# Influenza:
# Back to the Future, it never gets old

Tues., Sept. 22, 1987

Lifestyle

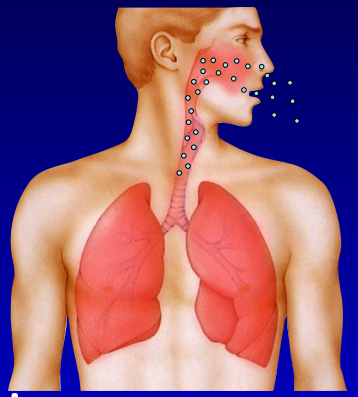
Dr. Jack Bernstein, of Wright State University, has found himself looking into an increasingly challenging area of study because of the emergence of AIDS and other virus-related maladies

JIM RUTLEDGE/ STAFF PHOTOGRAPHER

In search of the virus


Jack M. Bernstein, M.D.

Emeritus Professor, Wright State University

The New York Times

## Breaking News Alert

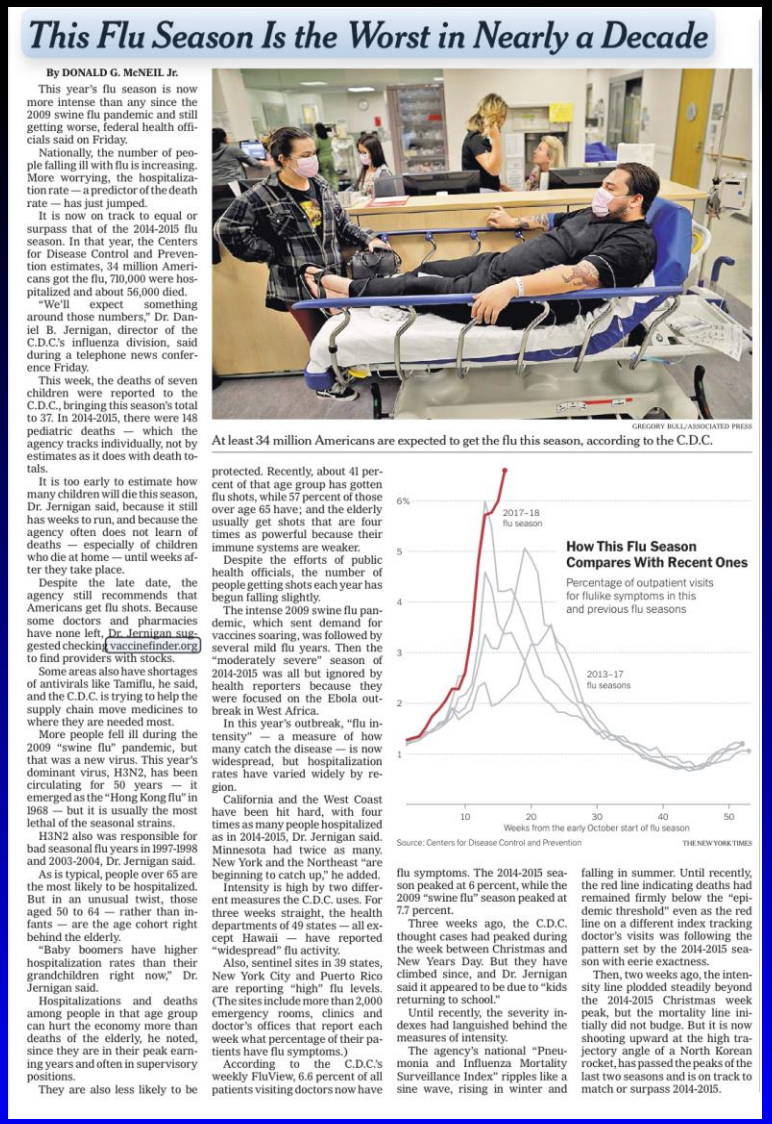
January 26, 2018 NYTimes.com »

BREAKING NEWS

# This year's flu season is now more intense than any since the 2009 swine flu pandemic and is still getting worse, federal health officials said

Friday, January 26, 2018 12:56 PM EST

Nationally, the number of people who are falling ill with flu is still increasing. More worrying, the hospitalization rate — a predictor of the death rate — has just jumped, and is now on track to equal or surpass that of the 2014-2015 flu season.



# This Flu Season Is the Worst in Nearly a Decade

By DONALD G. McNEIL Jr.

This year's flu season is now more intense than any since the 2009 swine flu pandemic and still getting worse, federal health officials said on Friday.

Nationally, the number of people falling ill with flu is increasing. More worrying, the hospitalization rate — a predictor of the death rate — has just jumped.

It is now on track to equal or surpass that of the 2014-2015 flu season. In that year, the Centers for Disease Control and Prevention estimates, 34 million Americans got the flu, 710,000 were hospitalized and about 56,000 died.

"We'll expect something around those numbers," Dr. Daniel B. Jernigan, director of the C.D.C.'s influenza division, said during a telephone news conference Friday.

This week, the deaths of seven children were reported to the C.D.C., bringing this season's total to 37. In 2014-2015, there were 148 pediatric deaths — which the agency tracks individually, not by estimates as it does with death totals.

It is too early to estimate how many children will die this season, Dr. Jernigan said, because it still has weeks to run, and because the agency often does not learn of deaths — especially of children who die at home — until weeks after they take place.

Despite the late date, the agency still recommends that Americans get flu shots. Because some doctors and pharmacies have none left, Dr. Jernigan suggested checking vaccinefinder.org to find providers with stocks.

Some areas also have shortages of antivirals like Tamiflu, he said, and the C.D.C. is trying to help the supply chain move medicines to where they are needed most.

More people fell ill during the 2009 "swine flu" pandemic, but that was a new virus. This year's dominant virus, H3N2, has been circulating for 50 years — it emerged as the "Hong Kong flu" in 1968 — but it is usually the most lethal of the seasonal strains.

H3N2 also was responsible for bad seasonal flu years in 1997-1998 and 2003-2004, Dr. Jernigan said.

As is typical, people over 65 are the most likely to be hospitalized. But in an unusual twist, those aged 50 to 64 — rather than infants — are the age cohort right behind the elderly.

"Baby boomers have higher hospitalization rates than their grandchildren right now," Dr. Jernigan said.

Hospitalizations and deaths among people in that age group can hurt the economy more than deaths of the elderly, he noted, since they are in their peak earning years and often in supervisory positions.

They are also less likely to be protected. Recently, about 41 percent of that age group has gotten flu shots, while 57 percent of those over age 65 have; and the elderly usually get shots that are four times as powerful because their immune systems are weaker.

Despite the efforts of public health officials, the number of people getting shots each year has begun falling slightly.

The intense 2009 swine flu pandemic, which sent demand for vaccines soaring, was followed by several mild flu years. Then the "moderately severe" season of 2014-2015 was all but ignored by health reporters because they were focused on the Ebola outbreak in West Africa.

In this year's outbreak, "flu intensity" — a measure of how many catch the disease — is now widespread, but hospitalization rates have varied widely by region.

California and the West Coast have been hit hard, with four times as many people hospitalized as in 2014-2015, Dr. Jernigan said. Minnesota had twice as many. New York and the Northeast "are beginning to catch up," he added.

Intensity is high by two different measures the C.D.C. uses. For three weeks straight, the health departments of 49 states — all except Hawaii — have reported "widespread" flu activity.

Also, sentinel sites in 39 states, New York City and Puerto Rico are reporting "high" flu levels. (The sites include more than 2,000 emergency rooms, clinics and doctor's offices that report each week what percentage of their patients have flu symptoms.)

According to the C.D.C.'s weekly FluView, 6.6 percent of all patients visiting doctors now have flu symptoms. The 2014-2015 season peaked at 6 percent, while the 2009 "swine flu" season peaked at 7.7 percent.

Three weeks ago, the C.D.C. thought cases had peaked during the week between Christmas and New Years Day. But they have climbed since, and Dr. Jernigan said it appeared to be due to "kids returning to school."

Until recently, the severity indexes had languished behind the measures of intensity.

The agency's national "Pneumonia and Influenza Mortality Surveillance Index" ripples like a sine wave, rising in winter and falling in summer. Until recently, the red line indicating deaths had remained firmly below the "epidemic threshold" even as the red line on a different index tracking doctor's visits was following the pattern set by the 2014-2015 season with eerie exactness.

Then, two weeks ago, the intensity line plodded steadily beyond the 2014-2015 Christmas week peak, but the mortality line initially did not budge. But it is now shooting upward at the high trajectory angle of a North Korean rocket, has passed the peaks of the last two seasons and is on track to match or surpass 2014-2015.

GREGORY BULL/ASSOCIATED PRESS

At least 34 million Americans are expected to get the flu this season, according to the C.D.C.

Weekly U.S. Influenza Surve | FluView Phase 8

gis.cdc.gov/grasp/fluview/FluView8.html

Lowe's Credit Card

FLUVIEW

CDC

# A Weekly Influenza Surveillance Report Prepared by the Influenza Division

## Weekly Influenza Activity Estimates Reported by State and Territorial Epidemiologists*

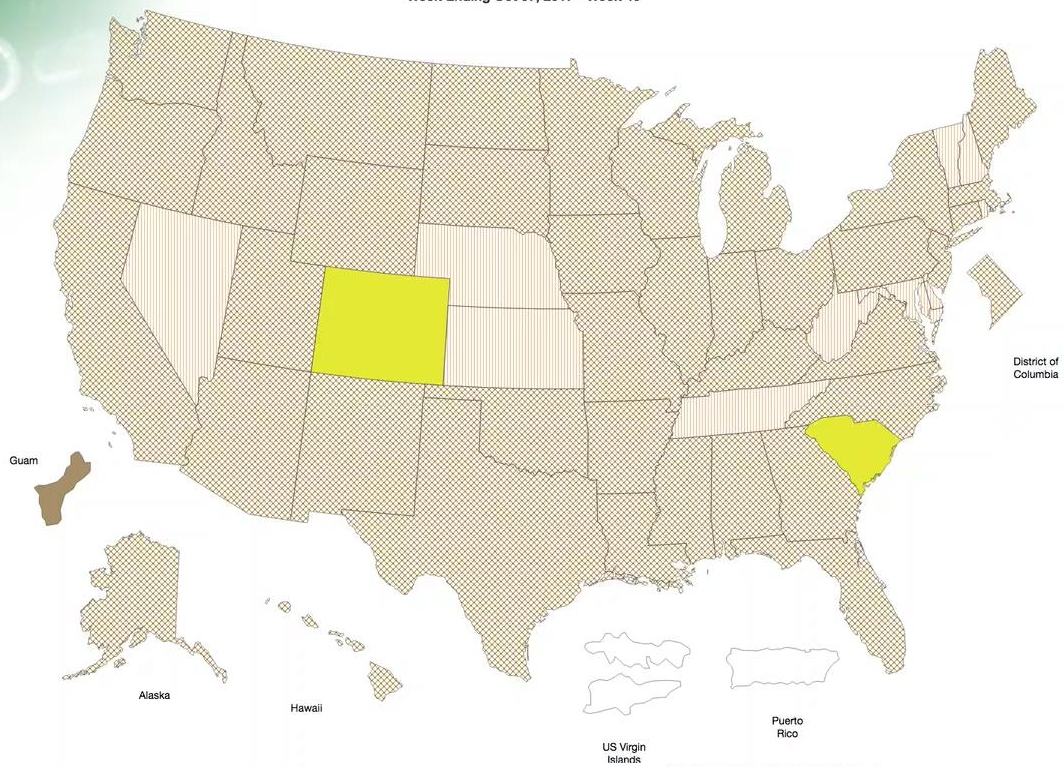
Season: 2017-18 | Play | Pause

<< 40 50 1 3 >>

Weeks

Download Image | Download Data

**Week Ending Oct 07, 2017 - Week 40**

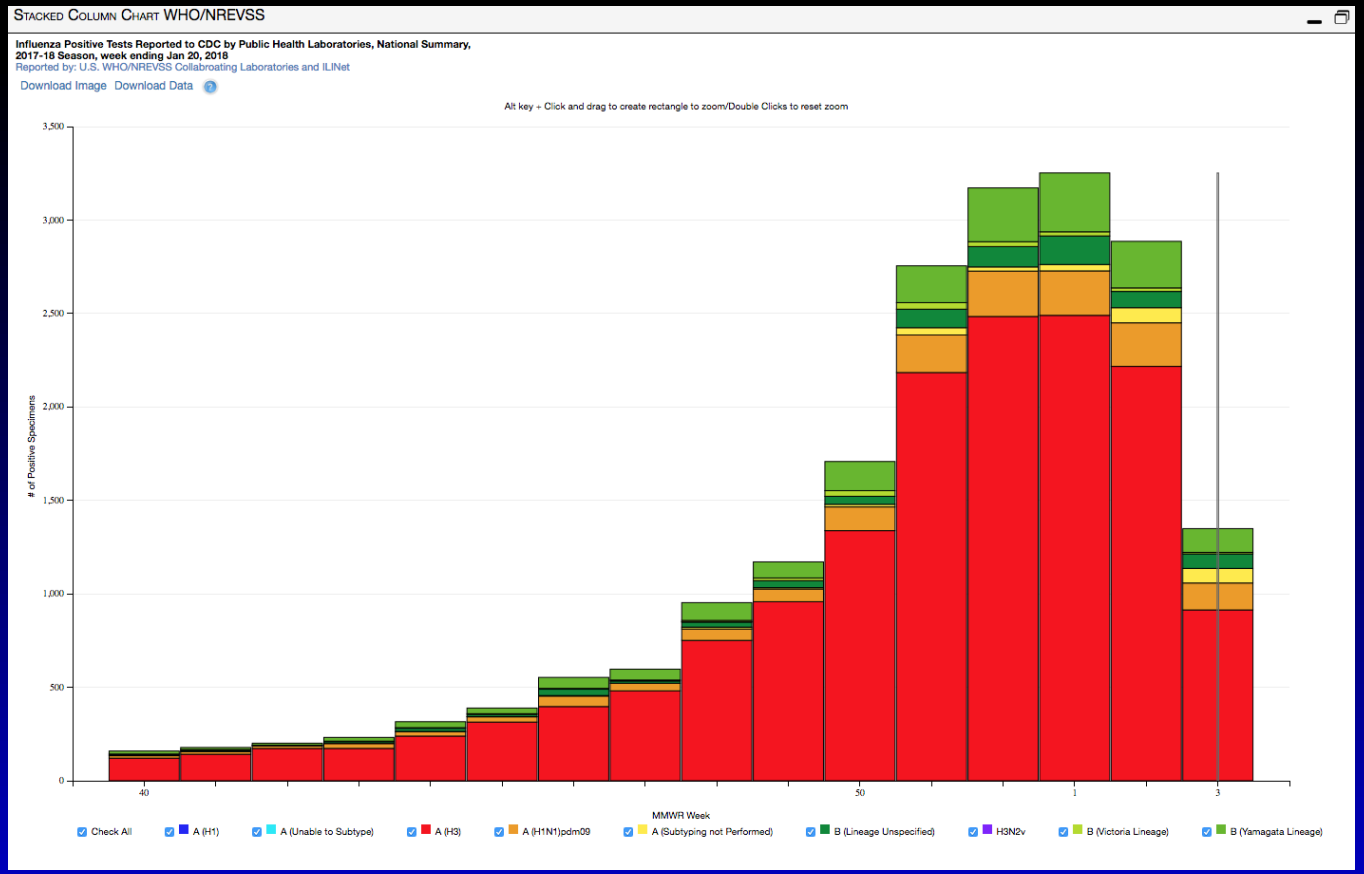



**Influenza Activity Estimates**

- No Activity
- Sporadic
- Local Activity
- Regional
- Widespread
- No Report

Most Recent Flu Activity data in XML Format

*This map indicates geographic spread and does not measure the severity of influenza activity.

