

H5N1 Infection; A Harbinger of Things to Come?

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The Backdrop for Interpreting and Responding to Pandemic Influenza

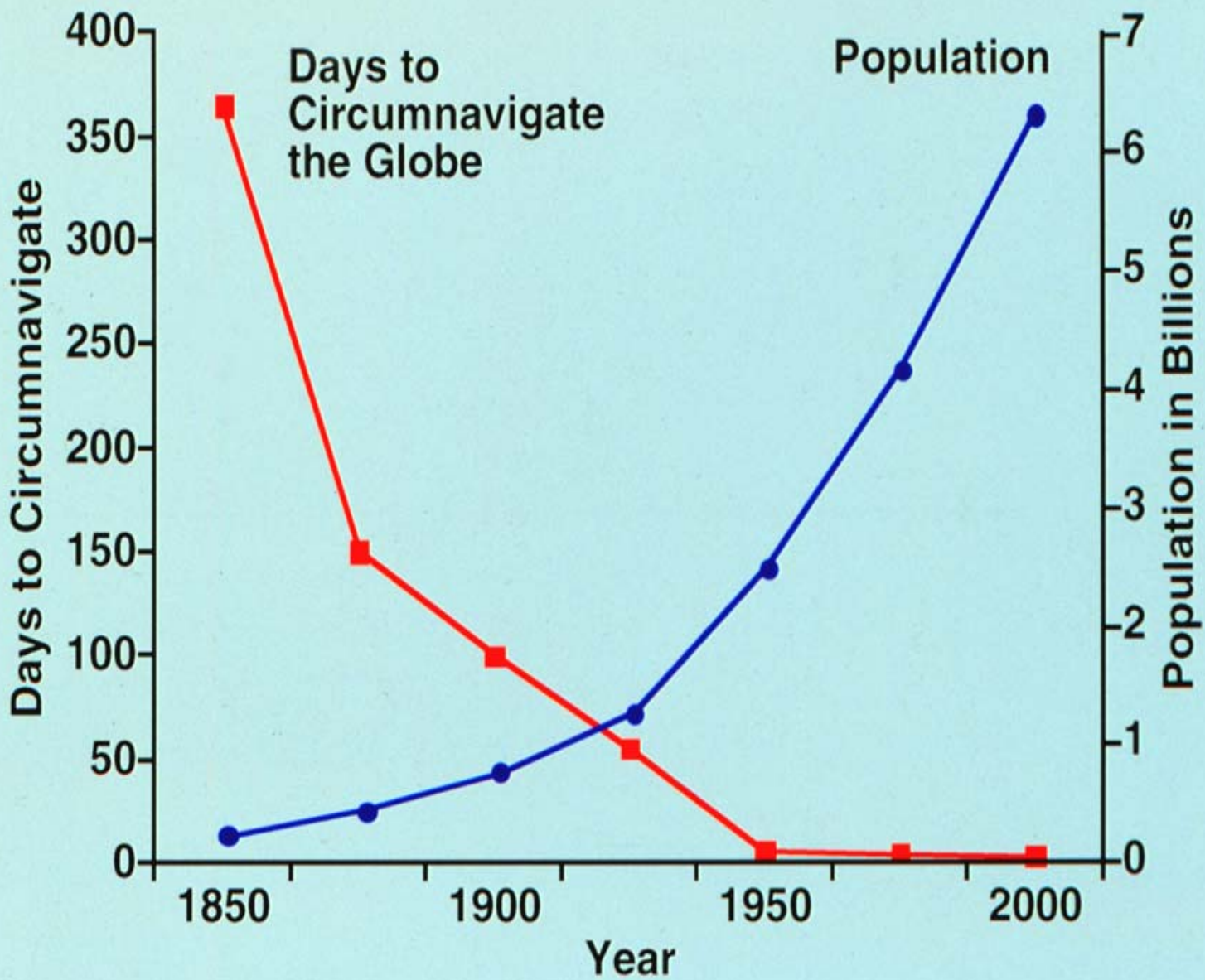
- A bunch of scaremongers who were wrong before....SARS, Ebola etc.
- Y2K, Swine flu and Iraq
- It can't happen
- Nothing we can do about it
- The public can't handle this

