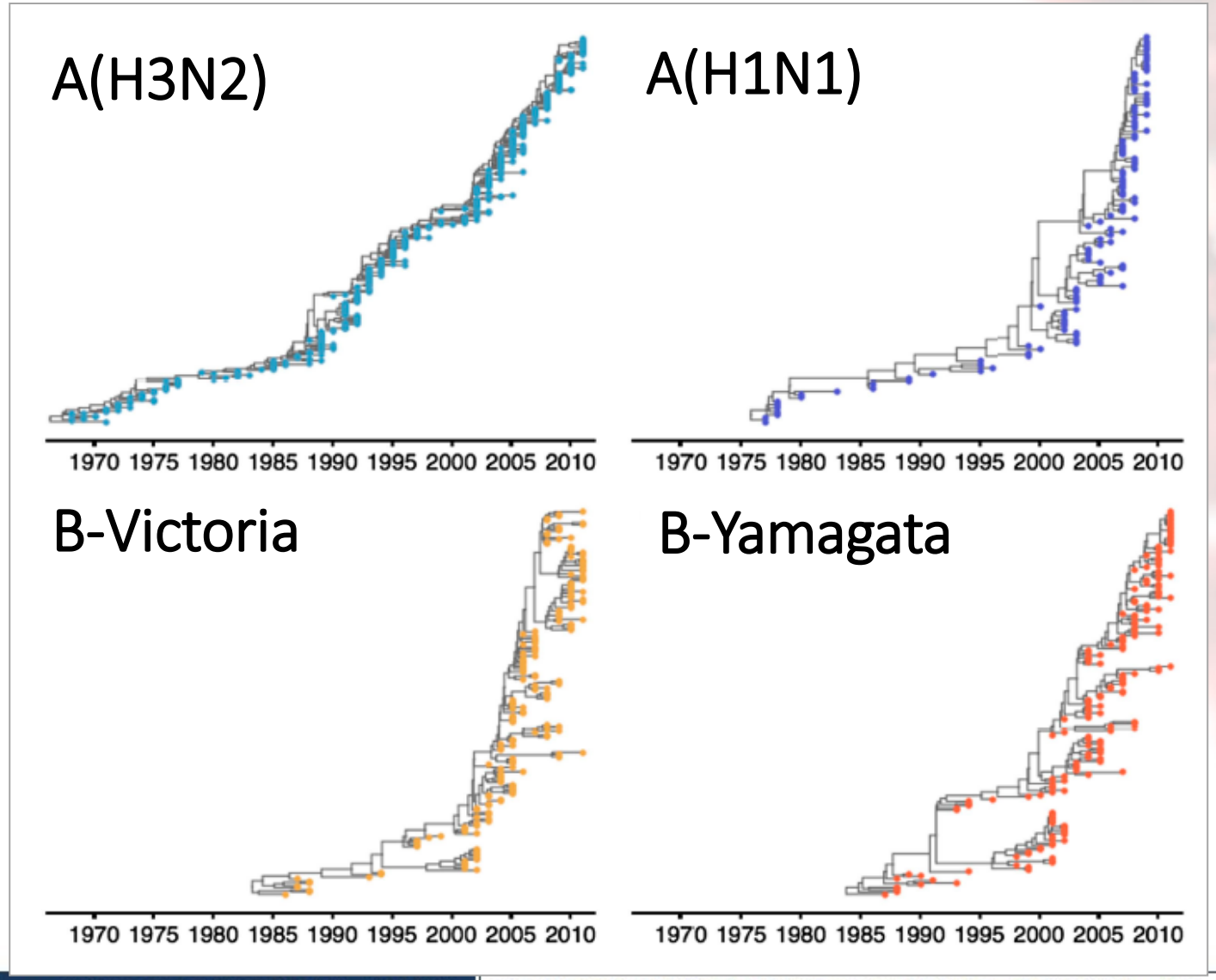





Nachbagauer R et al. 2020 Nat Med

- ✓ Historically, influenza A human infections have been caused by three subtypes of hemagglutinin (H1, H2 and H3) and two neuraminidase subtypes (N1 and N2)
- ✓ In the last 20 years human infections by previously avian-only subtypes H5, H7 and H9 have been consistently reported.

# Variability of influenza viruses



# Vaccine composition

Check for updates

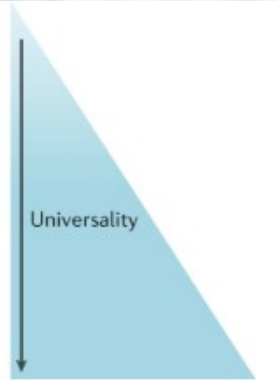
Next-generation influenza vaccines: opportunities and challenges

Chih-Jen Wei[1], Michelle C. Crank[2], John Shiver[3], Barney S. Graham[2], John R. Mascola[2] and Gary J. Nabel[1]


**Fig. 1: A spectrum of efficacy for influenza vaccines.**

From: Next-generation influenza vaccines: opportunities and challenges


| Vaccine | Coverage |
|---|---|
| Strain-specific | Circulating strains |
| Subtype-specific | Multiple strains within a single HA subtype |
| Multi-subtype | Multiple HA subtypes within group 1, group 2 or type B |
| Pan-group/lineage | Group 1 or 2 influenza A or influenza B lineages |
| Universal flu A | Influenza A |
| Universal flu A and B | Influenza A and B |
| 'TRUE' universal | All strains. Single product. Multiple years. |



# How influenza viruses change??

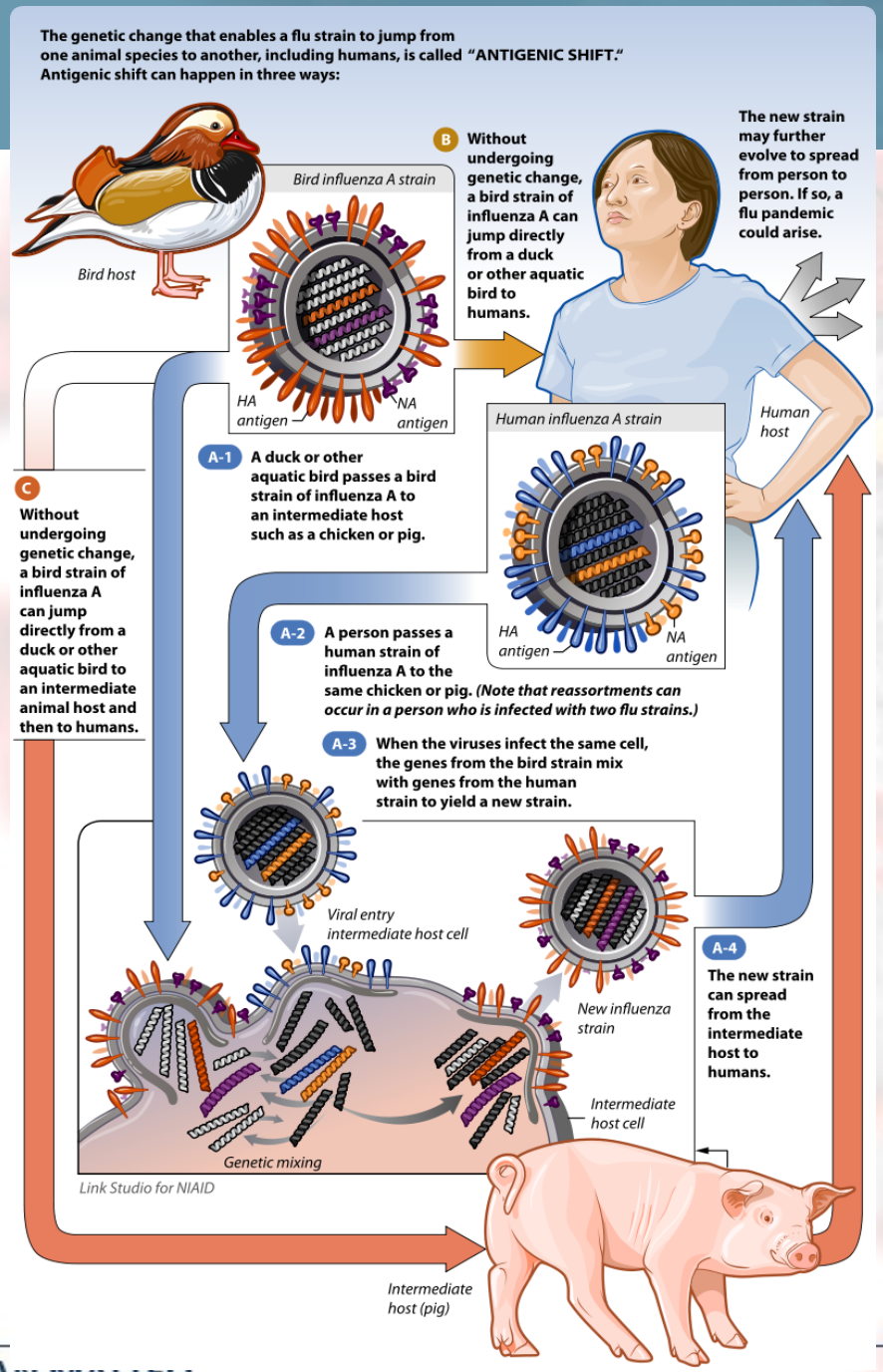
Influenza viruses are constantly changing.

They can change in two different ways:

- Antigenic «Drift»
- Antigenic «Shift»

While influenza viruses are changing by antigenic drift all the time, antigenic shift happens only occasionally.

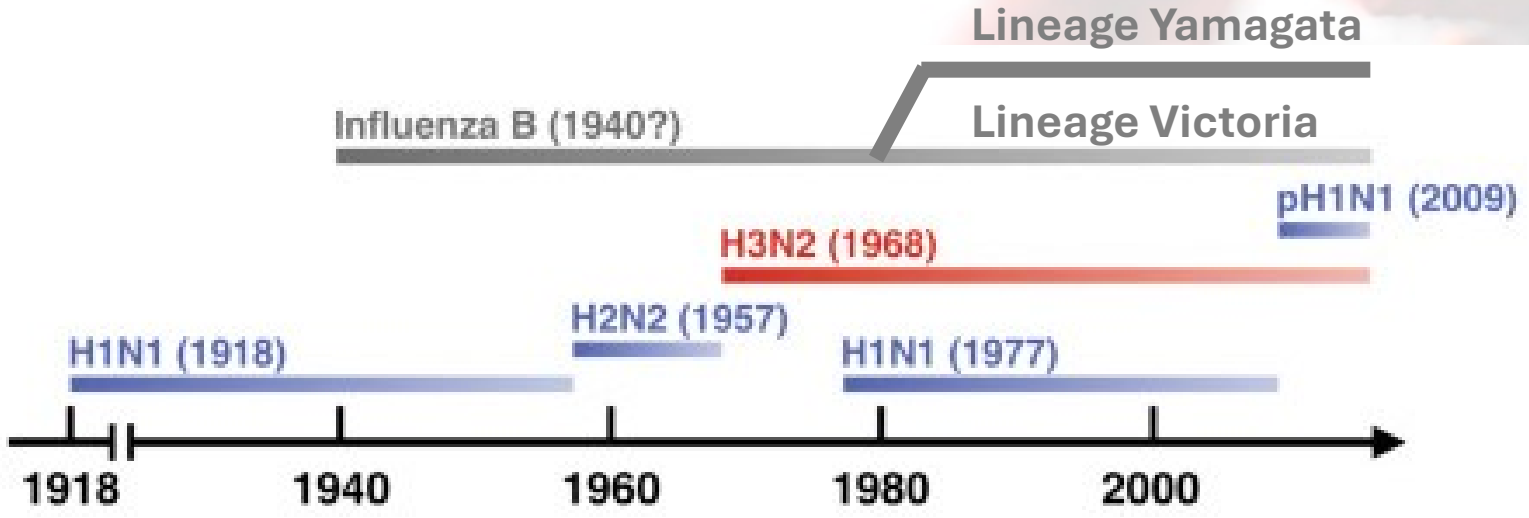
Type A viruses undergo both kinds of changes; influenza type B viruses change only by the more gradual process of antigenic drift.

