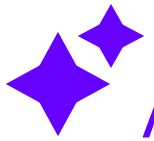
RESPIRATORY VIRUS PANDEMICS
CAN WE PREPARE FOR THEM?

Peter Palese
Icahn School of Medicine at Mount Sinai
New York

GVN Tampa
March 4, 2025

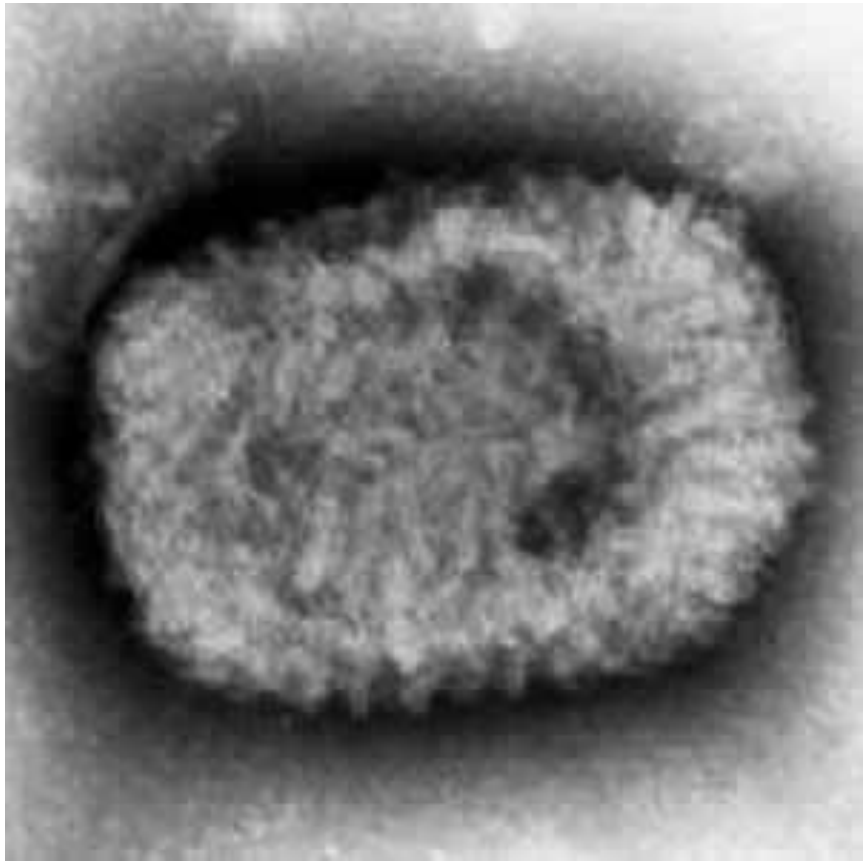


AI Summary

To understand the impact of smallpox in the 20th century, consider the following point:

- **Smallpox caused an estimated 300 million deaths globally during the 20th century.**

SMALLPOX



Mature Smallpox Virion. Micrograph from F. A. Murphy, University of Texas Medical Branch, Galveston, Texas.

- **May 14, 1796 - Jim Phipps vaccinated by Edward Jenner**
- **May 8, 1980 - WHO declares the world free of smallpox**

The Cow-Pock — or — the Wonderful Effects of the New Inoculation! — Vide the Publications of the Anti Vaccine Society

BRIEF EXTRACTS

FROM

HIGH AUTHORITIES

Exposing the Evils of Vaccination

THE GREAT MEDICAL DELUSION OF THE NINETEENTH CENTURY, NOW EXCITING POPULAR INDIGNATION.

