

# The "Flu"

Influenza is a viral infection of the lungs characterized by fever, cough, and severe muscle aches. In the elderly and infirm, it is a major cause of disability and death (often as a result of secondary infection of the lungs by bacteria). Even in the young and healthy, influenza produces a prostrating disease of a few days duration and one not soon forgotten.

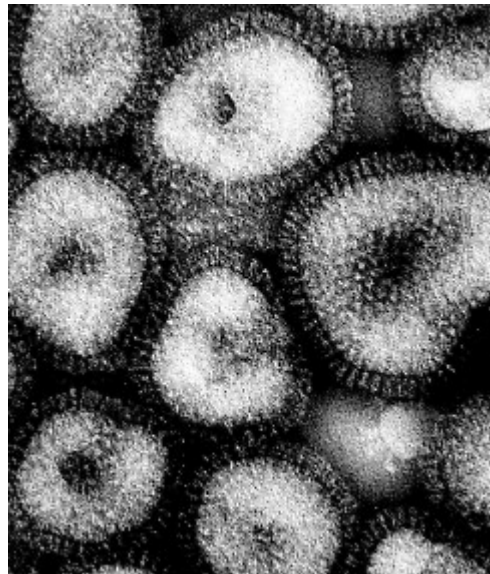
Influenza is **not**

- a case of low fever and sniffles that keeps you home in bed for a day
- a gastrointestinal upset ("stomach flu")

Influenza was responsible for the most devastating plague in human history — the ["Spanish" flu](#) that swept around the world in 1918 killing 675,000 people in the U.S. and an estimated 20–50 million people worldwide. (A disease that attacks a large fraction of the population in every region of the world is called a **pandemic**.) (It is uncertain where the flu first appeared, but it certainly wasn't in Spain.)

No one at the time even knew what disease agent was causing the pandemic. Not until 1930 (in pigs) and 1933 (in humans) was it established that influenza is caused by a **virus**.

This electron micrograph (courtesy of Dr. K. G. Murti) shows several influenza virus particles (at a magnification of about 265,000x). The surface projections are molecules of **hemagglutinin** and **neuraminidase** (see below).



There are three types of influenza:

- **Influenza C**

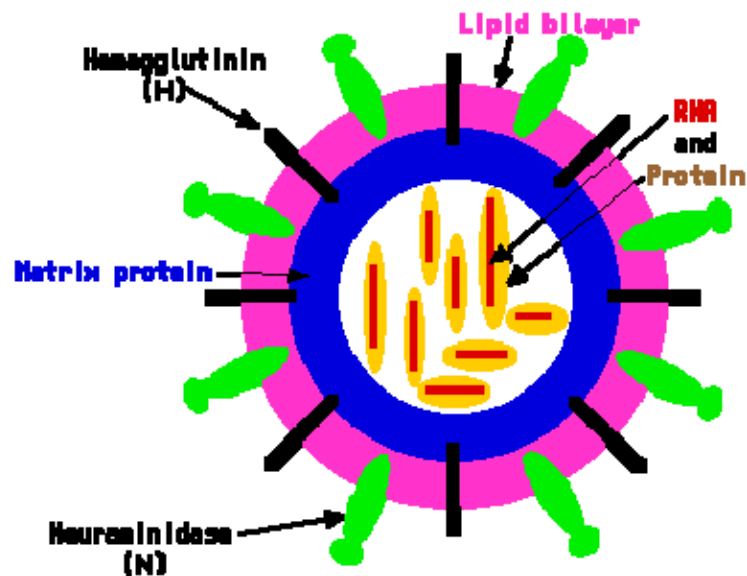
Common but seldom causes disease symptoms

- **Influenza B**

Often causes sporadic outbreaks of illness, especially in residential communities like nursing homes.

- **Influenza A**

Responsible for regular outbreaks, including the one of 1918. Influenza A viruses also infect domestic animals (pigs, horses, chickens, ducks) and some wild birds.



