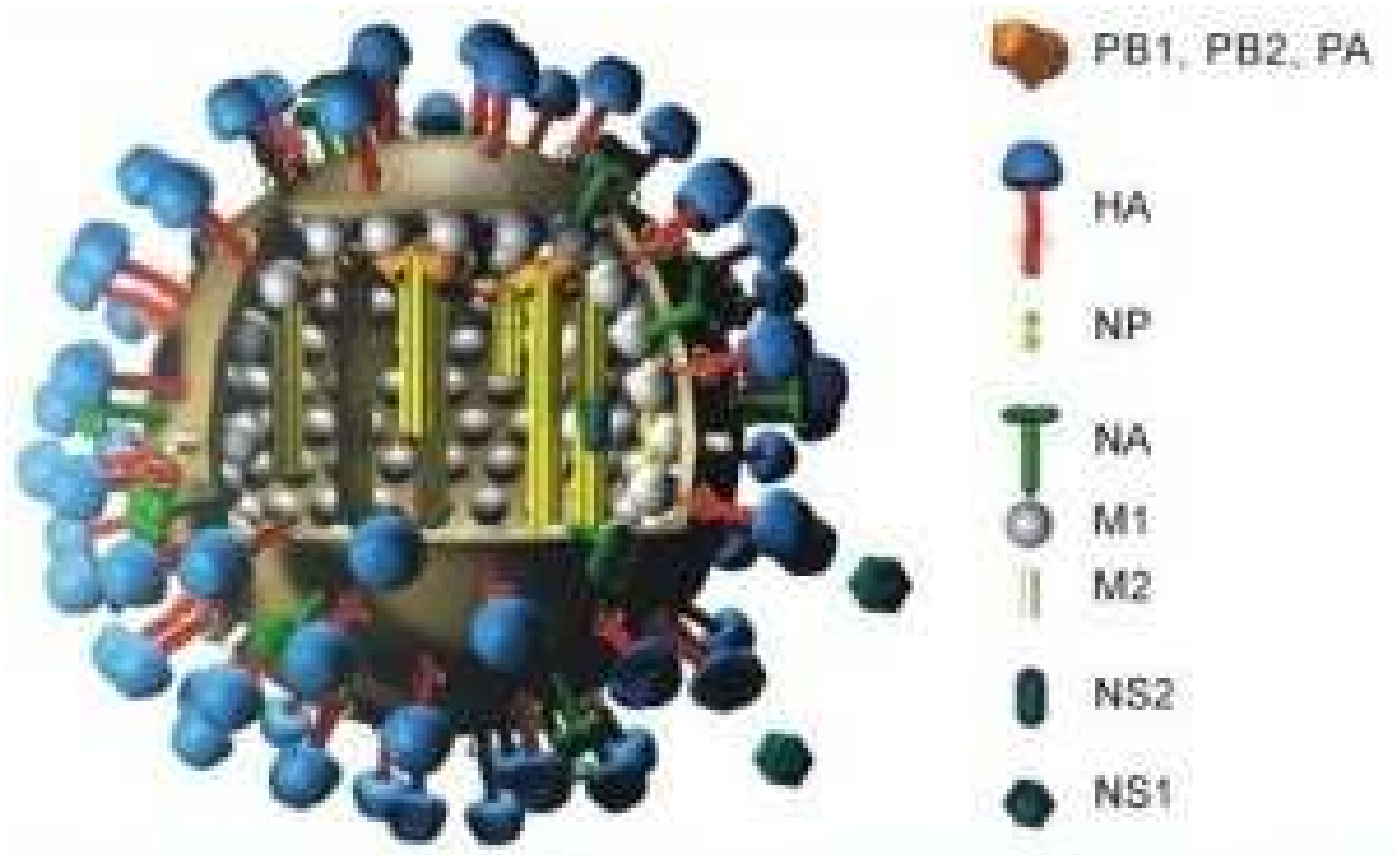


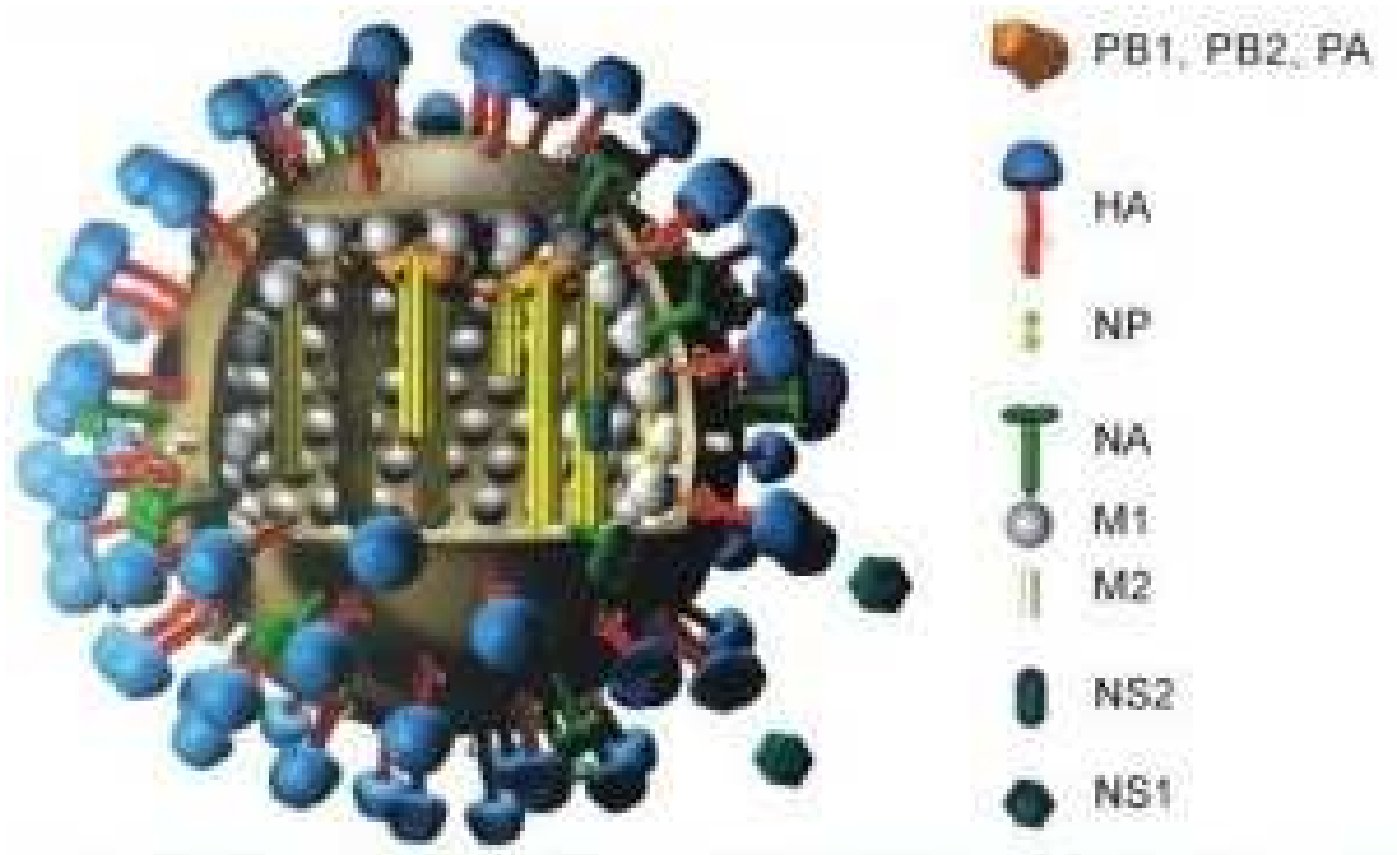
# What is H5N1?