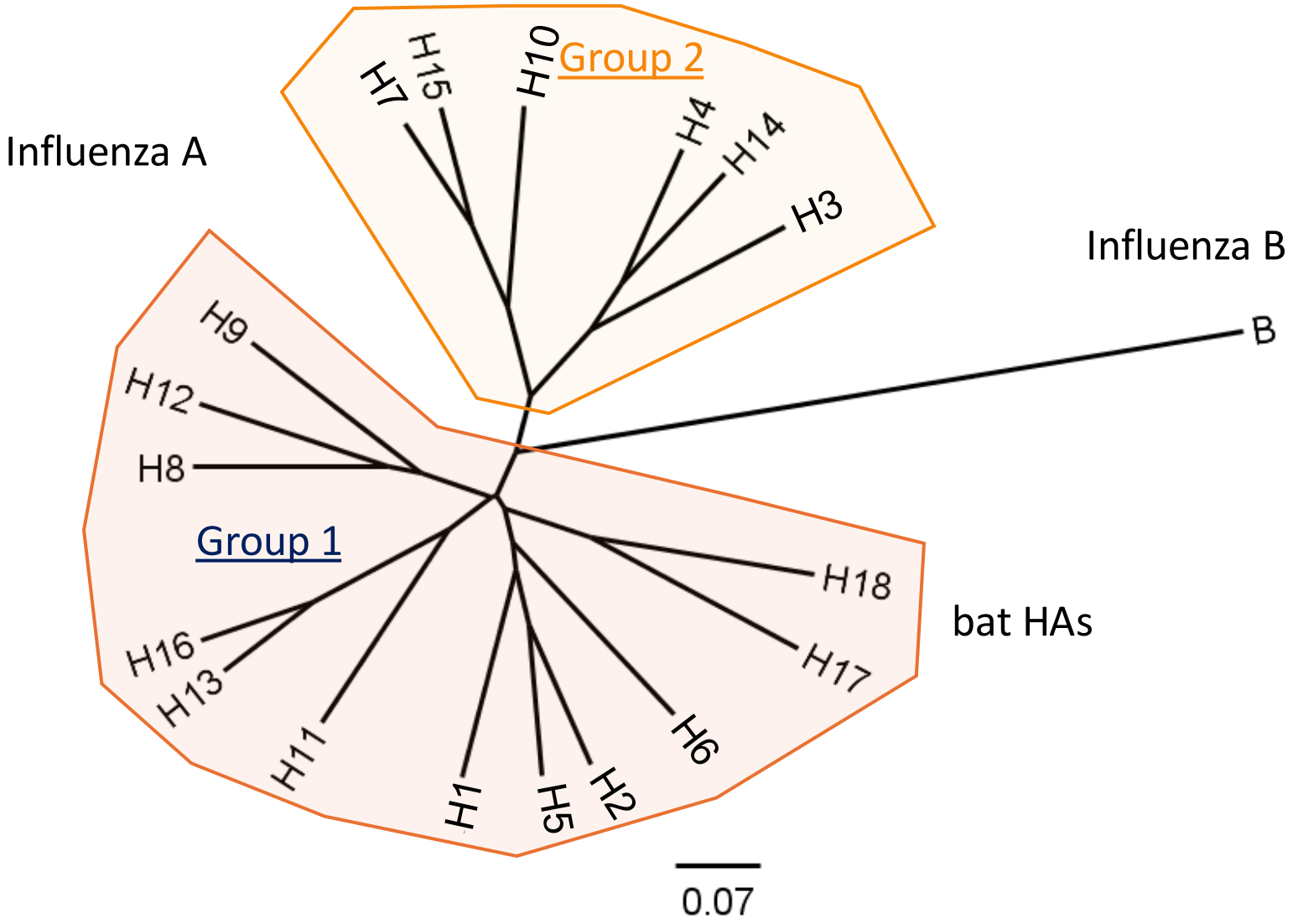
PROVIDENCE, R. I.
SNOW & FARNHAM, PRINTERS,
1891.

Camp Funston flu ward during the 1918 pandemic, Camp Funston, Kansas
Source: US Army – Public Domain