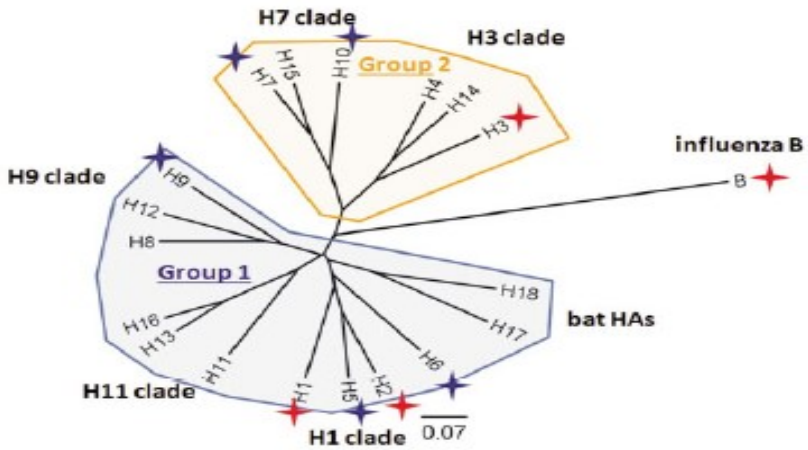


# From zoonosis to pandemia

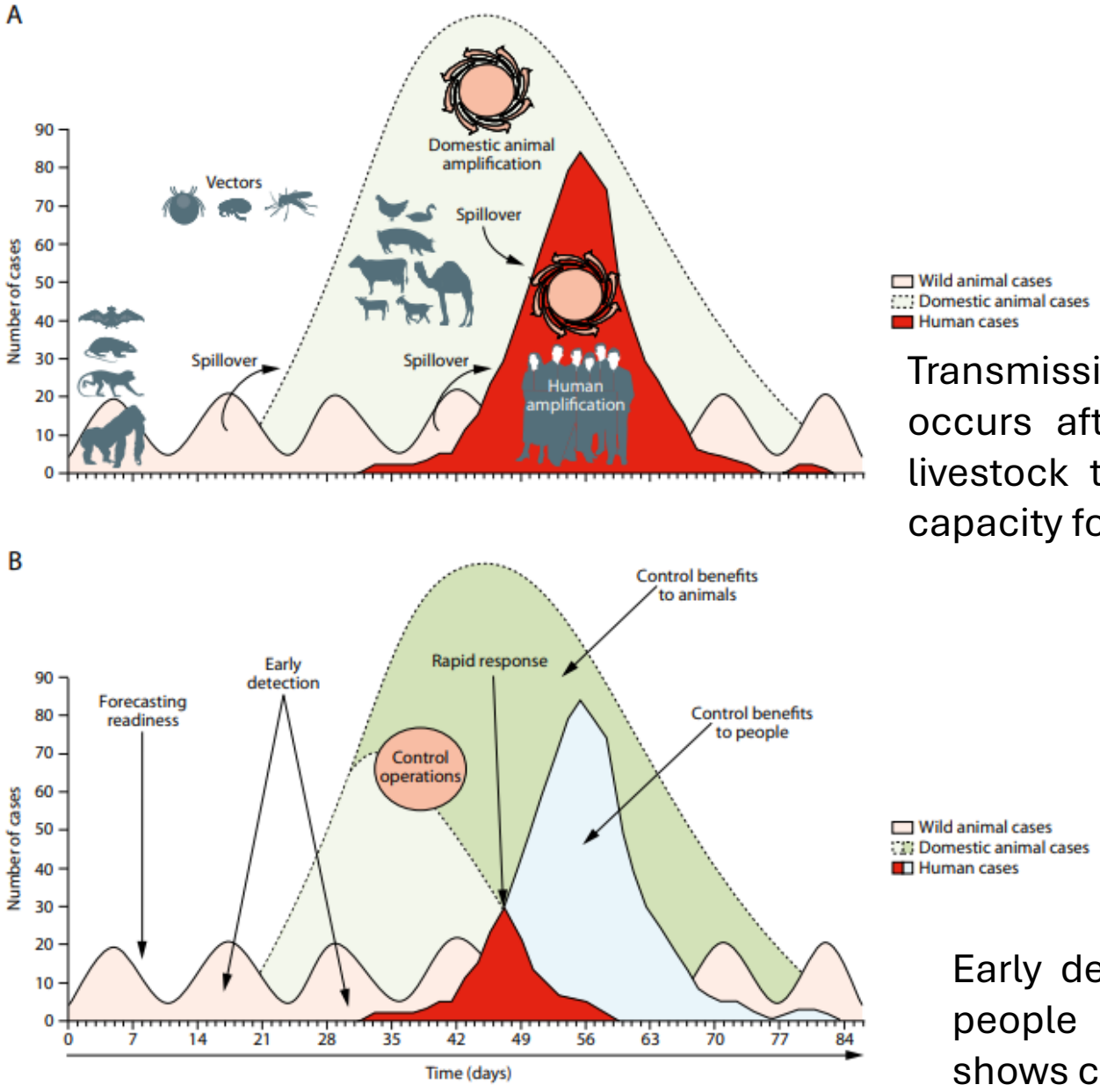
| Chracteristics of pandemic virus | |
|---|---|
| ✓ | Replication in humans |
| ✓ | Susceptibility of human population |
| ✓ | Human-human transmission |

# From pandemia to seasonal flu




*Nachbagauer & Krammer, Clin Microbiol Inf, 2017*




Series

Zoonoses 1

## Ecology of zoonoses: natural and unnatural histories

William B Karesh, Andy Dobson, James O Lloyd-Smith, Juan Lubroth, Matthew A Dixon, Malcolm Bennett, Stephen Aldrich, Todd Harrington, Pierre Formenty, Elizabeth H Loh, Catherine C Machalaba, Mathew Jason Thomas, David L Heymann

Transmission of infection and amplification in people (bright red) occurs after a pathogen from wild animals (pink) moves into livestock to cause an outbreak (light green) that amplifies the capacity for pathogen transmission to people

Early detection and control efforts reduce disease incidence in people (light blue) and animals (dark green). Spillover arrows shows cross-species transmission.

# Global Influenza Surveillance & Response System

GISRS
GLOBAL INFLUENZA SURVEILLANCE & RESPONSE SYSTEM
Uniting the world in the fight against influenza
SINCE 1952

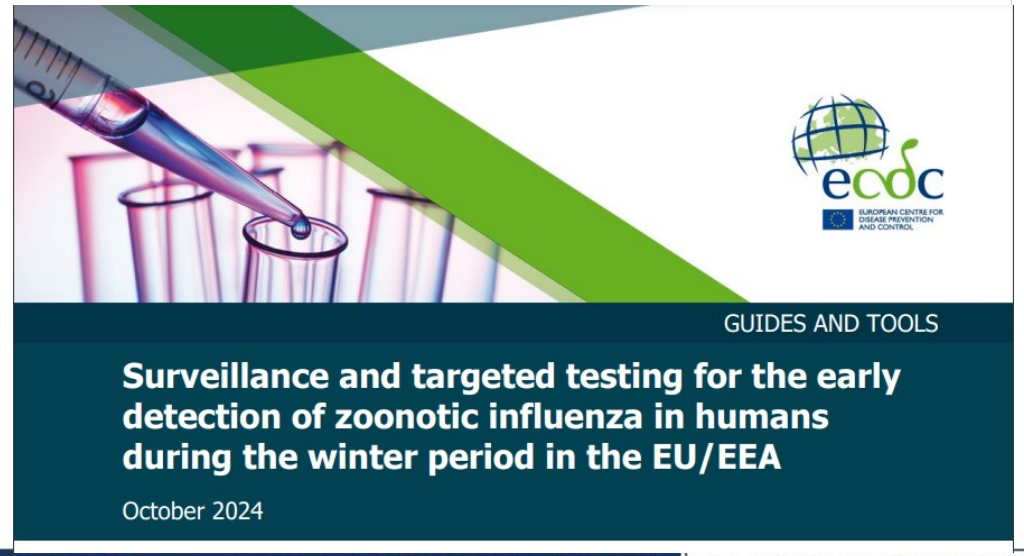
## Influenza pandemica

- Preparazione pandemica
- Monitoraggio e allerta

## Influenza stagionale

- Sorveglianza epidemiologica
  - Stimare l'impatto della mallattia
  - Definirne le caratteristiche epidemiologiche
- Sorveglianza virologica
  - Analizzare i virus stagionali circolanti
  - Formulare le raccomandazioni per la composizione vaccino

# Potenziamento della sorveglianza virologica

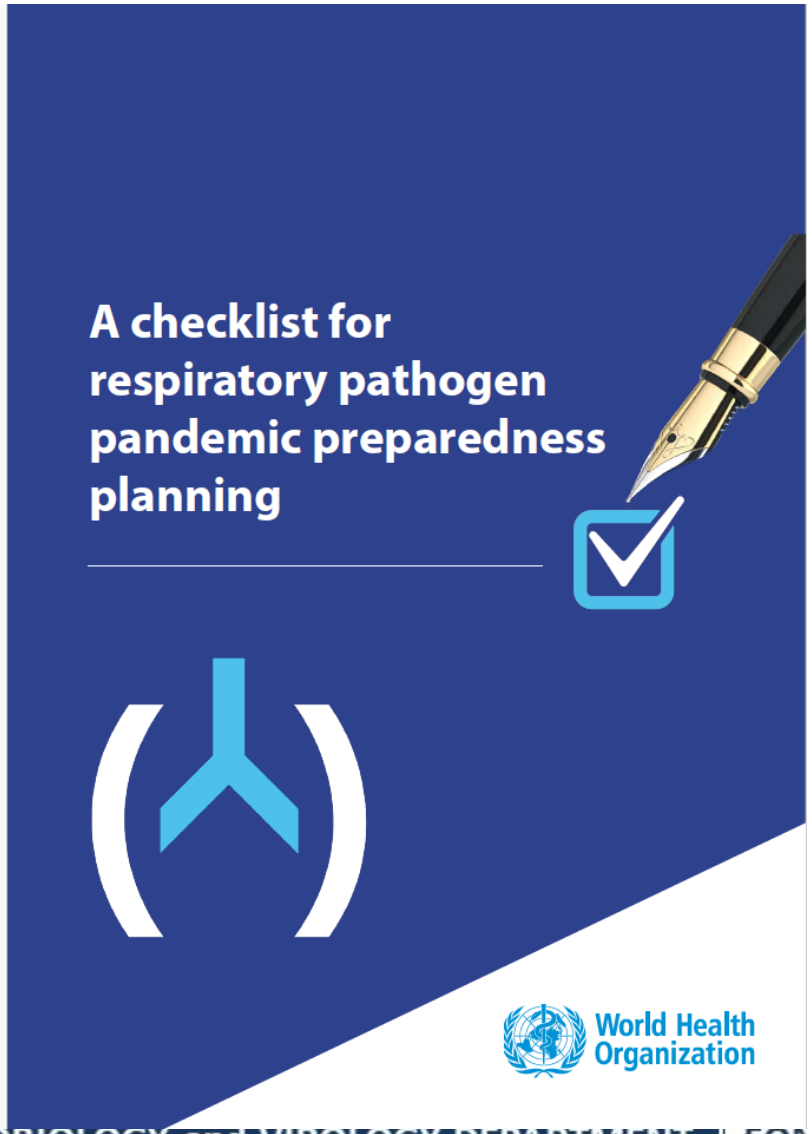




Monitoraggio virologico di:

