PANDEMIC INFLUENZA VIRUSES: PAST AND FUTURE

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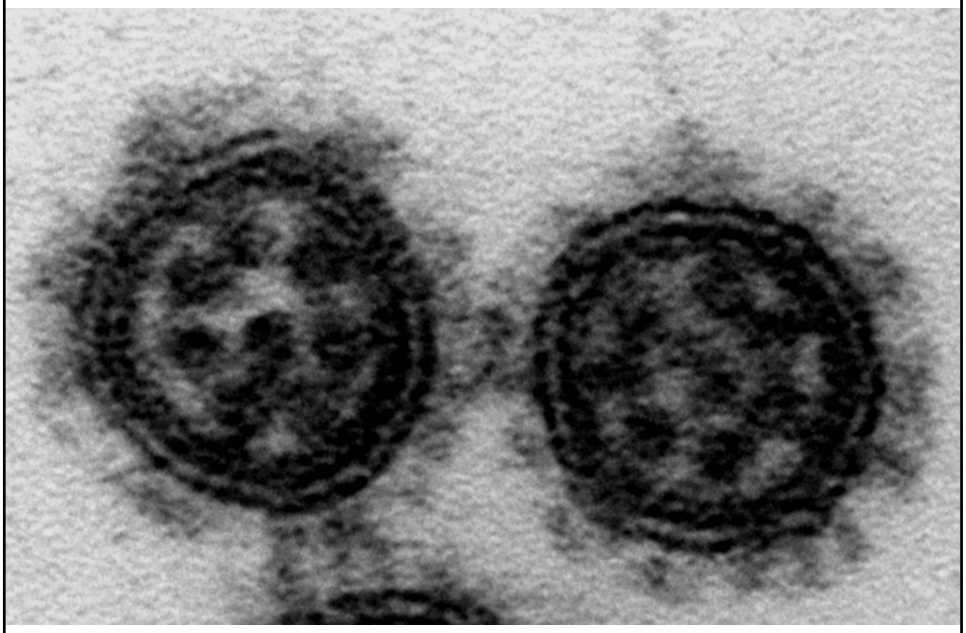
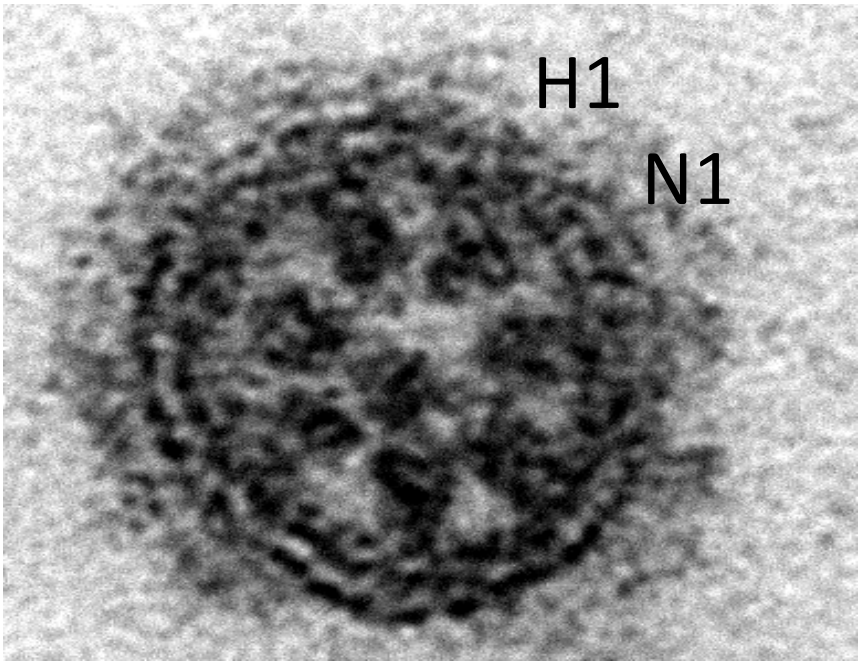
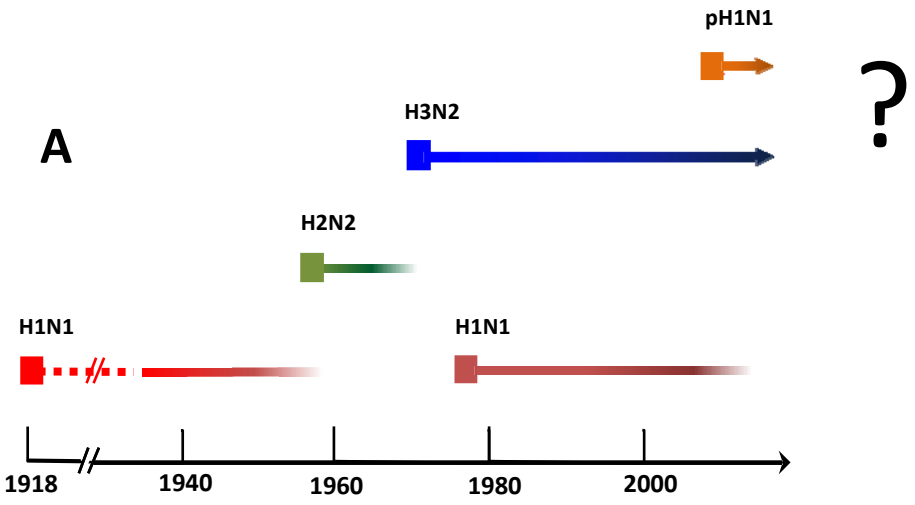