## The Influenza A Virus

The influenza A [virion](#) is

- a globular particle (about 100 nm in diameter)
- sheathed in a **lipid bilayer** (derived from the plasma membrane of its host)
- Studded in the lipid bilayer are two integral membrane proteins
  - some 500 molecules of **hemagglutinin** ("H") and
  - some 100 molecules of **neuraminidase** ("N")
- Within the lipid bilayer are
  - some 3000 molecules of **matrix protein**
  - **8 pieces of RNA**

Each of the 8 RNA molecules is associated with

- many copies of a **nucleoprotein**
- several molecules of the three subunits of its **RNA polymerase**
- some "non-structural" protein molecules of uncertain function

## The Genes of Influenza A

The 8 RNA molecules:

**1. The HA gene.** It encodes the **hemagglutinin**. 3 distinct hemagglutinins, **H1**, **H2**, and **H3**) are found in human infections; 13 others have been found in animal flu viruses.

2. The **NA gene**. It encodes the **neuraminidase**. 2 different neuraminidases (**N1** and **N2**) have been found in human viruses; 7 others in other animals.
3. The **NP gene** encodes the **nucleoprotein**. Influenza A, B, and C viruses have different nucleoproteins.
4. The **M gene** encodes two proteins (using different [reading frames](#) of the RNA): a **matrix protein** (M1 — shown in blue) and an ion channel (M2) spanning the lipid bilayer (not shown).
5. The **NS gene** encodes two different **non-structural proteins** (also by using different reading frames). These are found in the cytoplasm of the infected cell but not within the virion itself.
6. – 8. one RNA molecule (**PA, PB1, PB2**) for each of the 3 subunits of the **RNA polymerase**

## The Disease



The influenza virus invades cells of the respiratory passages.

- Its hemagglutinin molecules bind to sialic acid residues on the [glycoproteins](#) exposed at the surface of the epithelial cells of the host [respiratory system](#).
- The virus is engulfed by [receptor mediated endocytosis](#).
- The drop in [pH](#) in the [endosome](#) (endocytic vesicle) produces a change in the structure of the viral hemagglutinin enabling it to
- fuse the viral membrane with the vesicle membrane.
- This exposes the contents of the virus to the cytosol.
- The RNA enter the nucleus of the cell where fresh copies are made.
- These return to the cytosol where some serve as mRNA molecules to be translated into the proteins of fresh virus particles.
- Fresh virus buds off from the plasma membrane of the cell (aided by the neuraminidase) thus
- spreading the infection to new cells.

The result is a viral pneumonia. It usually does not kill the patient (the [1918 pandemic](#) was an exception; some victims died within hours) but does expose the lungs to infection by various bacterial invaders that can be lethal. Before the discovery of the flu virus, the bacterium [Hemophilus influenzae](#) was so often associated with the disease that it gave it its name.

# Pandemics and Antigenic Shift

Two pandemics of influenza have swept the world since the "Spanish" flu of 1918.

- The "Asian" flu pandemic of 1957 and
- the "Hong Kong" flu pandemic of 1968.

(The pandemic of 1957 probably made more people sick than the one of 1918. But the availability of antibiotics to treat the secondary infections, that are the usual cause of death, resulted in a much lower death rate.)

The hemagglutinin of the 1918 flu virus was H1, its neuraminidase was N1, so it is designated as an H1N1 "subtype". Here are some others.

## Some strains of influenza A

Date	Strain	Subtype	Notes
1918		H1N1	pandemic of <a href="#">"Spanish" flu</a>
1957	A/Singapore/57	H2N2	pandemic of "Asian" flu
1962	A/Japan/62	H2N2	epidemic
1964	A/Taiwan/64	H2N2	epidemic
1968	A/Aichi/68	H3N2	pandemic of "Hong Kong" flu
1976	A/New Jersey/76	H1N1	swine flu in recruits

These data suggest that flu pandemics occur when the virus acquires a **new** hemagglutinin and/or neuraminidase. For this reason, when an H1N1 virus appeared in a few recruits at Fort Dix in New Jersey in 1976, it triggered a massive immunization program (which turned out not to be needed). However, another H1N1 virus appeared the following year causing the "Russian" flu. Because most people born before the Asian flu pandemic of 1957 had been exposed to the H1N1 viruses circulating before, the Russian flu primarily affected children and young adults.

Where do the new H or N molecules come from?

Birds appear to be the source. Both the H2 that appeared in 1957 and the H3 that appeared in 1968 came from influenza viruses circulating in birds.

The encoding of H and N by separate RNA molecules probably facilitates the **reassortment** of these genes in animals **simultaneously infected by two different subtypes**. For example, H3N1 virus has been recovered from pigs simultaneously infected with swine flu virus (H1N1) and the Hong King virus (H3N2). Probably reassortment can also occur in humans with dual infections.