- *Persone ospedalizzate per sintomi respiratori* considerando anche il rischio di esposizione ad animali malati/morti
- *Casi di encefalite o meningoencefalite a eziologia non nota*
- *Cluster di infezioni respiratorie gravi*

In generale: qualsiasi campione positivo per virus influenzale A ma negativo per i sottotipi di virus influenzali stagionali deve essere caratterizzato prontamente

# Preparazione pandemica e sorveglianza




## CONTENTS





https://www.who.int/publications/i/item/9789240084513

# Potenziamento della sorveglianza virologica

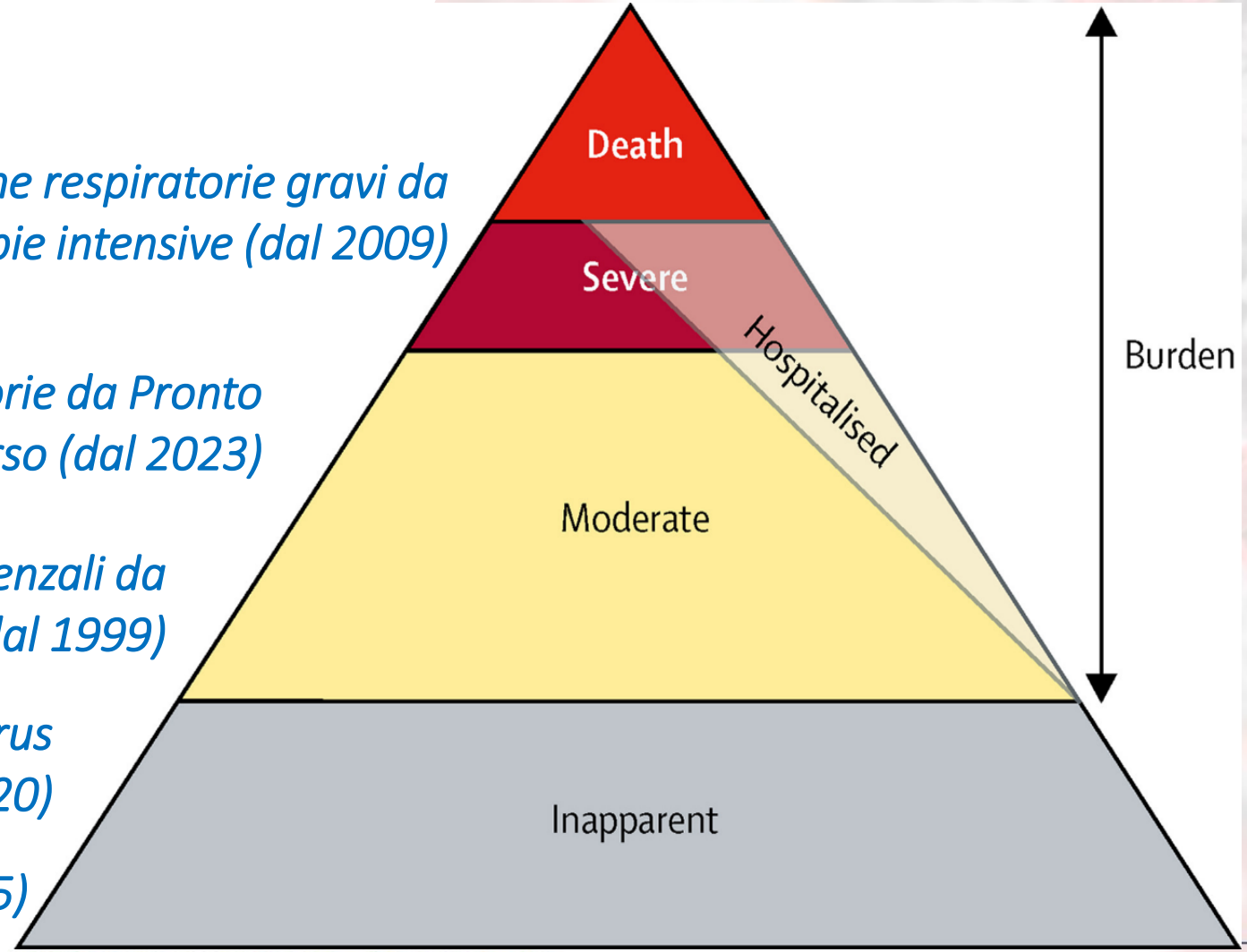
*Sorveglianza delle forme respiratorie gravi da terapie intensive (dal 2009)*

*Sorveglianza delle sindromi respiratorie da Pronto Soccorso (dal 2023)*

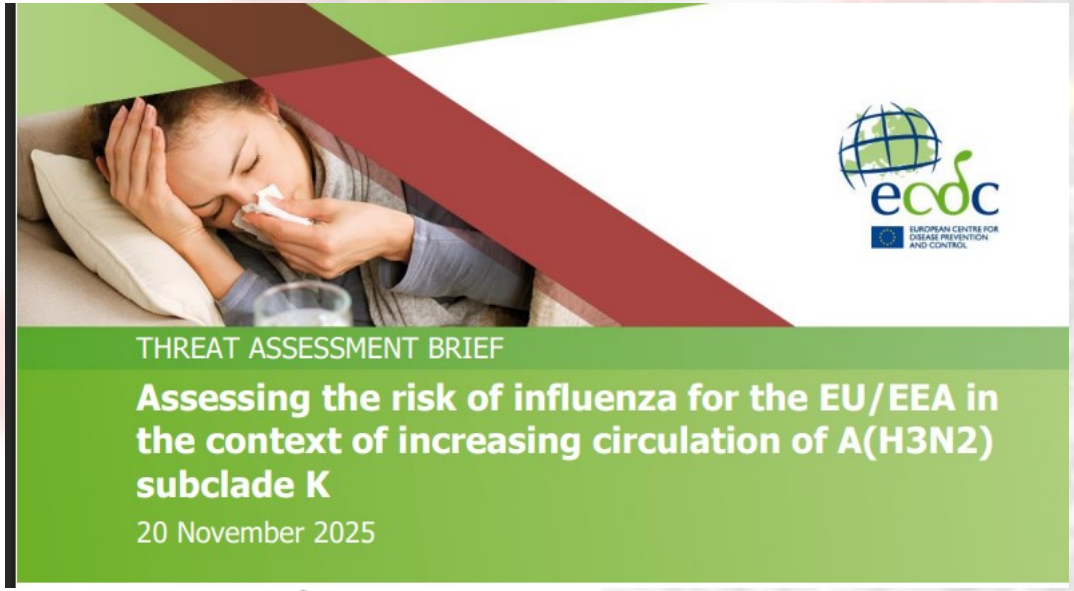
*Sorveglianza delle sindromi simil-influenzali da ambulatorio medico (dal 1999)*

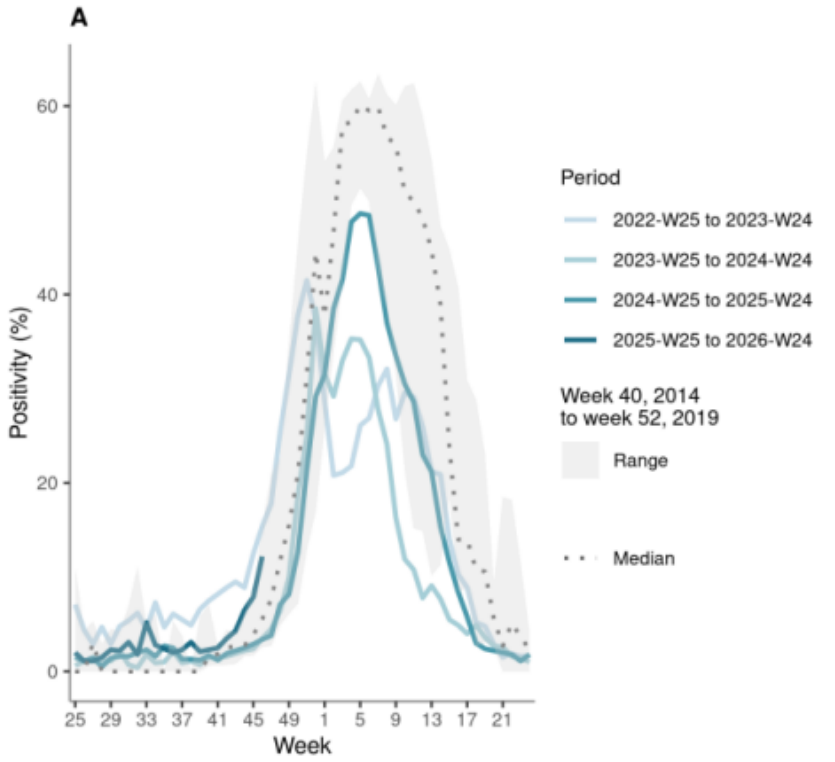
*Sorveglianza attiva degli esposti a virus aviari (dal 2020)*

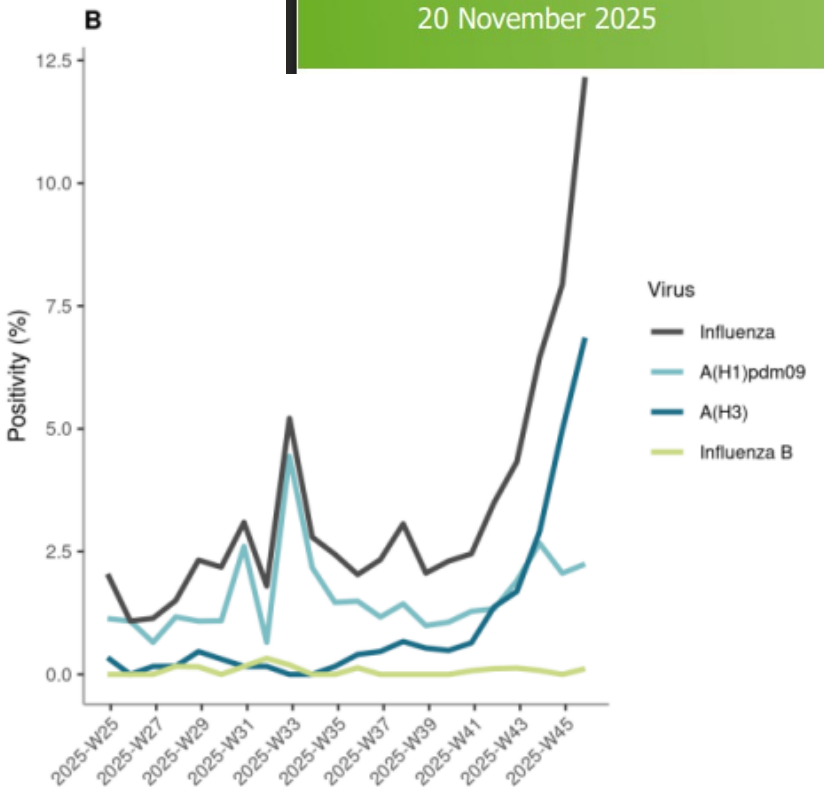
*Sorveglianza delle acque reflue (2025)*