# Definitions

- **Endemic**, means "belonging" or "native to", "characteristic of", or "prevalent in" a particular geography, group, field, area, or environment.  
An **infection** is said to be "endemic" in a human population when that infection is maintained in the population without the need for external inputs.
- An **Epidemic** occurs when new cases of a certain disease occur in a given human population, during a given period, substantially exceed what is "expected," based on recent experience (the number of new cases in the population during a specified period of time is called the "incidence rate").
- A **Pandemic** is an epidemic of infectious disease that is spreading through human populations across a large region; for instance a continent, or even worldwide. Flu pandemics exclude seasonal flu.  
Throughout history there have been a number of pandemics, such as smallpox and tuberculosis. More recent pandemics include HIV and the 2009 flu pandemic.

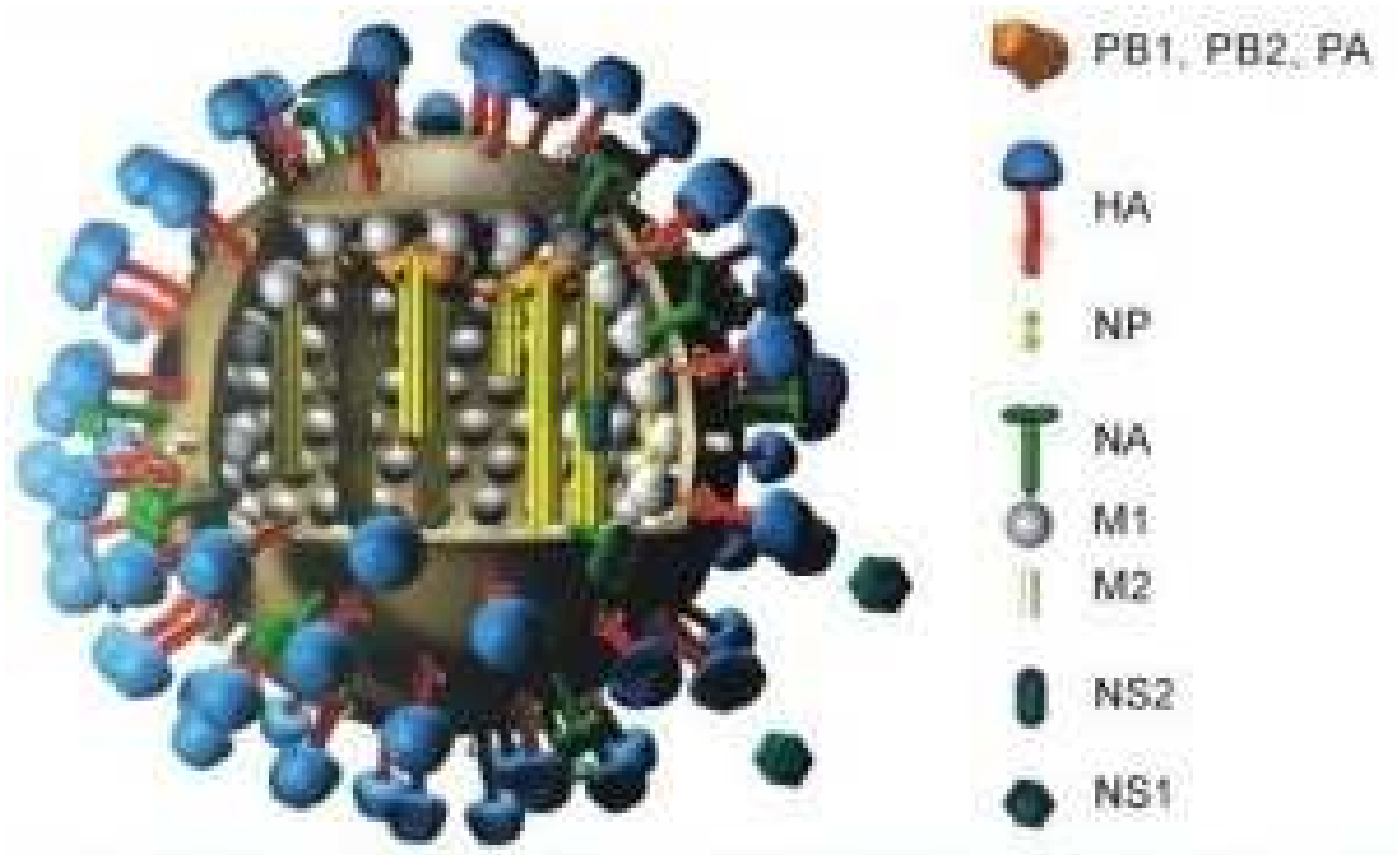
# What is a virus?