"Think of a fast-moving highly contagious disease that wipes out 5 per cent of the world population (50 million people). Half a million of them in the U.S. ...bodies pile up in the streets. There aren't enough morticians to bury the dead. Nor are there enough doctors and nurses to tend to the sick. The churches close, the schools shut. Telecommunications and transportation grind to a halt. The public succumbs to hysteria and panic. Police protection fails. Order decays. Productivity dives. Sounds like a scene from a science fiction film, doesn't it? But what if I told you, it already happened? What if I told you it was the pandemic flu that swept across America and around the globe in 1918? Or if I told you that this glimpse into the past might be a preview to our future. An avian flu pandemic is no longer a question of if, but a question of when."

Senator Bill Frist
Princeton, November 11, 2005

- “The present situation is markedly different for several reasons. First, the world has been warned in advanced. For more than a year, conditions favouring another pandemic have been unfolding in parts of Asia. Warnings that another pandemic may be imminent have come from both changes in the epidemiology of human and animal disease and an expanding geographical presence of the virus, creating further opportunities for human exposure.”

World Health Organization
September, 2005



Influenza

- Seasonal influenza disease (versus pandemic-related disease)
- Respiratory illness characterized by fever, headache, tiredness, dry cough, sore throat, runny nose, muscle aches and occasionally nausea, vomiting and diarrhea
- Complications occur mostly among “high risk” and include bacterial pneumonia, dehydration, and worsening of chronic conditions such as congestive heart disease, asthma and diabetes

Influenza

- Every year in the United States, five to 20% of the population develop influenza; 36,000 die
- Spreads by respiratory droplet (aerosol?)
- Seasonal influenza has largely been addressed through efforts to vaccinate up to 300 million “high risk” individuals in developed world countries

Understanding Pandemic Influenza

- Pandemic – An epidemic that becomes very widespread and affects a whole region, a continent or the world.
- Pandemics occur when a novel influenza strain emerges that has the following features:
 - readily transmitted between humans
 - genetically unique (i.e., lack of preexisting immunity in the human population)
 - increased virulence
- Pandemics are like earthquakes, hurricanes and tsunamis....they occur!

Severe Influenza Pandemics in History

- Pandemics recorded since Hippocrates
- The 1580 pandemic is classic example
 - Started in Asia and spread to Africa, Europe and the Americas
 - In six weeks afflicted all of Europe
 - Mortality was high, 9,000 died in Rome and in some Spanish cities were described as “nearly entirely depopulated by the disease”

Pandemics in the Past 300 Years

- Range; 10 to 49 years between pandemics. Average; 24 years

1732-33

1781-82

1800-02

1830-33

1847-48

1857-58

1889-90

1918-19

1957-58

1968-69

Comparison of Mortality Impact in the Three Influenza Pandemics of the 20th Century in the United States

	Antigenic shift (Pandemic event)	Number of Excess Deaths in the pandemic season (All-cause deaths)	Total Excess Mortality rate per 100,000 population (crude) (All-cause deaths)
1918-19 A(H1N1)	All novel?	~500,000	530
1957-58 A(H2N2)	H + N	~ 60,000	40
1968-69 A(H3N2)	H only	~ 40,000	18

Simonsen et al

Pandemic Influenza

- 1918-1919 (Spanish flu)
 - H1N1 strain
 - 200 million to 1 billion people were infected; more than 50-100 million died
 - killed a disproportionate number of healthy young adults (W curve)
- A summary of 13 studies in 1918-19 involving pregnant women demonstrated that the case-fatality rate ranged from 23 to 71%

Pandemic Influenza

- 1957-58 (Asian flu)
 - H2N2 strain
 - pandemic strain acquired three genes from the avian influenza gene pool in wild ducks by genetic reassortment and obtained five other genes from then-circulating human strain
 - 60 to 70,000 people in U.S. died