# Epidemics and Antigenic Drift

No antigenic shifts occurred between 1957 ("Asian") and 1968 ("Hong Kong"). So what accounts for the epidemics of 1962 and 1964?

Missense mutations in the **hemagglutinin (H) gene**.

Flu infections create a strong antibody response. After a pandemic or major epidemic, most people will be immune to the virus strain that caused it. The flu virus has two options:

- wait until a new crop of susceptible young people comes along
- change the epitopes on the hemagglutinin molecule (and, to a lesser degree, the neuraminidase) so that they are no longer recognized by the antibodies circulating in the bodies of previous victims.
  - By 1972, the H3 molecules of the circulating strains differed in 18 amino acids from the original "Hong Kong" strain
  - By 1975, the difference had increased to 29 amino acids.

The gradual accumulation of new epitopes on the H (and N) molecules of flu viruses is called **antigenic drift**. Spontaneous mutations in the H (or N) gene give their owners a selective advantage as the host population becomes increasingly immune to the earlier strains.

## Flu Vaccines

Although a case of the flu elicits a strong immune response against the strain that caused it, the speed with which new strains arise by antigenic drift soon leaves one susceptible to a new infection. Immunization with flu vaccines has proved moderately helpful in reducing the size and severity of new epidemics.

Some vaccines incorporate inactivated virus particles; others use the purified hemagglutinin. Both types incorporate antigens from the three major strains in circulation, currently:

- an A strain of the H1N1 subtype
- an A strain of the H3N2 subtype and
- a B strain.

Because of antigenic drift, the strains used must be changed periodically as new strains emerge that are no longer controlled by people's residual immunity.

Strains used in vaccines for the flu seasons shown. \* As the 86–87 season got underway, it was found that A/Chile/83 no longer gave protection so A/Taiwan/86 was offered as a second shot late in that season.

<b>Season</b>	<b>H1N1</b>	<b>H3N2</b>	<b>Type B</b>
86–87	A/Chile/83*	A/Mississippi/85	B/Ann Arbor/86
87–88	A/Taiwan/86	A/Leningrad/86	B/Ann Arbor/86
88–89	A/Taiwan/86	A/Sichuan/87	B/Victoria/87
89–90	A/Taiwan/86	A/Shanghai/87	B/Yamagata/88
90–91	A/Taiwan/86	A/Shanghai/89	B/Yamagata/88
91–92	A/Taiwan/86	A/Beijing/89	B/Panama/90
92–93	A/Texas/91	A/Beijing/89	B/Panama/90
93–94	unchanged	unchanged	unchanged
94–95	A/Texas/91	A/Shandong/93	B/Panama/90
95–96	A/Texas/91	A/Johannesburg/94	B/Harbin/94
96–97	A/Texas/91	A/Nanchang/95	B/Harbin/94
97–98	A/Johannesburg/96	A/Nanchang/95	B/Harbin/94
98–99	A/Beijing/95	A/Sydney/97	B/Beijing/93
99–00	A/Beijing/95	A/Sydney/97	B/Yamanashi/98
00–01	A/New Caledonia/99	A/Panama/99	B/Yamanashi/98
01–02	A/New Caledonia/99	A/Panama/99	B/Victoria/00 or similar
02–03	A/New Caledonia/99	A/Moscow/99	B/Hong Kong/2001
03–04	A/New Caledonia/99	A/Moscow/99	B/Hong Kong/2001
04–05	A/New Caledonia/99	A/Fujian/2002	B/Shanghai/2002
05–06	A/New Caledonia/99	A/California/2004	B/Shanghai/2002
06–07	A/New Caledonia/99	A/Wisconsin/2005	B/Malaysia/2004
07–08	A/Solomon Islands/06	A/Wisconsin/2005	B/Malaysia/2004

Because of antigenic drift, A/Wisconsin/2005 provided only limited protection against the H3N2 virus that circulated in the 07-08 season. The B/Malasia component of the vaccine provided no protection at all. All three components of next year's vaccine will be changed as shown on the next line.

08–09	A/Brisbane-59/2007	A/Brisbane-10/2007	B/Florida/2006
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## **FluMist®**

On 17 June 2003, the U. S. Food and Drug Administration (FDA) approved FluMist® – a live-virus vaccine that is given as a spray up the nose.