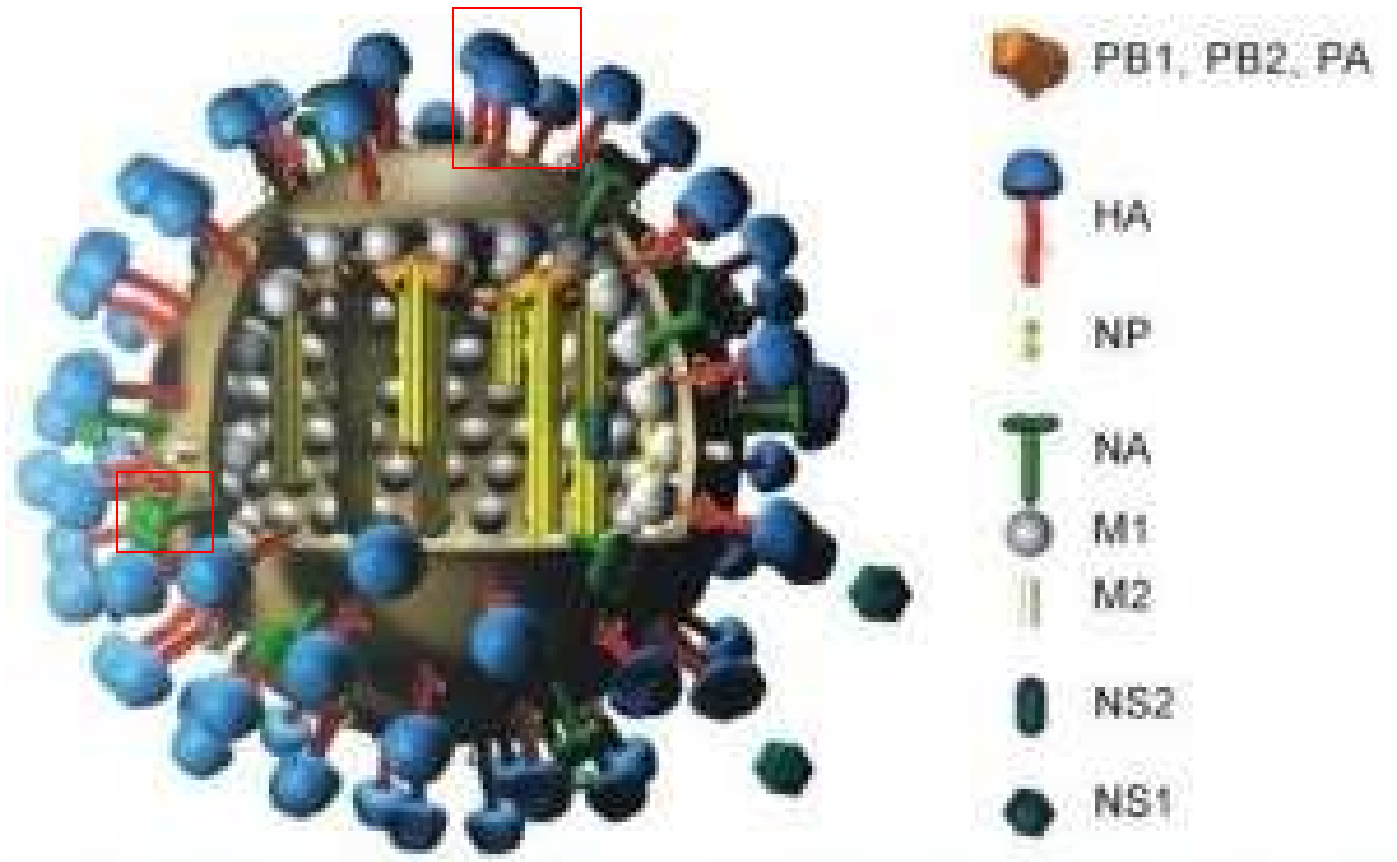


# Virus

- A virus (l. virus, toxin or poison) is a microscopic infectious agent that can only reproduce inside a host cell.  
Viruses infect all types of organisms: from animals and plants to bacteria.  
More than 5,000 types have been described although most types remain undiscovered.  
The study of viruses is known as virology, and is a branch of microbiology.
- Viruses consist of two or three parts:
  - all have genes made from either DNA or RNA, long molecules that carry genetic information;
  - all have a protein coat that protects these genes;
  - some have an envelope of fat that surrounds them when they are outside a cell.

# What is H5N1?

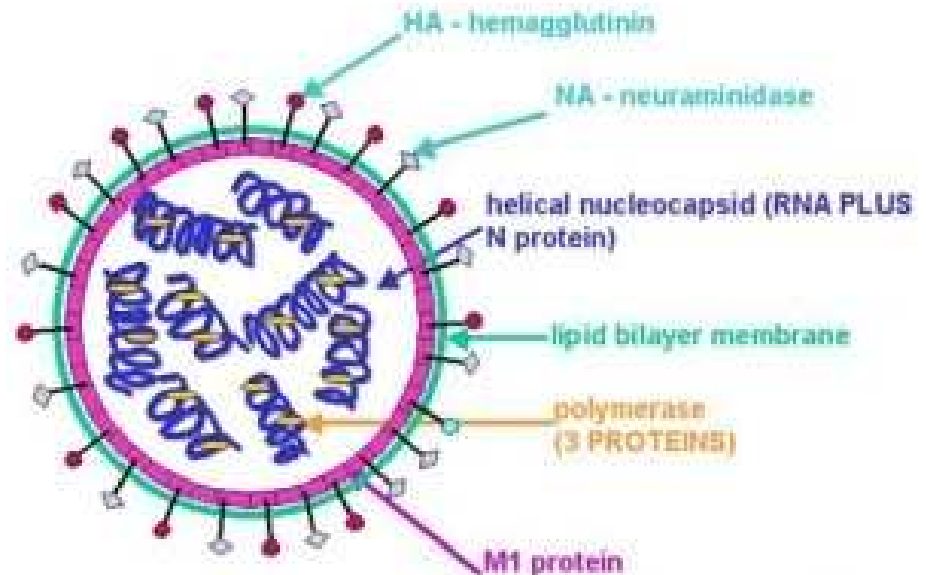




# Influenza A

- Virus subtypes are labeled by an **H number** (for hemagglutinin) and an **N number** (for neuraminidase)
- 16 different HA antigens (H1 to H16) and nine different NA antigens (N1 to N9) for influenza A
- Most known strains are extinct. e.g. - the annual flu subtype H3N2 no longer contains the strain that caused the Hong Kong Flu

## ORTHOMYXOVIRUSES



# Lethality

- Influenza A virus subtypes that have been confirmed in humans, ordered by the number of known human deaths, are:
- H1N1 caused "Spanish Flu"
- H2N2 caused "Asian Flu"
- H3N2 caused "Hong Kong Flu"
- H5N1 - the current pandemic threat
- H7N7 - unusual zoonotic potential
- H1N2 - currently endemic in humans and pigs
- H9N2, H7N2, H7N3, H10N7