Pandemic Influenza

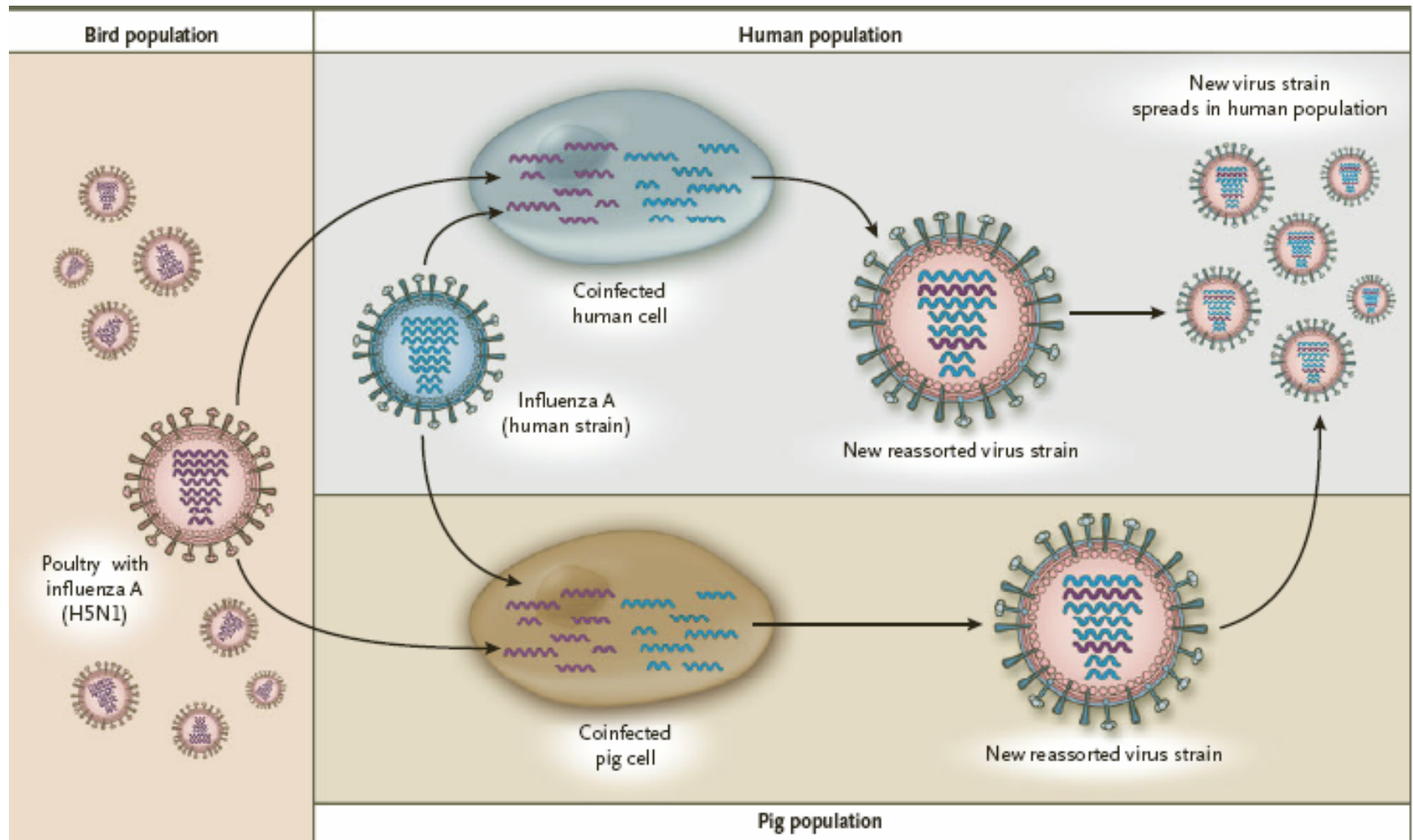
- 1968-69 (Hong Kong flu)
 - H3N2 strain
 - two genes from duck reservoir and six genes from human virus
 - 40,000 people died in the U.S.