INFLUENZA DEATHS WORLDWIDE 1918/1919

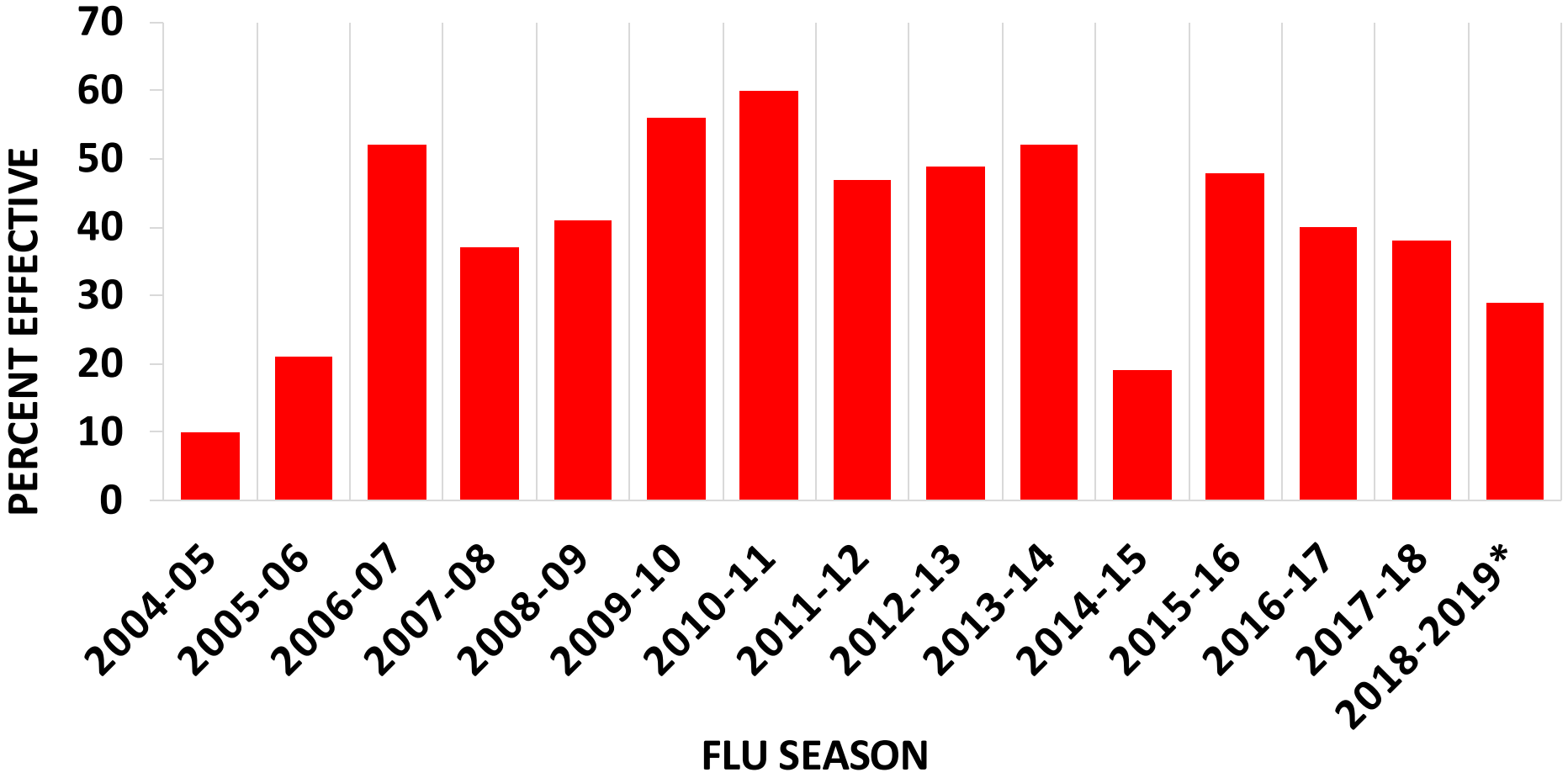
- **50-100 MILLION**

SUBTYPES OF INFLUENZA A VIRUS HEMAGGLUTININS



FLORIAN KRAMMER

SEASONAL FLU VACCINE EFFECTIVENESS



*Vaccine effectiveness estimates for 2018-2019 were presented to ACIP on June 27, 2019

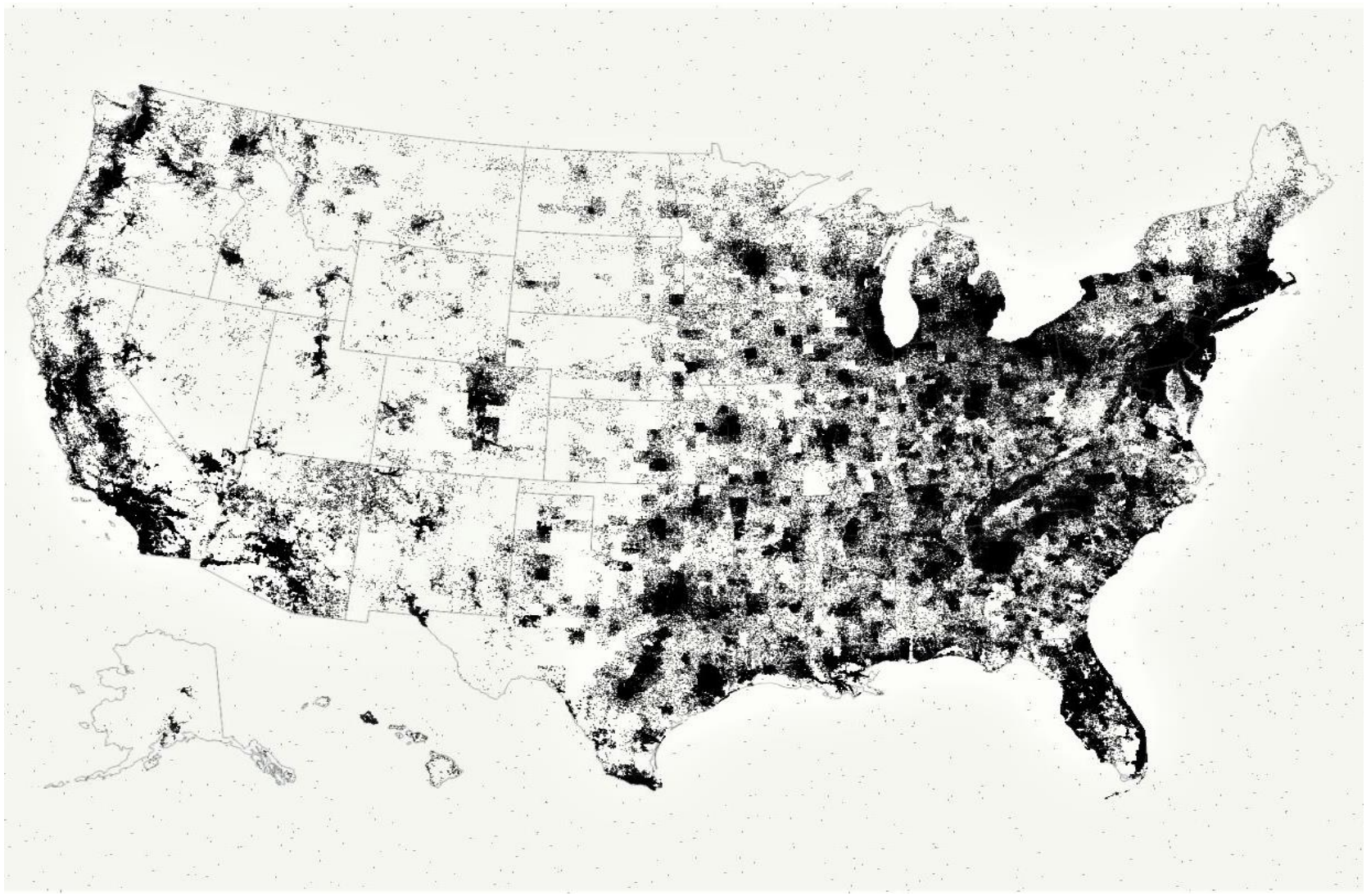
Source: CDC Seasonal Flu Vaccine Effectiveness Studies
https://www.cdc.gov/flu/vaccines-work/effectiveness-studies.htm