## ■ Pandemic Mortality, 1700 to Present Day

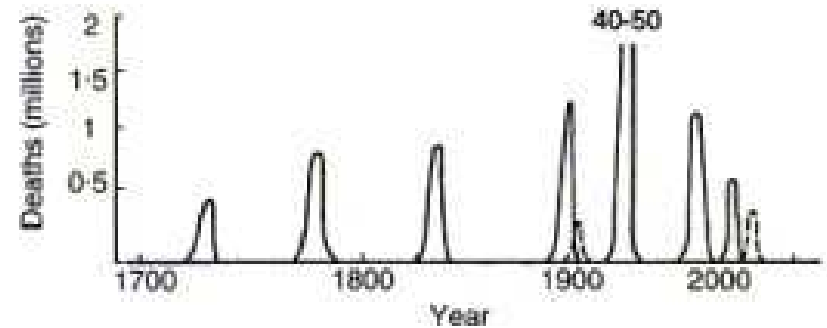
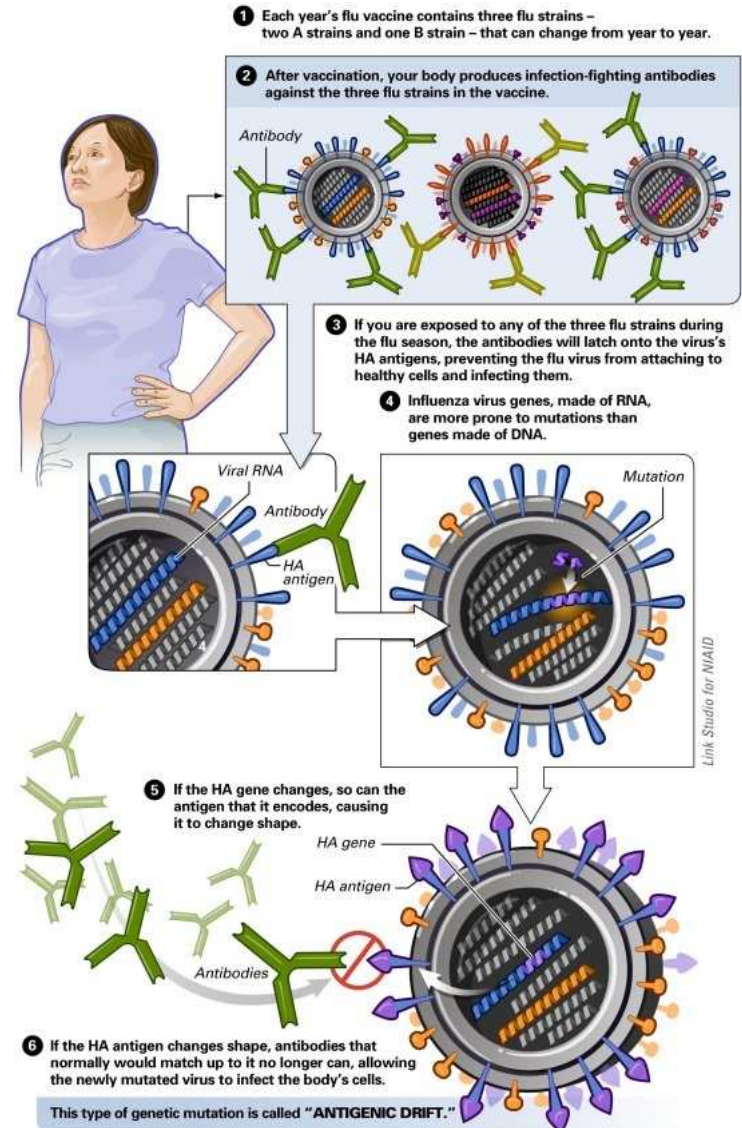


Fig. 2 History of influenza pandemics 1700-2000. Not to exact scale

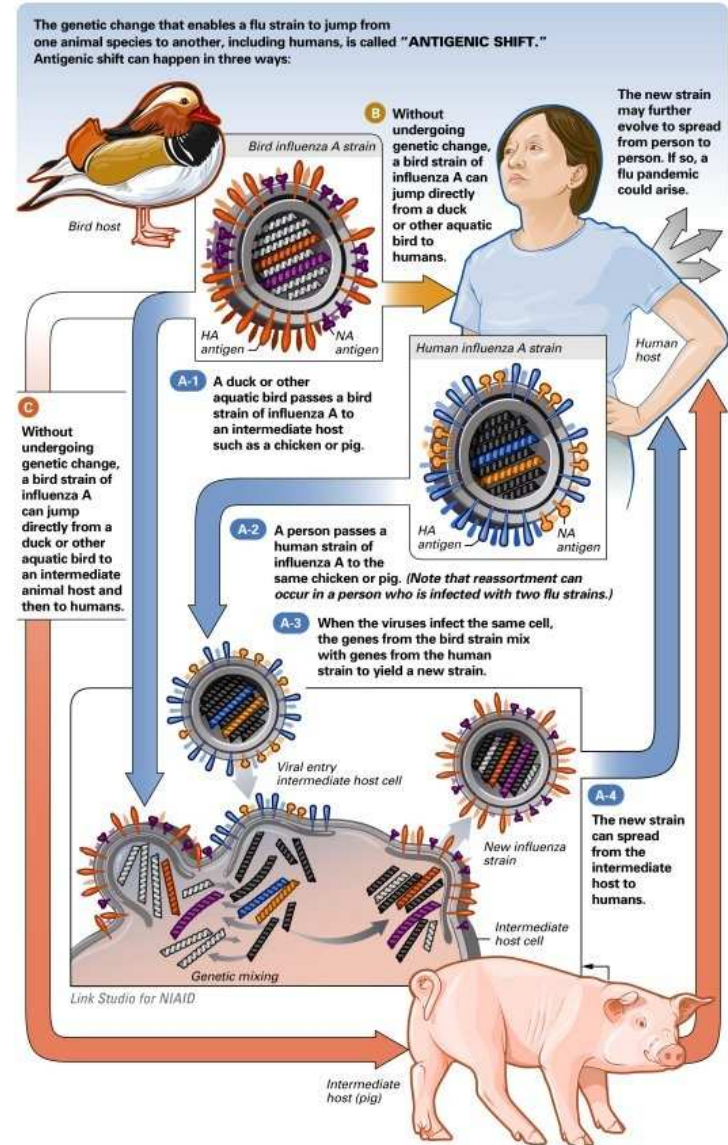
# Antigenic drift

- Most organisms contain built-in “proofreading” and error-correcting systems to ensure accurate genetic replication
- Influenza viruses lack this mechanism, so replication errors go uncorrected. Consequently, their genetic material constantly changes
- These changes, while usually small, are permanent. The new strain that emerges is called an antigenic variant, the process [antigenic drift](#)