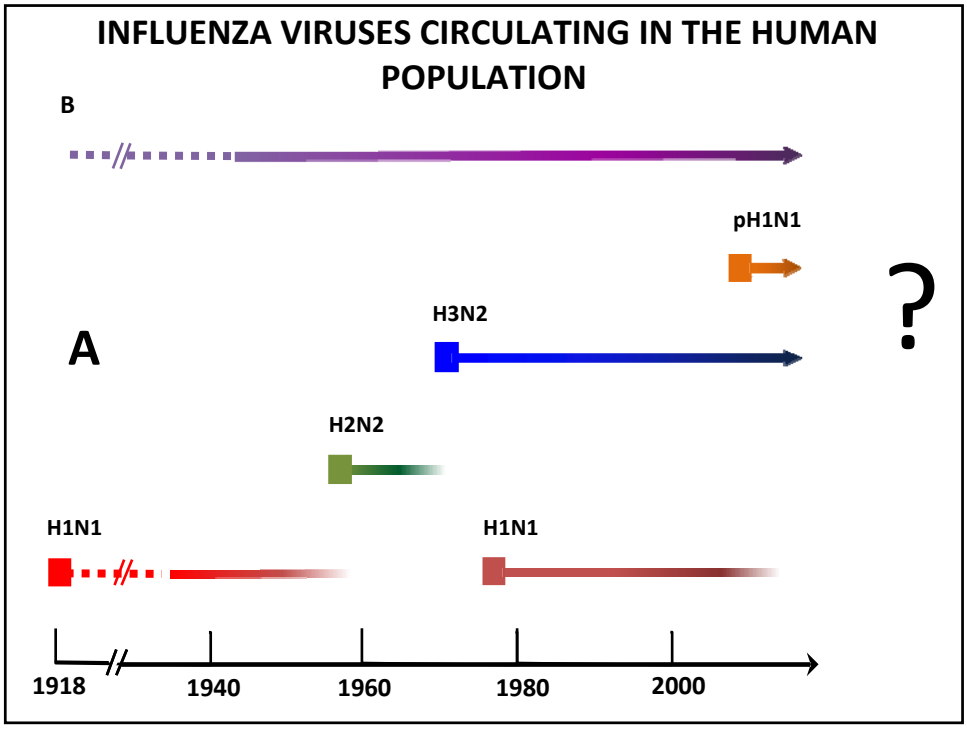
Yi-ying Chou

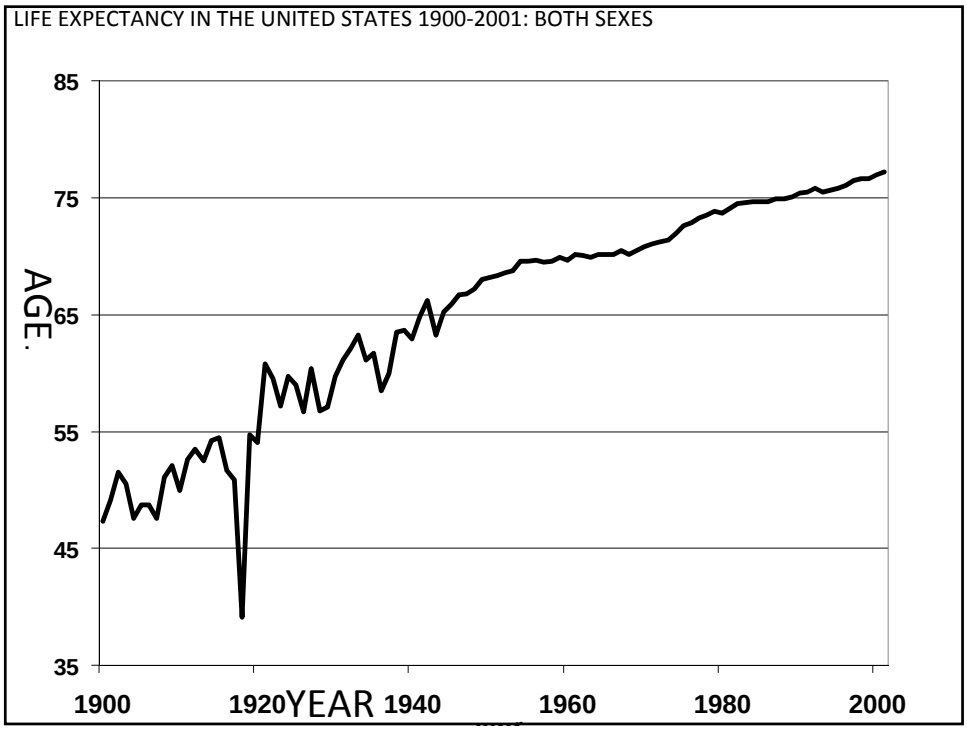


Yi-ying Chou

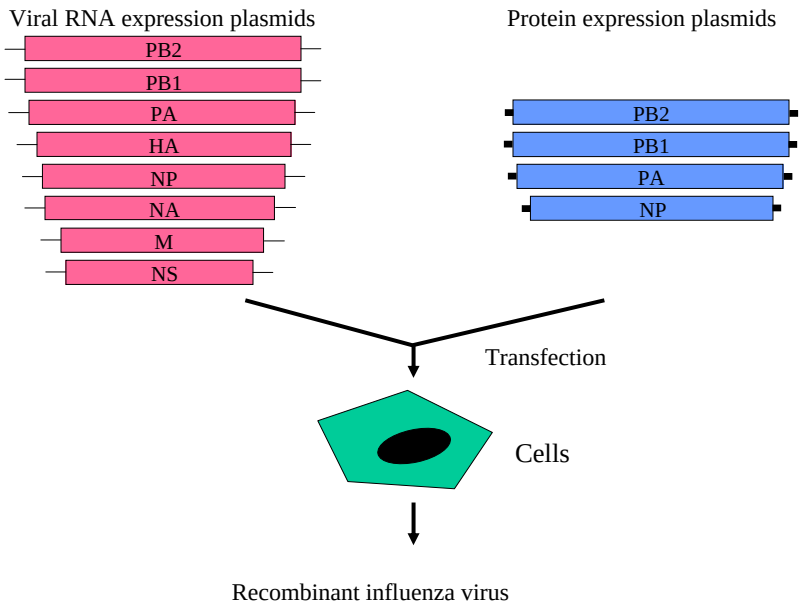
INFLUENZA VIRUSES CIRCULATING IN THE HUMAN POPULATION




INFLUENZA VIRUSES CIRCULATING IN THE HUMAN POPULATION
B
pH1N1
?
A
H3N2
H2N2
H1N1
H1N1
1918
1940
1960
1980
2000


LIFE EXPECTANCY IN THE UNITED STATES 1900-2001: BOTH SEXES
85
75
65
55
45
35
AGE
1900
1920
YEAR
1940
1960
1980
2000

REVERSE GENETICS



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.