# Current Flu season (2025-2026)

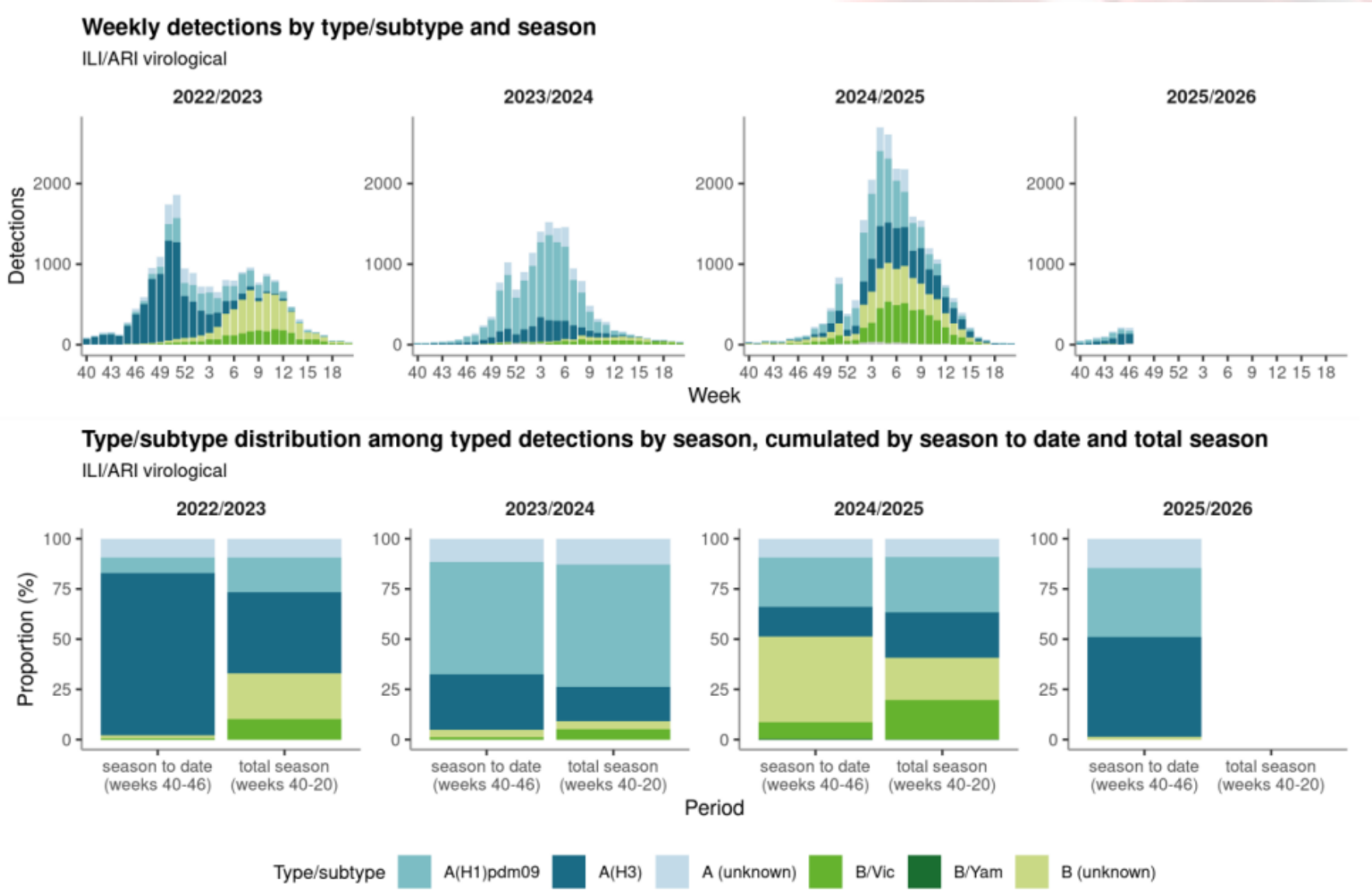


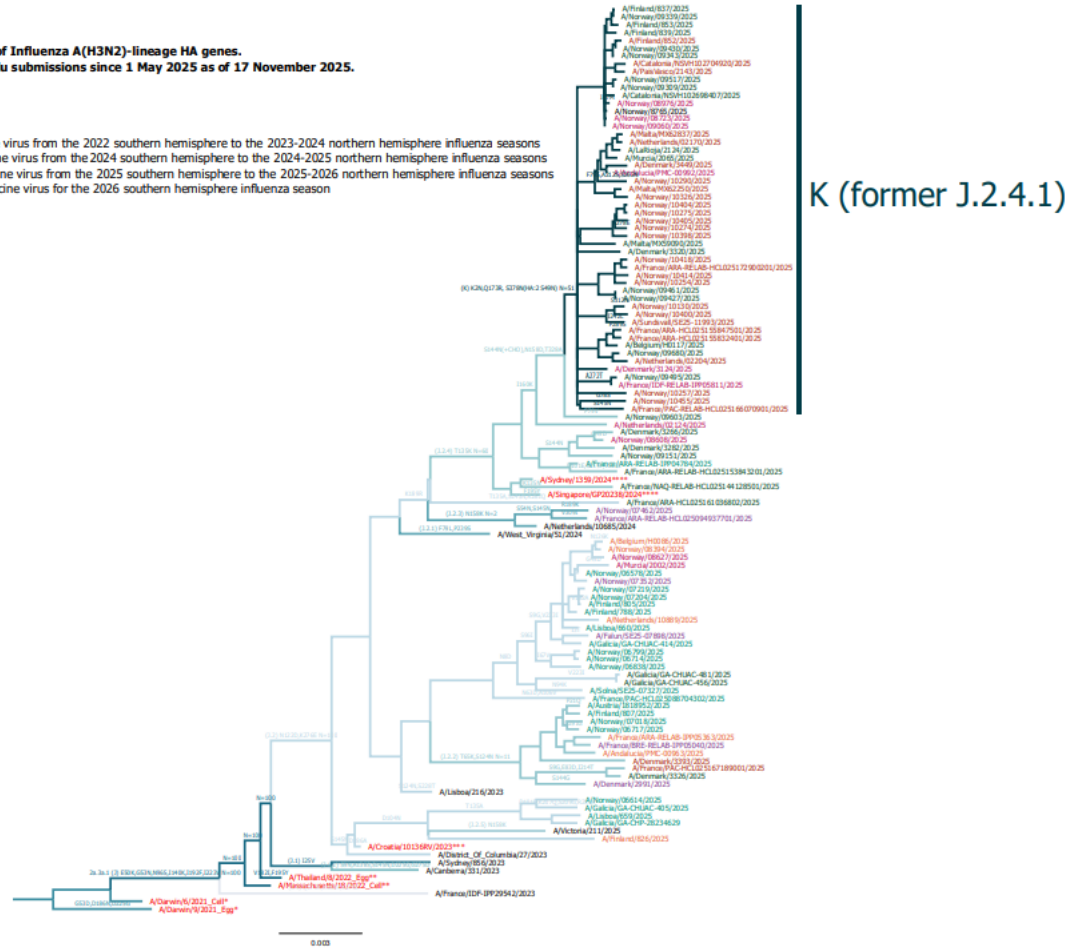



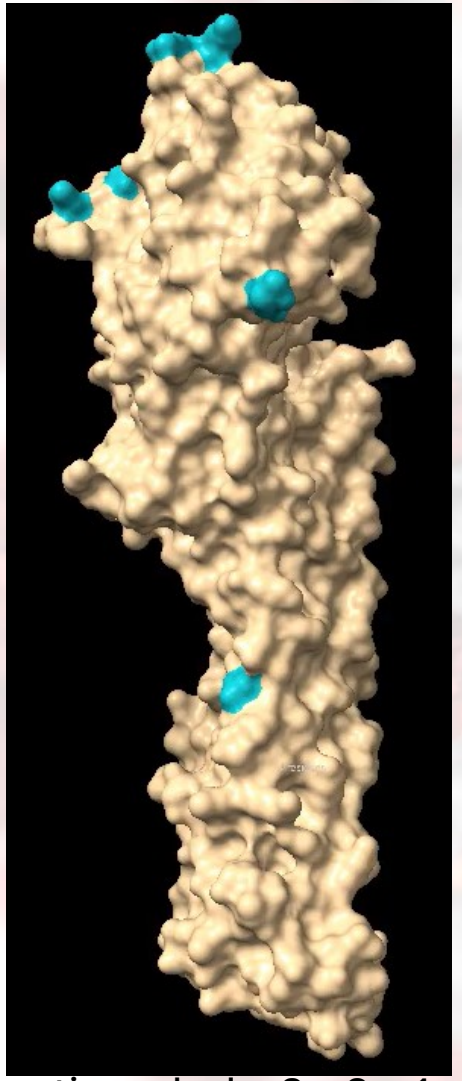

*ILI – influenza-like illness; ARI - acute respiratory infections*

# Current Flu season (2025-2026)



**GISAID).**



K2N,
T135K
S144N
N158D
I160K
Q173R
K189R
T328A
S378N

The newly emerged A(H3N2) subclade K (former J.2.4.1) belong to the dominating clade 2a.3a.1 and have K2N, T135K, S144N(+CHO), N158D, I160K, Q173R, K189R, T328A and S378N (haemagglutinin subunit 2: S49N) substitutions in haemagglutinin gene compared to A/Croatia/10136RV/2023, which is the WHO recommended eggpropagated vaccine virus for the 2025-2026 northern hemisphere influenza season.

# Current Flu season (2025-2026) strain in Pavia

**WHO recommended vaccine virus from the 2022 southern hemisphere to the 2023–2024 northern hemisphere influenza season

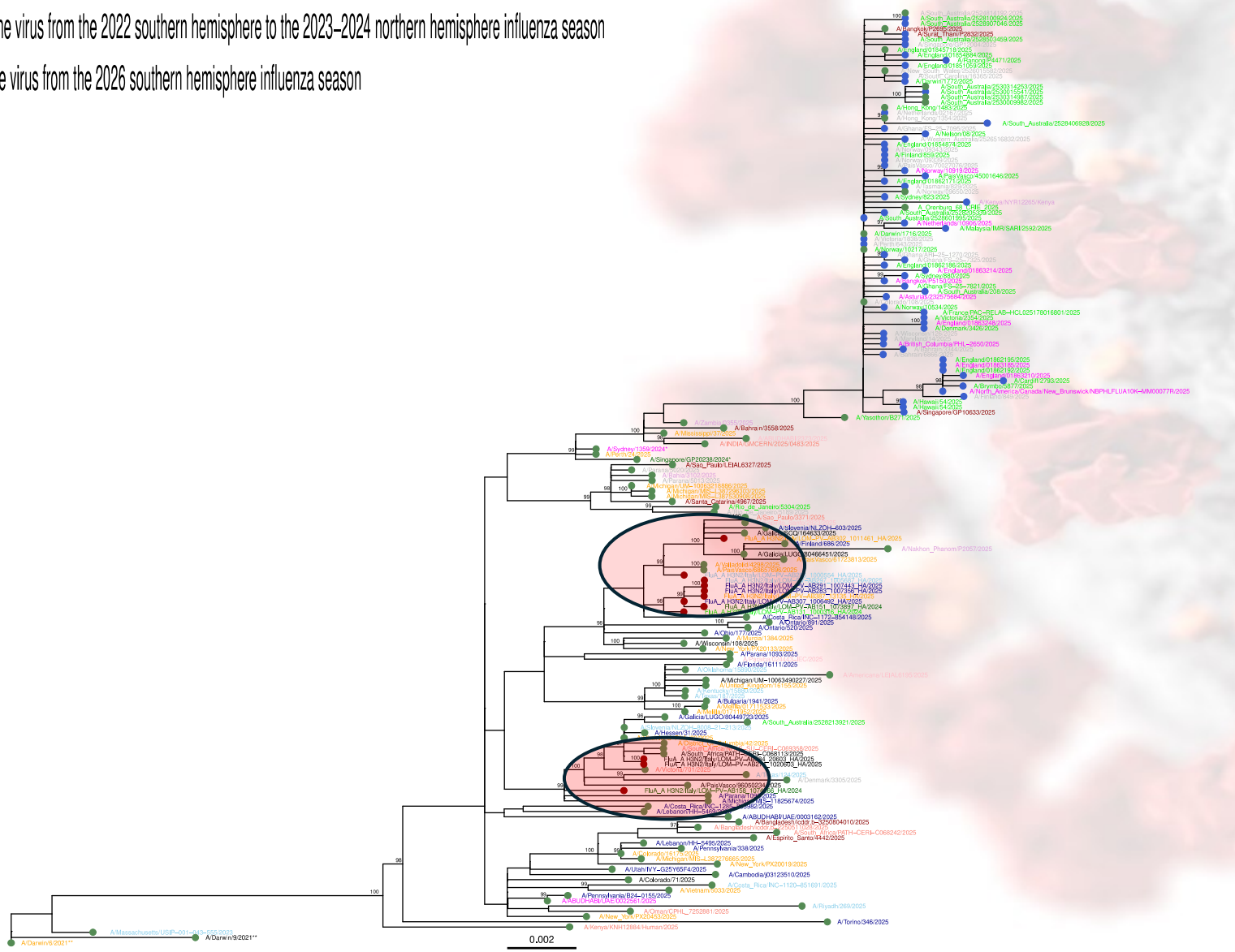
*WHO recommended vaccine virus from the 2026 southern hemisphere influenza season