CD388 (Cidara) is a neuraminidase inhibitor combined with an Fc antibody fragment to extend the drug's half-life.

The New York Times

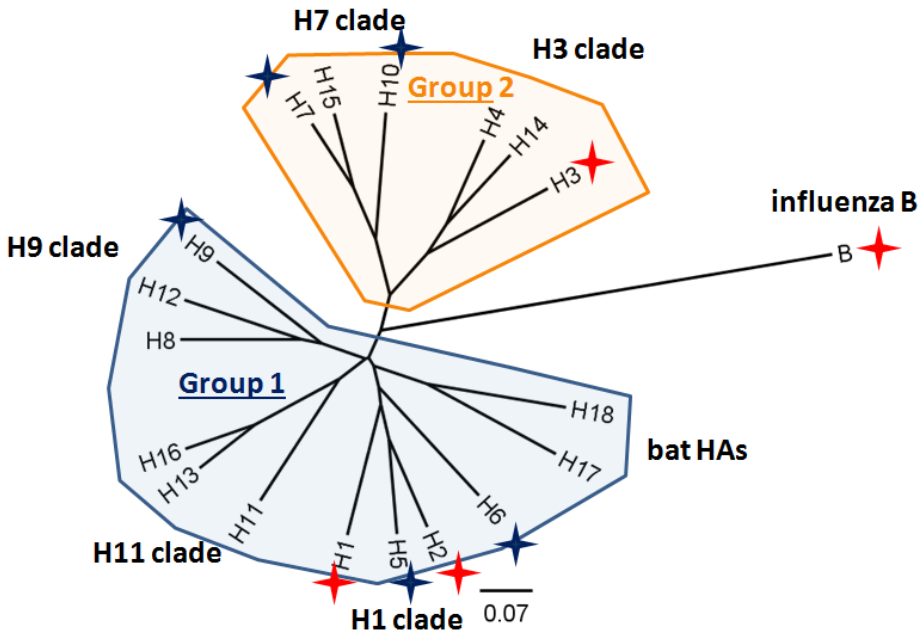
ONE MILLION
A NATION'S IMMEASURABLE GRIEF

By Jeremy White, Amy Harmon, Danielle Ivory, Lauren Leatherby, Albert Sun and Sarah Almukhtar - May 13, 2022

