

INFECTIOUS DISEASE

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BIRD FLU

Pandemic phase

Current status: PHASE 3

Human infection(s) with a new subtype, but no human-to-human spread

SWINE FLU

Current status: Pandemic declared over

Latest information from CDC

Stages of a pandemic

TEACHING OBJECTIVES

Brief review of influenza virus structure and properties

Discussion of viral pathogenesis and disease, genetics, epidemiology, prevention and treatment

WEB RESOURCES

Influenza CDC

Flu Weekly report CDC

Flu Facts and Myths CDC

Flu news CDC

VIROLOGY - CHAPTER THIRTEEN INFLUENZA VIRUS (ORTHOMYXOVIRUS)

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INTRODUCTION

True influenza is an acute infectious disease caused by a member of the orthomyxovirus family (figure 1): influenza virus A (figure 2), B or, to a much lesser extent, influenza virus C (figure 3). However, the term 'flu' is often used for any febrile respiratory illness with systemic symptoms that may be caused by a myriad of bacterial or viral agents as well as influenza viruses.

Influenza outbreaks usually occur in the winter in temperate climates. In the United States, the 'flu season usually starts in October or November and is at its height from December to March (figure 4 - 6).

The Myth of "Stomach flu"

Why do we get flu in the winter?



Figure 1A



Figure 1B
Properties of orthomyxoviruses

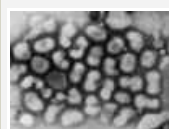


Figure 2A

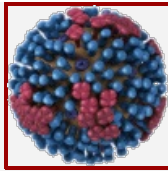


Figure 2B
Influenza virus. 3D reconstruction. CDC



Figure 3
Influenza C © Dr Linda M Stannard, 1995, University of Cape Town. Used with permission

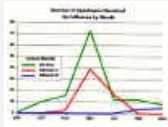


Figure 4
Number of specimens received for influenza testing per month South Carolina DHEC

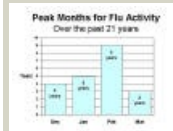


Figure 5
Peak months for flu activity over the past 21 years CDC

Disease potential

Major outbreaks of influenza are associated with influenza virus type A or B. Infection with type B influenza is usually milder than type A. Type C virus is associated with minor symptoms.

Proteins

The internal antigens (M1 and NP proteins - figure 1) are the type-specific proteins (type-specific antigens) used to determine if a particular virus is A, B or C. The M1 proteins of all members of each type show cross reactivity. The NP proteins of all members of each type also show cross reactivity.

The external antigens (HA and NA) show more variation and are the subtype and strain-specific antigens. These are used to determine the particular strain of influenza A responsible for an outbreak.

WEB RESOURCES

[Influenza information](#)
[Questions and answers](#)
CDC

[Flu Vaccine Information](#)
CDC

[World Influenza Program](#)
WHO

[Flu information](#)
Healthline

PATHOGENESIS AND DISEASE

Spread

The virus is spread person to person via small particle aerosols (less than 10µm diameter) that can get into the respiratory tract. It can also be spread via **fomites** since it can survive for a short time on surfaces and can be spread by this route if the virus is introduced into the nasal mucosa before it loses infectivity. The incubation period is short, about 18 to 72 hours.

Virus concentration in nasal and tracheal secretions remains high for 24 to 48 hours after symptoms start and may last longer in children. Titers are usually high and so there are enough infectious virions in a small droplet to start a new infection.

Site of infection

Influenza virus infects the epithelial cells of the respiratory tract. The cells die, in part due to the direct effects of the virus on the cell, and also possibly due to the effects of interferon. Cell death at later times may also result from the actions of cytotoxic T-cells. As a result, the efficiency of ciliary clearance is reduced, leading to impaired function of the mucus elevator; thus there is reduced clearance of infectious agents from the respiratory tract. Gaps in the protective epithelium provide other pathogens with access to other cells; however, **viremia** is very rare.

Recovery

Interferon may play a role by decreasing virus production. Many of the symptoms of uncomplicated influenza (muscle aches, fatigue, fever) are associated with the efficient induction of interferon. The cell-mediated immune response is important in viral clearance. The antibody response is usually not significant until after virus has been cleared. Repair of the respiratory epithelium begins rapidly, but may take some time to complete.