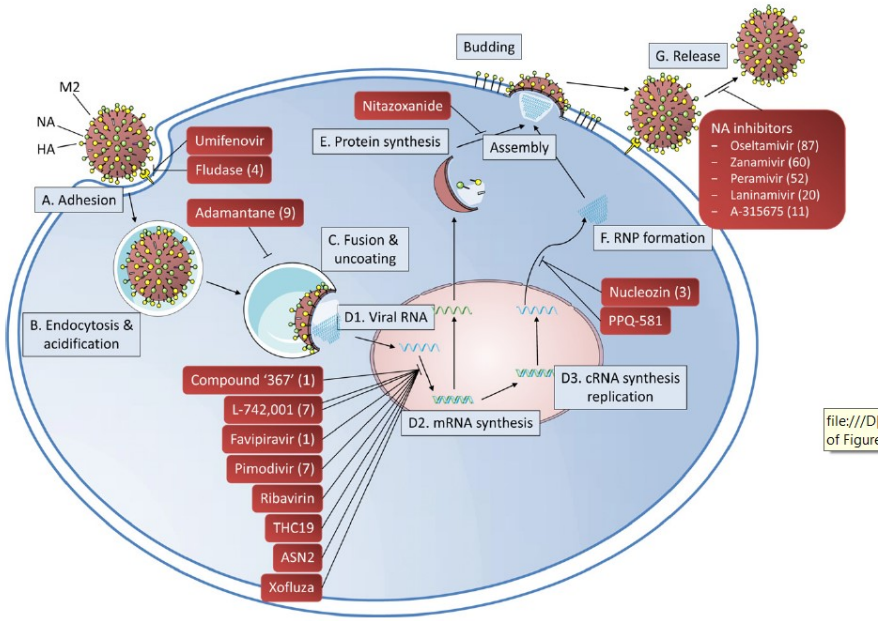
Month

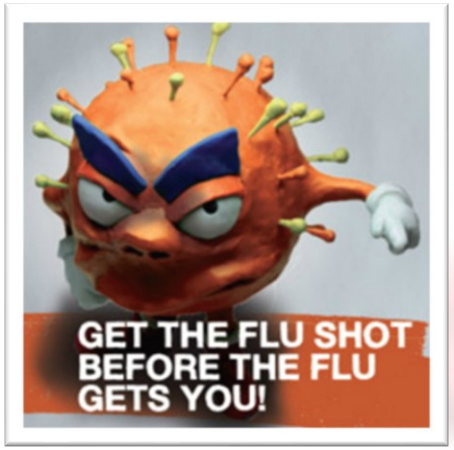
- a April
- a August
- a December
- a February
- a January
- a July
- a June
- a March
- a May
- a November
- a October
- a Septmber

Lineage

- K
- Other
- Pavia






Trends in Biotechnology

CellPress
REVIEWS

Opinion

# Next-Generation Sequencing: An Eye-Opener for the Surveillance of Antiviral Resistance in Influenza

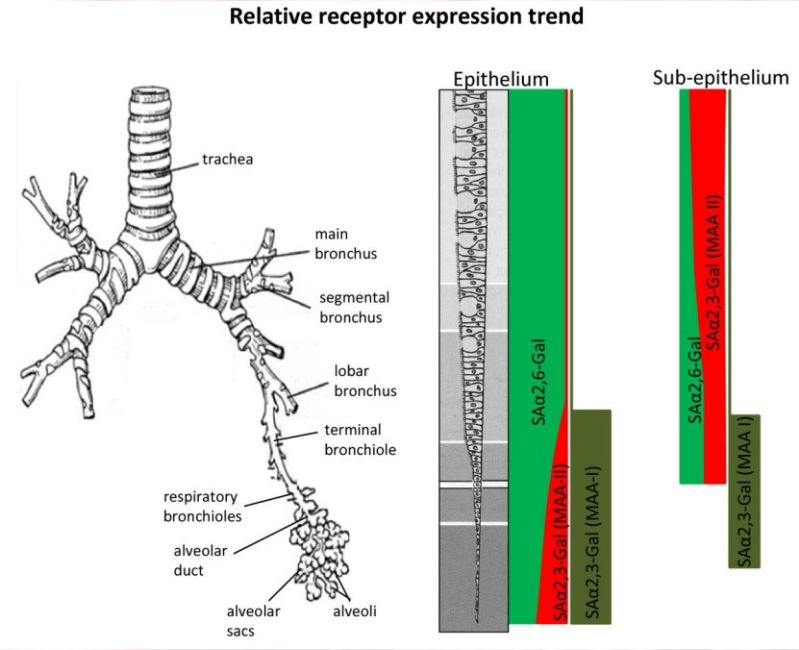
Laura A.E. Van Poelvoorde,[1,2,3,4,5,6] Xavier Saelens,[3,4] Isabelle Thomas,[2,6] and Nancy H. Roosens[1,5,*]

Van Poelvoorde, Laura A E et al. "*Trends in biotechnology* vol. 38,4 (2020): 360-367. doi:10.1016/j.tibtech.2019.09.009

Although vaccines are considered the best way to prevent influenza, the limited use and their generally poor effectiveness in the elderly (https://www.cdc.gov/flu/about/qa/vaccineeffect.htm) imply that efficient antiviral drugs are needed as a complementary or alternative line of defense.

Monitoring and detecting mutations in the influenza virus genome by NGS, especially those that confer antiviral resistance, is of paramount importance to *public health surveillance*. As the use of antiviral drugs continues to grow, more cases of drug-resistant viruses are expected to occur.

- The HA proteins of the human seasonal H1 and H3 virus subtypes mainly recognize receptors with terminal α-2,6-SA moieties, which are found on bronchial epithelial cells of the human upper respiratory tract (URT).
- By contrast, Avian viruses bind predominantly to galactose linked to α-2,3-SA54, which is found abundantly on epithelial cells in the intestine of birds and in the lower respiratory tract (LRT) of humans.



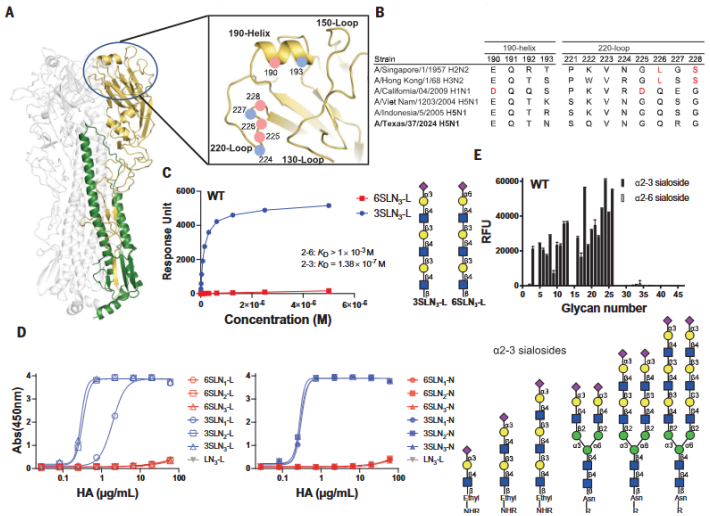

https://doi.org/10.1186/1746-6148-6-4

INFLUENZA

## A single mutation in bovine influenza H5N1 hemagglutinin switches specificity to human receptors

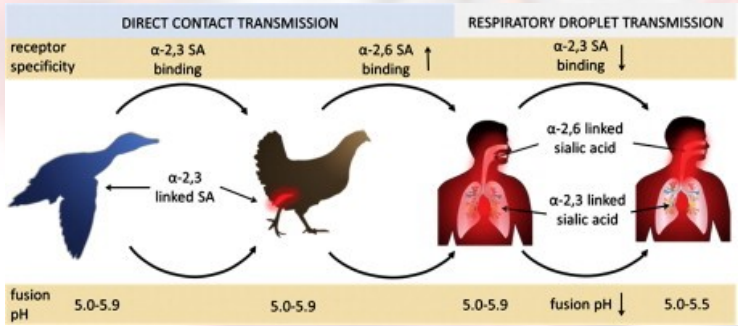
Ting-Hui Lin[1], Xueyong Zhu[1], Shengyang Wang[2,3], Ding Zhang[1], Ryan McBride[2,3], Wenli Yu[1], Simeon Babarinde[1], James C. Paulson[2,3]*, Ian A. Wilson[1]*

In 2024, several human infections with highly pathogenic clade 2.3.4.4b bovine influenza H5N1 viruses in the United States raised concerns about their capability for bovine-to-human or even human-to-human transmission. In this study, analysis of the hemagglutinin (HA) from the first-reported human-infecting bovine H5N1 virus (A/Texas/37/2024, Texas) revealed avian-type receptor binding preference. Notably, a Gln[226]Leu substitution switched Texas HA binding specificity to human-type receptors, which was enhanced when combined with an Asn[224]Lys mutation. Crystal structures of the Texas HA with avian receptor analog LSTa and its Gln[226]Leu mutant with human receptor analog LSTc elucidated the structural basis for this preferential receptor recognition. These findings highlight the need for continuous surveillance of emerging mutations in avian and bovine clade 2.3.4.4b H5N1 viruses.