# Antigenic shift

- Subtypes of influenza A viruses are able to exchange, or re-assort, genetic material
- The resulting virus contains a new combination of genetic material, part from both parent viruses. This process, called [antigenic shift](#), can lead to dramatic changes from one generation to another
- This process allows viruses to gain the ability to infect other species. There is concern that [H5N1](#) virus might, through antigenic shift, pick up a key piece of genetic material that will allow it to infect humans and spread easily between people



# H5N1

- Subtype of **Influenza A virus** capable of causing illness in many animal species, including humans
- A bird-adapted strain of H5N1, "highly pathogenic avian influenza virus of type A of subtype H5N1", is the causative agent
- One strain is spreading globally. It is **epizootic** and panzootic, killing tens of millions of birds
- Most media references to "bird flu" and H5N1 are about this specific strain



# H5N1

- Believed it might mutate to transmit easily from person to person
- Has mutated by **antigenic drift** into dozens of highly pathogenic varieties, all currently belonging to genotype Z of avian virus H5N1
- Genotype Z emerged through reassortment in 2002 from earlier highly pathogenic genotypes of H5N1 first appearing in **China** in 1996 in birds and in **Hong Kong** in 1997 in humans



# H5N1 transmission

- Infected birds pass on H5N1 through saliva, nasal secretions, and feces
- Other birds may pick up virus through direct contact with excretions or with contact with contaminated surfaces
- Migratory birds may spread it to all parts of the world
- Past outbreaks of avian flu have often originated in crowded conditions in southeast and east Asia, where humans, pigs, and poultry live in close quarters
- In these conditions a virus is more likely to mutate into a form that more easily infects humans



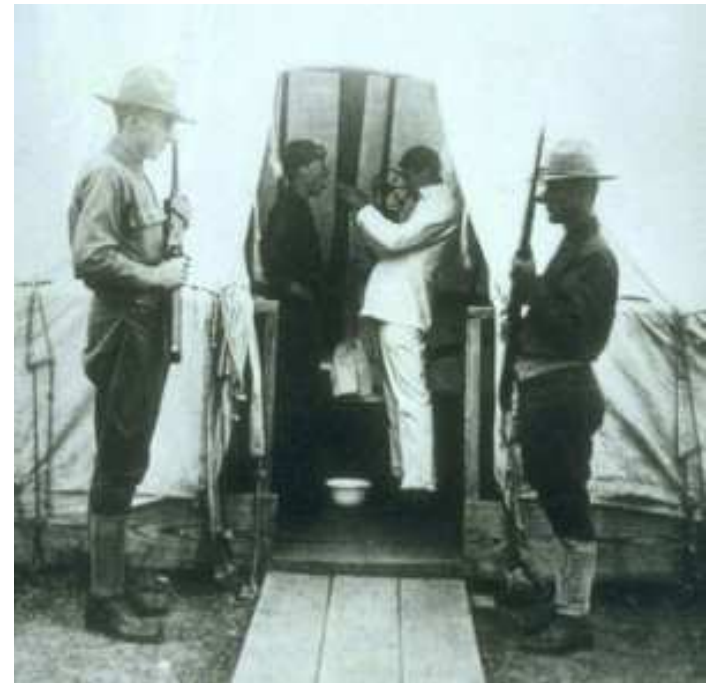
# Epidemiology

- Majority of **H5N1** flu cases have been reported in southeast and east Asia
- Once an outbreak is detected, local authorities often order a mass slaughter of birds or animals affected. If this is done promptly, an outbreak of avian flu may be prevented
- However, the **United Nations** (UN) **World Health Organization** (WHO) has expressed concern that not all countries are reporting outbreaks completely. (China, SARS)



# 1918

- At Fort Riley, Kansas, an Army private reports to the camp hospital before breakfast on March 11 complaining of fever, sore throat, and headache. He is quickly followed by another with similar complaints.
- By noon, the camp's hospital has dealt with over 100 ill soldiers.
- By week's end that number has jumped to 500.



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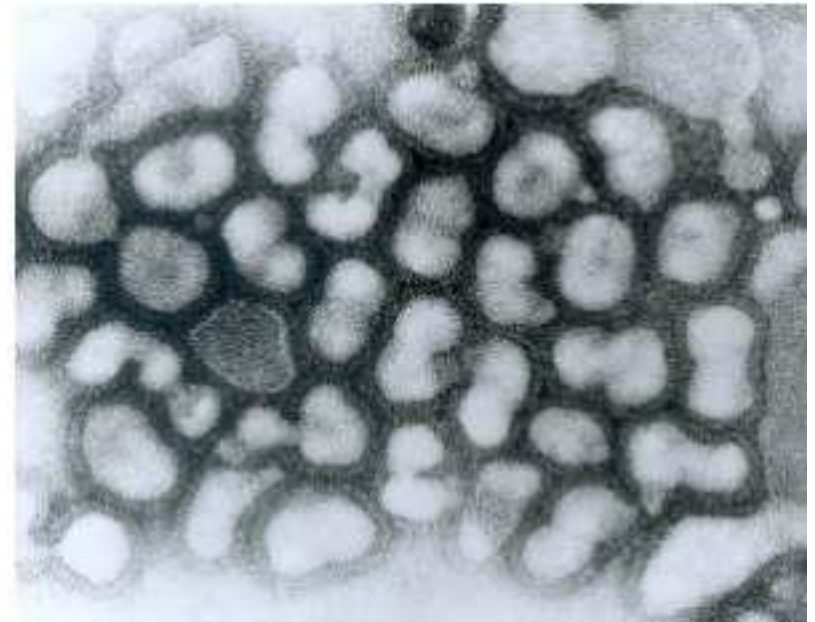
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# 1918

- The **Spanish Flu Pandemic**, *La Grippe Espagnole*, *La Pesadilla*, or the **1918 flu**, was caused by unusually severe, deadly strain of subtype **H1N1** of the species **Influenza A virus**.
- 50 million to 100 million worldwide were killed between 1918 and 1919.
- Called the "**Spanish Flu**" because it received greatest press in Spain which was neither involved in the war nor wartime censorship.