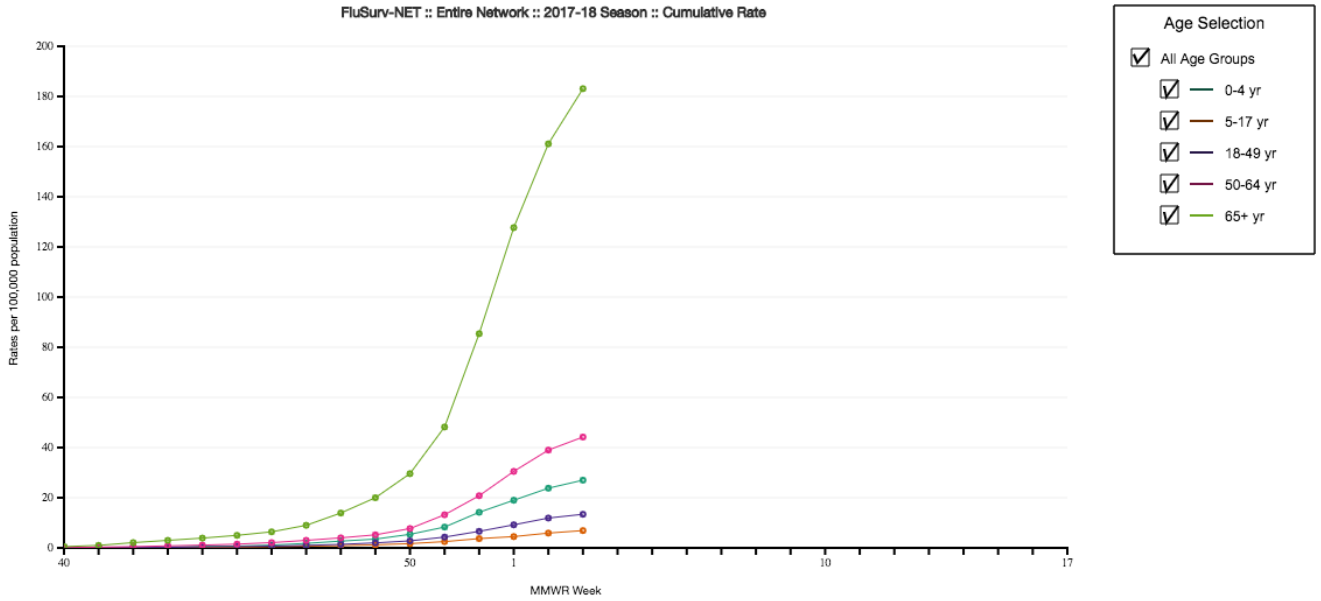

Stacked Column Chart WHO/NREVSS
Influenza Positive Tests Reported to CDC by Public Health Laboratories, National Summary,
2017-18 Season, week ending Jan 20, 2018
Reported by: U.S. WHO/NREVSS Collaborating Laboratories and ILINet
Download Image Download Data
Alt key + Click and drag to create rectangle to zoom/Double Clicks to reset zoom
# of Positive Specimens
3,500
3,000
2,500
2,000
1,500
1,000
500
0
40
50
1
3
MMWR Week
Check All
A (H1)
A (Unable to Subtype)
A (H3)
A (H1N1)pdm09
A (Subtyping not Performed)
B (Lineage Unspecified)
H3N2v
B (Victoria Lineage)
B (Yamagata Lineage)

FluView

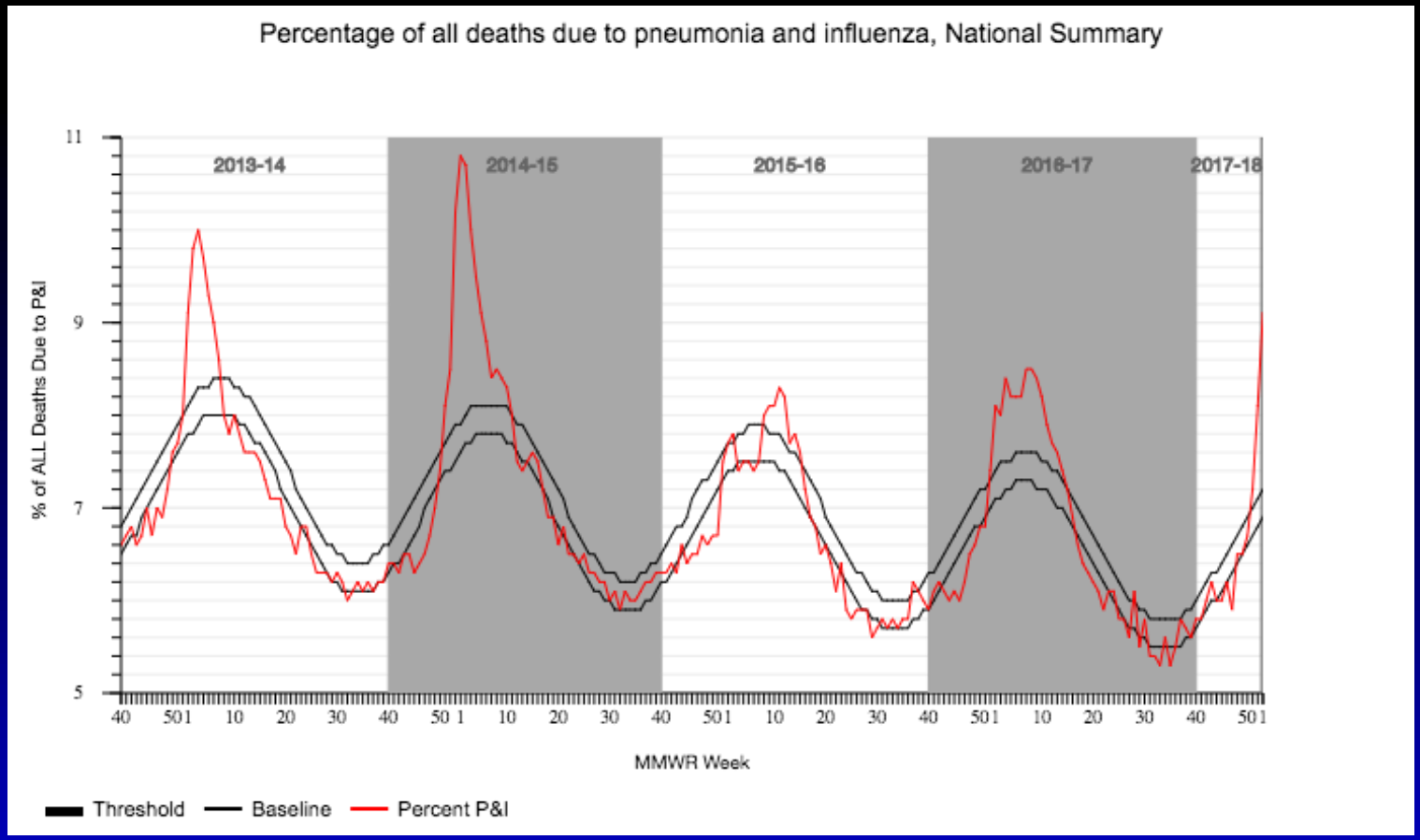
CDC

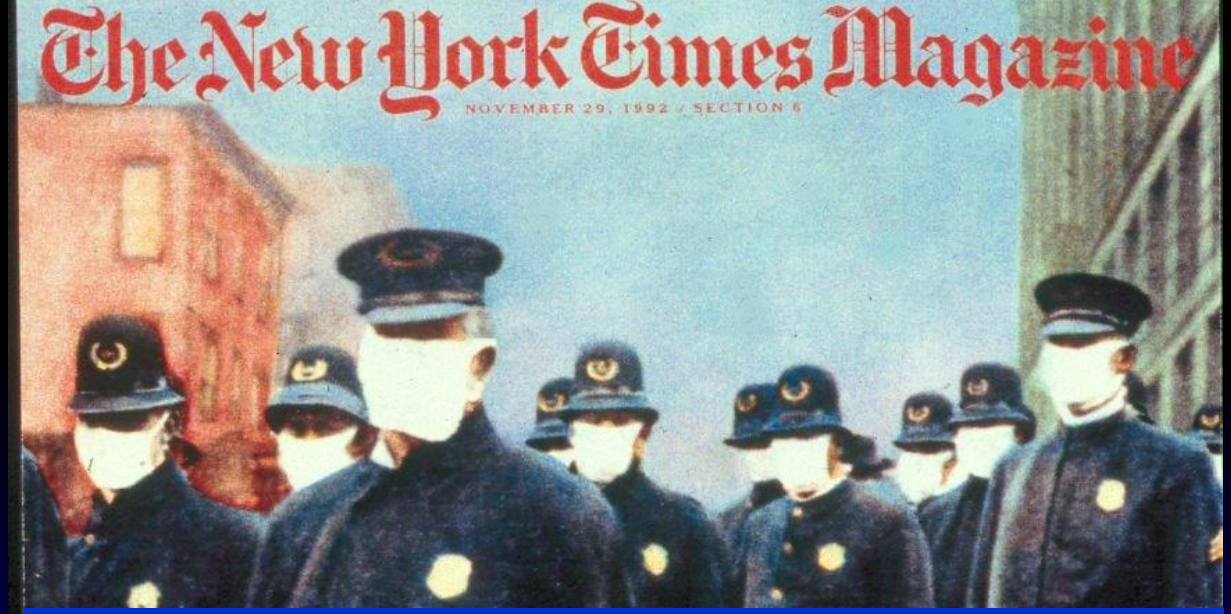
# Laboratory-Confirmed Influenza Hospitalizations

## Preliminary cumulative rates as of Jan 20, 2018




The Influenza Hospitalization Surveillance Network (FluSurv-NET) conducts population-based surveillance for laboratory-confirmed influenza-associated hospitalizations in children (persons younger than 18 years) and adults. The current network covers over 70 counties in the 10 Emerging Infections Program (EIP) states (CA, CO, CT, GA, MD, MN, NM, NY, OR, and TN) and three additional states (MI, OH, and UT). The network represents approximately 9% of US population (~27 million people). Cases are identified by reviewing hospital, laboratory, and admission databases and infection control logs for patients hospitalized during the influenza season with a documented positive influenza test (i.e., viral culture, direct/indirect fluorescent antibody assay (DFA/IFA), rapid influenza diagnostic test (RIDT), or molecular assays including reverse transcription-polymerase chain reaction (RT-PCR)). Data gathered are used to estimate age-specific hospitalization rates on a weekly basis, and describe characteristics of persons hospitalized with associated influenza illness. Laboratory-confirmation is dependent on clinician-ordered influenza testing. Therefore, the unadjusted rates provided are likely to be underestimated as influenza-associated hospitalizations can be missed if influenza is not suspected and tested for. FluSurv-NET hospitalization data are preliminary and subject to change as more data become available. All incidence rates are unadjusted. Please use the following citation when referencing these data: "FluView: Influenza Hospitalization Surveillance Network, Centers for Disease Control and Prevention. WEBSITE. Accessed on DATE".


Percentage of all deaths due to pneumonia and influenza, National Summary
2013-14
2014-15
2015-16
2016-17
2017-18
% of ALL Deaths Due to P&I
11
9
7
5
40
50
1
10
20
30
40
50
1
10
20
30
40
50
1
10
20
30
40
50
1
10
20
30
40
50
1
MMWR Week
Threshold
Baseline
Percent P&I




*"If the epidemic continues its mathematical rate of acceleration, civilization could easily disappear from the face of the earth."*

The Army Surgeon General

# FLU PANDEMIC

**A lethal strain of the virus killed more than 20 million in 1918. Scientists say it's time for another, and modern medicine may not be of much help.**

BY ROBIN MARANTZ HENIG

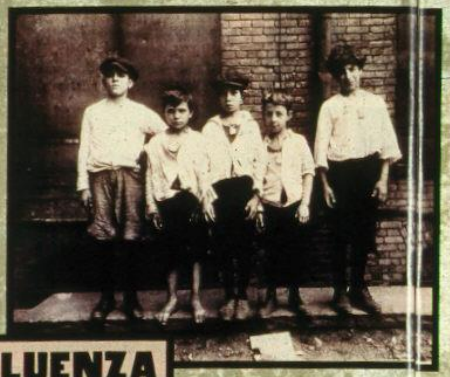
DURING THE FLU EPIdemic of 1918, accrding to medical lore, victims were struck down almost in midstride. Four women in a bridge group played cards together until 11 o'clock in the evening. By the next morning three of them were dead. One man got on a streetcar feeling well enough to go to work, rode six blocks and died. During the single month of October, influenza killed 196,000 people in this country — more than twice as many as would die of AIDS during the first 10 years of that epidemic. By the end of the winter of 1918-19, two billion people around the world had come down with influenza, and between 20 million and 40 million had died.

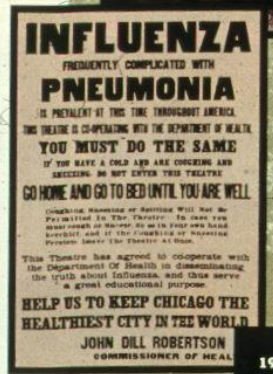
The flu outbreak of 1918 was "the most devastating epidemic that we have ever had in history," says John R. La Montagne, chief of infectious diseases at the National Institute of Allergy and Infectious Diseases in Bethesda, Md. "And it happened in this century. No one really knows why it occurred, but there's every expectation that if it occurred once, it can occur again." The 1918 influenza pandemic killed as many people in a single year as died in the four-year Black Death, the bubonic plague that ravaged Europe from 1347 to 1351.

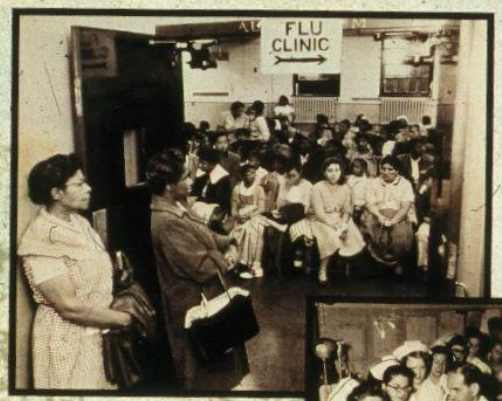
We like to believe such plunder is an ancient relic; whatever was killing people so ruthlessly in 1918 must be something we can treat by now. Modern medicine has given us an influenza vaccine, an anti-influenza drug (amantadine) and plenty of antibiotics to prevent or treat secondary bacterial infections. But in the face of a virus that kills so rapidly, all the antiviral drugs in the physician's armamentarium would be impotent. If a strain similar to the 1918 variant were to emerge today — a strain that, last time around, killed literally overnight — some experts believe that even modern medicine would be helpless to prevent many related deaths.

THE EXISTENCE OF the influenza vaccine — not to mention that pervasive phrase "just the flu," conveying as it does a certain harmless inevitability — may give us a sense of false security when it comes to the possibility of a pandemic outbreak of influenza. (A pandemic is an international epidemic, with disease occurring at a higher-than-expected

*Robin Marantz Henig is the author of "A Dancing Matrix: Voyages Along the Viral Frontier," from which this article is adapted. The book will be published in February by Alfred A. Knopf Inc.* 






**1957: THE ASIAN FLU**

**Less virulent than the 1918 strain, it still killed 70,000 Americans. ABOVE: Anxious patients await treatment at the Central Harlem District Health Center. RIGHT: Staff inoculations at Montefiore Hospital in the Bronx.**

**1968: THE HONG KONG FLU**

**Most people had some immunity to this strain, which was similar to the Asian flu; 28,000 Americans died. ABOVE: Masks were in on a Florida campus in 1969. LEFT: A crowded public-health clinic in New York, 1968. BACKGROUND: An electron microscope photograph from 1969 of influenza viruses attacking a cell from a human trachea.**

**1918: THE SPANISH FLU**

**In a single month, influenza killed 196,000 in the United States. ABOVE: Mayor Andrew J. Peters of Boston being inoculated with the flu serum; there was no vaccine in 1918. LEFT: A warning poster issued by the Chicago commissioner of health. TOP LEFT: Bags of camphor were thought to ward off the virus.**



TOP ROW, FROM LEFT: BETTMANN ARCHIVE; THE NEW YORK TIMES; BROWN BROTHERS; BETTMANN NEWSPHOTOS. BOTTOM ROW, FROM LEFT: NATIONAL LIBRARY OF MEDICINE; BROWN BROTHERS; ROBERT WALKER/THE NEW YORK TIMES. BACKGROUND: ROBERT DOWNCROSS/SCIENCE PHOTO LIBRARY/PHOTO RESEARCHERS

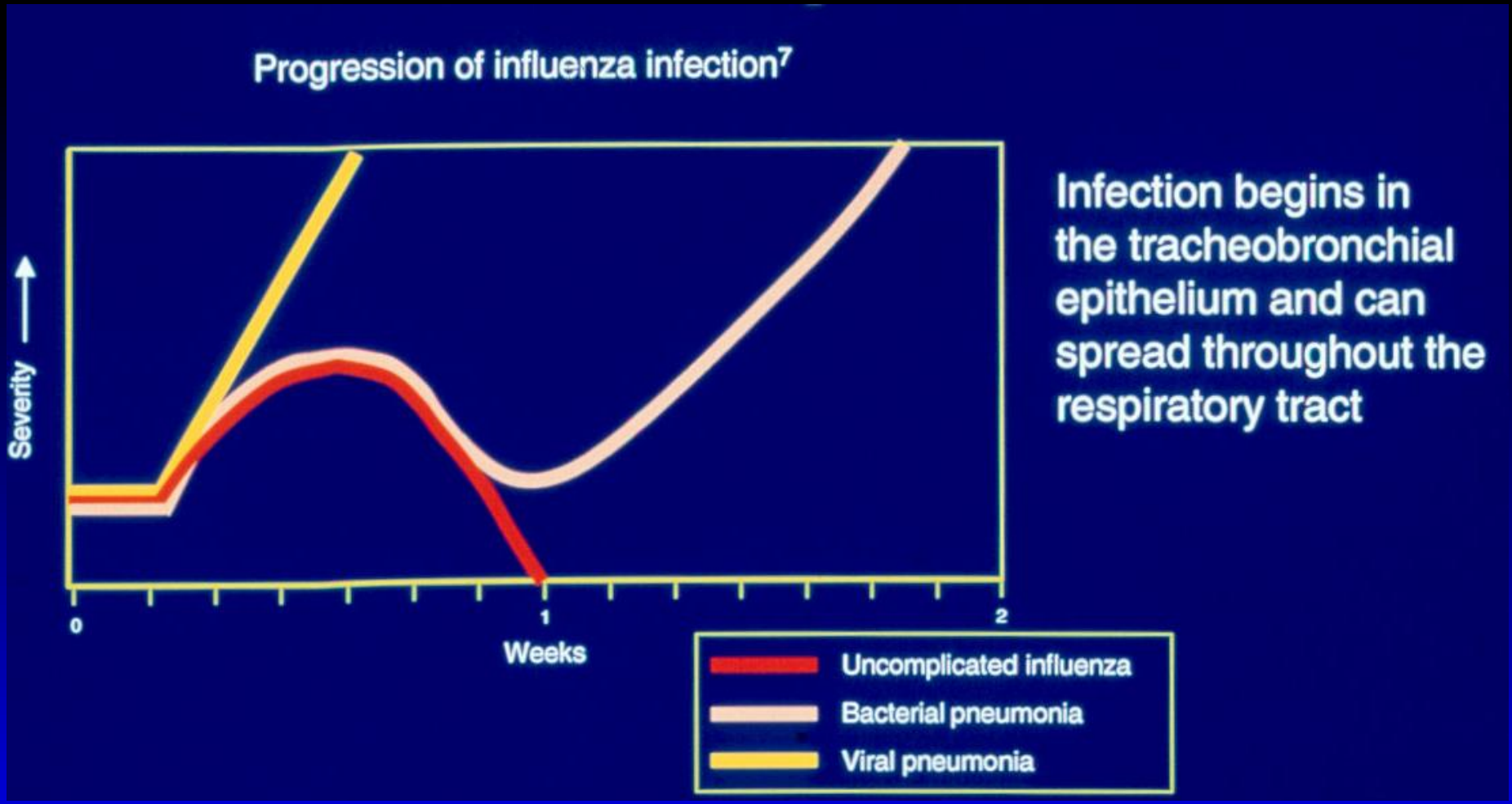
# The 1918 “Spanish flu”

Military physicians were baffled by the mysterious illness that was striking young, healthy soldiers.

- Started in the U.S. during March.