HA Gln226 → Leu

Shift from α-2,3-SA to α-2,6-SA




**Thus, it is important to continue to monitor for signs of such changes in the currently circulating H5N1 viruses**

https://doi.org/10.1002/embj.201387442

frontiers in Veterinary Science

REVIEW
published: 22 January 2019
doi: 10.3389/fvets.2018.00347

# Adaptation of Human Influenza Viruses to Swine

*Daniela S. Rajao[1]*, Amy L. Vincent[2] and Daniel R. Perez[1]*

[1] Department of Population Health, University of Georgia, Athens, GA, United States, [2] Virus and Prion Research Unit, USDA-ARS, National Animal Disease Center, Ames, IA, United States

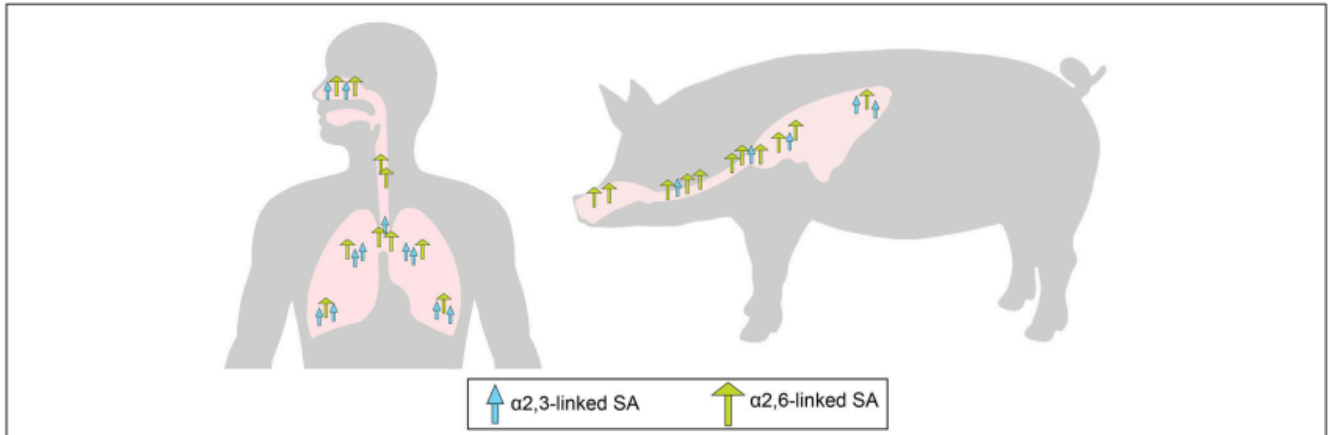



**FIGURE 1 |** Overall distribution of α2,6-linked sialic acid (SA; green long arrow) and α2,3-linked SA (blue short arrow) in the epithelium of the respiratory tract of pigs (18, 19) and humans (14, 15). Adapted from de Graaf and Fouchier (20).

A large diversity of influenza A viruses (IAV) within the H1N1/N2 and H3N2 subtypes circulates in pigs globally, with different lineages predominating in specific regions of the globe. A common characteristic of the ecology of IAV in swine in different regions is the periodic spillover of human seasonal viruses.

Such human viruses resulted in sustained transmission in swine in several countries, leading to the establishment of novel IAV lineages in the swine host and contributing to the genetic and antigenic diversity of influenza observed in pigs.

The frequent occurrence of reverse-zoonosis of IAV from humans to pigs that have contributed to the global viral diversity in swine in a continuous manner, describe host-range factors that may be related to the adaptation of these human-origin viruses to pigs, and how these events could affect the swine industry.


**FIGURE 3 |** Proportion of amino acids found in influenza A viruses circulating in pigs globally at the HA receptor-binding site positions previously shown to impact receptor-specificity for H1, H3, and H9. Analysis was performed using the Influenza Research Database Sequence Variation (SNP) tool (44). Sequences with 100% identity were removed resulting in a set of 8076 H1 HA, 2287 H3 HA, and 46 H9 HA swine IAV sequences. The amino acids previously shown to change receptor-binding specificity are displayed on the right.

# Swine influenza virus infection in humans: NGS approach

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 21, No. 7, July 2015

**DISPATCHES**

## Swine Influenza A(H3N2) Virus Infection in Immunocompromised Man, Italy, 2014

Antonio Piralla, Ana Moreno, Maria Ester Orlandi, Elena Percivalle, Chiara Chiapponi, Fausto Vezzoli, Fausto Baldanti, and the Influenza Surveillance Study Group[1]

subtypes H1 and H3, as well as avian influenza subtype H7N9, were unsuccessful.

The clinical sample was inoculated onto a mixed-cell (Mv1Lu and A549 cells) monolayer. After 48 h incubation,

**RAPID COMMUNICATIONS**

## Swine influenza A (H1N1) virus (SIV) infection requiring extracorporeal life support in an immunocompetent adult patient with indirect exposure to pigs, Italy, October 2016

F Rovida [1,2], A Piralla [1,2], FC Marzani [3], A Moreno [4], G Campanini [1], F Mojoli [3,5], M Pozzi [3], A Girello [1], C Chiapponi [6], F Vezzoli [7], P Prati [8], E Percivalle [1], A Pavan [9], M Gramegna [10], GA Iotti [3,5], F Baldanti [1,11]

frontiers | Frontiers in Cellular and Infection Microbiology

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OPEN ACCESS

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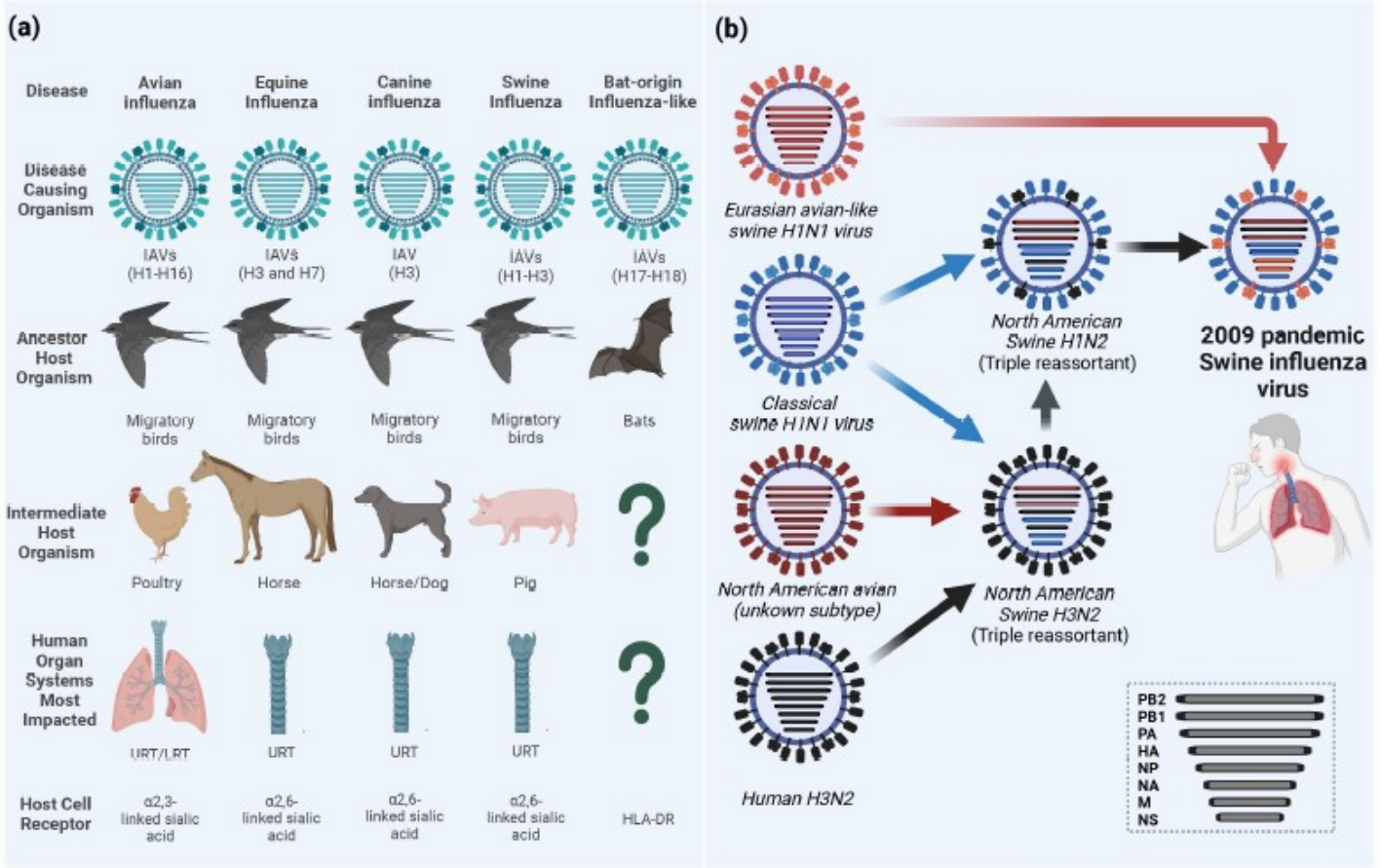
# Zoonosis and zooanthroponosis of emerging respiratory viruses

Ahmed Magdy Khalil[1,2], Luis Martinez-Sobrido[1*] and Ahmed Mostafa[1,3*]

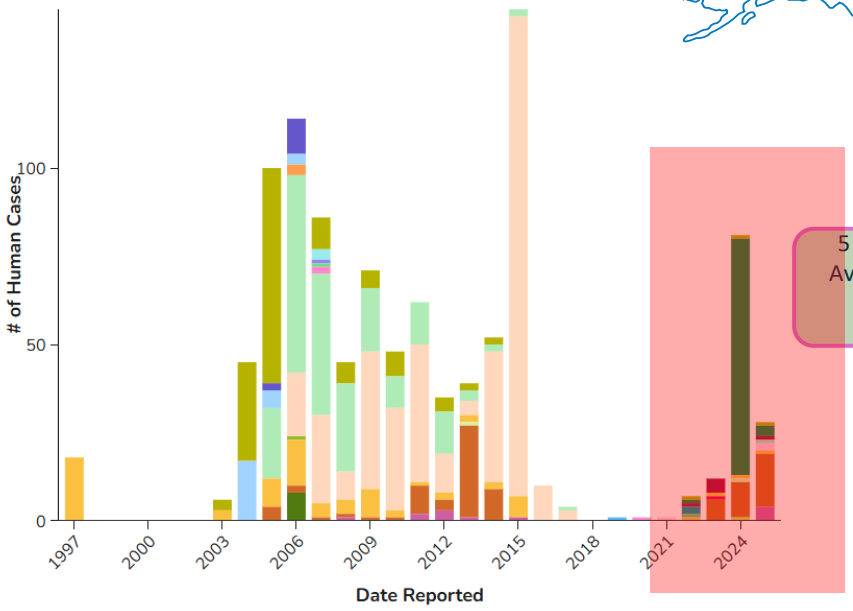
IAVs are categorized according to their intermediate or ancestor animal host species into avian influenza viruses (AIVs), equine influenza viruses (EIVs), canine influenza viruses (CIVs), swine influenza viruses (SIVs) or bat-origin influenza-like viruses (BIVs).