More on
interferon

Protection

A humoral antibody response is the main source of protection. IgG and IgA are important in protection against reinfection. Antibody to the HA protein is most important since this can neutralize the virus and prevent the virus initiating the infection. Neutralization frequently involves blocking of the binding of the virus to host cells and may work at other steps involved in the entry and uncoating of the virus. Antibody to the NA protein has some protective effect since it seems to slow the spread of the virus. IgG persists longer than IgA and so plays a more important role in long term immunity.

Clinical findings

The disease is usually most severe in very young children (under 5 years of age) and the elderly. Young children often lack antibodies to the influenza virus because of no prior exposure. In addition, the small diameter of components of the respiratory tract in the very young also means that inflammation and swelling can lead to blockage of parts of respiratory tract, sinus system or Eustachian tubes. Although children with risk factors for influenza complications have a higher case fatality rate, the majority of pediatric deaths occur among children with no high-risk conditions. In the elderly, influenza is often severe because of an underlying decreased effectiveness of the immune system and/or chronic obstructive pulmonary disease or chronic cardiac disease.

CDC surveys show that each year about 114,000 people in the U.S. are hospitalized and about 36,000 people die because of the flu. Flu and pneumonia together constitute the sixth leading cause of deaths in the United States. Most flu fatalities are 65 years and older. Children younger than 2 years old are as likely as those over 65 to have to be hospitalized because of the flu. The 1918 Spanish flu outbreak killed more than 500,000 people in the United States and more than 20 million worldwide. The 1968-69 "Hong Kong flu" outbreak led to more than 34,000 deaths in the United States.

Symptoms and complications

1. Uncomplicated influenza

- Fever (38 - 40 degrees C)
- Myalgias, headache
- Ocular symptoms - photophobia, tears, ache
- Dry cough, nasal discharge
- H1N1 strain, the 2009 "swine flu", also gives rise to gastro-intestinal symptoms (e.g. vomiting, diarrhea)

2. Pulmonary complications, sequelae:

- **Croup** (acute laryngotracheobronchitis) in young children - symptoms include cough (like a barking seal), difficulty breathing, stridor (crowing sound during inspiration)
- Primary influenza virus pneumonia
- Secondary bacterial infection: This often involves *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Hemophilus influenzae*

The build up of fluids and lack of mucociliary clearance in the respiratory tract provide a good environment for bacterial growth.

Complications often occur in patients with underlying chronic obstructive pulmonary or heart disease. The underlying problems may not have been recognized prior to the influenza infection.

3. Non-pulmonary complications of influenza:

- **Myositis** - This is rare and more likely to be seen in children after influenza type B infection
- Cardiac complications
- **Encephalopathy** - Increased surveillance of hospital patients less than 21 years of age in the state of Michigan in the United States during the 2002 -

CASE REPORT MMWR - Flu fatalities in Michigan

Sign or Symptom	No.	%
Headache	100	100
Fatigue	95	95
Myalgia	90	90
Malaise	85	85
Loss of appetite	80	80
Nausea	75	75
Diarrhea	70	70
Vomiting	65	65
Cough	60	60
Sore throat	55	55
Runny nose	50	50
Red, swollen eyes	45	45
Photophobia	40	40
Tears	35	35
Ache	30	30
Dry cough	25	25
Nasal discharge	20	20
H1N1 strain	15	15
2009 "swine flu"	10	10
Gastro-intestinal symptoms	5	5
Vomiting	5	5
Diarrhea	5	5

Figure 6A

Number and percentage of signs and symptoms and conditions among influenza patients in Michigan

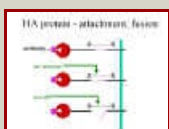


Figure 7

The HA protein has a pocket that binds to the

cell receptor. Antibodies cannot get into the pocket. Since antigenic domains are on the surface of the HA, these can be altered without altering receptor binding. Cell enzymes cleave the receptor outside the cell but the HA is only activated in an endosome

2003 flu season revealed eight cases of influenza-associated encephalopathy (figure 6A). Two of these patients (aged two and five years) died. Similar complications of influenza have been reported from Japan. Even when not fatal, encephalopathy can have serious sequelae and this emphasizes the importance of vaccination. Neither of the Michigan fatalities had been vaccinated.