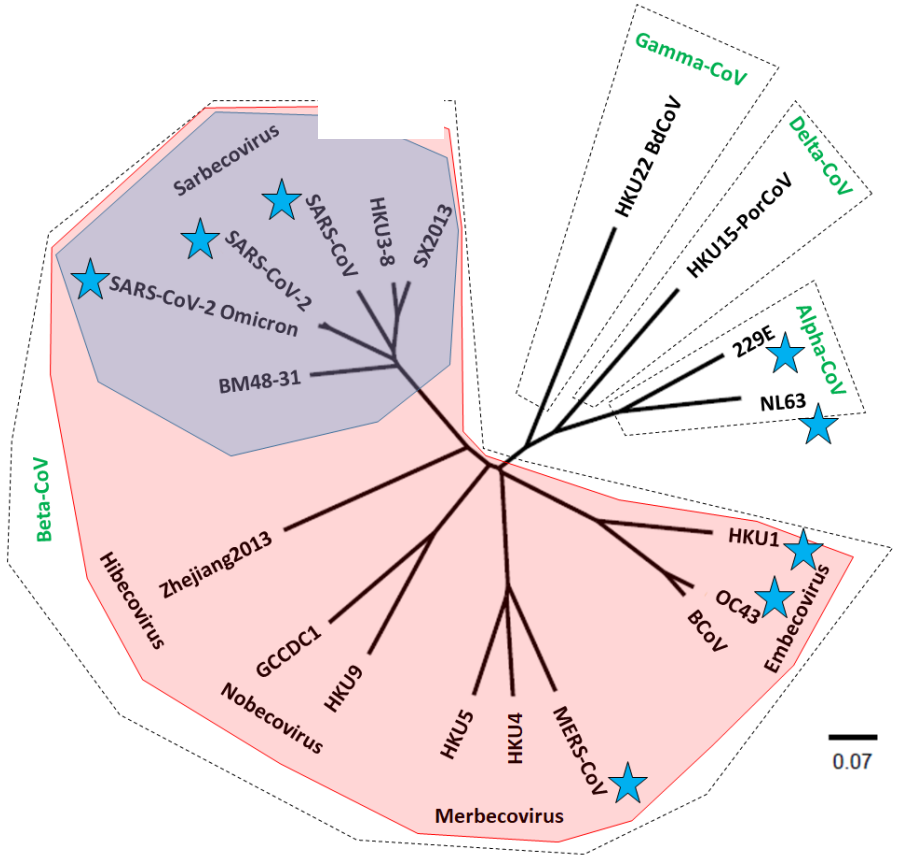


SURFACE GLYCOPROTEIN DIVERSITY OF CORONA AND OF INFLUENZA VIRUSES

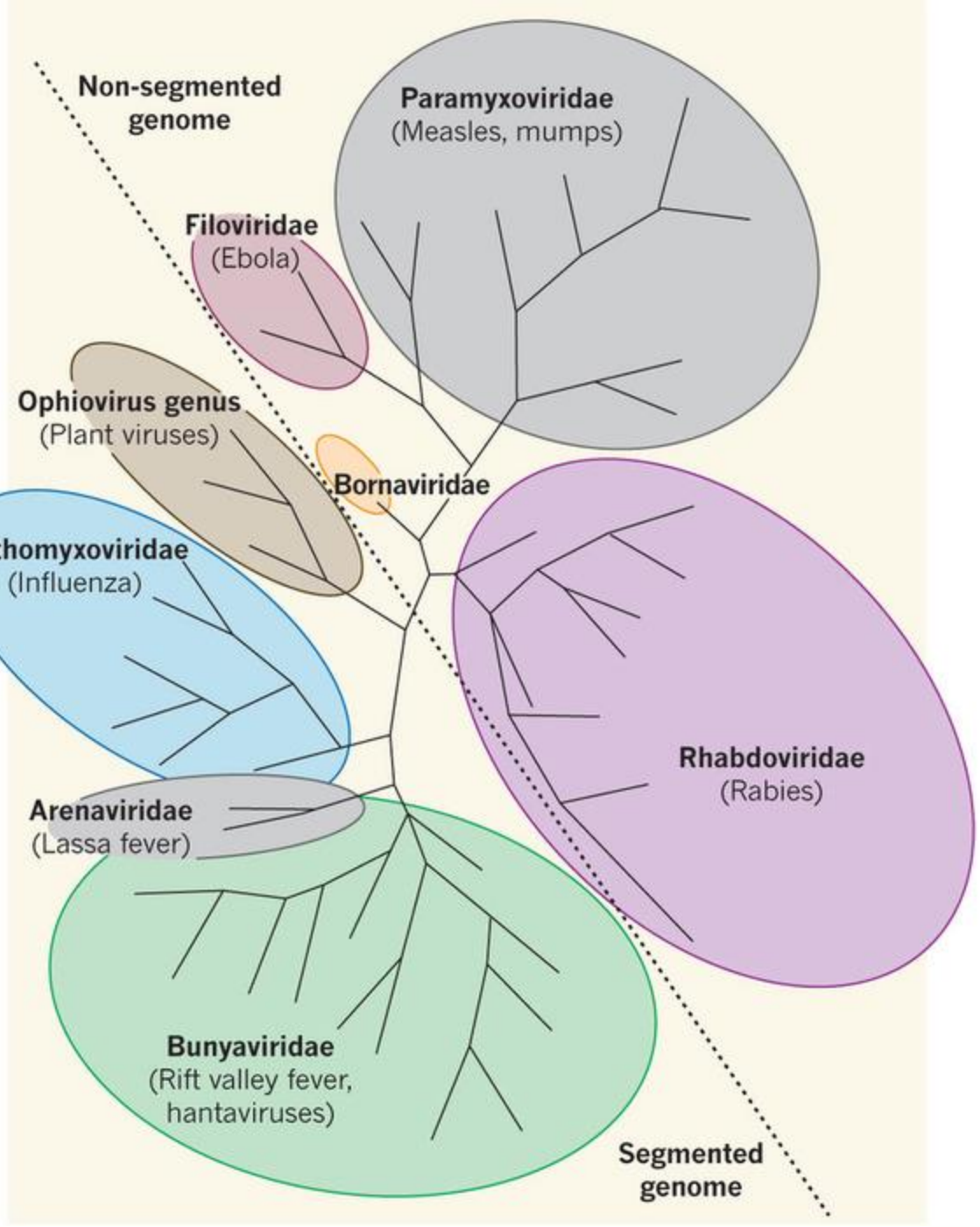
INFLUENZA



CORONA



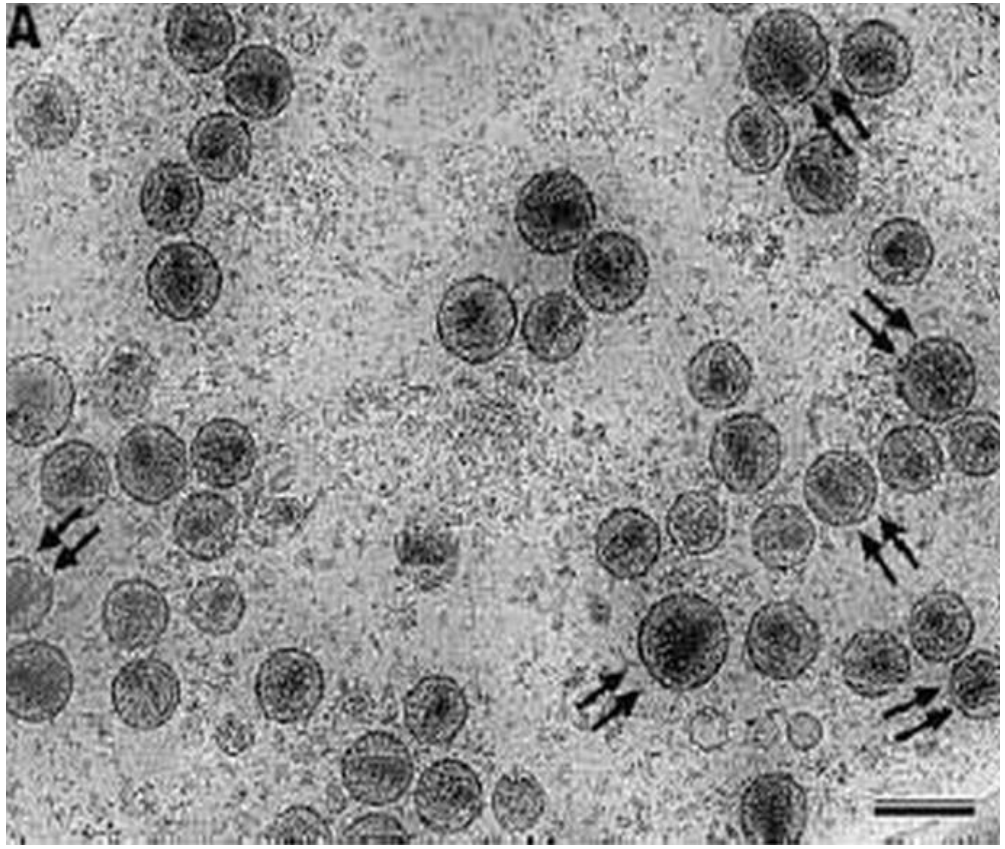
FLORIAN KRAMMER



PHYLOGENETIC TREES OF NEGATIVE STRAND RNA VIRUSES

https://www.nature.com/articles/468773a

HIV



Mature HIV-1 Virions. Briggs, J.A.G., Wilk, T., Welker, R. et al. Structural organization of authentic, mature HIV-1 virions and cores. EMBO J 22, 1707–1715 (2003).

- **NOT A RESPIRATORY VIRUS**
- **40.8 MILLION INFECTED AS OF 2024, 44.1 MILLION DEATHS TO DATE (WHO)**

Lenacapavir (Gilead) is a first-in-class, twice-yearly subcutaneous injection used to treat multi-drug resistant HIV-1. It works by inhibiting the HIV-1 capsid, disrupting viral replication at multiple stages. It is also highly effective for HIV prevention (PrEP).

Lenacapavir is *Science*'s breakthrough of the year 2024.