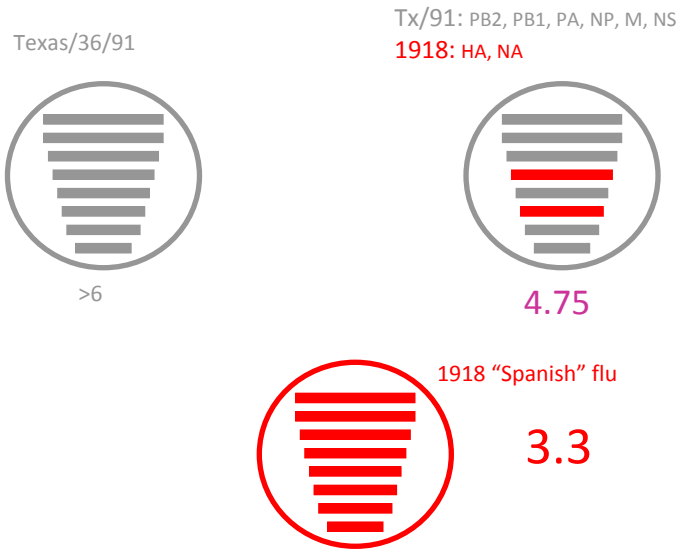
the HA from the Tx/91 virus with the remaining seven genes from the 1918 virus (Tx/91 HA:1918); a virus having the NA from 1918 with the remaining seven genes from the Tx/91 virus (1918 NA:Tx/91); and recombinant viruses having two 1918 (1918 HA/NA:Tx/91) or five 1918 genes (1918 HA/NA/M/NP/NS:Tx/91) 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

Virulence of the 1918 virus in mice: mouse lethal dose 50 (log pfu)

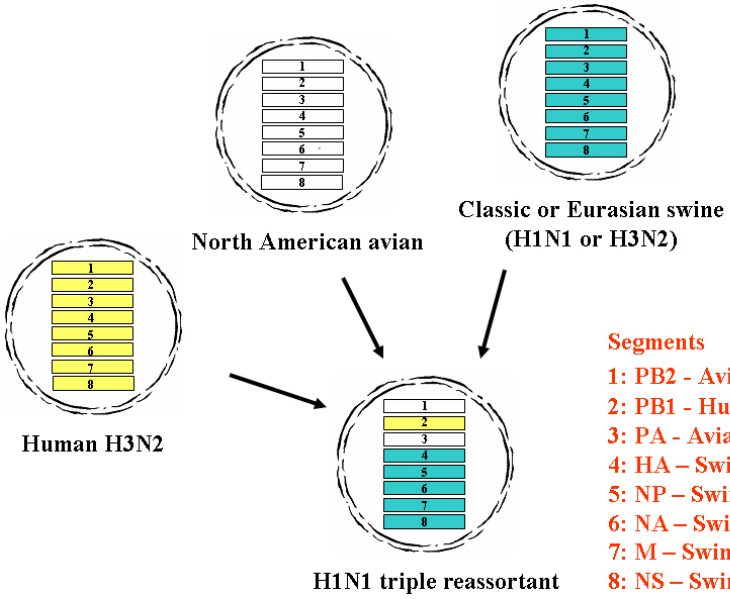


SEVERITY OF INFLUENZA PANDEMICS (deaths/US numbers)