Leading causes of death in the US

- **Reye's syndrome** - The effects of influenza virus infection on the liver and brain are particularly serious. In the liver fatty deposits are seen while in the brain edema occurs. Reye's syndrome includes vomiting, lethargy and may result in coma. It is rare, but approximately 40% of cases are fatal. The origin of Reye's syndrome is unclear but seems to follow certain viral infections such as influenza or chicken pox (varicella zoster/herpes zoster), especially if they are in the young and especially if they have been treated with aspirin. Aspirin is contraindicated for childhood or adolescent fevers because it is a risk factor in the development of Reye's syndrome. Acetaminophen and Ibuprofen are apparently not associated with Reye's syndrome.
- **Guillain-Barré syndrome** (acute idiopathic polyneuritis) - The cause of this syndrome in the central nervous system is mysterious. It is an autoimmune disease that can follow a viral or bacterial (e.g. *Campylobacter jejuni*) infection. Recent anti-influenza vaccines do not seem to increase the risk of developing Guillain-Barre Syndrome.

Reye's Syndrome	Guillain-Barre Syndrome
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The major causes of influenza-associated death are bacterial pneumonia and cardiac failure. Ninety per cent of deaths are in people over 65 years of age.

DIAGNOSIS

Firm diagnosis is by means of virus isolation and serology. The virus can be isolated from the nose or a throat swab. This is used to infect cells in culture (or eggs). **Hemadsorption** may be used to detect infected cells. Polymerase chain reaction (PCR) tests are being developed to detect viral RNA. Recently, rapid tests that can be used in a physician's office have been approved. Provisional diagnosis is often made clinically, based on knowledge of a current outbreak of influenza combined with appropriate clinical symptoms (fever, cough, runny nose, malaise).

EPIDEMIOLOGY

HA (hemagglutinin) protein

The HA protein is involved in attachment and membrane fusion in the endosome of the infected cell. The receptor binding site on the virus is in a pocket (figure 7) that is not exposed to the immune system. The antigenic domains are on the surface. These can be altered and the virus can thus avoid a humoral response without affecting its ability to bind to the receptor.

NA (neuraminidase) protein

The neuraminidase protein digests sialic acid (neuraminic acid) - which most cells have on their surface. Since sialic acid is part of the virus receptor, when the virus binds to the cell, it will be internalized (endocytosed). By late in infection, the sialic acid will have been removed from the infected cell surface by the neuraminidase making it easier for the progeny virions to diffuse away once they exit the cell. Neuraminidase is also involved in penetration of the mucus layer in the respiratory tract.

Antigenic drift

Antigenic drift is due to mutation. Antibodies to the HA protein are the most important in

WEB RESOURCES

[Guillain-Barré syndrome](#)
NIH Information
[Reye's syndrome](#)
NIH Information

protection, although those to NA also play a role. Both proteins undergo antigenic drift (i.e. accumulate mutations) and accumulate changes such that an individual immune to the original strain is not immune to the drifted one. Antigenic drift results in sporadic outbreaks and limited epidemics.

Antigenic shift

Antigenic shift is due to reassortment. In the case of influenza A, antigenic shift periodically occurs. Apparently "new" HA and/or NA are found in the circulating viral strains. There is little immunity (particularly if both proteins change, or if new HA is present) and an epidemic/pandemic is seen.

PANDEMICS CAUSED BY INFLUENZA A		
<i>Major antigenic shifts associated with influenza A pandemics</i>		
Year	Sub type	Prototype strain
1947	H1N1	A/FM1/47
1957 (Asian flu)	H2N2	A/Singapore/57
1968 (Hong Kong flu)	H3N2	A/Hong Kong/68
1977	H1N1	A/USSR/77
1987	H3N2	No pandemic Various strains circulated worldwide

Where does a new HA and/or NA come from? All sixteen HA and nine NA types circulate in ducks, some also circulate in other animals. It appears that some animal, somewhere (possibly a pig), becomes infected with both human and animal viruses, and that one of the reassortants contains genes for human internal components but a new HA and/or NA segment from the animal virus. If this virus reassortant can infect humans, it will have mainly the same internal components as the current human virus, but new envelope components resulting in little immunity in the population. Influenza A subtypes are therefore classified according to the type of HA and NA protein. It is possible that we do not see such a shift in influenza B because there is no animal reservoir for this virus.

Classification of influenza strains:

- Type A, B or C/place isolated/number of isolate/year isolated
- In the case of influenza A, also: HA subtype (H) and NA subtype (N)

For example, the three strains for the 2010/2011 vaccine for the northern hemisphere were:

- A/California/7/2009 (H1N1)-like virus
- A/Perth/16/2009 (H3N2)-like virus
- B/Brisbane/60/2008-like virus.