THE NEXT PANDEMIC

IS NOT A QUESTION OF IF

BUT WHEN

It’s our Wits versus their Genes

Joshua Lederberg

Influenza A and B viruses circulating in the human population

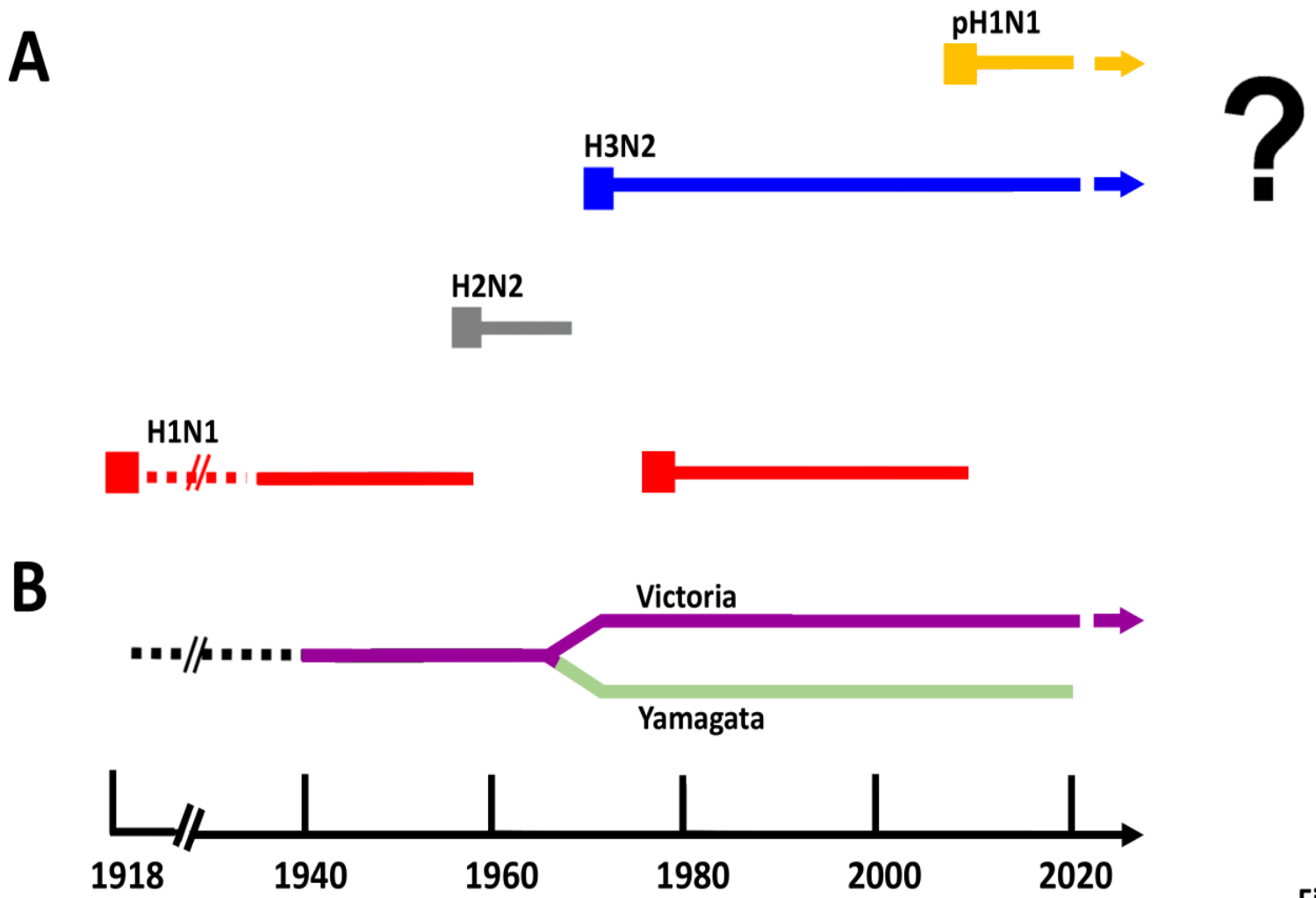
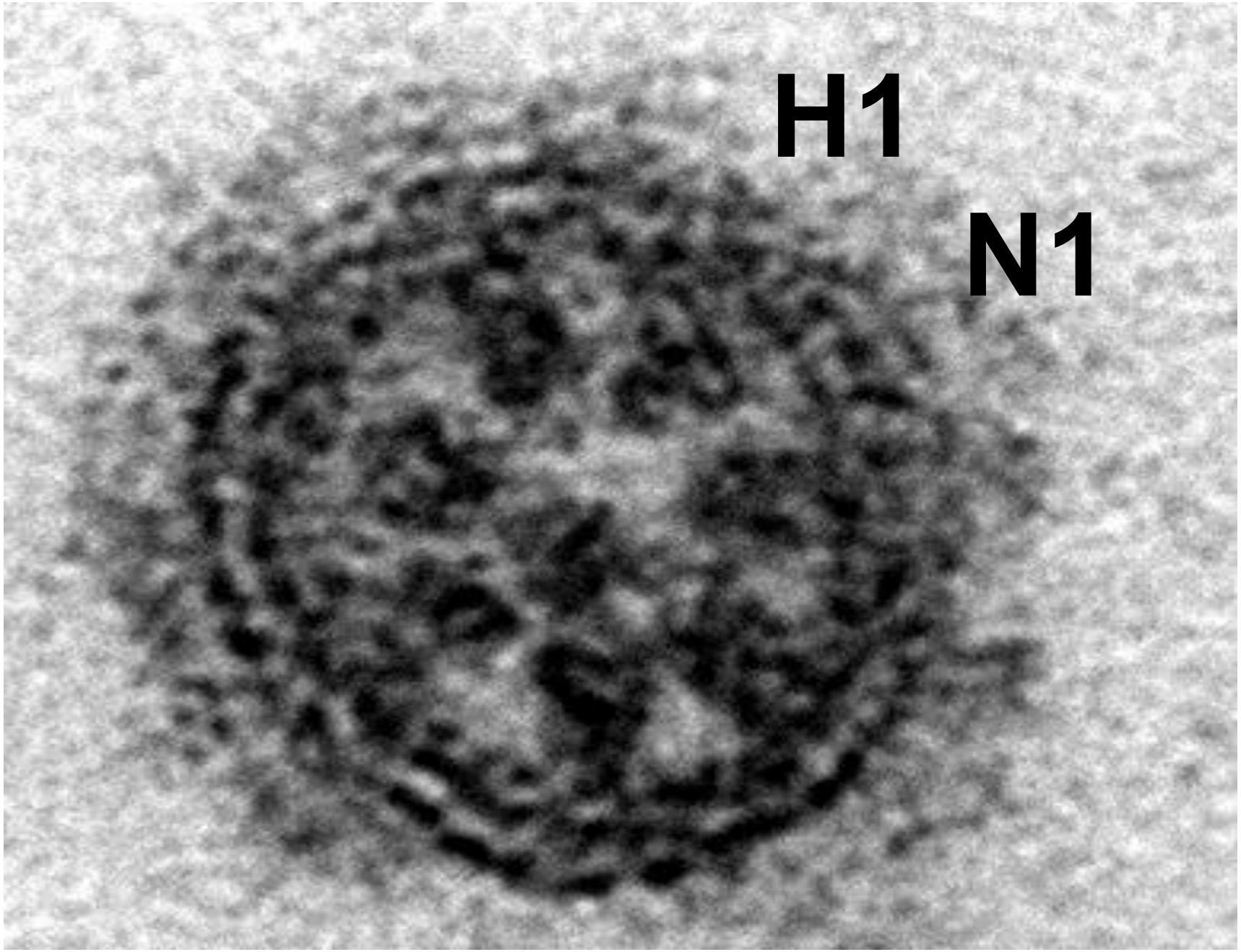