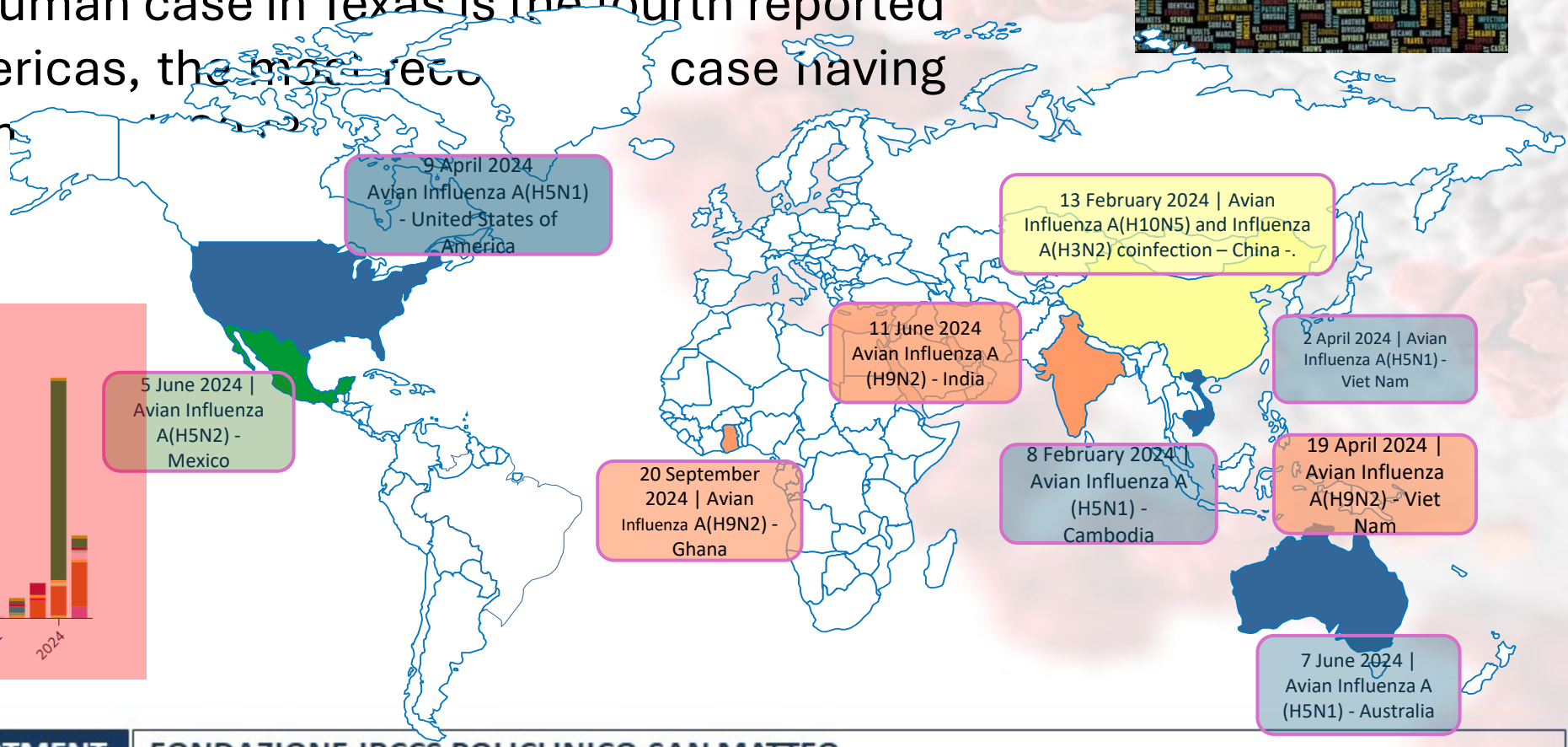


# April 2025 – Avian Influenza Virus (AIV) H5N1



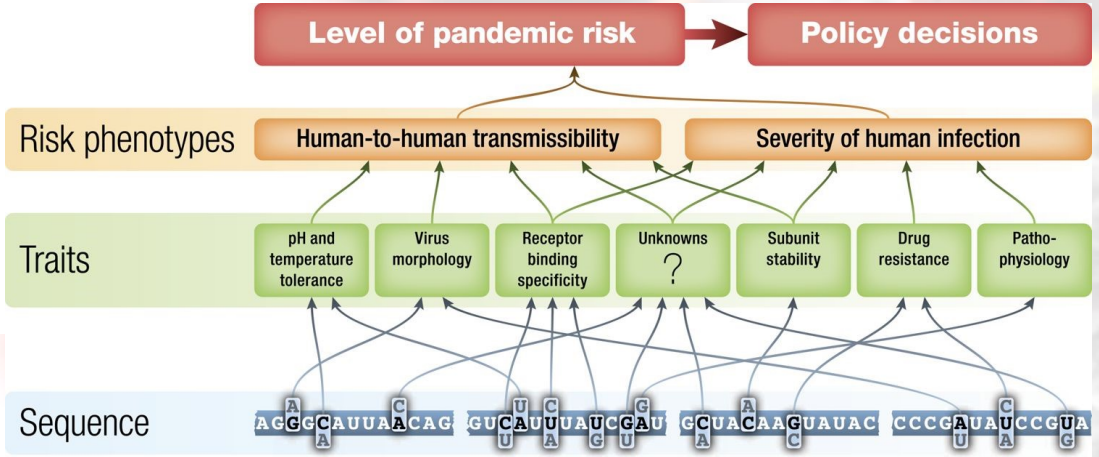
From 2003 to August 2025, a total of 972 cases and 470 deaths (CFR 52%) caused by influenza A(H5N1) virus have been reported worldwide from 23 countries. The most recently reported case in humans prior to the current case, was in March 2024 in Viet Nam. The human case in Texas is the fourth reported in the region of the Americas, the most recent case having been reported in Chile in [illegible]



## Pandemic risk characterisation of zoonotic influenza A viruses using the Tool for Influenza Pandemic Risk Assessment (TIPRA)

Reina Yamaji, Wenqing Zhang, Akiko Kamata, Cornelia Adlhoch, David E Swayne, Dmitriy Pereyaslov, Dayan Wang, Gabriele Neumann, Gounalan Pavade, Ian G Barr, Malik Peiris, Richard J Webby, Ron A M Fouchier, Sophie Von Dobschütz, Thomas Fabrizio, Yuelong Shu, Magdi Samaan




### 1. Scores viruses across two dimensions

TIPRA evaluates a zoonotic influenza virus using two main axes:
(a) Risk of Emergence (how likely the virus is to gain sustained human-to-human transmission) and
(b) Potential Public-Health Impact (how severe a pandemic would be if it emerged).

### 2. Uses a set of predefined indicators

Each axis is broken down into quantitative and qualitative indicators (e.g., transmissibility in mammals, genetic markers, human case severity, population immunity, global spread in animals). Experts assign standardized scores to each indicator.

### 3. Relies on multidisciplinary expert judgment

TIPRA integrates evidence from virology, epidemiology, surveillance data, ecology, clinical severity, and immunology. Experts review available data, discuss uncertainties, and assign final consensus scores for each indicator.

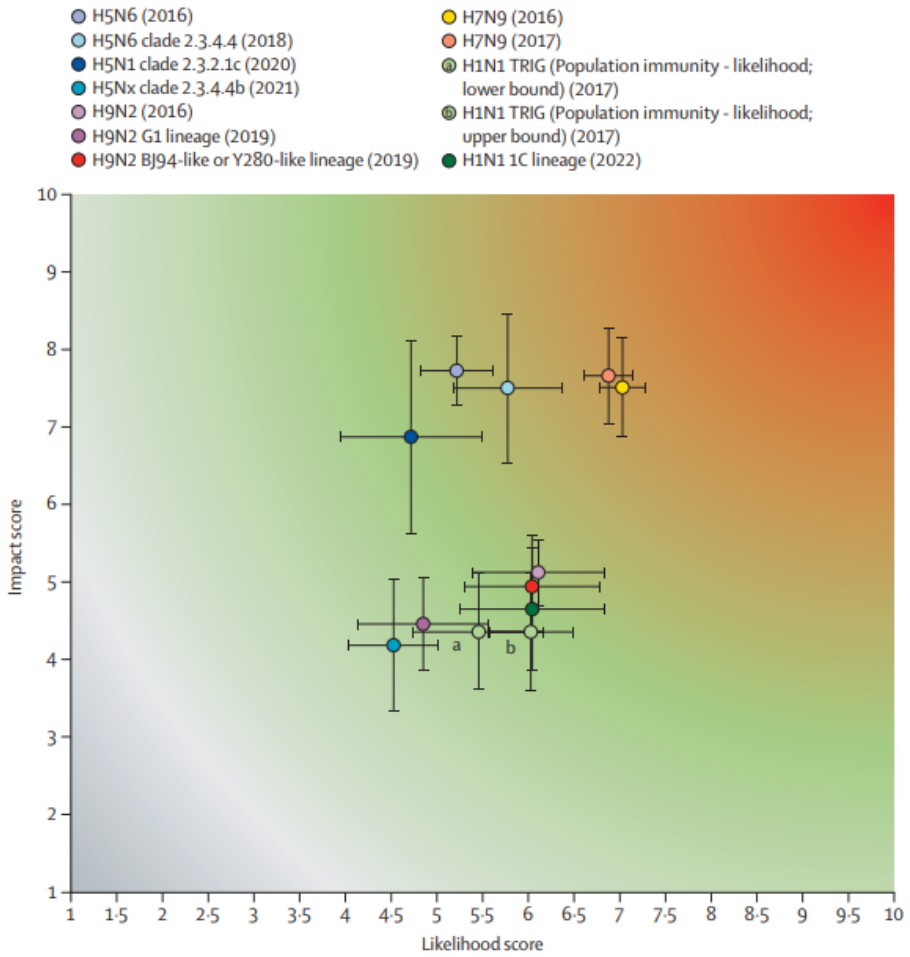
### 4. Produces a comparable "risk profile" across viruses

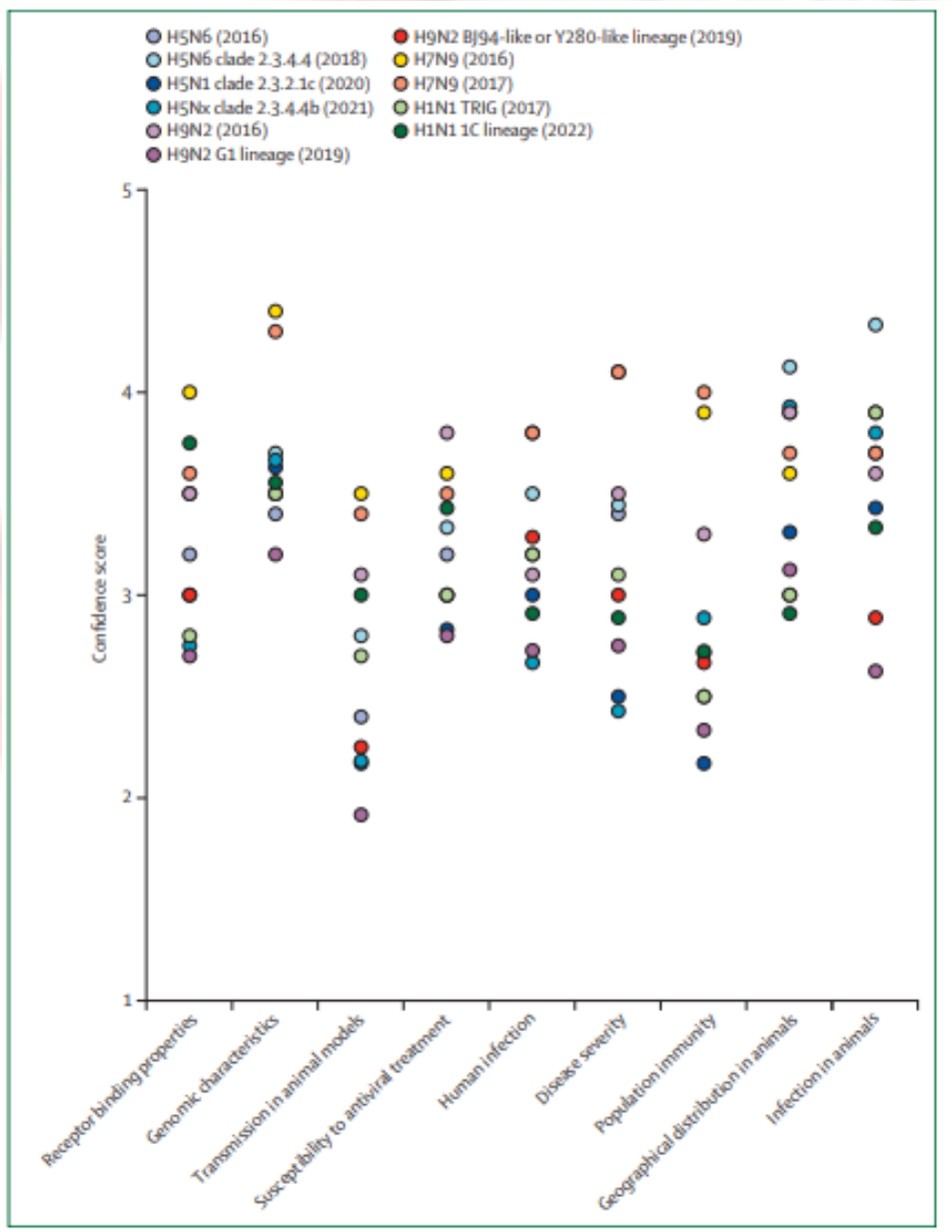
The tool summarizes the scoring into an emergence-risk score, an impact score, and an overall risk characterization, allowing WHO and member states to compare different zoonotic influenza viruses, prioritize surveillance, and guide preparedness actions.