The H1N1 virus recommended for inclusion in the 2010-2011 seasonal influenza vaccine was a pandemic 2009 H1N1 virus and is the same vaccine virus as was used in the 2009 H1N1 monovalent vaccine.

For the 2013-2014 flue season, the vaccine composition is as follows:

- A/California/7/2009(H1N1)pdm09-like virus
- A(H3N2) virus antigenically like the cell-propagated A/Victoria/361/2011 virus (A/Texas/50/2012)
- B/Massachusetts/2/2012-like (B/Yamagata lineage) virus.

From CDC: A/Texas/50/2012 is an egg-propagated A(H3N2) virus antigenically similar to cell-propagated A/Victoria/361/2011. A/Texas/50/2012 is used as the H3N2 vaccine component because of antigenic changes in A/Victoria/361/2011 vaccine virus resulting from mutations acquired during growth in eggs. CDC also recommended that quadrivalent vaccines contain a B/Brisbane/60/2008-like

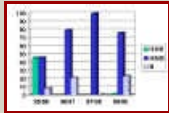


Figure 8
Types of influenza that predominated from 1995/6 to 1998/99 CDC

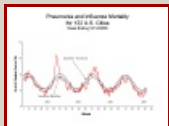


Figure 9
Pneumonia and Influenza Mortality Surveillance for 122 US cities 2003-2006

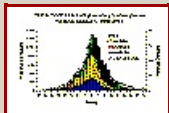


Figure 10A
2001-2001 weekly US summary



Figure 10B
Avian influenza A (H5N1) virion, a type of bird flu virus which is a subtype of avian influenza A. At this magnification, one may note the stippled appearance of the roughened surface of the proteinaceous coat encasing the virion. CDC



Figure 10 C
H7N9 Avian Flu. Negative stain



Figure

10C
 Genetic Evolution of
 H7N9 flu in China in
 2013.

The eight genes of the H7N9 virus are closely related to avian influenza viruses found in domestic ducks, wild birds and domestic poultry in Asia. The virus likely emerged from "reassortment," a process in which two or more influenza viruses co-infect a single host and exchange genes. This can result in the creation of a new influenza virus. Experts think multiple reassortment events led to the creation of the H7N9 virus. These events may have occurred in habitats shared by wild and domestic birds and/or in live bird/poultry markets, where different species of birds are bought and sold for food. As the above diagram shows, the H7N9 virus likely obtained its HA (hemagglutinin) gene from domestic ducks, its NA (neuraminidase) gene from wild birds, and its six remaining genes from multiple related H9N2 influenza viruses in domestic poultry.
 CDC

H1N1 and H3N2 Swine Flu

Swine flu, as its name suggests, is a type A influenza of pigs and does not normally infect humans. However, swine flu variants do sometimes spread to humans and in 2009, a new H1N1 swine flu started to circulate. This virus is unusual because it possesses a combination of genes that have not previously been observed in animal or human populations. Although the virus is most like the H1N1 viruses that are found in pigs and was therefore termed "swine flu", it was found only in humans and did not circulate in pig herds. In response to the potential for a major pandemic, a mass vaccination campaign using an H1N1 monovalent vaccine (in addition to the usual trivalent vaccine against seasonal flu) was carried out. In June 2010, WHO declared the pandemic over; however, the H1N1 "swine" flu continues to circulate around the globe along with the seasonal flu. It will likely continue to do so. In fact, H1N1 is one of the seasonal flu strains in the seasonal flu vaccine. Other swine flu variants that have infected humans include H3N2 and H1N2.

Swine Influenza A H3N2 was first found in the United States in pigs in 2010 but in recent years a number of human infections have occurred in people with close contact to pigs. Although the virus can spread directly from human to human, there has been little spread.

H5N1 Avian Flu

There is concern about a recent outbreak of avian influenza due to a strain of H5N1 influenza A virus (figure 10B). This bird virus seems to be able to infect humans without having to undergo a recombination event in some other animal. The case fatality rate is high (~60%) in humans. Fortunately, as yet the virus does not readily spread from birds to humans or one human to another. However, there is concern that it might mutate, or undergo reassortment with a human influenza virus, and acquire the ability to spread rapidly from human to human while still being as virulent.

H7N9 Avian Flu

Human infections by this variant have occurred recently in China and most infections occur in people in close contact with birds. No cases have been reported outside China.