The viruses have been weakened so that they do not cause illness, but are able to replicate in the relatively cool tissues of the nasopharynx where they can induce an immune response. Presumably this is tilted towards [IgA](#) production, a better defense against infection by inhaled viruses than blood-borne IgG antibodies. In any case, FluMist® induces a more rapid response than inactivated vaccine and there is some evidence that it provides better protection against antigenic drift as well.

All three currently-circulating strains of flu (H1N1, H3N2, and B) are included. As new strains appear, they can be substituted.

At present, this new vaccine (technically known as **LAIIV** "Live Attenuated Influenza Vaccine") is only approved for children older than 24 months and adults younger than 50. People with immunodeficiency (e.g., [AIDS](#)) should also be cautious about taking it.

## **Other weapons against flu**

It takes a while for the flu vaccine to build up a protective level of antibodies. What if you neglected to get your flu shot and now an epidemic has arrived?

### **Amantadine and Rimantadine**

These drugs inhibit one of the [matrix proteins](#) needed to get viral RNA into the cytosol. They work against A strains only and resistance to the drugs evolves quickly. By the 2008-2009 flu season, virtually all strains of H3N2 had developed resistance.

### **Zanamivir (Relenza®) and Oseltamivir (Tamiflu®)**

These drugs block the neuraminidase and thus inhibit the release and spread of fresh virions. Spraying zanamivir into the nose or inhaling it shortens the duration of disease symptoms by one to three days. Unfortunately, by the 2008-2009 flu season, all H1N1 strains circulating in the U.S. had become resistant to Tamiflu.

### **Antibiotics**

Antibiotics are of absolutely no value against the flu virus. However, they are often given to patients to combat the secondary bacterial infections that occur and that are usually the main cause of serious illness and death.

## Why so few drugs?

The mechanisms by which amantadine and zanamivir work provide a clue.

There are far fewer anti-viral drugs than antibacterial drugs because so much of the virus life cycle is dependent on the machinery of its host. There are many agents that could kill off the virus, but they would kill off host cell as well. So the goal is to find drugs that target molecular machinery unique to the virus. The more we learn about these molecular details, the better the chance for developing a successful new drug.

## "Bird Flu"

In October 2003, an epidemic of influenza in chickens began sweeping through several countries in the Pacific Rim (Vietnam, Thailand, Japan, China, South Korea, Cambodia). The virus is **H5N1**. The H5 molecule is common among bird influenza viruses but has not been seen on flu viruses that cause human epidemics. However, sporadic human cases of H5N1 (with an alarmingly-high fatality rate) have been occurring ever since.

As a glance at the tables above will show, humans have had long experience with infections and vaccines by both H1 and H3 flu viruses. But the human population has absolutely no immunity against any H5 viruses. Has the ground been prepared for another worldwide pandemic?

So far, person-to-person spread seems to account for only a few cases. Most cases seem to have been acquired from close contact with infected birds.

However, there are reports that the virus has been found in pigs. This is very troubling as simultaneous infection of a pig by a human strain could provide the opportunity for genetic reassortment between the two strains [[Link](#)] with the creation of an H5 virus able to spread rapidly between humans.

Work is going forward on an H5N1 vaccine. However, this is a virus that kills chickens so it is not surprising that it does not grow well in the eggs used for vaccine production.

## The "Spanish" Flu

For almost a decade, Jeffery Taubenberger and his colleagues have been sequencing the genes of the influenza virus that had been recovered from

- preserved lung tissue of a U.S. soldier who died from influenza in 1918;
- lung tissue from a flu victim whose body had remained frozen in the permafrost of Alaska since she died in 1918.

In the 6 October 2005 issue of the journal **Nature**, they reported completing the task.



Why had they bothered? Because:

The knowledge of the genome of the 1918 virus may provide clues to help us avoid — or at least prepare for — another pandemic. In fact, its genome turns out to resemble bird flu genomes more closely than those of human strains. If a bird flu virus could create the pandemic of 1918, what may we expect from the current rapid spread of bird flu?

But even with all of its genes now completely sequenced, why the 1918 strain was so deadly is not fully understood. But deadly it is. They have even been able to replace the 8 genes of a laboratory strain of flu virus with all 8 genes of the 1918 strain (using strict biosafety containment procedures!). The resulting virus kills mice faster than any other human flu virus tested. (Reported in the 7 October 2005 issue of **Science**.)

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<http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/I/Influenza.html>