# Pandemics

- Some pandemics are relatively minor and contained quickly
- 1957 pandemic "only" killed a million people.
- Mutation that causes high infection rate may also cause the virus to be less virulent during **passage** from host to host and replication. **Serial passage – Louis Pasteur, 1880**
- 

## ■ Pandemic Mortality, 1700 to Present Day

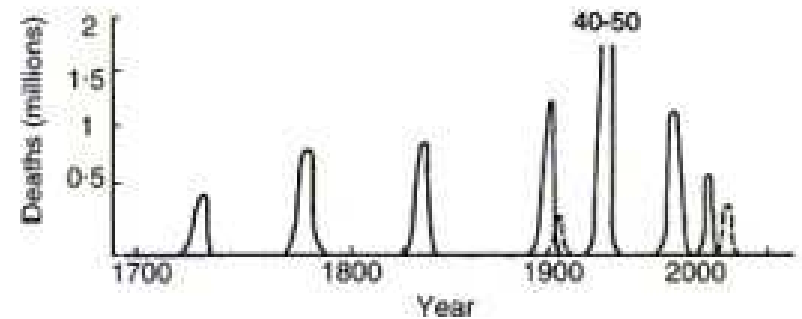
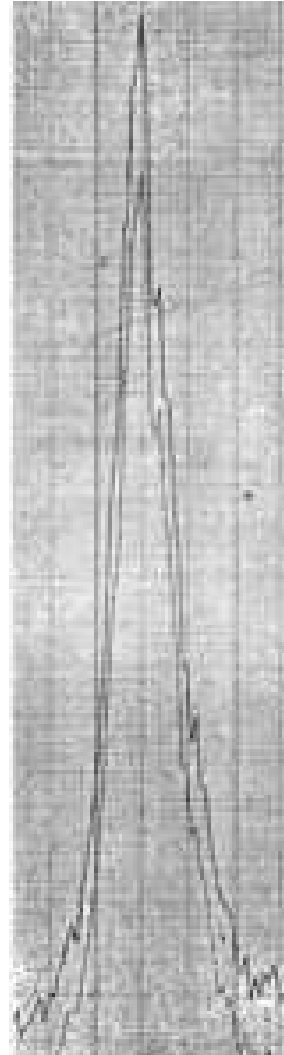


Fig. 2 History of influenza pandemics 1700-2000. Not to exact scale

# Flu pandemics

- Typically come in waves.
- Mortality varies widely.
- 1889 –1890 and 1918 -1919 flu pandemics each came in three or four waves of increasing lethality.
- Within each wave, mortality was greater at beginning.



The massive mortality due to the influenza epidemic in October of 1918 in Kansas. This is representative of what happened in every state in the nation.

# 1918 pandemic

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**Approximate beginning of the epidemic, 1918**

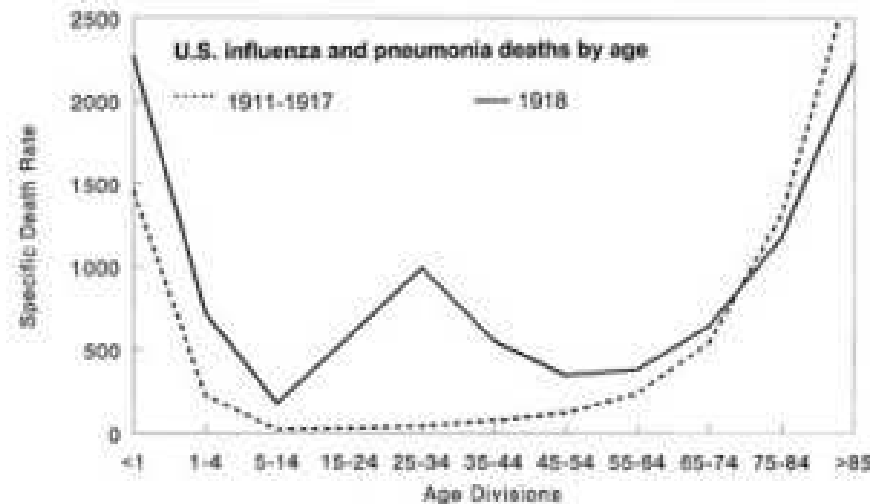


before sept. 14	between sept. 14 - 21	between sept. 21 - 28	between sept. 28 - oct. 5	after oct. 5
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*Source: America's Forgotten Pandemic - The Influenza of 1918 - 1989*

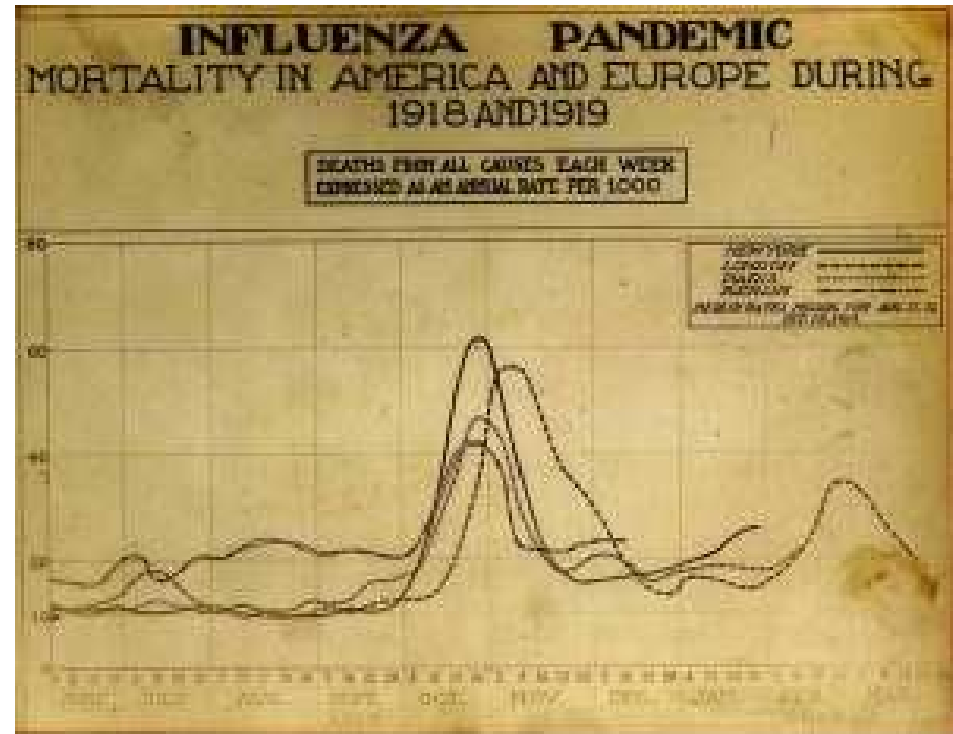
# 1918 pandemic

- Strain killed young and healthy compared to newborns, old and infirm
- Progression from asymptomatic to too feeble to walk within hours; many died the next day
- In fast-progressing cases, mortality was primarily from virus-induced consolidated pneumonia
- Slower-progressing cases featured secondary bacterial pneumonias.
- Some deaths resulted from malnourishment and even animal attacks in overwhelmed communities.