Influenza Virus Change and Pandemic Potential

- Reassortment
- Recombination: point mutations

Reassortment

- Occurs when an avian virus and human-adapted virus “swap genes” in a co-infected cell of an animal or human and a “third virus” results that can be readily transmitted by and between humans



Generation of a Potentially Pandemic Strain of Influenza through Reassortment.

Reassortment of genes between avian and human strains of influenza, which is facilitated by the division of the influenza A genome into eight segments, can occur during coinfection with both strains. Such coinfection may occur in pigs, which would support the growth of both avian and human viruses, or it may occur in humans.

Recombination

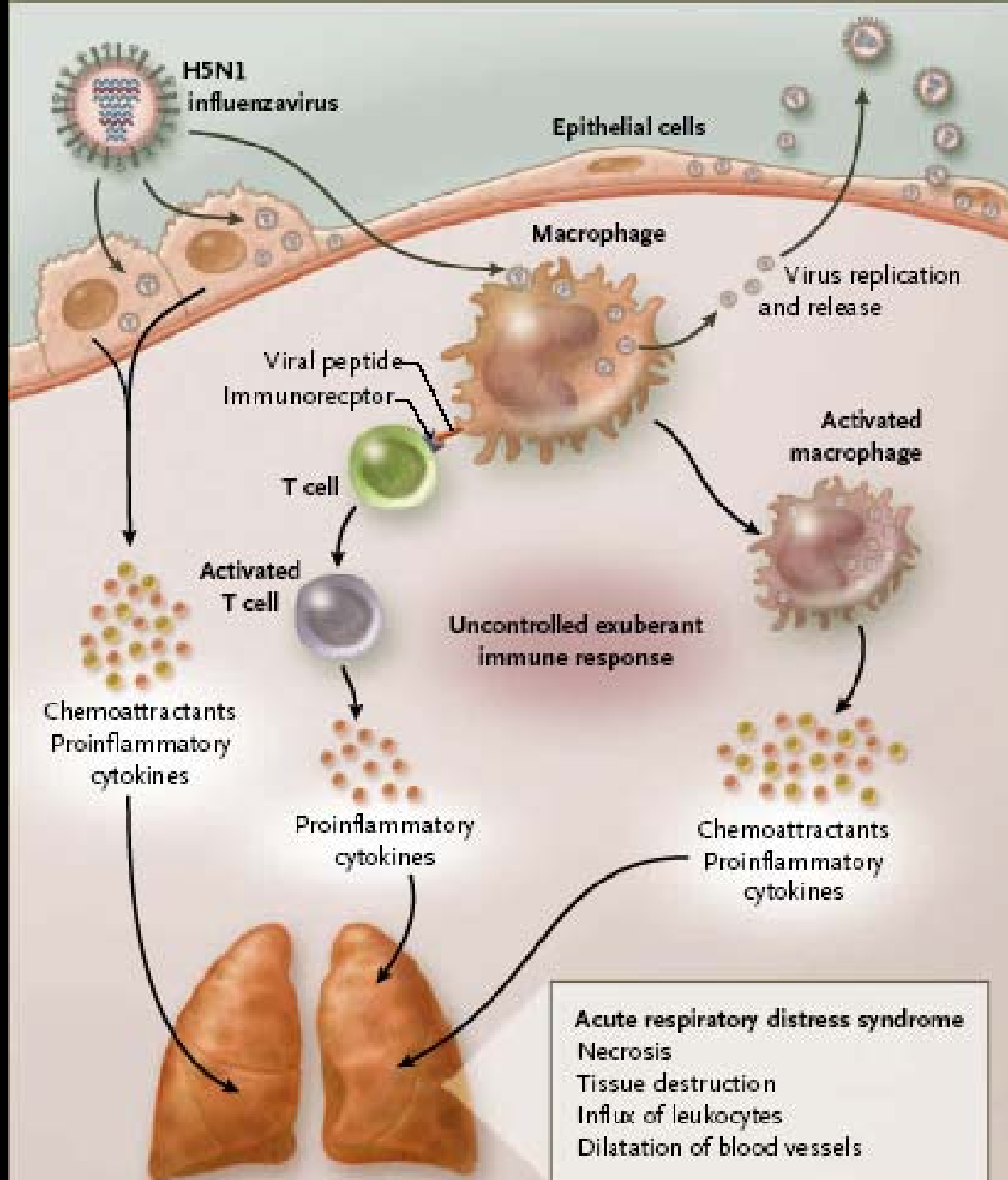
- As a result of a series of point mutations in the hemagglutinin of an avian influenza virus, the virus becomes a competent human-to-human transmitted agent while retaining the essential properties of the original avian virus
- Definitively proven to have been the mechanism for the evolution of the 1918 pandemic-associated virus