Review

# Pandemic risk characterisation of zoonotic influenza A viruses using the Tool for Influenza Pandemic Risk Assessment (TIPRA)

*Reina Yamaji, Wenqing Zhang, Akiko Kamata, Cornelia Adlhoch, David E Swayne, Dmitriy Pereyaslov, Dayan Wang, Gabriele Neumann, Gounalan Pavade, Ian G Barr, Malik Peiris, Richard J Webby, Ron A M Fouchier, Sophie Von Dobschütz, Thomas Fabrizio, Yuelong Shu, Magdi Samaan*



# Emergenet: Fast Scalable Pandemic Risk Assessment of Influenza A Strains Circulating In Non-human Hosts

Kevin Wu[1], Jin Li[1], Aaron Esser-Kahn[2,3], and Ishanu Chattopadhyay[1,4,5]★

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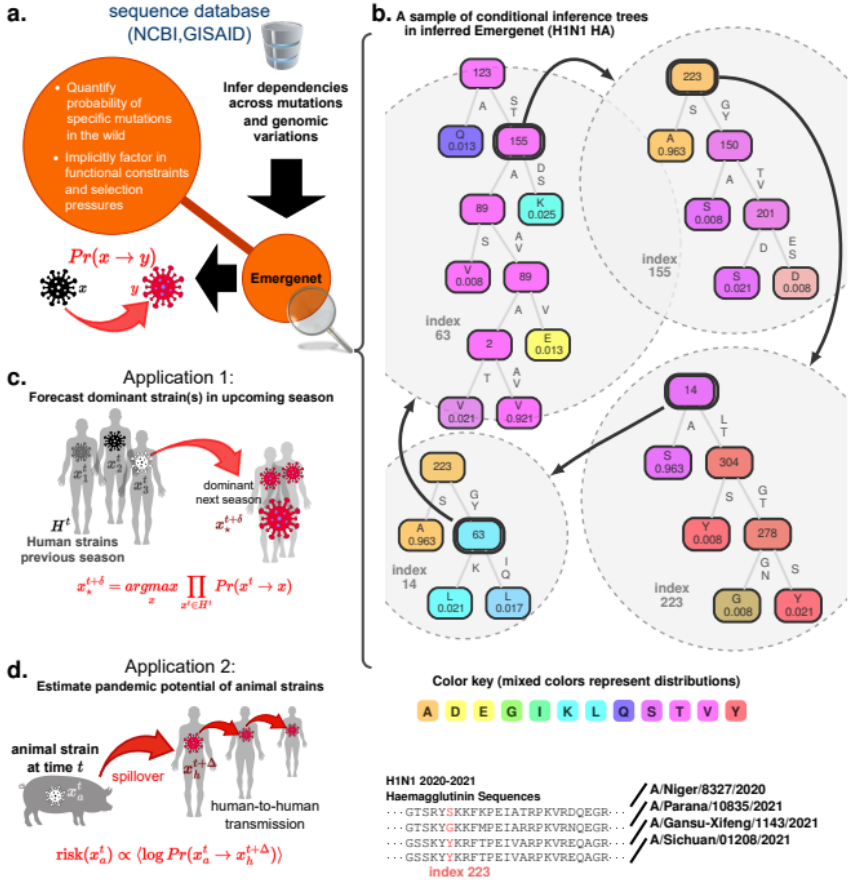
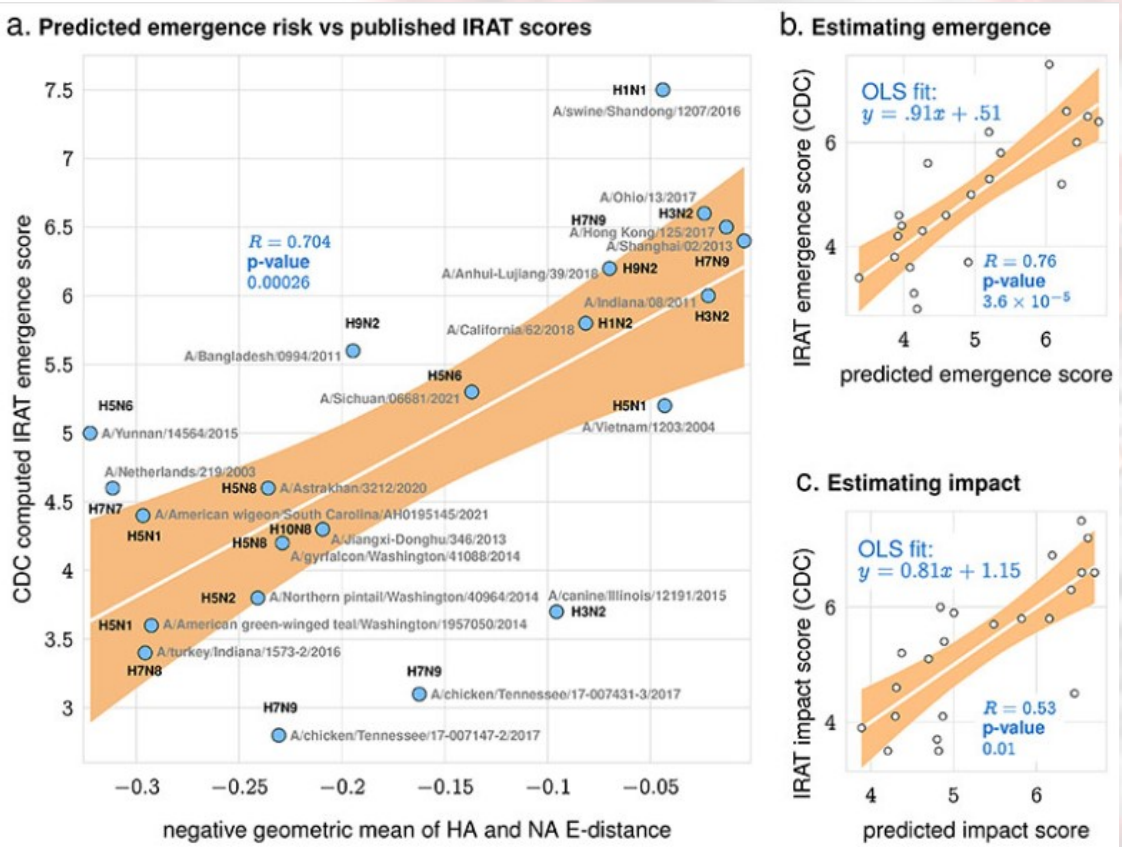
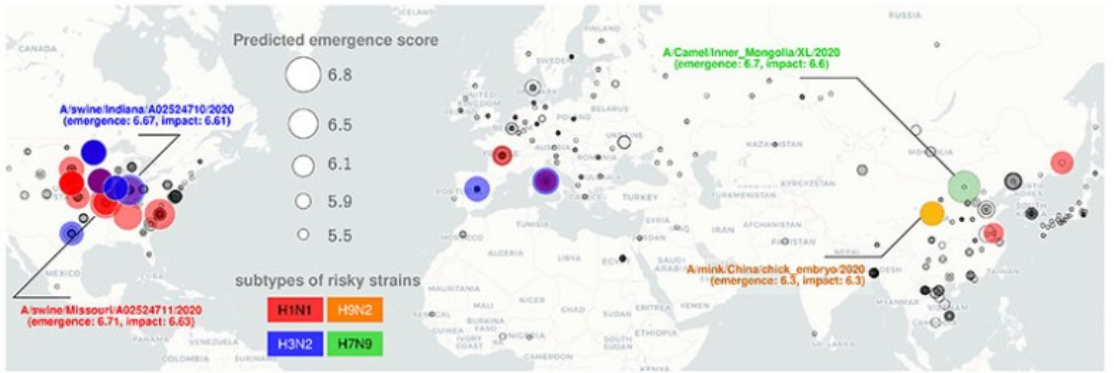
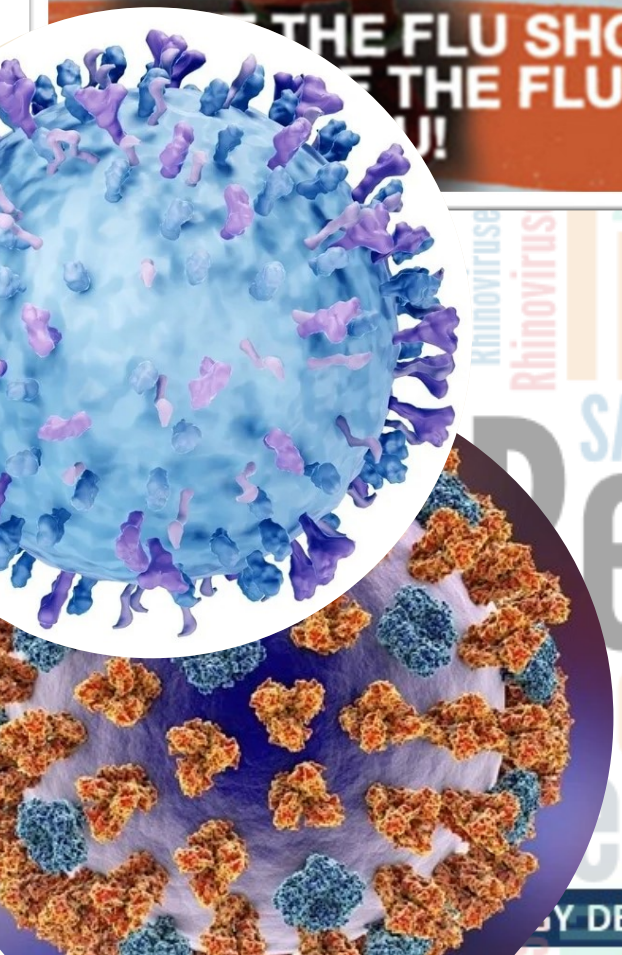
[2] Pritzker School of Molecular Engineering, University of Chicago, Chicago, IL, USA
[3] Committee on Immunology, University of Chicago, Chicago, IL, USA
[5] Committee on Quantitative Methods in Social, Behavioral, and Health Sciences, University of Chicago, IL, USA



# Grazie per l'attenzione