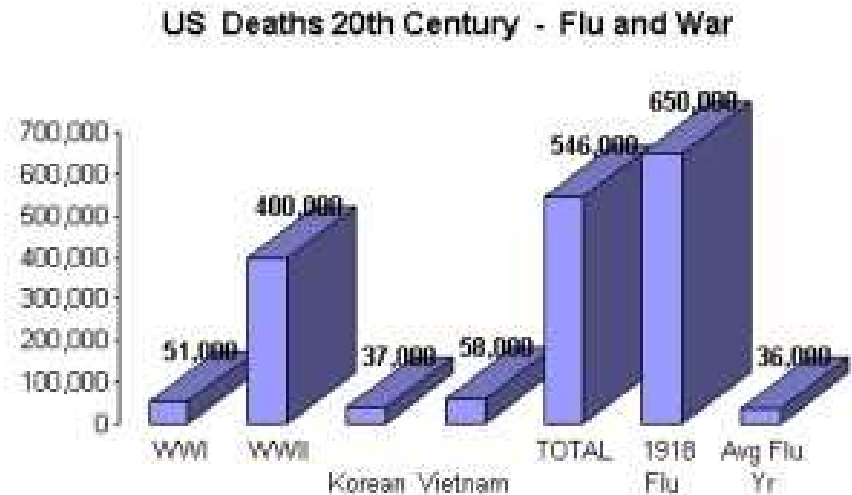
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# 1918 pandemic

- Global mortality is estimated at 2.5 - 5% of the human population.
- 20% of world population infected.
- 25 million died in six months.
- An estimated 17 million died in India, about 5% of the population
- Some estimates place total mortality at 100 million



# 1918 pandemic

In U.S. Army camps:

- case mortality exceeded 5%
- in some circumstances exceeded 10%
- greater than combat losses

In the British Army in India, case mortality was:-

- white troops was 9.6%
- Indian troops 21.9 %

In isolated populations, mortality rates even higher:-

- Fiji islands – 14% of entire population in 16 days
- Labrador and Alaska – 33% of entire native population.



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# 1918 pandemic

- President Woodrow Wilson suffered from the flu in 1919 while negotiating the Treaty of Versailles.
- Public health ordinances enforced to restrain spread:
  - Gauze masks distributed to be worn in public
  - stores could not hold sales
  - funerals limited to 15 minutes
  - Some towns required a signed certificate to enter and railroads would not accept passengers without them
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# Social consequences

- Not enough doctors, hospital rooms, or medical supplies
- Bodies often lay unburied as few were available to deal with them
- Great social disruption and sense of fear
- Selfishness, lack of trust, illegal behavior, and ignorance
- “Horrific disconnect between reassurances and reality destroyed the credibility of those in authority. People felt they had no one to turn to, no one to rely on, no one to trust.”



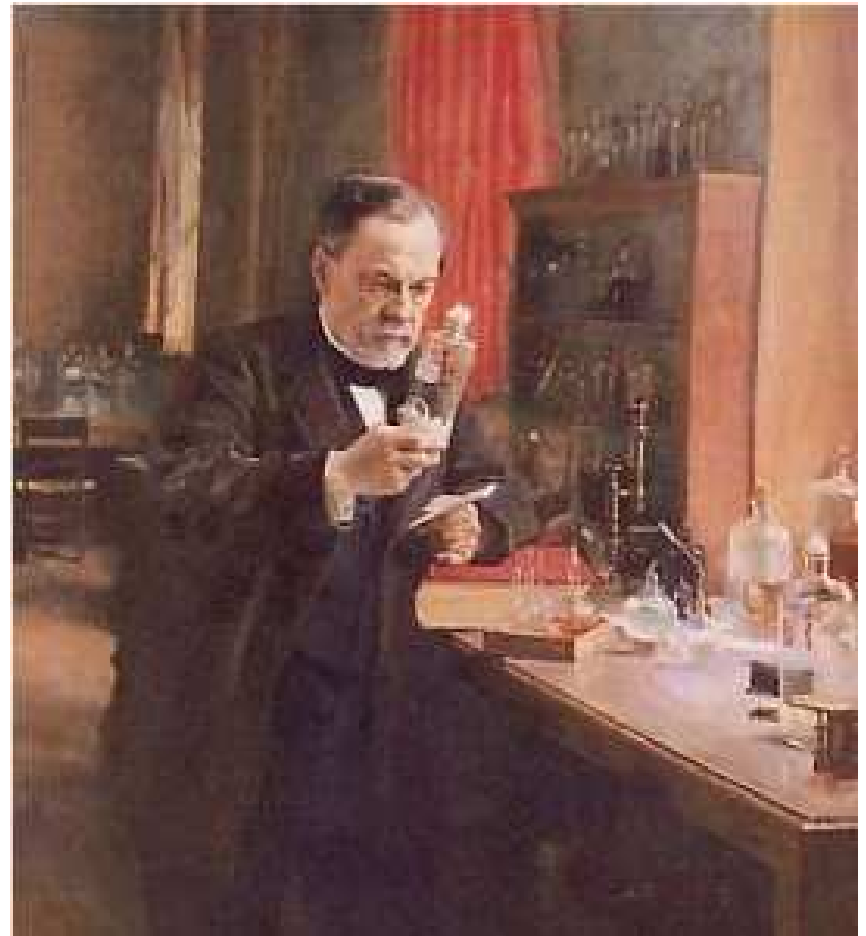
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# What did they think?

- Trench warfare and mustard gas
- Climate, weather and racial composition of cities
- Humidity ([Committee on Atmosphere and Man, 1923](#)).
  
- Germ theory
  - Pasteur and Koch
- Immunity
  - Erlich
  
- “.....in all cases of pneumonia...a sputum study, white blood and differential count, blood culture and urine examinations were made as routine,” ([JAMA, 1/25/1919](#)).
- “.....commonly found were *pneumococcus*, *streptococcus*, *staphylococcus* and *Bacillus influenzae* ([JAMA, 4/12/1919](#)).