Fig. 1



Yi-ying Chou

Influenza virus vaccine based on chimeric hemagglutinin split vaccine: clinical trial data

- **Universal influenza virus vaccine: Mishra et al., Molecular Therapy, 2026; https://pubmed.ncbi.nlm.nih.gov/41883166/**
- **Main GSK study: Forschweiller *et al.*, Lancet ID, 2022; https://pubmed.ncbi.nlm.nih.gov/35461522/**
- **T-cell responses: Bliss *et al.*, eBioMedicine, 2024; https://pubmed.ncbi.nlm.nih.gov/38805853/**
- **Breadth of antibody response CVIA 057: Meade *et al.*, JVI, 2023; https://pubmed.ncbi.nlm.nih.gov/36533948/**
- **Passive transfer experiments into FcR humanized mice: Edgar *et al.*, PNAS, 2023; https://pubmed.ncbi.nlm.nih.gov/37871218/**
- **Main CVIA 047 results: Nachbagauer *et al.*, Nature Medicine, 2021; https://pubmed.ncbi.nlm.nih.gov/33288923/**
- **Interim analysis CVIA 057: Bernstein *et al.*, Lancet ID, 2020; https://pubmed.ncbi.nlm.nih.gov/31630990/**

RESEARCH ARTICLE

Characterization of the Reconstructed 1918 Spanish Influenza Pandemic Virus

Terrence M. Tumpey,[1]* Christopher F. Basler,[2] Patricia V. Aguilar,[2] Hui Zeng,[1] Alicia Solórzano,[2] David E. Swayne,[4] Nancy J. Cox,[1] Jacqueline M. Katz,[1] Jeffery K. Taubenberger,[3] Peter Palese,[2] Adolfo García-Sastre[2]

The pandemic influenza virus of 1918–1919 killed an estimated 20 to 50 million people worldwide. With the recent availability of the complete 1918 influenza virus coding sequence, we used reverse genetics to generate an influenza virus bearing all eight gene segments of the pandemic virus to study the properties associated with its extraordinary virulence. In stark contrast to contemporary human influenza H1N1 viruses, the 1918 pandemic virus had the ability to replicate in the absence of trypsin, caused death in mice and embryonated chicken eggs, and displayed a high-growth phenotype in human bronchial epithelial cells. Moreover, the coordinated expression of the 1918 virus genes most certainly confers the unique high-virulence phenotype observed with this pandemic virus.

the HA from the Tx/91 virus with the remaining seven genes from the 1918 virus (Tx/91 HA:1918); a virus having the NA from 1918 with the remaining seven genes from the Tx/91 virus (1918 NA:Tx/91); and recombinant viruses having two 1918 (1918 HA/NA:Tx/91) or five 1918 genes (1918 HA/NA/M/NP/NS:Tx/91) with the remaining genes derived from the Tx/91 virus. The HA of the 1918 viruses used throughout these studies was derived from A/South Carolina/1/18 strain that was shown to preferentially bind the α2,6 sialic acid (human) cellular receptor (*16*). The identity of the 1918 and Tx/91 influenza virus genes in the rescued viruses was confirmed by reverse transcription polymerase chain reaction and sequence analysis.

The infectivity of the 1918 virus and the ability to form plaques in the presence and in the absence of the protease trypsin were assayed in MDCK cells by the plaque method. The proteolytic cleavage of the HA molecule is a prerequisite for multicycle replication, and the ability of an influenza virus to replicate in the absence of

THE LANCET PAPER OF THE YEAR 2005

Tumpey et al., Science, 310, 77, 2005