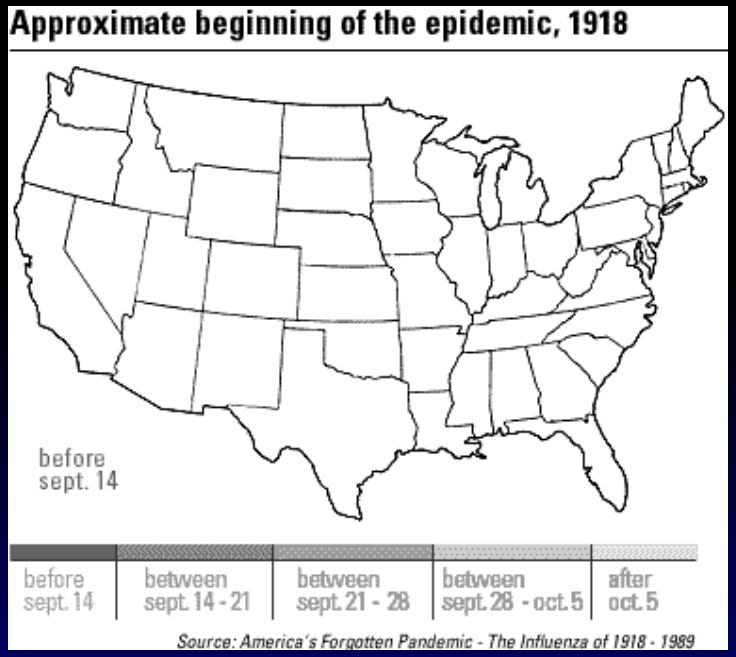
As sailors and soldiers fell ill, doctors puzzled over the mystery illness they were confronting.

# Course of Untreated Influenza

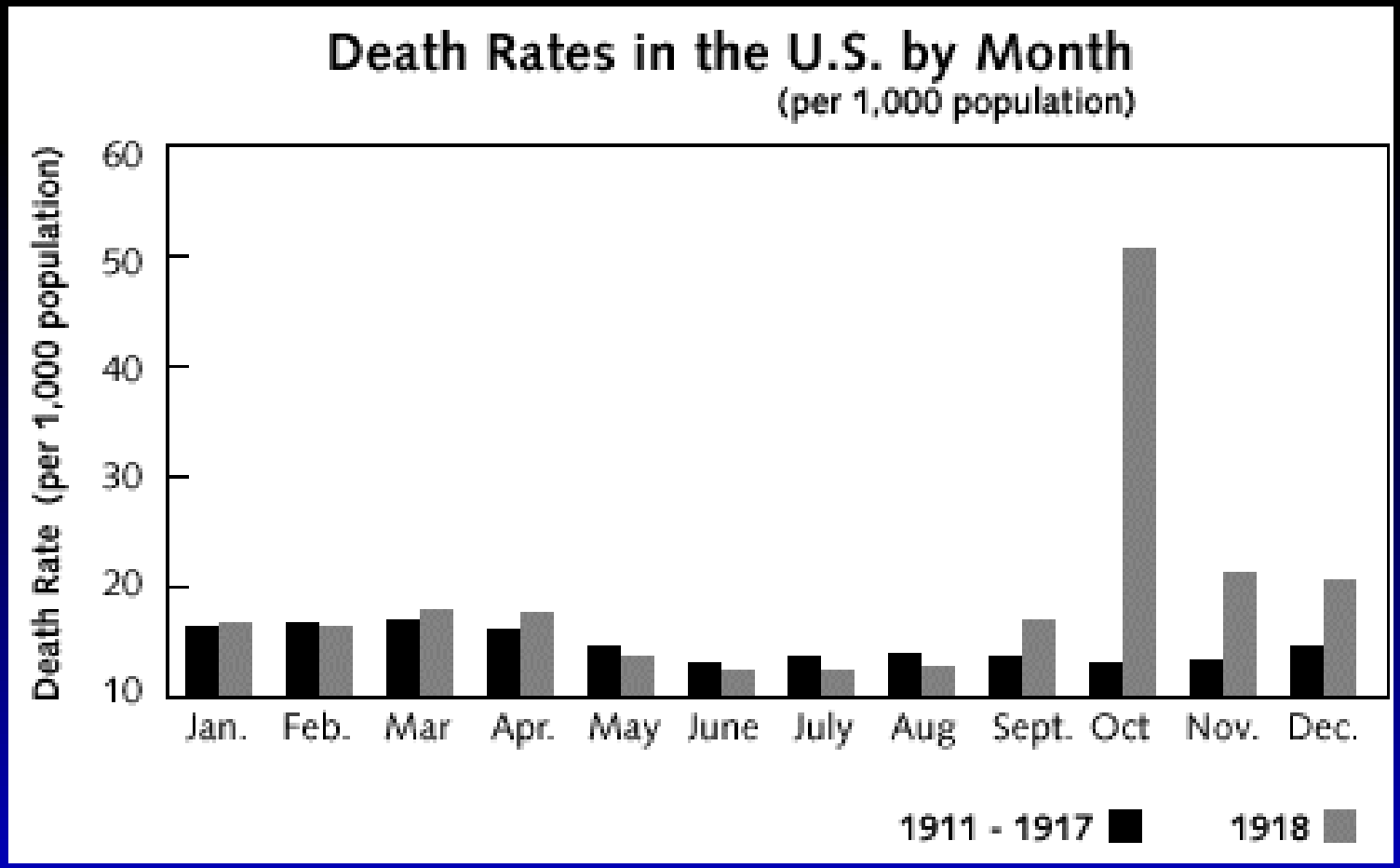



Small PA Jr Hospital Practice 1990

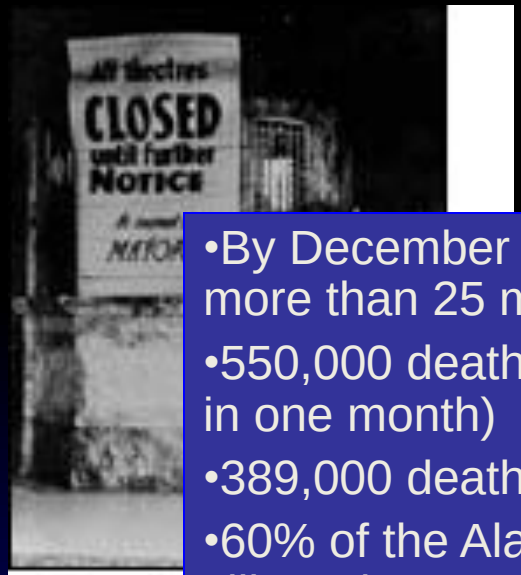
By September 11, 1918, influenza had spread to Boston's civilian population.




Vaccines intended to prevent Spanish influenza proved ineffective.


Death Rates in the U.S. by Month
(per 1,000 population)
Death Rate (per 1,000 population)
60
50
40
30
20
10
Jan.
Feb.
Mar
Apr.
May
June
July
Aug
Sept.
Oct
Nov.
Dec.
1911 - 1917
1918

Surgical facemasks became an everyday fashion accessory. Their effectiveness was debated.



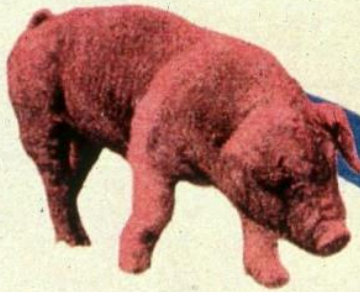

Public gath
ordered clo
of many m

- By December there had been 200 - 1000 million cases which killed more than 25 million people worldwide
- 550,000 deaths within the US (20,000 in NYC; 11,000 in Philadelphia in one month)
- 389,000 deaths in Japan.
- 60% of the Alaskan Eskimo population died (100% mortality in some villages)
- 25% of the Samoan population died.
- The strain (H1N1) was so virulent that many people died within hours of symptom onset.

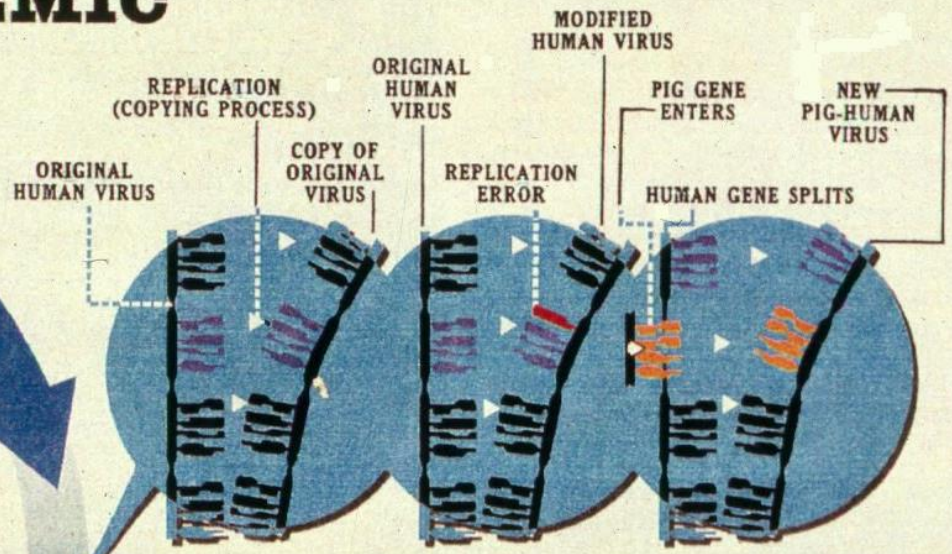
A nationwide casket shortage was evidence of a mounting death toll.

San Francisco residents, still fearful of influenza, wear masks during an armistice parade.

# BREEDING A PANDEMIC



Many influenza strains originate in Asia, where the most common animal hosts for the influenza virus — pigs, ducks and chickens — live in close proximity to each other and to human beings. These animal species serve as "mixing vessels," or reservoirs, for influenza viruses of both animal and human types. Inside a reservoir animal's intestines, viruses flutter about and recombine, falling in line in random new combinations. This kind of genetic reassortment is known as antigenic shift.




**NORMAL REPLICATION**

If replication were limited to this error-free process, influenza would not pose much of a threat to human beings, who build up resistance when first exposed to a particular viral strain.

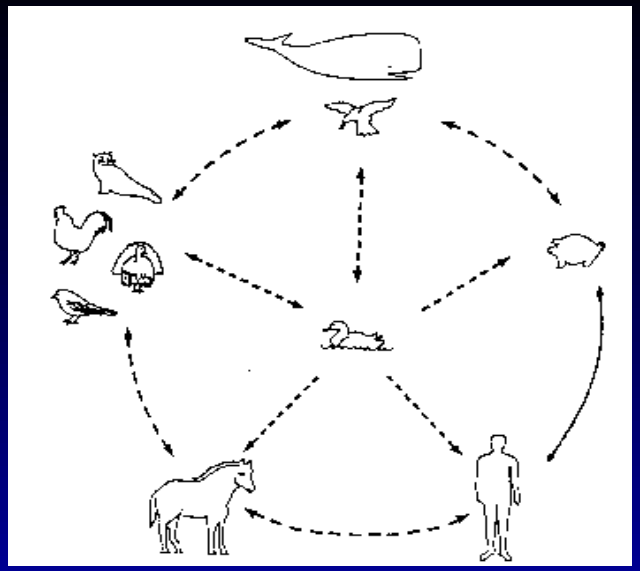
**ANTIGENIC DRIFT**

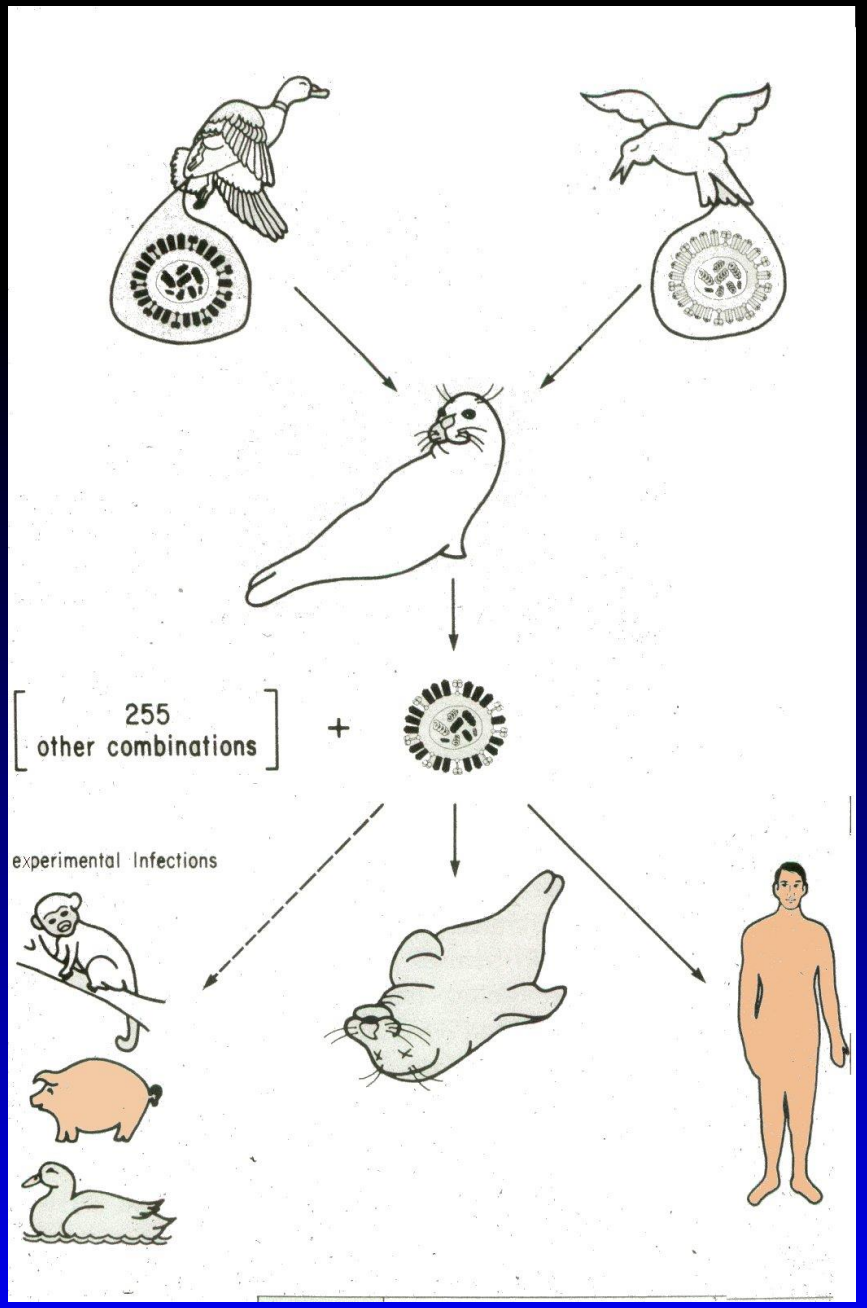
This is akin to the virus changing a purple coat for a red one, making it harder for the immune system to recognize the virus. Antigenic drift explains why people who had the flu or got a flu shot are soon vulnerable again.

**ANTIGENIC SHIFT**

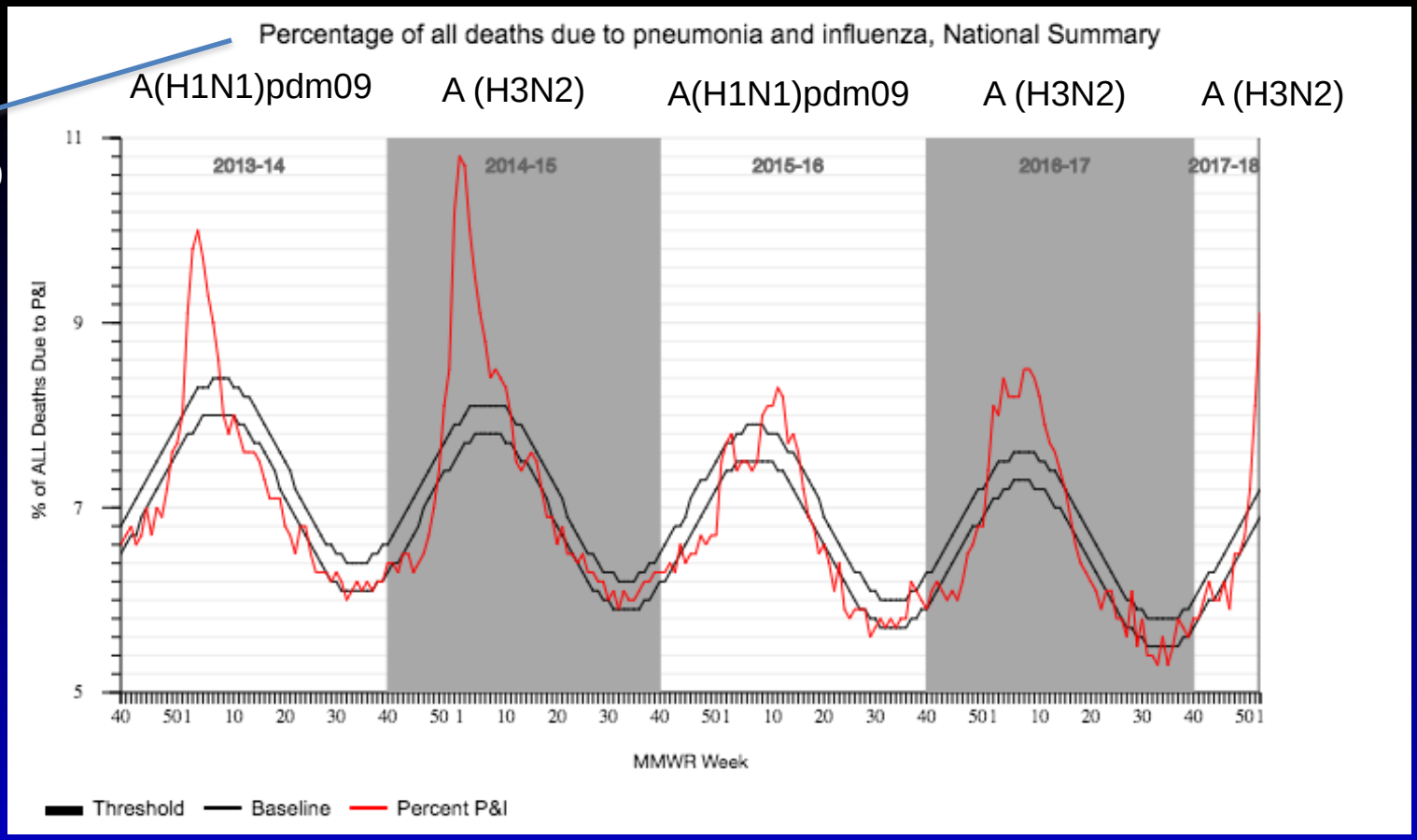
This rare strain — part human, part bird or pig — is unrecognizable to the immune system. It's as if the virus replaced its purple coat with a spangly orange cloak. The potential for an influenza pandemic has arrived.