- **1918-1919 (H1N1)** **675 K**
- **1957-1958 (H2N2)** **70 K**
- **1968-1969 (H3N2)** **34 K**

- **2009-2010 (pH1N1)** **8-18K**

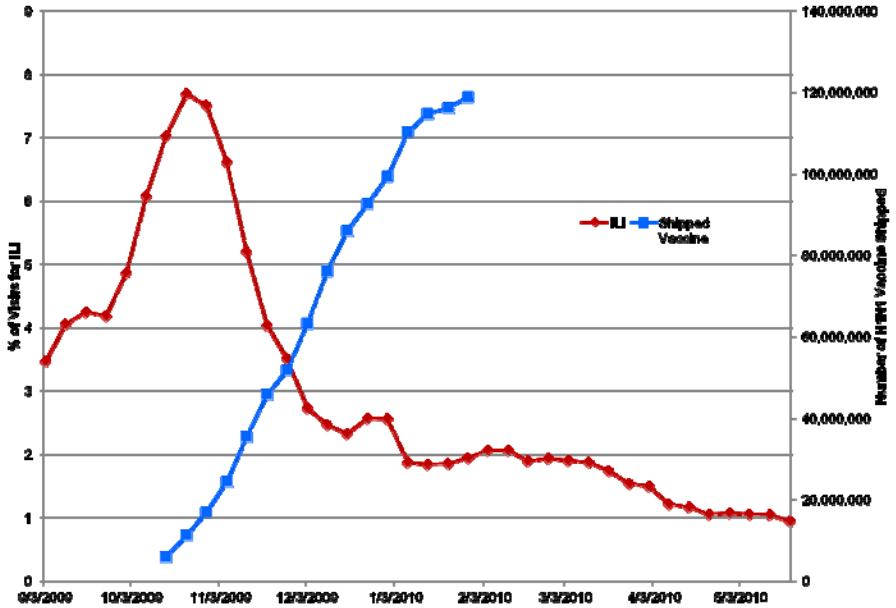
ORIGIN OF GENES OF THE 2009 SWINE H1N1 INFLUENZA VIRUS



Segments

1: PB2 - Avian
2: PB1 - Human
3: PA - Avian
4: HA – Swine (Classic)
5: NP – Swine (Classic)
6: NA – Swine (Eurasian)
7: M – Swine (Eurasian)
8: NS – Swine (Classic)

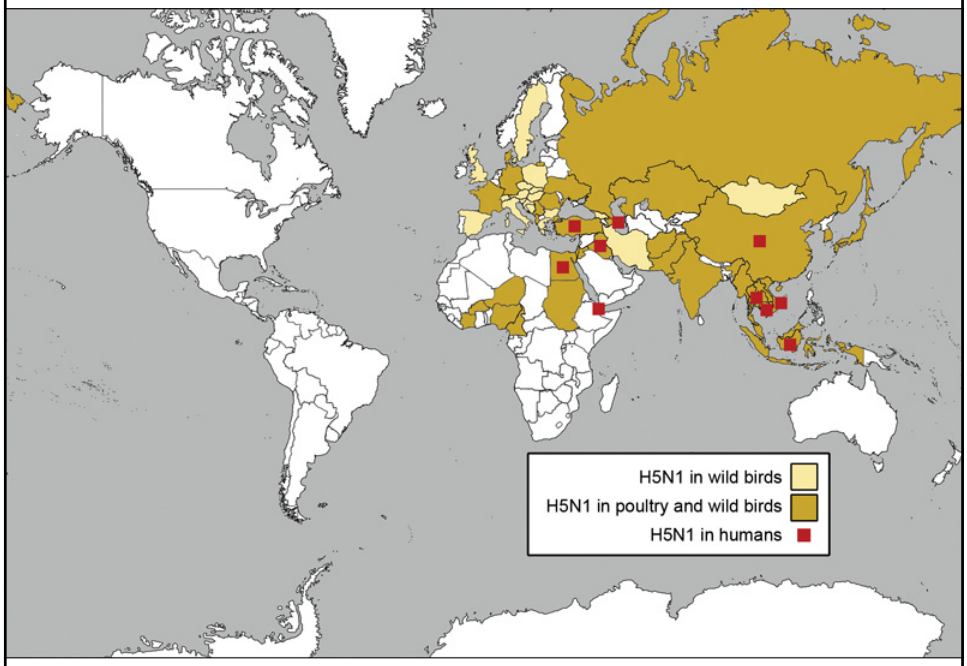
Visits for Influenza-like-Illness (ILI) and pH1N1 Vaccine Distribution
Sep 2009 – May 2010



Source: CDC ILI and Vaccine Distribution Data

Pandemic Influenza: What's Next?