# What did they think?

- Nicolle and Le Bailly's experiments suggested that influenza was a "filter-passing virus," (BMJ, 11/2/1918)
- .....bacteria from expectoration of an influenza patient were filtered out and injected into eyes and nose of two monkeys who developed fever and marked depression
- .....Filtrate was later administered to a volunteer subcutaneously who developed typical signs of influenza
- .....inoculated person developed influenza from filtrate since no one else in their quarters developed influenza (JAMA, 12/28/1918)



The Nobel Prize in Physiology or  
Medicine 1928

"for his work on typhus"



**Charles Jules Henri Nicolle**

France

Institut Pasteur  
Tunis

b. 1866  
d. 1936

# What did they think?

- [O'Malley and Hartman](#) ..... serum of convalescent patients, utilizing the contained antibodies to boost immune system of sick patients
- Other treatments were "digitalis," and the administration of isotonic glucose and sodium bicarbonate intravenously which was done in military camps ([JAMA, 1/4/1919](#))
- Ross and Hund .....neutralize or render the intoxicant inert...and prevent the blood destruction with its destructive leukopenia and lessened coagulability," ([JAMA, 3/1/1919](#))



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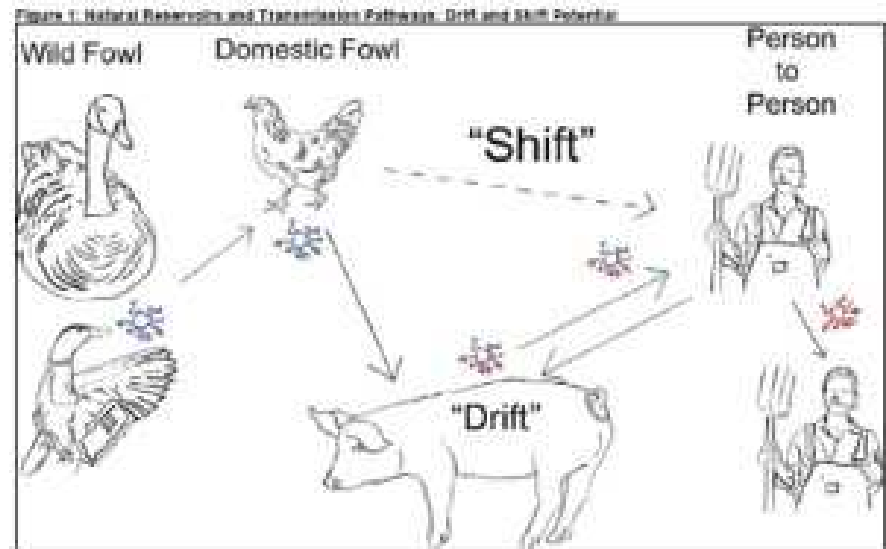
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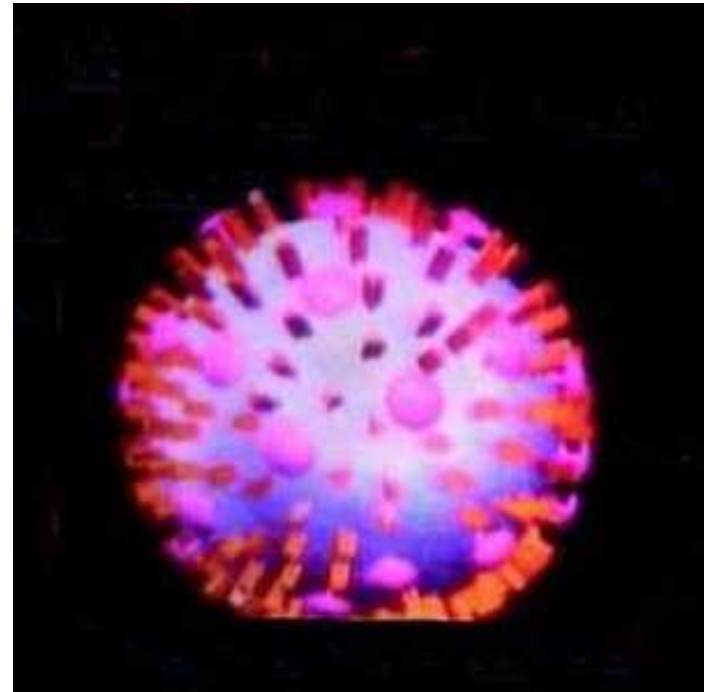
# Modern theory

- ..... the virus strain originated at **Fort Riley, Kansas**, by two **genetic mechanisms** — **genetic drift** and **antigenic shift** — in viruses in poultry and swine which the fort bred for local consumption
- However, recent reconstruction of the virus suggests that it **could** have jumped directly from birds to humans, without traveling through swine



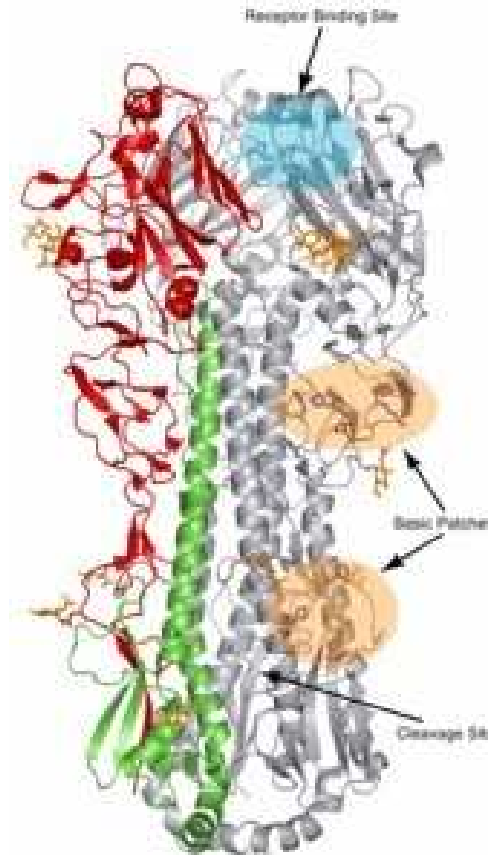
# Virus recovery

- **1998** - The **Molecular Pathology** Division of the US **Armed Forces Institute of Pathology** (AFIP) recovers samples of 1918 influenza from Native Alaskan woman buried in permafrost near Brevig Mission, Alaska, which lost about 85% of population in November 1918
- One of four recovered samples contained viable viral genetic material which was inactivated with **guanidinium** thiocyanate before transport



# Progress

- **October 2002:** AFIP together with Mount Sinai School of Medicine creates a virus much more deadly to mice than other constructs containing genes from contemporary influenza virus.
- **February 6, 2004:** synthesis of hemagglutinin protein responsible for 1918 outbreak of Spanish Flu reported. DNA from a lung sample from an Inuit woman buried in the tundra spliced with a number of preserved samples from American soldiers of the First World War.



# Reconstruction

- **October 5, 2005** - researchers announce that the genetic sequence of the 1918 flu strain has been reconstructed using historic tissue samples