# Flu as zoonoses





A(H1N1)pdm09
2009



# The Faces of Flu

**INFLUENZA POSTER GIRL**
**MARCH, 1988**

REBECCA BERNSTEIN, AGE 6

CULTURE + INFLUENZA A (H3N2)
WEEK OF 2/28/88
CULTURE + INFLUENZA B
WEEK OF 3/13/88

**INFLUENZA POSTER GIRL**
**JANUARY, 1989**

REBECCA BERNSTEIN, AGE 7

CULTURE + INFLUENZA A (H1N1)
WEEK OF 1/16/89

**INFLUENZA POSTER CHILD**
**1988-1989**

JONATHAN BERNSTEIN, AGE 4

CULTURE + INFLUENZA A (H1N1) 2/6/89
CULTURE + INFLUENZA B 2/6/89

Married. Works for EPA in Columbus.

Married. Pediatric social worker in Cleveland.

# Bernstein Family

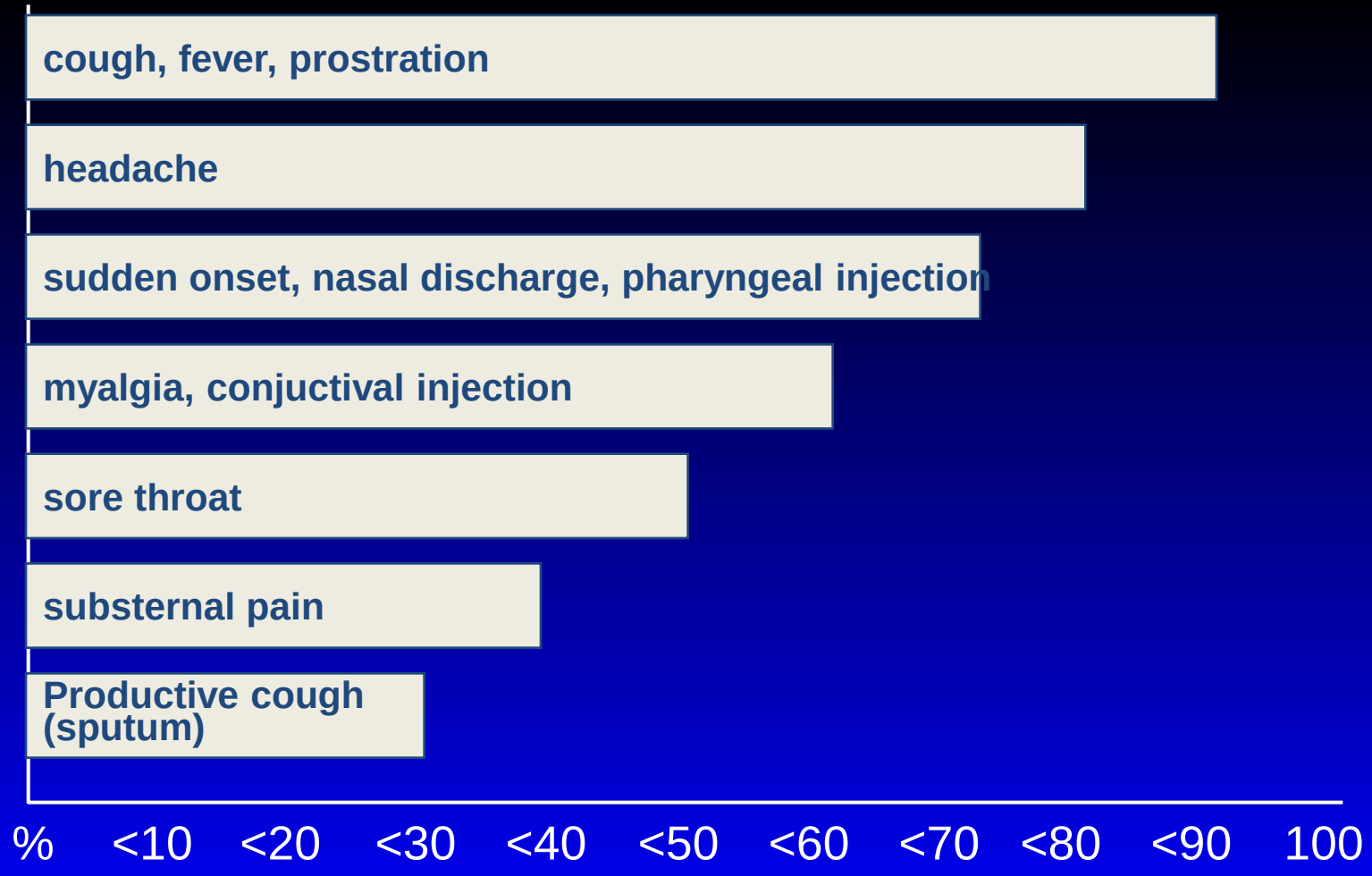
## Viral Cultures

Fourth beer book coming out soon. Married with a 4 year old daughter

| | *Joshua* | *Rebecca* | *Jonathan* |
|---|---|---|---|
| **1986** | Flu A | |  |
| **1988** |  | Flu A/H3<br>Flu B | |
| **1989** | | Flu A/H1  | Flu A/H1<br>+Flu B |
| **1991** | Flu B (2/91)<br>Flu A (12/91) | | Para 2 (11/91) |

# Influenza A In Young Adults

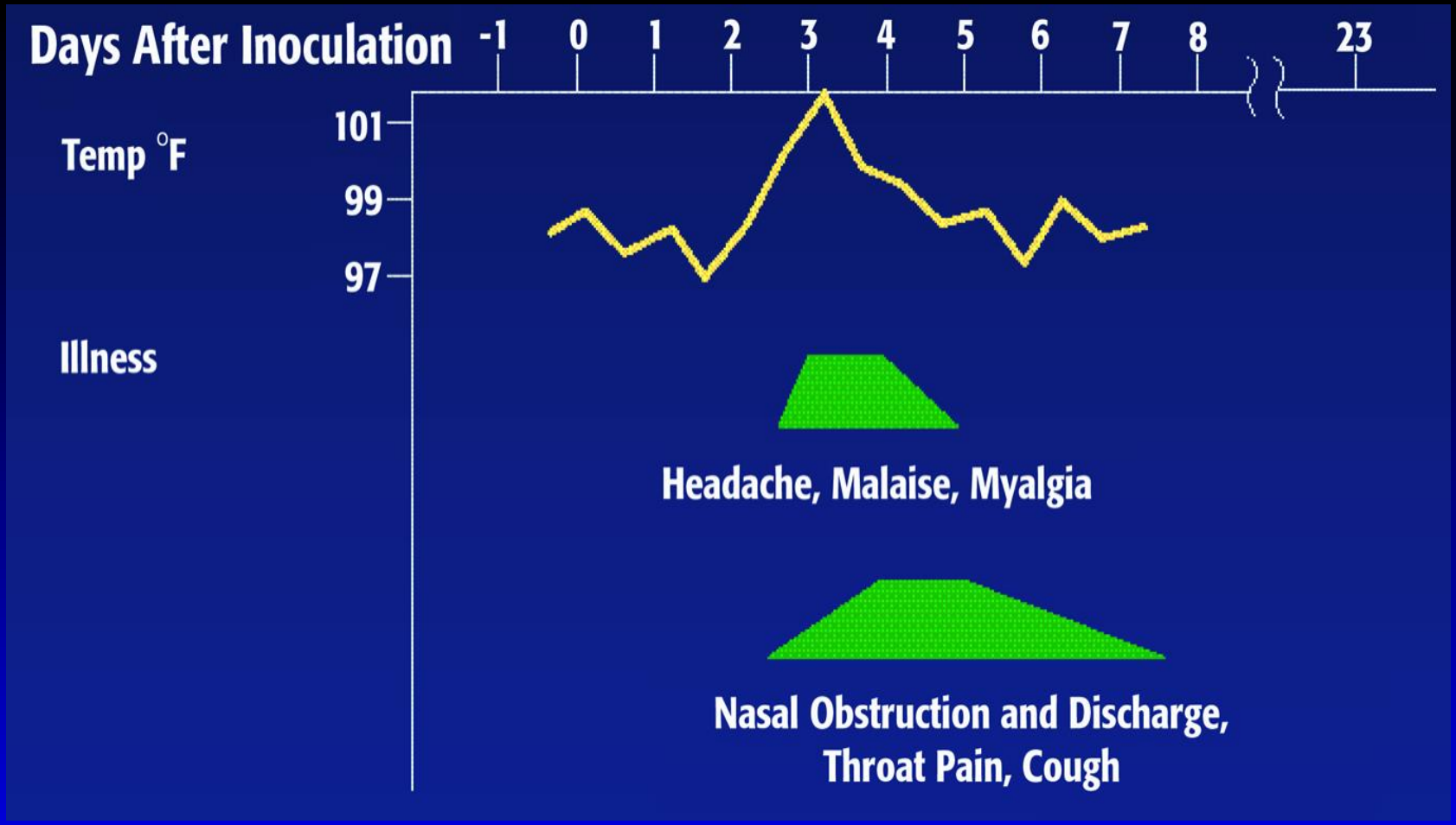
(Taken from Kilbourne: Influenza, 1987, p159)



## Flu vs Cold

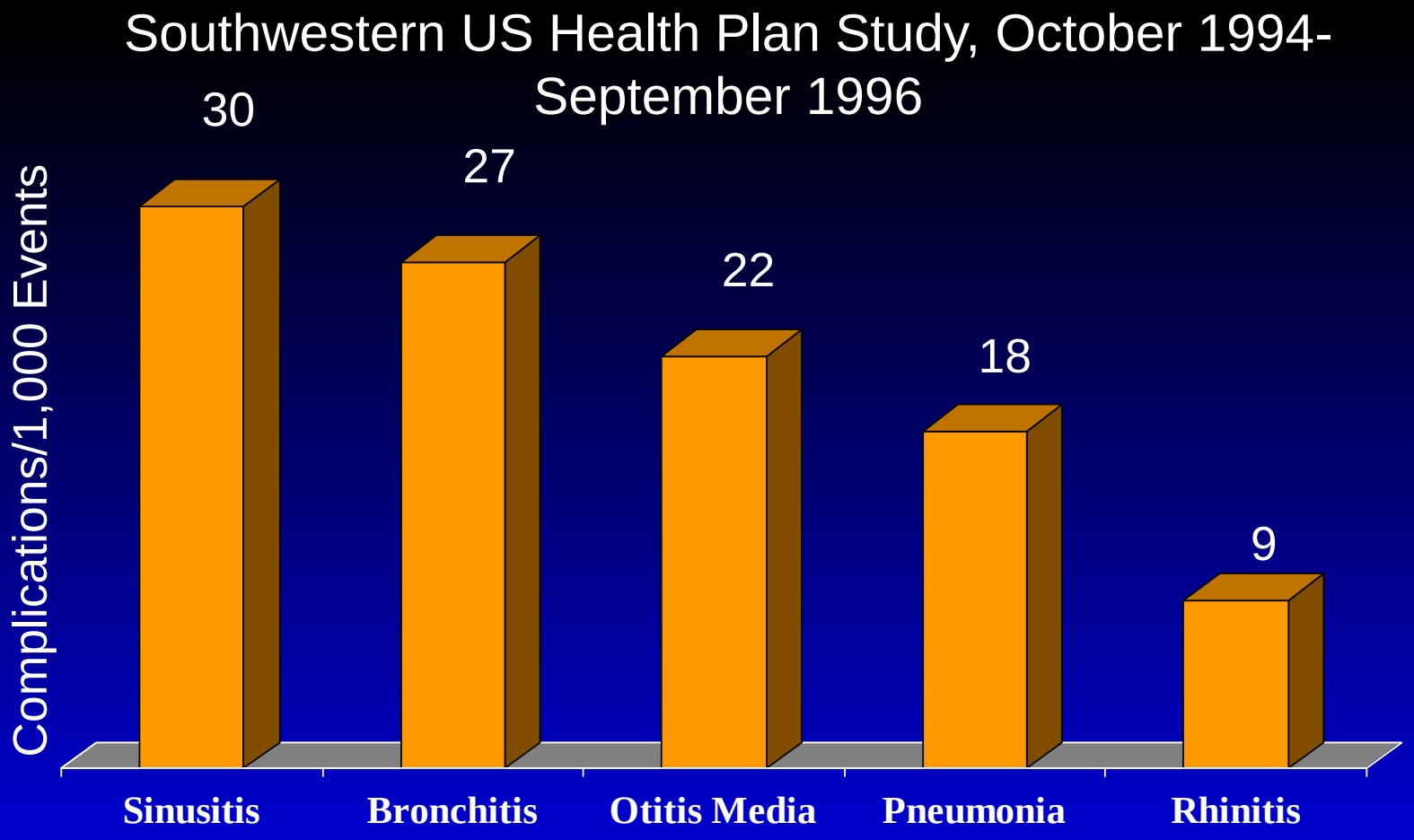
| Signs and Symptoms | Influenza | Cold |
|---|---|---|
| **Symptom onset** | Abrupt | Gradual |
| **Fever** | Usual; lasts 3-4 days | Rare |
| **Aches** | Usual; often severe | Slight |
| **Chills** | Fairly common | Uncommon |
| **Fatigue, weakness** | Usual | Sometimes |
| **Sneezing** | Sometimes | Common |
| **Stuffy nose** | Sometimes | Common |
| **Sore throat** | Sometimes | Common |
| **Chest discomfort, cough** | Common; can be severe | Mild to moderate; hacking cough |
| **Headache** | Common | Rare |

# Shedding of Influenza A in Volunteer

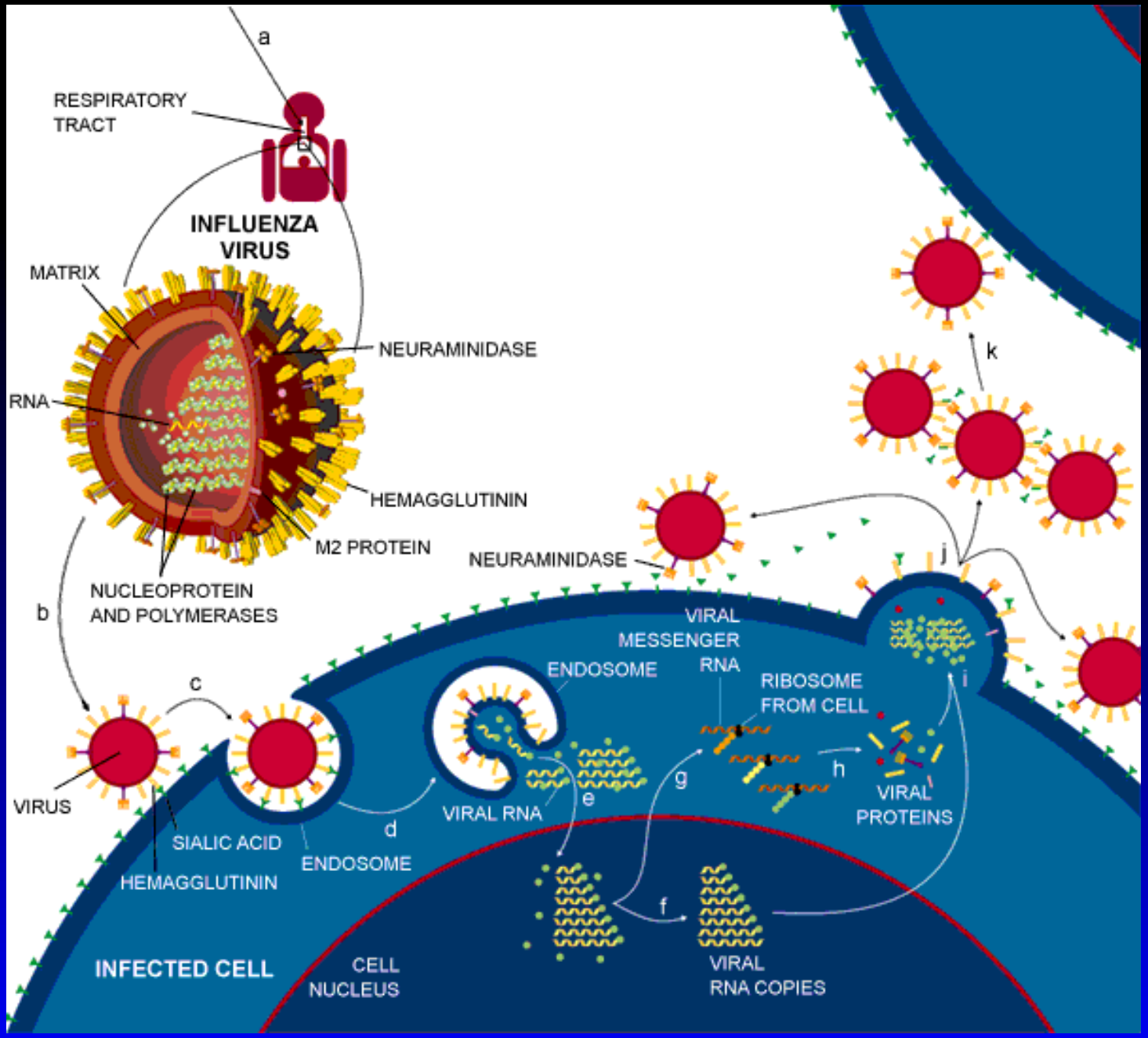



Adapted from Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas and Bennett's Principles and Practice of Infectious Disease.* 4th ed. 1995:1554.

# Secondary Complications of Influenza



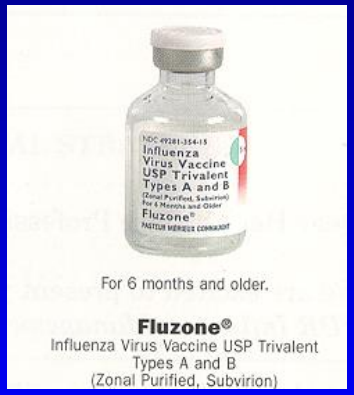

Synergy Health Care, Inc. data, data on file, Outcomes Management, Roche Laboratories. Slide 5.


a
RESPIRATORY TRACT
INFLUENZA VIRUS
MATRIX
NEURAMINIDASE
RNA
HEMAGGLUTININ
M2 PROTEIN
NUCLEOPROTEIN AND POLYMERASES
b
NEURAMINIDASE
k
j
VIRAL MESSENGER RNA
ENDOSOME
RIBOSOME FROM CELL
i
c
VIRUS
SIALIC ACID
HEMAGGLUTININ
ENDOSOME
d
VIRAL RNA
e
g
h
VIRAL PROTEINS
f
INFECTED CELL
CELL NUCLEUS
VIRAL RNA COPIES

# Inactivated Influenza Virus Vaccine

Content — Updated yearly to protect against anticipated strains, consists of type A (2) and type B (1)

Process — Grown in embryonated chicken eggs and formalin inactivated




*MMWR*. 1999;48:4-5.