What has the 1918 Influenza Virus Foreshadowed for a Potential H5N1 Pandemic?

- Taubenberger et al. **Nature 2005: 437;889**
 - Demonstrated that the 1918 pandemic H1N1 “jumped” directly from an avian species to humans
 - “Notably, a number of the same changes have been found in recently circulating highly pathogenic H5N1 viruses that have caused illness and death in humans and are feared to be precursors of a new influenza pandemic.”

What has the 1918 Influenza Virus Foreshadowed for a Potential H5N1 Pandemic?

- Tumpey et al. **Science 2005: 310;77**
 - Reconstructed the 1918 pandemic virus using reverse genetics and “recovered genes”
 - The coordinated expression of the 1918 virus genes most certainly confers the unique high-virulence phenotype observed in this virus
 - At 16 and 24 hours, 1918 virus release orders of magnitude higher than current H1N1 viruses



A Letter from 1918

“These men start with what appears to be an ordinary attack of LaGrippe or Influenza, and when brought to Hosp. they rapidly develop the most vicious type of Pneumonia that has ever been seen....and a few hours later you can begin to see Cyanosis extending from their ears and spreading all over the face, until it is hard to distinguish the colored men from the white. It is only a matter of a few hours then until death comes....It is horrible. One can stand to see one, two or twenty men die, but to see those poor devils dropping like flies...We have been averaging about a hundred deaths per day...Pneumonia means in about all cases death...We have lost an outrageous number of Nurses and Drs. It takes special trains to carry away the dead. For several days there were no coffins and the bodies piled up something fierce...It beats any sight they ever had in France after a battle. An extra long barracks has been vacated for the use of the Morgue, and it would make any man sit up and take notice to walk down the long lines of dead soldiers all dressed and laid out in double rows...Good Bye old Pal, God be with you till we meet again”