AVIAN INFLUENZA IS A THREAT



Confirmed Human H5N1 Cases

	Cases	Deaths
Azerbaijan	8	5
Bangladesh	3	0
Cambodia	16	14
China	40	26
Djibouti	1	0
Egypt	150	52
Indonesia	178	146
Iraq	3	2
Lao	2	2
Myanmar	1	0
Nigeria	1	1
Pakistan	3	1
Thailand	25	17
Turkey	12	4
Viet Nam	119	59
Total	**562**	**329**

WHO

THE AVIAN H5N1 INFLUENZA VIRUS DOES NOT EFFICIENTLY TRANSMIT FROM HUMAN TO HUMAN

The New York Times

ARTHUR OCHS SULZBERGER JR., *Publisher*

Founded in 1851

ADOLPH S. OCHS
Publisher 1896-1935

ARTHUR HAYS SULZBERGER
Publisher 1935-1961

ORVIL E. DRYFOOS
Publisher 1961-1963

ARTHUR OCHS SULZBERGER
Publisher 1963-1992

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An Engineered Doomsday

A lethal virus needs to be destroyed, or better contained, and future research closely reviewed

Scientists have long worried that an influenza virus that has ravaged poultry and wild birds in Asia might evolve to pose a threat to humans. Now scientists financed by the National Institutes of Health have shown in a laboratory how that could happen. In the process they created a virus that could kill tens or hundreds of millions of people if it escaped confinement or was stolen by terrorists.

We nearly always champion unfettered scientific research and open publication of the results. In this case it looks like the research should never have been undertaken because the potential harm is so catastrophic and the potential benefits from studying the virus so speculative.

Unless the scientific community and health officials can provide more persuasive justifications than they have so far, the new virus, which is in the Netherlands, ought to be destroyed. Barring that, it should be put in a few government-controlled laboratories with the highest containment rating, known as biosafety level 4. That is how the United States and Russia contain samples of smallpox, which poses nowhere near the same danger of global devastation.

In the future, it is imperative that any such experiments be rigorously analyzed for potential dangers — preferably through an international review mechanism, but also by governmental funding agencies — before they are undertaken, not after the fact as is happening in this case.

The most frightening research was done by scientists at the Erasmus Medical Center in Rotterdam, who sought to discover how likely it is that the "bird flu" virus, designated A(H5N1), might mutate from a form that seldom infects or spreads among humans into a form highly transmissible by coughing or sneezing. Thus far the virus has infected close to 600 humans and killed more than half of them, a fatality rate that far exceeds the 2 percent rate in the 1918 influenza pandemic that killed as many as 100 million people.

Working with ferrets, the animal that is most like humans in responding to influenza, the researchers found that a mere five genetic mutations allowed the virus to spread through the air from one ferret to another while maintaining its lethality. A separate study at the University of Wisconsin, about which little is known publicly, produced a virus that is thought to be less virulent.

These findings led to an unprecedented request from an American federal advisory board that the researchers and the two scientific journals that plan to publish the studies omit any details that might help terrorists figure out how to unleash a devastating pandemic. That presumably includes details on how the engineered virus was made and details on the precise mutations that allowed it to go airborne.

We doubt that anything at all should be published, but it seems clear that something will be.

The two journals reviewing the papers seem inclined to follow the advisory board's recommendations that the research be published in a redacted form, provided there is some way for researchers who need the information to gain access to the full details. The Erasmus team believes that more than 100 laboratories and perhaps 1,000 scientists around the world need to know the precise mutations to look for. That would spread the information far too widely. It should suffice to have a few of the most sophisticated laboratories do the analyses.

Defenders of the research in Rotterdam claim it will provide two major benefits for protecting global health. First, they say the findings could prove helpful in monitoring virus samples from infected birds and animals. If genetic analysis found a virus somewhere that was only one or two mutations away from going airborne, public health officials would then know to bear down aggressively in that area to limit human contact with infected poultry and ramp up supplies of vaccines and medicines.

But it is highly uncertain, even improbable, that the virus would mutate in nature along the pathways prodded in a laboratory environment, so the benefit of looking for these five mutations seems marginal.

A second postulated benefit is that the engineered virus can be used to test whether existing antiviral drugs and vaccines would be effective against it and, if they come up short, design new drugs and vaccines that can neutralize it. But genetic changes that affect transmissibility do not necessarily change the properties that make a virus susceptible to drugs or to the antibodies produced by a vaccine, so that approach may not yield much useful new information.

We cannot say there would be no benefits at all from studying the virus. We respect the researchers' desire to protect public health. But the consequences, should the virus escape, are too devastating to risk.

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