# Efficacy of the Influenza Vaccine

- Most effective (70%-90%) in preventing illness in persons aged <65 yrs
- 30%-70% in preventing P/I hospitalization in elderly not in chronic care facility
- 30%-40% in preventing illness in frail elderly
- 50%-60% in preventing P/I hospitalization in nursing home elderly
- 80% in preventing death in nursing home elderly

*MMWR*. 1999;48:4.

| Outcome | Risk Ratio or Odds Ratio (95% CI)* | *P* Value |
|---|---|---|
| Hospitalizations for pneumonia and influenza | 0.48 (0.28–0.82) | 0.008 |
| Hospitalizations for all respiratory conditions | 0.76 (0.53–1.09) | 0.13 |
| Death | 0.30 (0.21–0.43) | <0.001 |
| Outpatient visits for pneumonia and influenza | | |
| ≥1 outpatient visit | 0.95 (0.73–1.25) | >0.2 |
| Number of outpatient visits† | 0.64 (0.49–0.84) | 0.002 |
| Outpatient visits for all respiratory conditions | | |
| ≥1 outpatient visit | 0.95 (0.84–1.07) | >0.2 |
| Number of outpatient visits† | 0.89 (0.83–0.96) | 0.002 |

**Relation between Influenza Vaccination and Outpatient Visits, Hospitalization, and Mortality in Elderly Persons with Chronic Lung Disease.** Nichol KL, Baken L, Nelson A. *Ann Intern Med.* 1999;130:397-403.

# THE JAPANESE EXPERIENCE WITH VACCINATING SCHOOLCHILDREN AGAINST INFLUENZA

THOMAS A. REICHERT, PH.D., M.D., NORIO SUGAYA, M.D., DAVID S. FEDSON, M.D., W. PAUL GLEZEN, M.D., LONE SIMONSEN, PH.D., AND MASATO TASHIRO, M.D., PH.D.

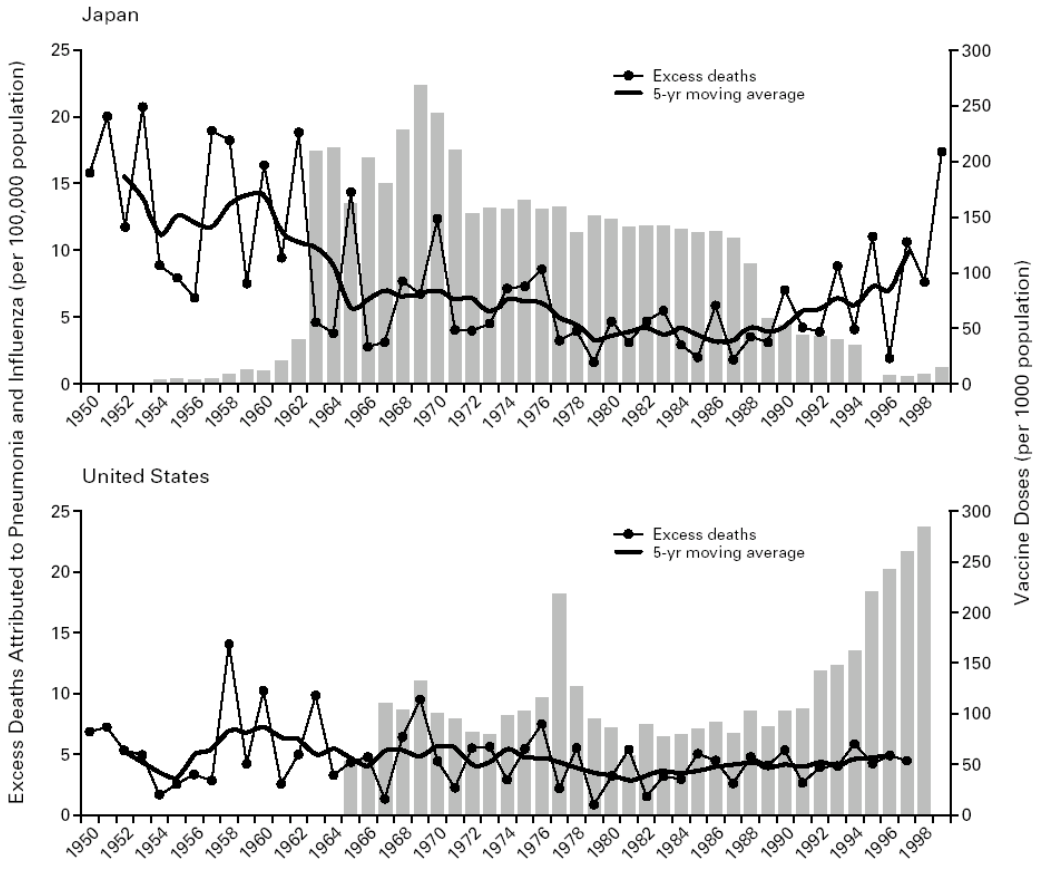



**Figure 4.** Excess Deaths Attributed to Pneumonia and Influenza over a 50-Year Period in Japan and the United States. The five-year moving average is also shown. The history of the rates of use of vaccine in each country is superimposed (shaded bars). Tick marks represent the beginning of the years indicated.

N Engl J Med 2001; 344:889-96

# THE JAPANESE EXPERIENCE WITH VACCINATING SCHOOLCHILDREN AGAINST INFLUENZA

THOMAS A. REICHERT, PH.D., M.D., NORIO SUGAYA, M.D., DAVID S. FEDSON, M.D., W. PAUL GLEZEN, M.D., LONE SIMONSEN, PH.D., AND MASATO TASHIRO, M.D., PH.D.

***Conclusions***

The effect of influenza on mortality is much greater in Japan than in the United States and can be measured about equally well in terms of deaths from all causes and deaths attributed to pneumonia or influenza. Vaccinating schoolchildren against influenza provides protection and reduces mortality from influenza among older persons. (N Engl J Med 2001; 344:889-96.)

# CDC Recommendations: Who Should Receive Influenza Vaccine?

- Persons at increased risk (age ≥6 mos)
- Hospital and outpatient employees
- Nursing home employees with patient contact
- Home health care providers working with high-risk persons
- Household members of high-risk persons
- Persons desiring to avoid influenza infection

*MMWR*. 1999;48:5-7.

# Composition of the 2017-18 InfluenzaVaccine

- A/Michigan/45/2015 (H1N1)pdm09-like virus (updated)
- A/Hong Kong/4801/2014 (H3N2)-like virus
- B/Brisbane/60/2008-like (B/Victoria lineage) virus

Four component vaccines are recommended to include the same three viruses above, plus B/Phuket/3073/2013-like virus (B/Yamagata lineage).

- Standard dose flu shots.
- A high-dose shot for people 65 and older.
- A shot made with adjuvant for people 65 and older.

*Live attenuated influenza vaccine (LAIV) – or the nasal spray vaccine – is not recommended*

Contents lists available at ScienceDirect

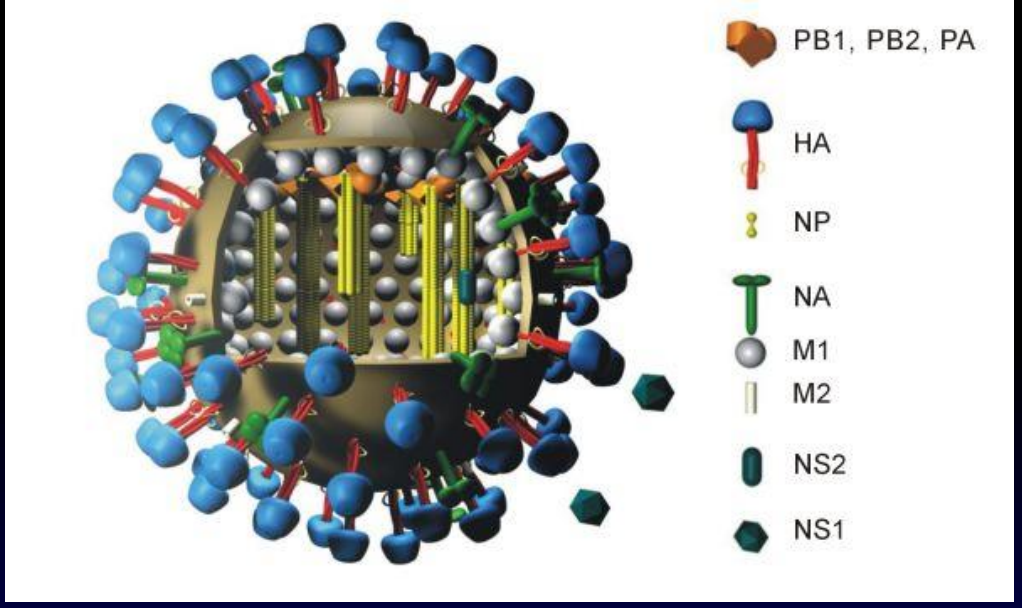
Vaccine

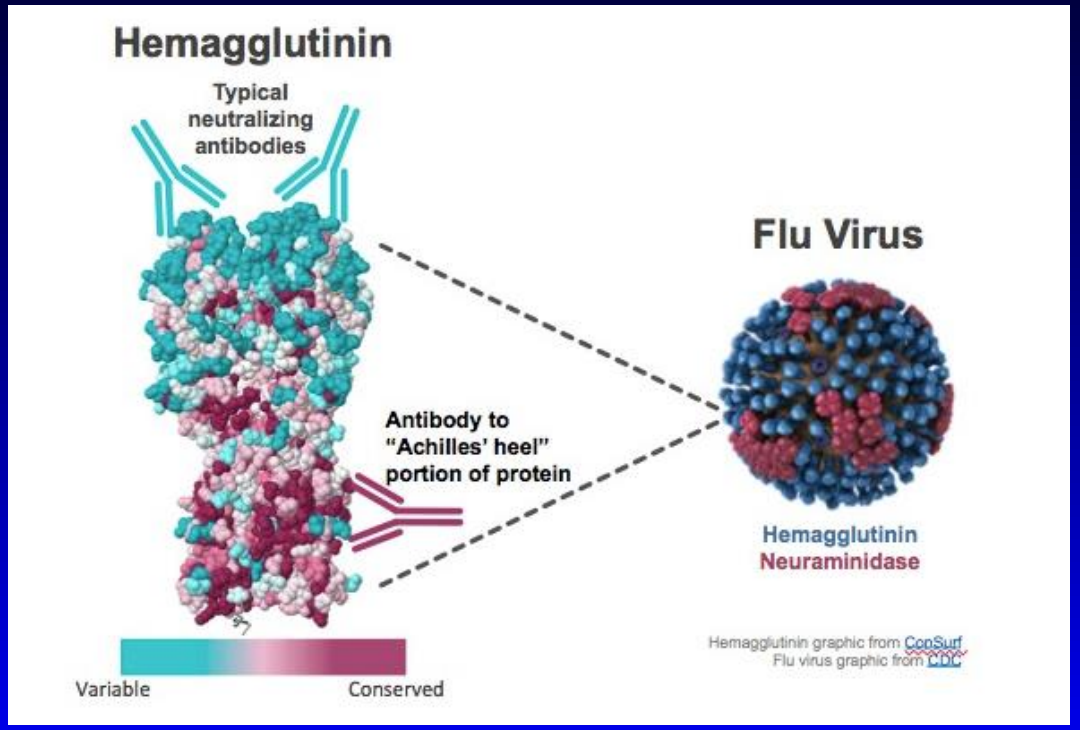
journal homepage: www.elsevier.com/locate/vaccine

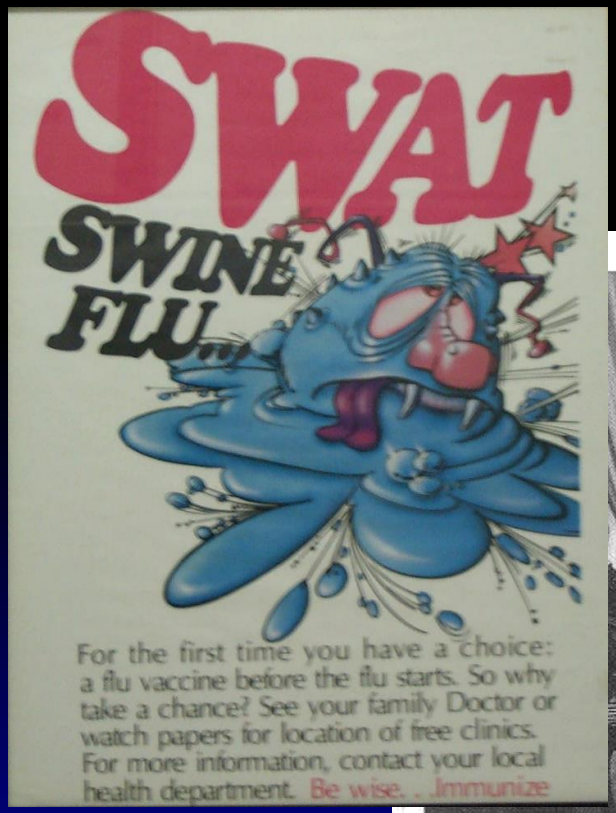
# Universal influenza vaccines: Shifting to better vaccines

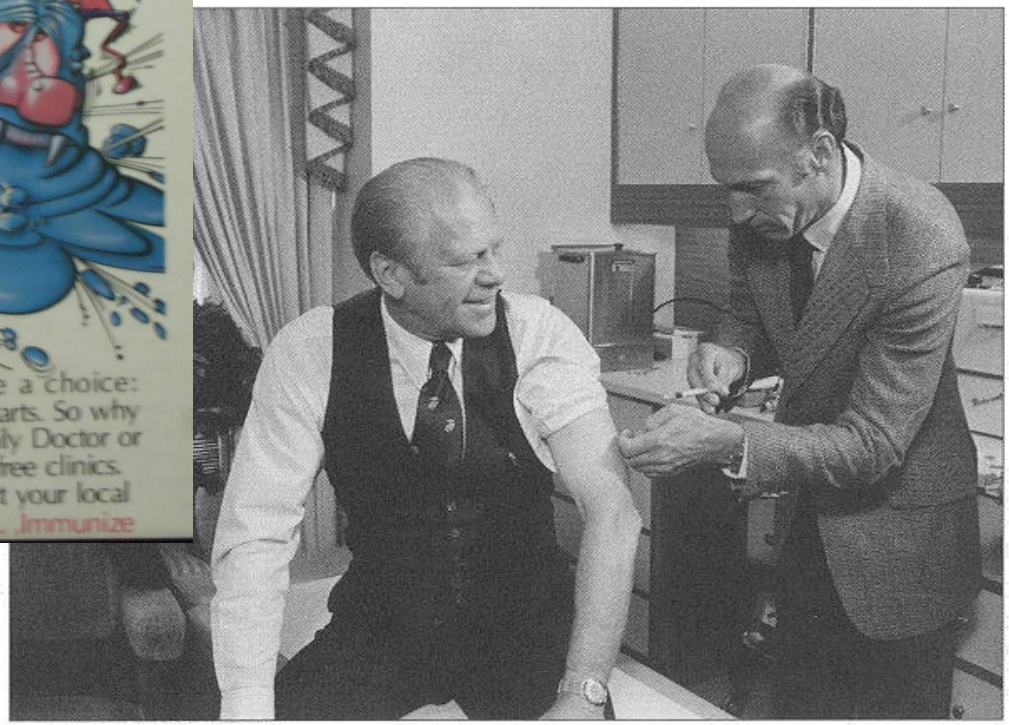
Francesco Berlanda Scorza*, Vadim Tsvetnitsky[1], John J. Donnelly

*PATH, 2201 Westlake Avenue Suite 200, Seattle, WA 98121, USA*

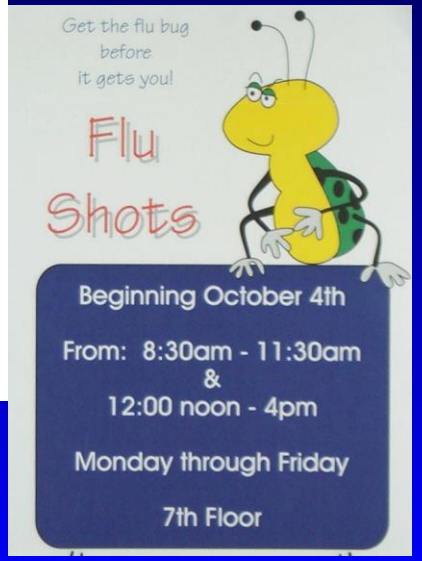

PB1, PB2, PA
HA
NP
NA
M1
M2
NS2
NS1


Hemagglutinin
Typical neutralizing antibodies
Antibody to "Achilles' heel" portion of protein
Flu Virus
Hemagglutinin
Neuraminidase
Variable
Conserved
Hemagglutinin graphic from ConSurf
Flu virus graphic from CDC