Letter Dr Roy Grist to Burt; Published in BMJ, Dec, 1979

The Great Influenza

THE EPIC STORY OF THE 1918 PANDEMIC



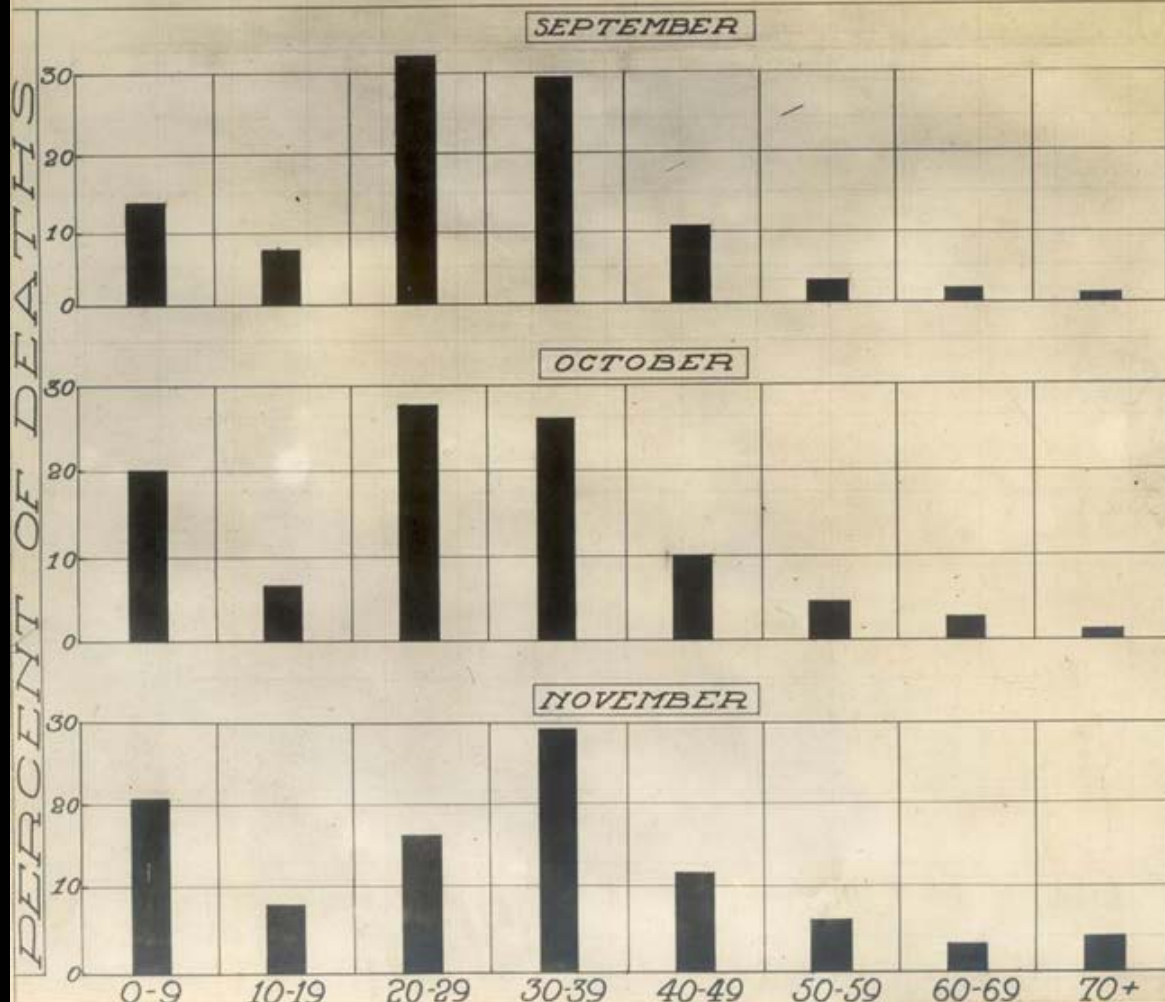
John M. Barry

author of *Rising Tide*

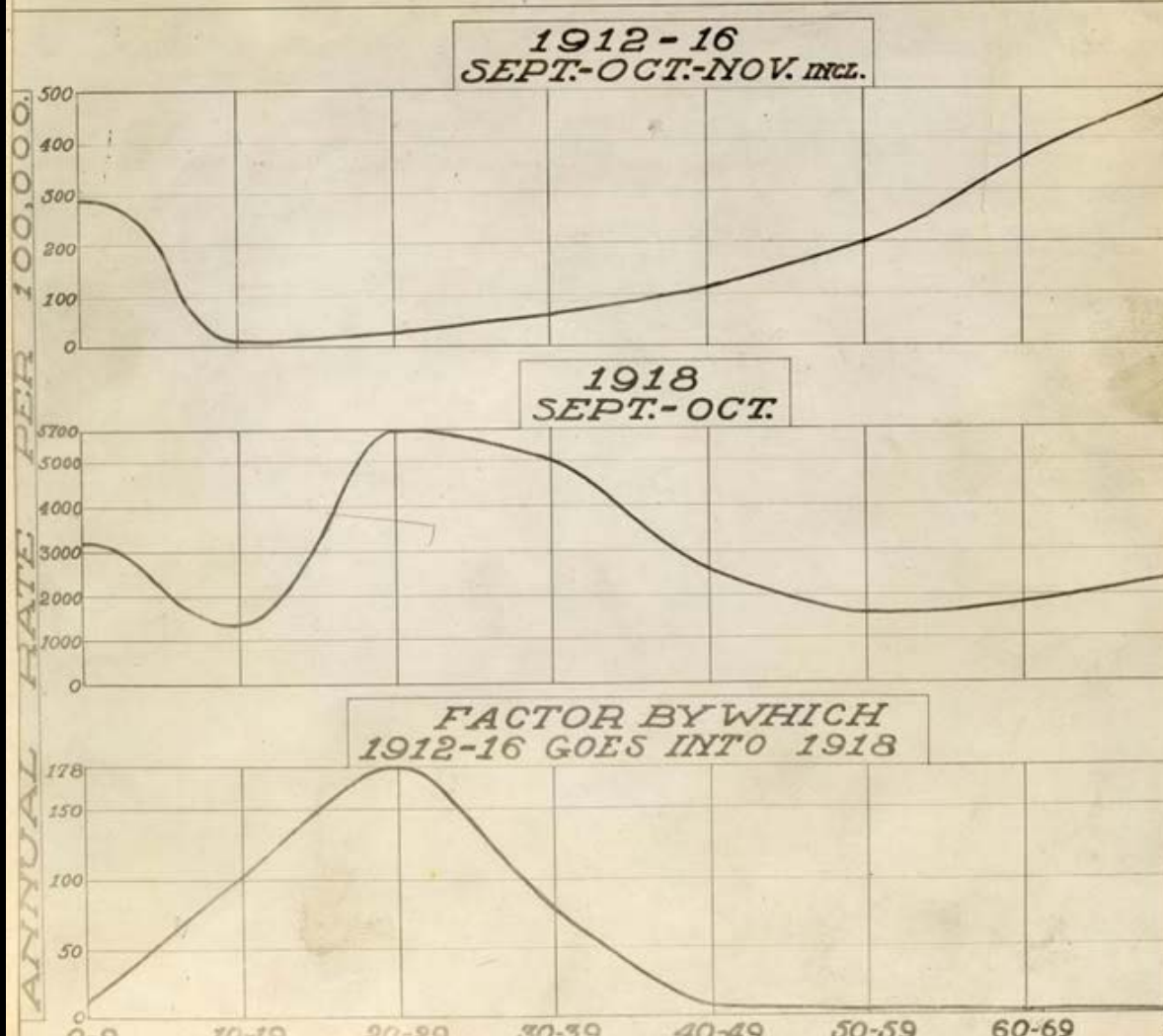




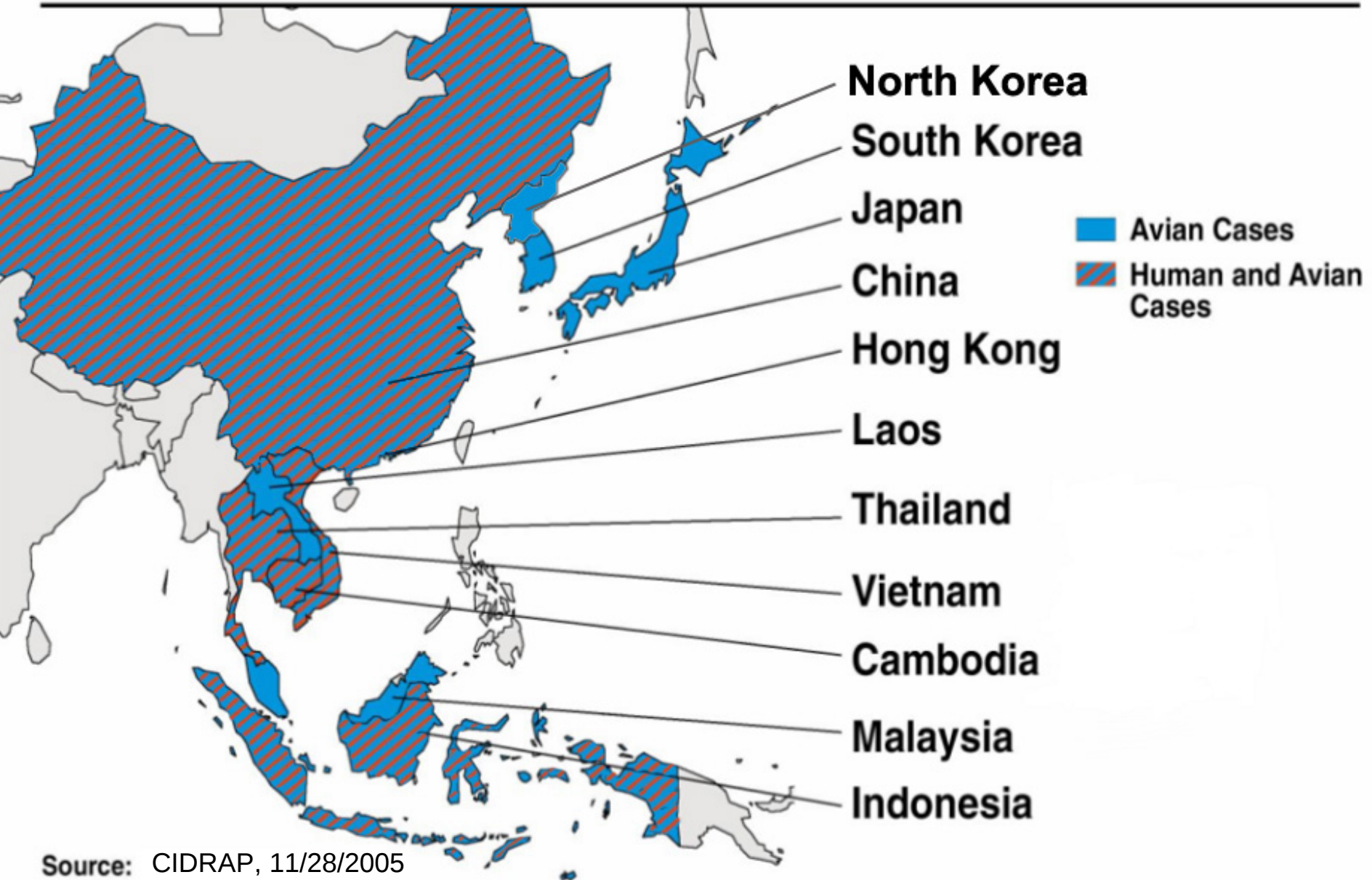
AGE DISTRIBUTION OF INFLUENZA AND PNEUMONIA DEATHS AT BOSTON DURING SEPT.-OCT.-NOV. 1918.



AGE DISTRIBUTION OF DEATHS FROM INFLUENZA AND PNEUMONIA AT BOSTON



H5N1 Influenza in Asia, 2004-2005



Source: CIDRAP, 11/28/2005

Case and Death Estimates for the Next Pandemic

- Assuming the next pandemic will be caused by H5N1
- Most estimate that 30 to 60 percent of the world's population will become infected
- 1968-like pandemic; 2 to 7.5 million deaths
- 1918-like pandemic; 180 to 360 million deaths
- Based on current H5N1 case fatality rate; 1.6 billion deaths

Projected Influenza-Associated Deaths in the United States Based on the 1918-19 Experience

<u>Age in Years</u>	<u>Projected Deaths Based on Current Population and Deaths in 1918-19</u>
<5	233,200
5-14	74,553
15-24	214,582
25-34	378,639
35-44	268,602
45-54	43,948
55-65	123,451
>65	426,689
Total	1,763,664

Conclusions

- Not a matter of if, just when and where
- At minimum, assume we will not have vaccine for the first 6-8 months and then supplies will be extremely limited even in the developed world
- Even if a 1918-like scenario unfolds, 98 out of every 100 people will still be alive at the end of the pandemic; how do minimize their pain and suffering?