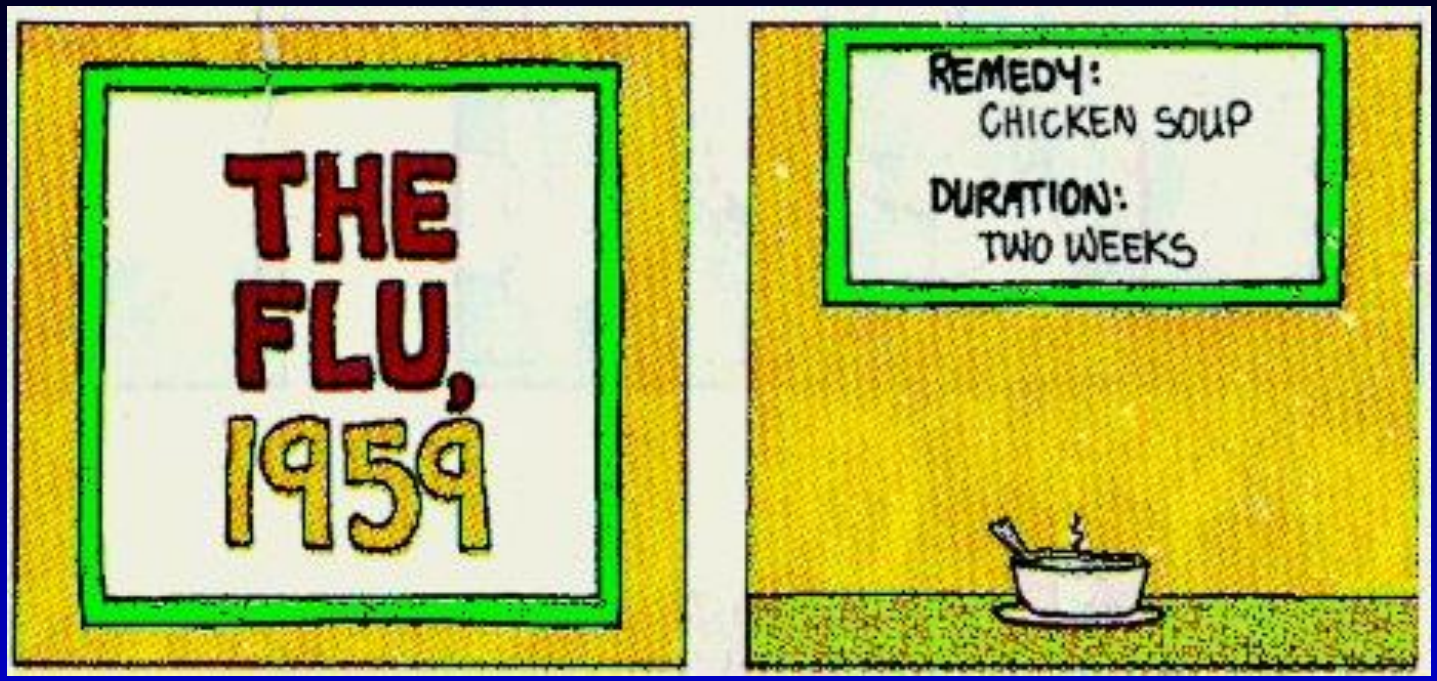


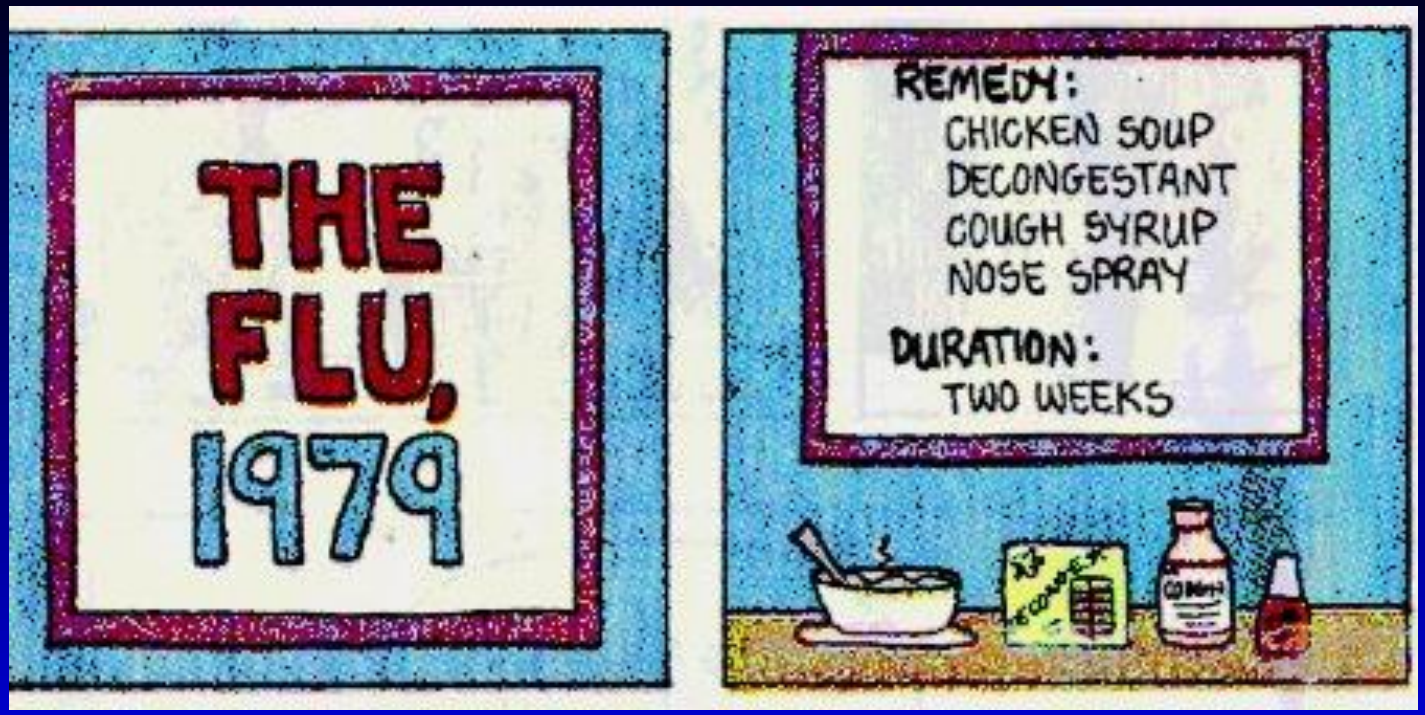



In 1976, afraid that the 1918 virus had reappeared in the form of swine flu, the Federal government instituted a national immunization campaign. When some who had been vaccinated died, President Gerald Ford was immunized in an effort to assuage public fears. Here he receives his flu shot from Dr. William Lukash (*Courtesy of the Gerald R. Ford Library*)



# Antiviral Therapy




THE FLU, 1979
REMEDY:
CHICKEN SOUP
DECONGESTANT
COUGH SYRUP
NOSE SPRAY
DURATION:
TWO WEEKS

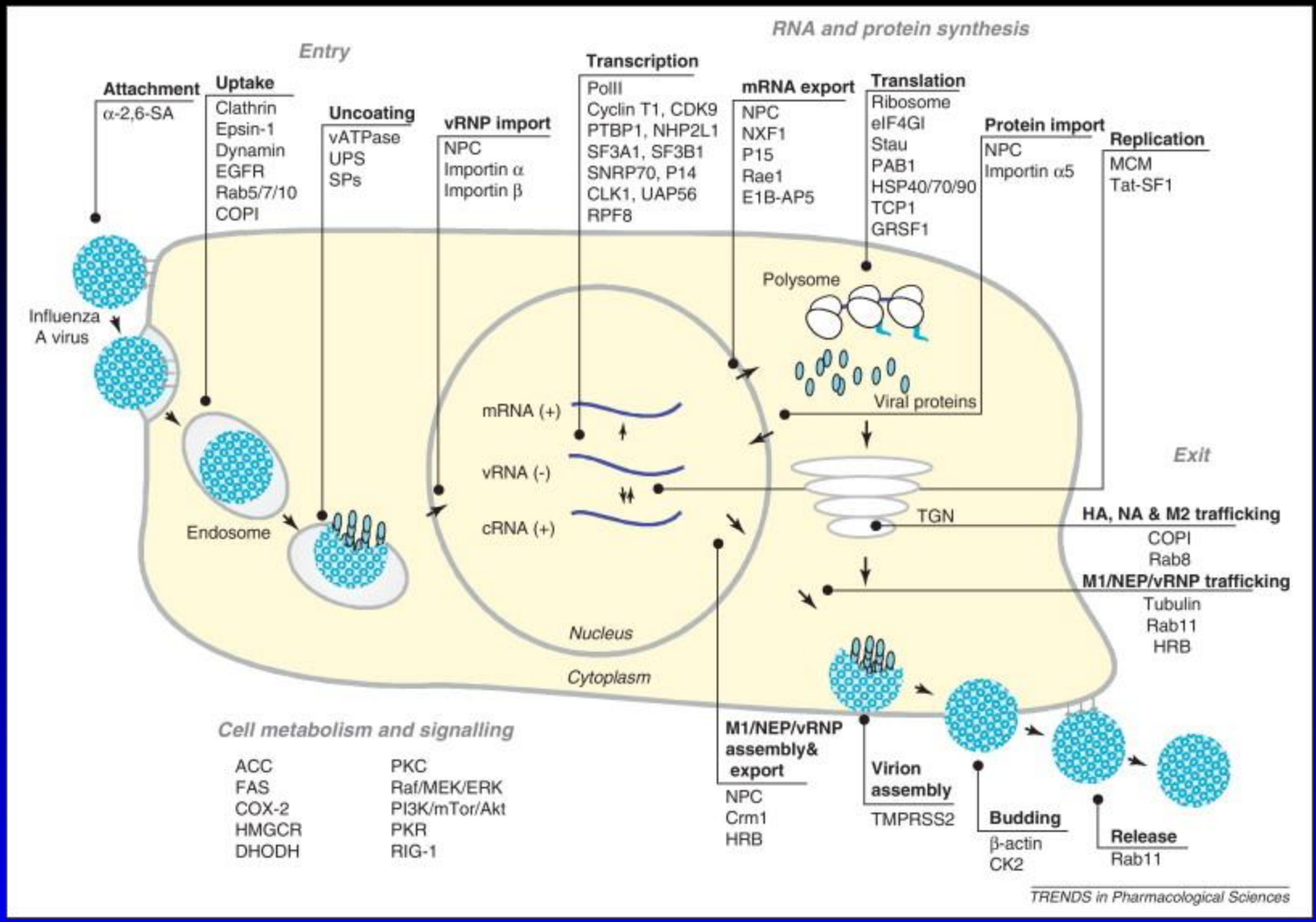

THE FLU, 1999


ANCIENT HEALING FORMULA
Cold and Flu Tea
YOGI TEA
FRONTIER
FRONTIER
FRONTIER
FRONTIER


REMEDY:
CHICKEN SOUP
DECONGESTANT
COUGH SYRUP
NOSE SPRAY
ECHINACEA
GOLDENSEAL
ELDERBERRY TEA
GARLIC EXTRACT
ZINC LOZENGES
GINGERROOT
SELENIUM
GINSENG
SLIPPERY ELM
SPIRULINA
EUCALYPTUS
DURATION: TWO WEEKS
ZINC


HOW DO YOU FEEL, CATHY?
STILL COUGHING, MOM...BUT I THINK I HAVE ALL THE CASH FLUSHED OUT OF MY SYSTEM.

# Influenza: Mechanisms and Targets

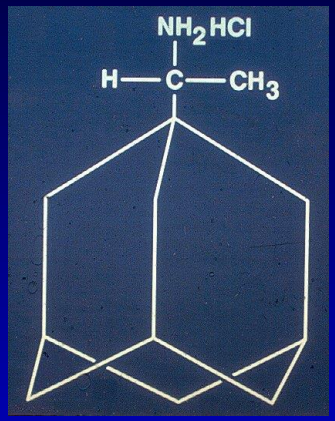


# Previously available medications for influenza

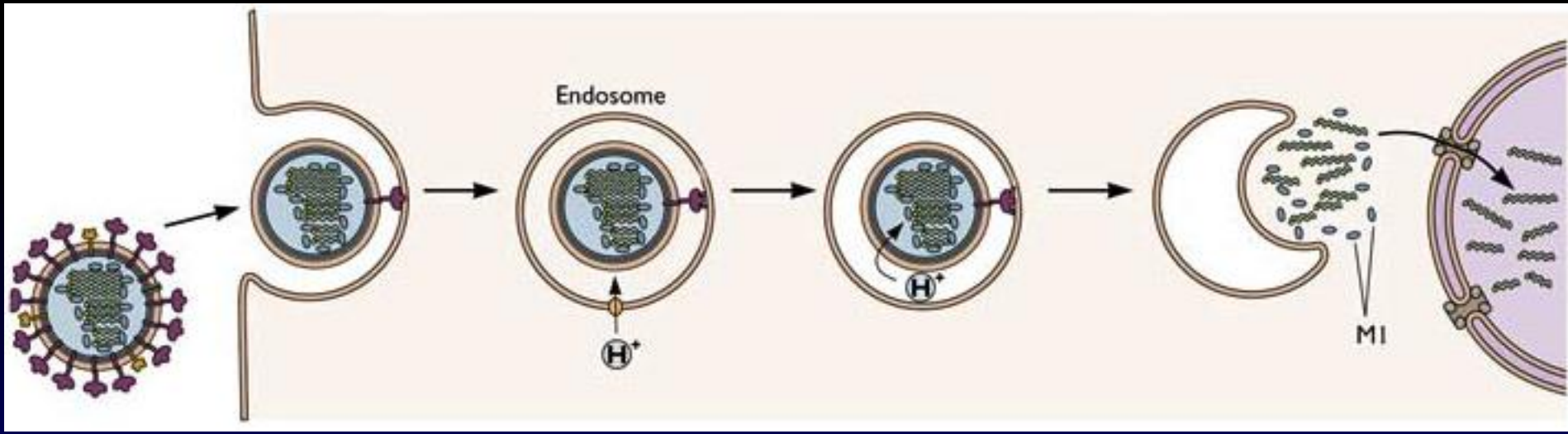
(THAT HAVE EFFICACY)

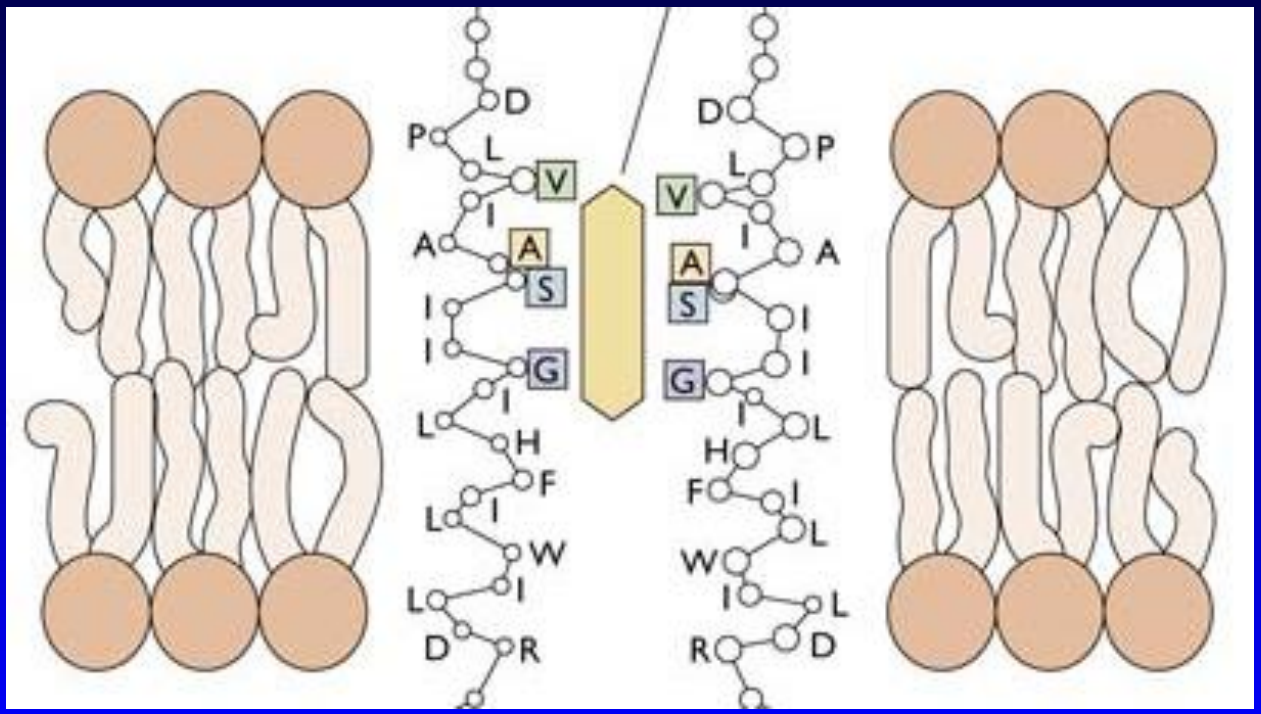
ADAMANTADINES

- Amantadine (Symmetral®)
  - Originally utilized for Parkinson's
  - Prophylactic and therapeutic efficacy
  - Problems with CNS toxicity
- Rimantadine (Flumadine®)
  - Same as amantadine but less CNS toxicity



# Adamantines: How and Why?



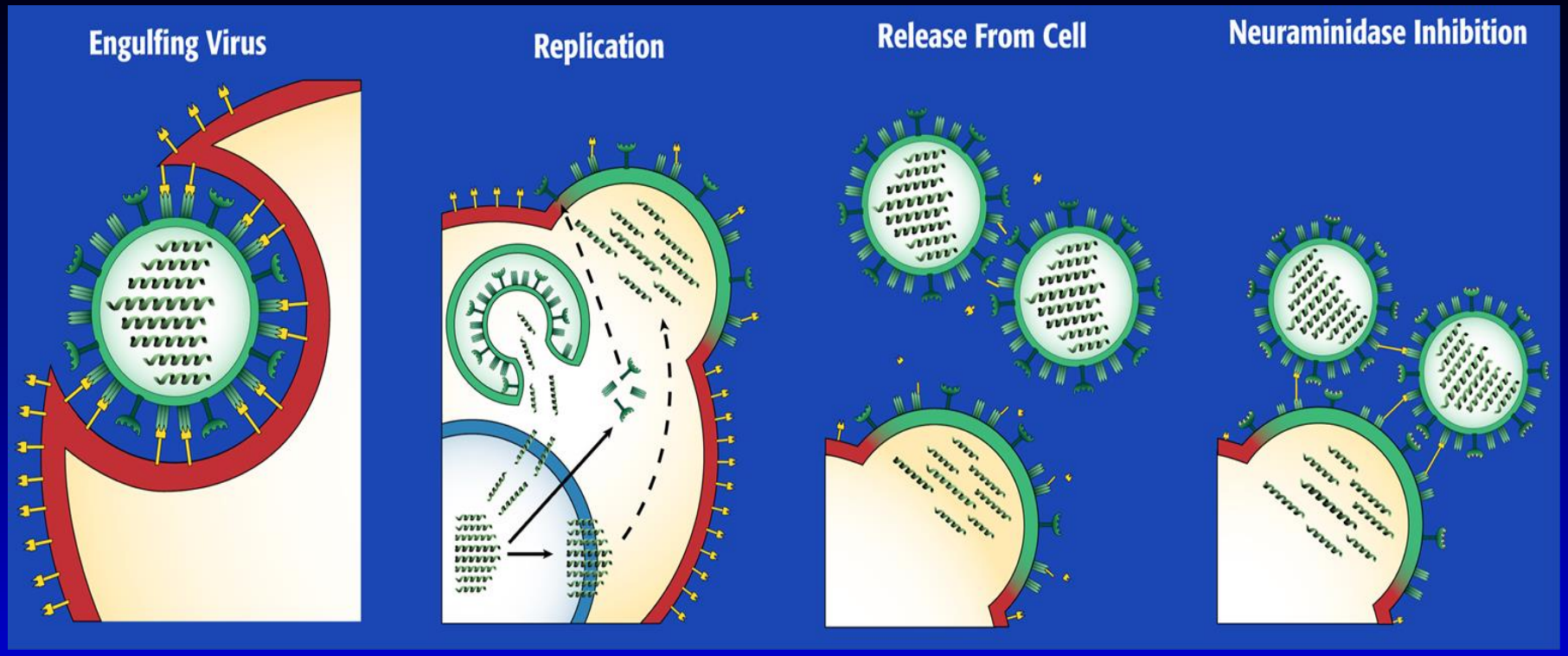

**Problem:**

100% of seasonal H3N2 and 2009 pandemic flu samples tested showed resistance to rimantadine and it is no longer recommended for treatment of influenza A.

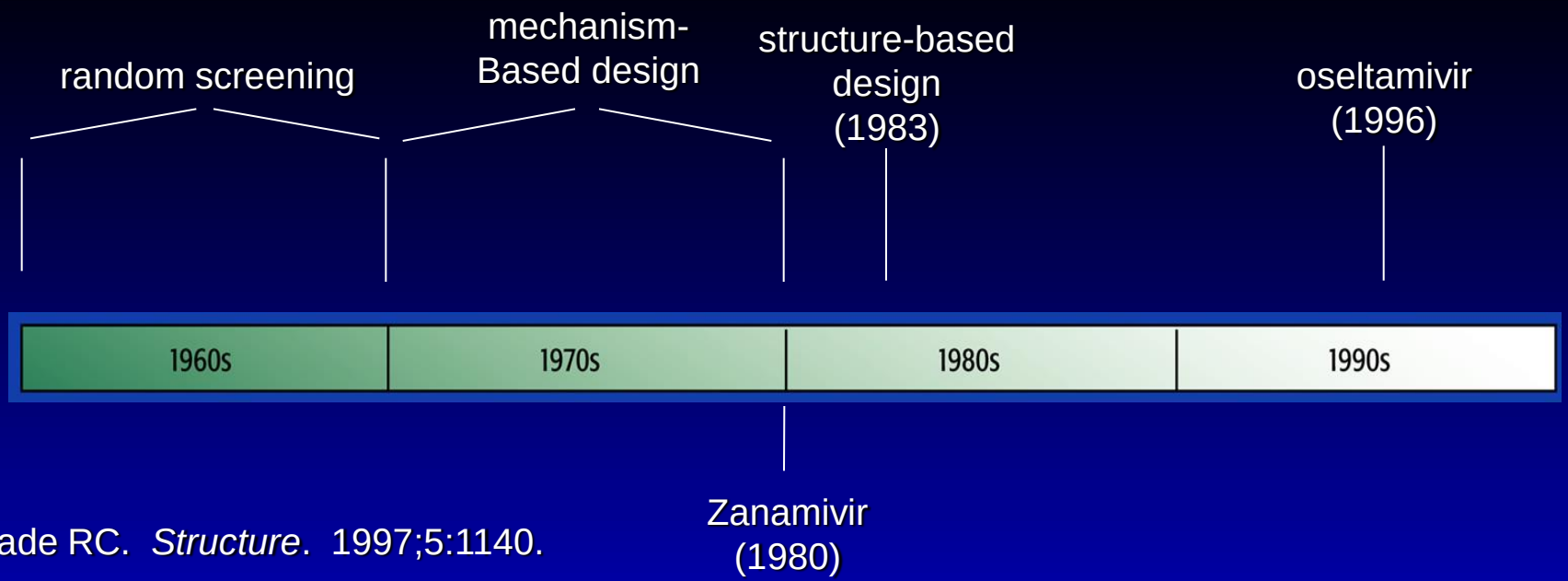
# Amantadine Therapy….. 2000

Fri 1/28/00 Becky: “just thought i would write you and tell you that i am feeling tons better. *dad that medicine was a wonder drug. i was feeling better by wed. night.* now all i have is a stuffy nose but that can't be helped.”

# Neuraminidase Inhibition



# The Search for Influenza Neuraminidase Inhibitors




Wade RC. *Structure*. 1997;5:1140.

# Use of the Oral Neuraminidase Inhibitor Oseltamivir in Experimental Human Influenza

## Randomized Controlled Trials for Prevention and Treatment

Frederick G. Hayden, MD
John J. Treanor, MD
R. Scott Fritz, PhD
Monica Lobo, MD
Robert F. Betts, MD
Madeline Miller, DVM
Nelson Kinnersley, MSc
Roger G. Mills, MD
Penelope Ward, MD
Stephen E. Straus, MD

**Context** Influenza virus neuraminidase is thought to be essential for virus replication in humans; however, to date, available neuraminidase inhibitors are limited to zanamivir, which is topically administered.

**Objective** To determine the safety, tolerability, and antiviral activity of oral neuraminidase inhibitor oseltamivir (GS4104/Ro64-0796) for prevention and the early treatment of influenza in experimentally infected humans.

**Design** Two randomized, double-blind, placebo-controlled trials conducted between June and July 1997.

**Setting** Individual hotel rooms; 2 large US university medical schools.

**Participants** A total of 117 healthy adult volunteers (aged 18-40 years; median age, 21 years) who were susceptible (hemagglutination-inhibition antibody titer ≤1:8).

**Interventions** All subjects were inoculated intranasally with influenza A/Texas/36/91 (H1N1) virus. For the prophylaxis study, oral oseltamivir (100 mg once daily [n = 12], 100 mg twice daily [n = 12], or matching placebo [n = 13], starting 26 hours before virus inoculation) was administered. For the treatment study, the same drug was given (20 mg, 100 mg, or 200 mg twice daily, 200 mg once daily, or matching placebo [n = 16], in each group starting 28 hours after inoculation). All regimens were continued for 5 days.

**Main Outcome Measures** Comparing placebo groups with pooled treatment groups, for prophylaxis, outcomes included frequency of infection and viral shedding; for treatment, viral shedding in titers.

**Results** In the prophylaxis study, 8 (67%) of 12 placebo and 8 (38%) of 21 oseltamivir recipients became infected ($P = .16$; efficacy, 61%); 6 (50%) placebo compared with 0 oseltamivir recipients shed virus ($P < .001$; efficacy, 100%), and 33% of placebo but no oseltamivir recipient had infection-related respiratory illness ($P < .01$). Among infected subjects in the treatment study (n = 69), the viral titer area under the curve of the combined oseltamivir groups (n = 56) was lower (median [interquartile range {IQR}], 80 [23-151] vs 273 [79-306] $\log_{10}$ tissue culture-infective $\text{doses}_{50}$ per milliliter × hour; $P = .02$) than the placebo group (n = 13), and the median (IQR) duration of viral shedding with therapy was reduced from 107 (83-131) to 58 (35-59) hours ($P = .003$). Oseltamivir treatment also reduced symptom scores (median [IQR] score-hours, 225 [97-349] vs 400 [189-645]; $P = .05$), and nasal proinflammatory cytokine levels. Transient mild to moderate nausea after dosing was observed in 15 (17%) of 88 oseltamivir and 2 (7%) of 29 placebo recipients (95% confidence interval for difference, −11% to 68%), which was largely prevented by ingestion with food.

**Conclusions** In these trials, prophylaxis and early treatment with oral oseltamivir were both associated with significant antiviral and clinical effects in experimental human influenza.

*JAMA. 1999;282:1240-1246* www.jama.com

A CONTINUING NEED EXISTS FOR antiviral agents against influenza A and B virus infections for treatment of influenza and as a supplementation to vaccines for prevention. The influenza virus neuraminidase is 1 of 2 major surface glycoproteins of influenza A and B viruses. It cleaves terminal sialic acid (*N*-acetylneuraminic acid) residues from cellular and viral glycoconjugates and is essential for sustained viral replication in vitro[1] and probably also in humans.[2] Inhibition of neuraminidase enzymatic action by antibody, mutation, or chemicals causes virus particles to aggregate at the cell surface and with each other. In addition, neuraminidase prevents inactivation of influenza virus by respiratory mucus and likely facilitates infection of the airway mucosa.[3] The enzyme active site is highly conserved across influenza A and B viruses,[4-6] and several novel antiviral compounds have been designed based on the neuraminidase crystallographic structure.[5,7]

**Author Affiliations and Financial Disclosures** are listed at the end of this article.
**Corresponding Author and Reprints:** Frederick G. Hayden, MD, University of Virginia Health Sciences Center, Department of Internal Medicine, Box 473, Charlottesville, VA 22908 (e-mail: fgh@virginia.edu).

**Roche Receives FDA Approval Of TAMIFLU™, First Pill To Treat The Most Common Strains Of Influenza (A&B)**

**NUTLEY, N.J. – October 27, 1999**

- Jon came home from Bob Evans on 20 Jan c/o sore throat, backache and chills. Temp 101.5 F. Duration sx <6 h.
- Started on neuraminidase inhibitor therapy immediately. Afebrile by morning 21 Jan. Back at work and school

# Neuraminidase Therapy 2001

# Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: A randomized controlled trial.

Treanor JJ, Hayden FG, Vrooman PS, Barbarash R, Bettis R, Riff D, Singh S, Kinnersley N, Ward P, Mills RG.

Reduced illness duration (76.3 h & 74.3 h for 75 mg and 150 mg, respectively, vs 97.0 h for placebo; P = .004

Reduced illness severity (686 score-hours and 629 score-hours for 75 mg and 150 mg, respectively, vs 887 score-hours for placebo; P < .001 for both comparisons).

JAMA 2000 Feb 23;283(8):1016-24.

*Journal of Antimicrobial Chemotherapy* (2003) **51**, 123–129
DOI: 10.1093/jac/dkg007

# Early administration of oral oseltamivir increases the benefits of influenza treatment

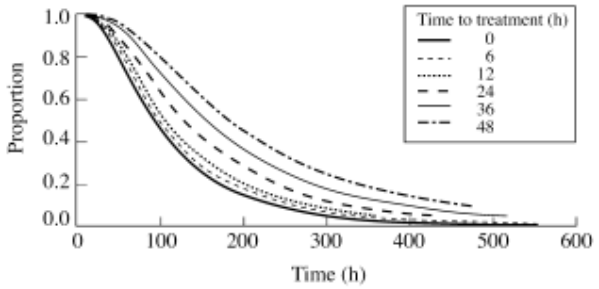



**Figure 1.** The duration of influenza illness is shorter the earlier that oseltamivir treatment 75 mg twice a day for 5 days is initiated (intent-to-treat infected population).

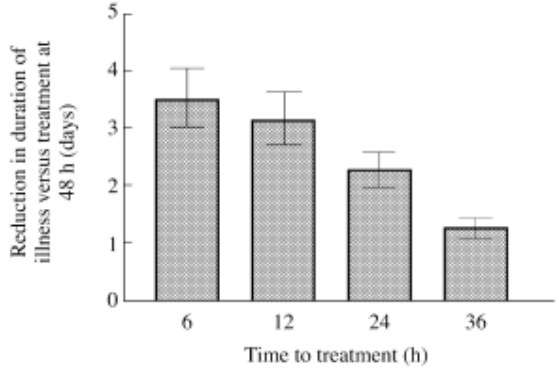



**Figure 2.** The reduction in days of illness duration with earlier treatment with oseltamivir 75 mg twice a day in comparison with delayed treatment at 48 h (intent-to-treat infected population). The data are median and 95% CI.

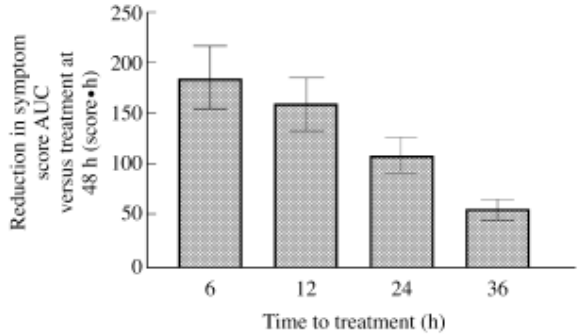



**Figure 3.** The reduction in total symptom score AUC with earlier treatment with oseltamivir 75 mg twice a day in comparison with delayed treatment at 48 h. The data are median and 95% CI.

*Journal of Antimicrobial Chemotherapy* (2003) **51**, 123–129
DOI: 10.1093/jac/dkg007

# Early administration of oral oseltamivir increases the benefits of influenza treatment

*Journal of Antimicrobial Chemotherapy* (2003) **51**, 123–129
DOI: 10.1093/jac/dkg007

# Early administration of oral oseltamivir increases the benefits of influenza treatment

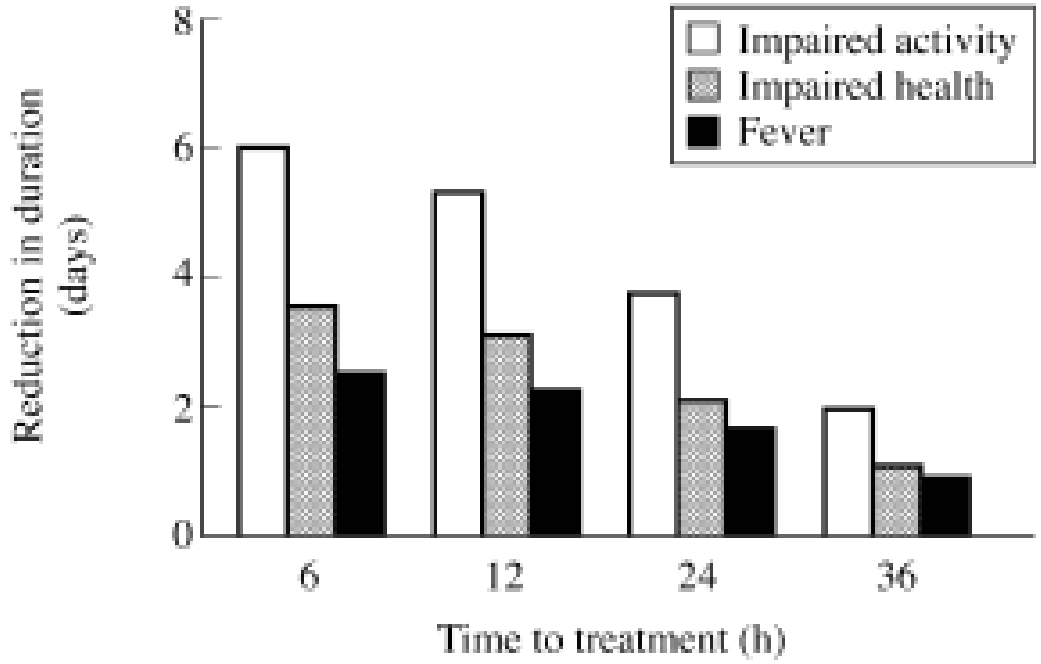



**Figure 4.** The median reduction in days of impaired activity and health and duration of fever with earlier treatment with oseltamivir 75 mg twice a day in comparison with delayed treatment at 48 h (intent-to-treat infected population).

# Clinical Experience in Adults and Children Treated with Intravenous Peramivir for 2009 Influenza A (H1N1) Under an Emergency IND Program in the United States

**Jaime E. Hernandez,[1] Raghavendra Adiga,[4] Robert Armstrong,[5] Jose Bazan,[7] Hector Bonilla,[8] John Bradley,[6] Robin Dretler,[9] Michael G. Ison,[10] Julie E. Mangino,[7] Stacene Maroushek,[11] Avinash K. Shetty,[2] Anna Wald,[12] Christine Ziebold,[13] Jenna Elder,[3] Alan S. Hollister,[1] and William Sheridan,[1] on behalf of the eIND Peramivir Investigators**

[1]ID Clinical Development, Clinical Pharmacology, and Clinical Development, BioCryst Pharmaceuticals, Durham, [2]Department of Pediatric Infectious Diseases, Wake Forest University Health Sciences, Winston-Salem, [3]Pharpoint Research, Wilmington, North Carolina; [4]Liberty Hospital, Liberty, Missouri; [5]Good Samaritan Hospital, San Jose, [6]Division of Infectious Diseases, Rady Children's Hospital, San Diego, California; [7]Division of Infectious Diseases, Department of Internal Medicine Ohio State University Medical Center, Columbus, [8]Division of Infectious Diseases, Department of Internal Medicine, Summa Health System, Akron, Ohio; [9]Dekalb Medical Center, Atlanta, Georgia; [10]Department of Internal Medicine, Division of Infectious Diseases and Organ Transplantation, Northwestern University Feinberg School of Medicine, Chicago, Illinois; [11]Department of Pediatrics, Hennepin County Medical Center, Minneapolis, Minnesota; [12]Department of Medicine, Epidemiology, and Laboratory Medicine, Division of Infectious Diseases, University of Washington Medical Center, Seattle, Washington; and [13]Department of Pediatrics, Division of Infectious Diseases, University of Iowa Children's Hospital, Iowa City, Iowa

**(See the editorial commentary by Jain et al, on pages 707–709.)**

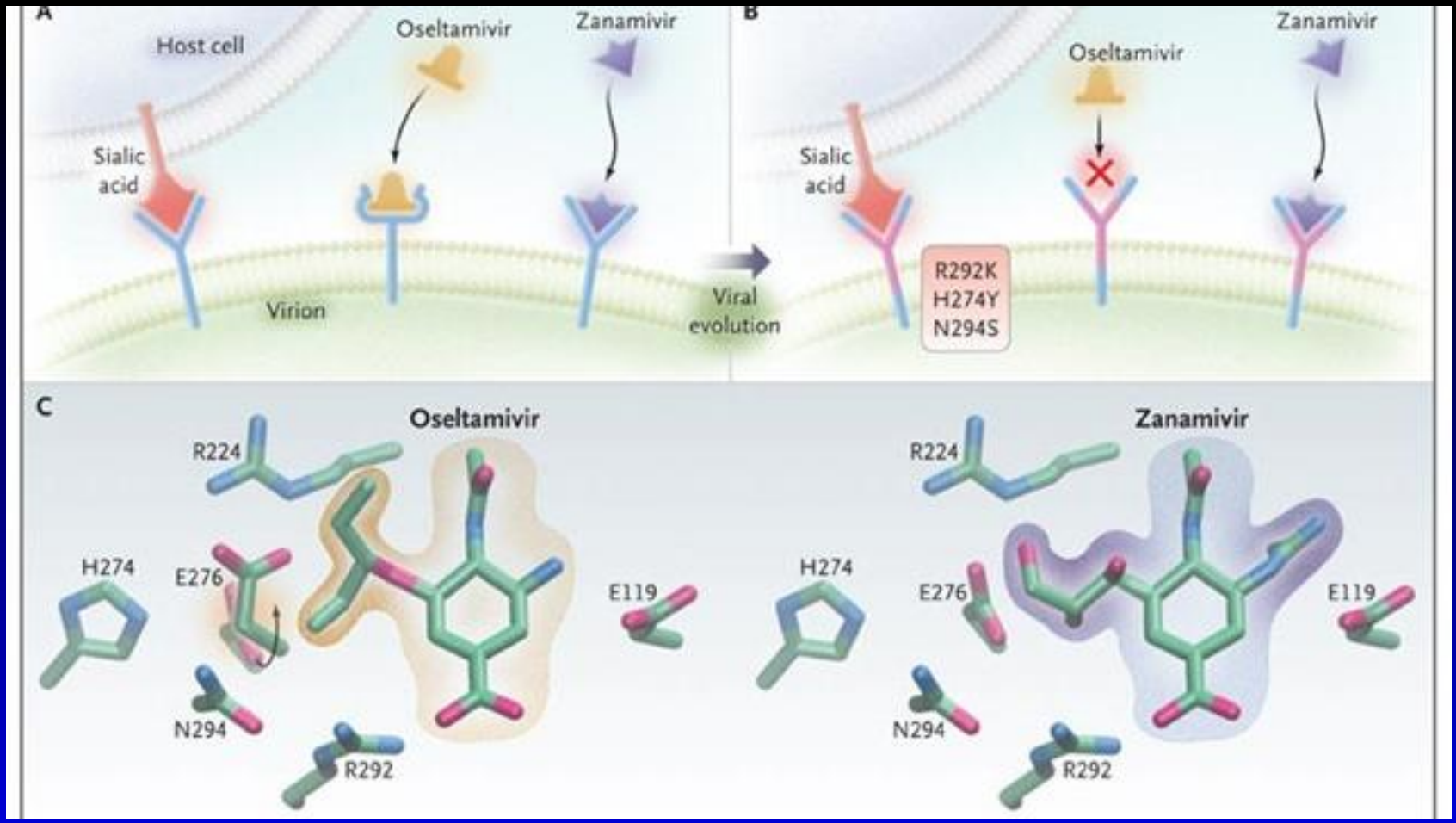
***Background.*** Peramivir, an investigational intravenous neuraminidase inhibitor in Phase 3 trials for hospitalized patients, was made available during the 2009 H1N1 influenza pandemic under the Emergency Investigational New Drug (eIND) regulations. We describe the clinical characteristics and outcomes of all patients for whom peramivir was requested under the eIND.

***Methods.*** After obtaining eIND approval from the Food and Drug Administration and local institutional review board approval, clinicians caring for hospitalized patients with influenza administered intravenous peramivir and collected information on demographic characteristics, clinical characteristics, and outcomes.

***Results.*** From April through October 2009, peramivir was requested for 42 patients and administered to 20 adults and 11 children. At hospitalization, all patients had rapidly progressing, radiographically confirmed viral pneumonia with respiratory failure, and all but 1 patient required mechanical ventilation. In most patients, including 1 person with documented oseltamivir-resistant infection, the illness had progressed despite oseltamivir treatment. Peramivir was administered for 1–14 days (median duration, 10 days). The 14-day, 28-day, and 56-day survival rates were 76.7%, 66.7%, and 59.0%, respectively. Peramivir was generally well tolerated.

***Conclusions.*** Intravenous peramivir was well tolerated and was associated with recovery in most patients hospitalized with severe 2009 H1N1 influenza viral pneumonia and treated under an eIND.

# Resistance to Neuraminidase Inhibitor




January - April, 2012, 16 oseltamivir-resistant 2009 H1N1 viruses were detected

# Oseltamivir Resistance during Treatment of Influenza A (H5N1) Infection

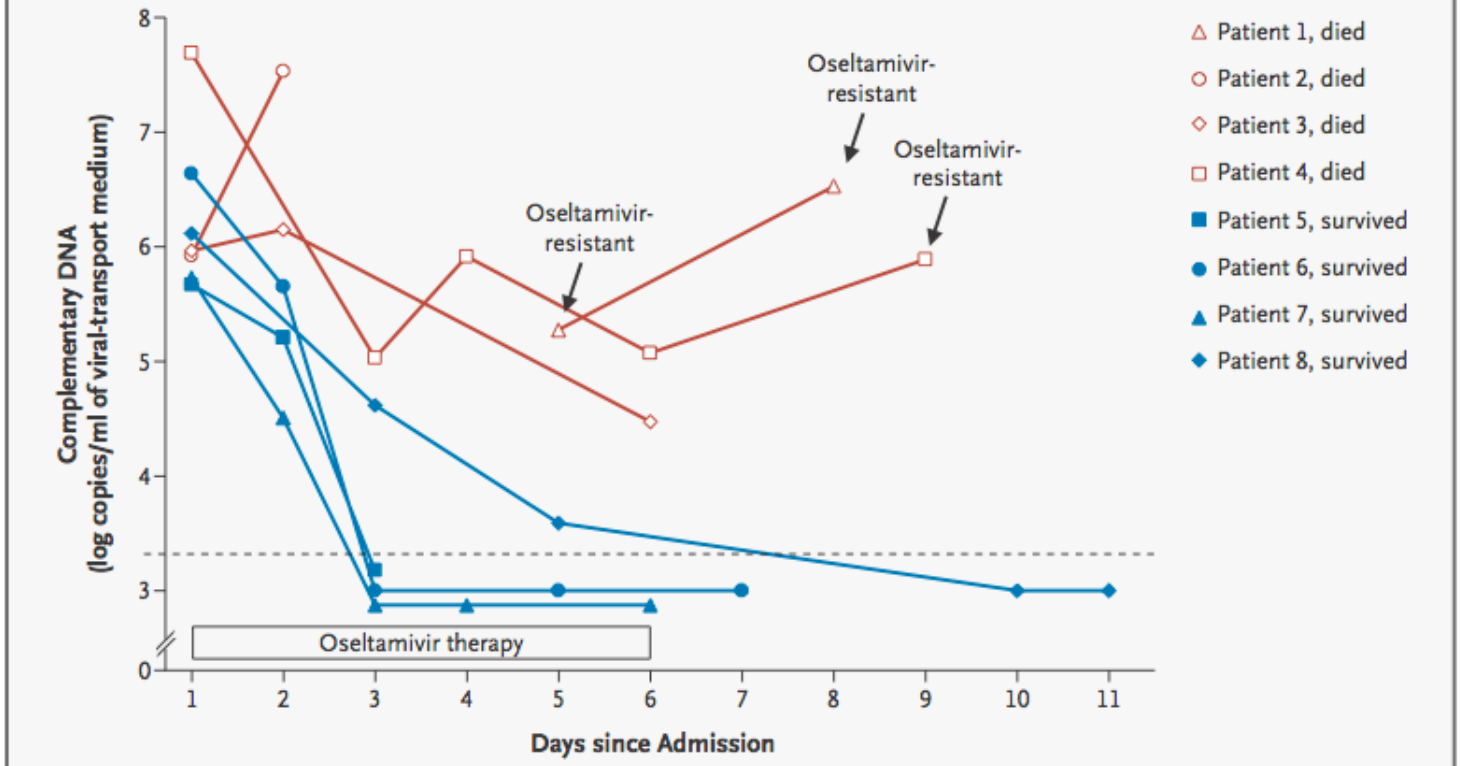



**Figure 3. Influenza A (H5N1) Viral RNA Load in Throat Swabs from Eight Patients.**

Blue lines represent patients who survived influenza A (H5N1) virus infection, and red lines represent patients who died. The dashed horizontal line denotes the limit of detection of the RT-PCR assay. The arrows indicate the specimens from which oseltamivir-resistant influenza A (H5N1) variants were isolated. No virus was isolated from any other specimen besides samples obtained at admission.

de Jong, Menno D. et al. N Engl J Med 2005; 353:2667-2672

## Table 1

Summary of influenza antivirals currently in phase II or III clinical trials

| Host/Viral targeted | Name | Type of antiviral | Specific target | Administration Route | Clinical trial phase | Manufacturer/Research Group |
|---|---|---|---|---|---|---|
| Host targeting | DAS181–F03/F04[a] | Sialidase | Neu5Ac α(2,3)- and Neu5Ac α(2,6)-Gal linkages of sialic acid | Oral, inhalation | I, II | Ansun Biopharma, USA |
| | Nitazoxanide | Thiazolide | Haemagglutinin maturation | Oral, tablet | III | Romark, USA |
| Viral targeting | JNJ-63623872 | PB2 Inhibitor | Small molecule inhibitor of PB2 | Oral, tablet | I, II | Janssen, Belgium |
| | T705 | RNA-dependent RNA polymerase | Purine pseudobase (incorporates in viral RNA) | Oral, tablet | II, III | Toyama, Japan |
| | S-033188 | Cap-dependent endonuclease inhibitor | Small molecule inhibitor of cap-dependent endonuclease | Oral, tablet | III | Shionogi, Japan |
| | CR6261 | Monoclonal antibody | HA stem | Intravenous | I, II | Crucell/Janssen |
| | CR8020 | Monoclonal antibody | HA stem | Intravenous | I, II | Crucell/Janssen |
| | MEDI8852 | Monoclonal antibody | HA stem | Intravenous | I, II | MedImmune, USA |
| | MHAA4549A | Monoclonal antibody | HA stem | Intravenous | II | Genentech, USA |
| | VIS410 | Monoclonal antibody | HA stem | Intravenous | II | Visterra, USA |

[a]F03 and F04 refer to formulations of DAS181. DAS181-F03 and DAS181-F04 are 10 μm particles, however, F04 differs via the addition of $MgSO_4$.

# Traditional Herbal Medicine

Numerous reports of the anti-influenza activity of medicinal plant extracts and plant products

Korrossy-Horwood et al. (P-458) Glycyrrhizin from licorice roots
Tsai et al. (P-450) Platform to screen Chinese herbal medicines
Ehrhardt et al. (O-871) Cystus052, a polypenol-rich extract from pink rockrose

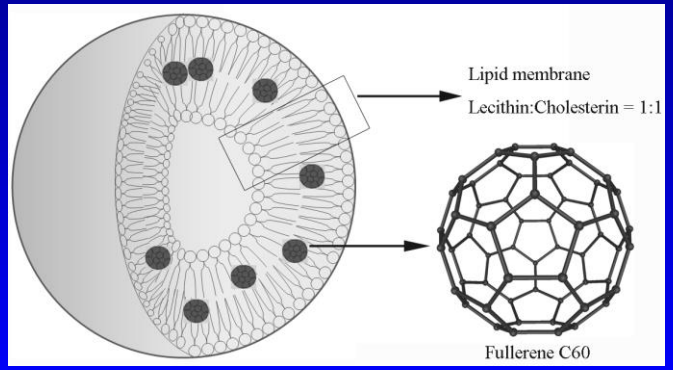
Plant polyphenols possess ant-influenza activity:

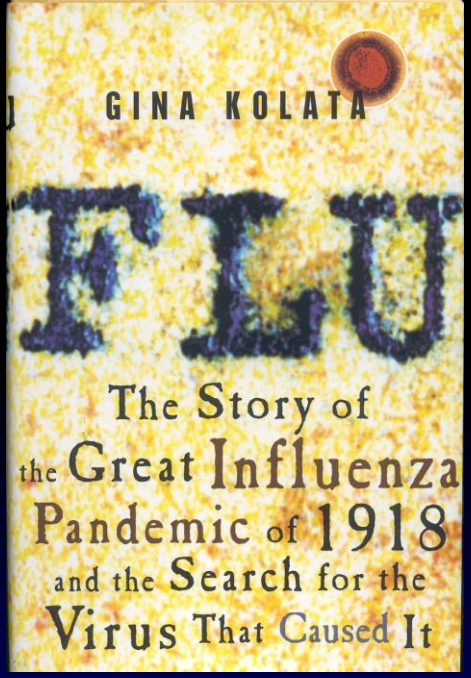
Anti-influenza activity of resveratrol from red grapes:
Improved survival and reduced lung titers in infected mice
(Palamara et al. J.Infect. Dis.191,1719–1729)

Epigallocatechin-3-gallate and theaflavindigallate from green tea:
Unspecific binding of the HA and agglutination of virus particles
(Nakayama et al.; Antiviral Res. 21,289–299)

Chun-Xian Du1, Hai-Rong Xiong, Hong Ji, Qiang Liu, Hong Xiao and Zhan-Qiu Yang The antiviral effect of fullerene-liposome complex against influenza virus (H1N1) *in vivo.* Scientific Research and Essays Vol. 7(6), pp. 706-711, 16 February, 2012

Influenza viruses are important pathogens for humans and the discovery of novel anti-influenza drugs with low toxicity deserves great efforts. Fullerenes have attracted considerable attention in different fields of sciences including antiviral activity. We synthesized a fullerene-liposome incorporated compound and investigated its antiviral activity on influenza virus infection in a mouse model. The results showed that fullerene-liposome could reduce mean pulmonary virus yields, decrease the lung index and eventually significantly prolong mean time to death (MTD) and decrease mortality of H1N1 virus-infected mice. Our data indicated that fullerene-liposome has the anti-influenza activity in vivo at much lower concentrations as compared to the Rimantadine, and then reveals that fullerene-liposome is a promising agent in the clinical therapy of influenza infection with favorable water-solubility and low toxicity.



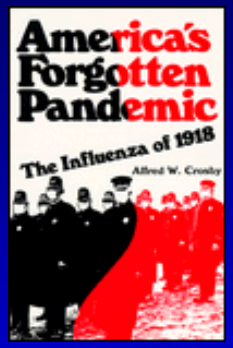


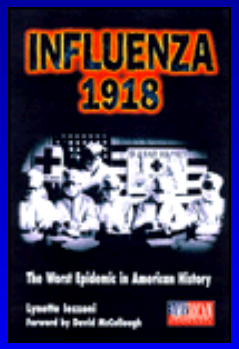

# Flu : The Story of the Great Influenza Pandemic of 1918 and the Search for the Virus That Caused It

by Gina Bari Kolata

Feeling tired, achy, and congested? You'll hope not after reading science writer Gina Kolata's engrossing *Flu*, a fascinating look at the 1918 epidemic that wiped out around 40 million people in less than a year and afflicted more than one of every four Americans. This tragedy, just on the heels of World War I and far more deadly, so traumatized the survivors that few would talk about it afterward. Kolata reports on the scientific investigation of this bizarre outbreak, in particular the attempts to sequence the virus' DNA from tissue samples of victims. She also looks at the social and personal effects of the disease, from improved public health awareness to the loss of productivity. (The disease affected 20- to 40-year-olds disproportionately.)

How could this disease, now almost trivial to healthy young people, have become so virulent? The answer is complex, invoking epidemiology, immunology, and even psychology, but Kolata cuts a swath through medical papers and statistical reports to tell a story of an out-of-control virus exploiting an exhausted world on the brink of transition into modern society. Through letters, interviews, and news reports, she pieces together a cautionary tale that captures the horror of a devastating illness. Research marches onward, but we're still at the mercy of something as simple as the flu. *--Rob Lightner*



# New York Times 3 Feb. 1999

EATING WELL

*Marian Burros*

## So Listen to Mother Already: For Flu, Take Chicken Soup

With more people sneezing and coughing their way through winter in New York than anywhere else in the country, it's helpful to remember that the therapeutic value of "Jewish penicillin" is not a myth.

Chicken soup has been served to billions of cold and flu victims around the globe for centuries, almost always with the same result: the patients feel better. And according to at least one pulmonary specialist, they probably get better sooner, too — even those who would rather lie in bed and moan.

Dr. Irwin Ziment, chief of medicine at Olive View-UCLA Medical Center in Silmar, Calif., and an expert in respiratory pharmacology, is one physician who goes beyond the scientific evidence to site the historical tradition of chicken soup as a legitimate natural remedy. He points out that as early as the 12th century, the rabbi and physician Maimonides wrote that "soup made from an old chicken is of benefit against chronic fevers" and that it "also aids the cough."

It was not until 1978 that researchers at Mount Sinai Medical Center in Miami Beach conducted a randomized flu trial using hot water, cold water and hot chicken soup. The soup proved the most effective liquid in clearing up the nasal passages. The subjects who drank hot water were also helped, but not as much as those who got the soup.

Dr. Ziment said scientists know that cystine, an amino acid plentiful in chicken, is chemically similar to a drug prescribed for bronchitis and other respiratory infections. The drug, acetylcysteine, was originally made from chicken feathers and skin.

Ingredients that make eyes water and noses run also turn out to be very useful in relieving cold and flu symptoms — so chicken soup made with hot, pungent additions works better than blander recipes.

Garlic, hot peppers, wasabi, horseradish, mustard, ginger and even curry powder are spices that will break up congestion and flush out sinuses.

If you can't find someone to dote on you by making soup from scratch, buy the best you can — made with real chickens — and simmer it with one or two of these.

A few years ago, Dr. Stephen Rennard, who specializes in lung diseases at the University of Nebraska Medical Center in Omaha, did another chicken soup study — "without matzoh balls," he cautioned.

Dr. Rennard found that in a test tube at least, chicken soup made by his wife from her grandmother's recipe inhibited the ability of certain white blood cells to promote inflammation involved in some cold symptoms, like irritated airways and phlegm production. "The soup may make you feel better, temporarily, but won't affect the virus itself, which has to run its course," concluded the January 1994 Berkeley Wellness Letter, which published his findings.

Dr. Ziment, isn't so sure. "This is where religion or poetry comes into it," he said. "If people think it makes them feel better, it will help. Placebos work if people believe in them."

Corbis/Bettmann

She was right: Mom's chicken soup was best, but any will help a cold sufferer.

### YOU WILL GET BETTER SOUP

*Time: 40 minutes*

**6 cups rich turkey or chicken stock**
**2 heads garlic, cloves separated and peeled**
**4 to 6 small fresh jalapeños, seeded and coarsely chopped, or less if desired**
**1 tablespoon fresh oregano or 1 teaspoon dried**
**1 tablespoon fresh thyme or 1 teaspoon dried**
**Salt to taste**
**Freshly grated Parmigiano-Reggiano or pepper Jack cheese.**

1. Combine the stock, garlic, jalapeños and herbs in a saucepan, and bring to a boil. Reduce the heat, and simmer until the garlic is very soft, about 30 minutes.

2. Transfer to a blender, and purée until smooth. Season with salt, and serve in mugs, garnished with the Parmigiano-Reggiano or pepper Jack cheese if you're up to it.

**Yield**: 3 or 4 servings.