Although human to human cases have not been reported, the H7N9 virus has genetic changes that may allow it to spread more easily to mammals, causing more severe disease that spreads rapidly. The case fatality rate is about 20% and the patients experience a severe respiratory disease that can lead to pneumonia, acute respiratory distress syndrome and multi-organ failure.

This variant may have arisen as a result of several reassortments in which the virus acquired its hemagglutinin from domestic ducks and its neuraminidase from wild birds with the other genes coming from flu viruses infecting poultry (Figure 10C).

WEB RESOURCES

WHO/NREVSS
 Collaborating Laboratories
 Regional Influenza-Like
 Illness
 (Map with linked bar
 charts with latest
 surveillance information)

AVIAN INFLUENZA
 WHO Site
 CDC Site

Avian Flu	A new pandemic?	Why is the current avian flu resistant to amantadine and rimantadine?
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Avian flu incidence in poultry from 2004 maps (FAO)	Avian Flu and pig density in South East Asia (FAO)	Avian Flu and poultry density in South East Asia (FAO)
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Current human and bird distribution of H5N1 flu (CDC)	Avian Flu: Symptoms in poultry (FAO)	Stages of a pandemic
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SURVEILLANCE

A measure of the severity of influenza in any one year is the excess of deaths due to pneumonia or influenza compared to the seasonally adjusted norm (figure 9).

The World Health Organization (WHO) maintains constant surveillance of influenza outbreaks world wide and has a series of 'sentinel' labs to look at what is happening in the circulating virus population. The CDC does the same in the United States and co-operates with WHO.

Usually the most important influenza virus is influenza A, but in some seasons influenza B is the major cause of influenza. In recent years H1N1 and H3N2 have often co-circulated (figure 10A); the proportions of each can change dramatically from year to year.

PREVENTION

Vaccines

There are two types of vaccine

- **TRIVALENT INACTIVATED VACCINE (TIV)**

The trivalent inactivated vaccine (TIV) is an inactivated preparation of egg-grown virus and is given by injection. Only certain formulations of the vaccine are FDA certified for young children - the annual ACIP recommendations (see below) give details. Protection is via IgG antibodies.

- **LIVE, ATTENUATED INFLUENZA VIRUS VACCINE (LAIV)**

The live, attenuated influenza virus (LAIV - marketed as *FluMist*) vaccine (see [Viral Genetics](#)) is prepared from egg-grown virus. It is approved for healthy (those not at risk for complications from influenza infection), non-pregnant individuals 2 to 49 years old but should not be given to children under 5 years of age who have possible reactive airways disease (for example, a history of recurrent wheezing). It is given nasally and should provide mucosal, humoral and cell-mediated immunity. It is contraindicated for children and adolescents on any therapy containing aspirin due to the potential risk of Reye's syndrome since the virus is a live virus.

Both influenza vaccines are formulated annually using the types and strains of influenza predicted to be the major problems for that year (the predictions are based on worldwide monitoring of influenza). The vaccines are multivalent, the current ones are trivalent and have two strains of influenza A and one of influenza B. Vaccination needs to be given every year because the most effective strains for the vaccine will change due to drift and/or shift. The vaccines are usually given in the Fall (figure 11), once the strains to be used for the influenza season have been determined in the earlier part of the year. By giving the vaccine in the fall, protection should be high at the time the influenza season peaks. Since both vaccines are grown in eggs, they are contraindicated for those allergic to eggs.

(see also [Anti-viral Vaccines](#))

The CDC recommends: "Physicians should administer influenza vaccine to any person who wishes to reduce the likelihood of becoming ill with influenza (the vaccine can be administered to children as young as 6 months). Persons who provide essential community services should be considered for vaccination to minimize disruption of essential activities during influenza outbreaks. Students or other persons in institutional settings (e.g., those who reside in dormitories) should be encouraged to receive vaccine to minimize the disruption of routine activities during epidemics."

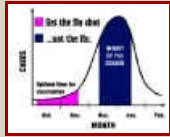


Figure 11
When to get a 'flu shot
CDC

Prevention and Control of Influenza
 Recommendations of the Advisory Committee on Immunization Practices (ACIP)
 Recommendations for Using Antiviral Agents for Influenza for the Influenza
 Season

Chemotherapy

• **Zanamivir (Relenza) and Oseltamivir (Tamiflu)**

Two neuraminidase inhibitors have been approved by the FDA (Zanamivir [Relenza] and Oseltamivir [Tamiflu]). They are active against both influenza A and influenza B and can reduce the duration of uncomplicated influenza (by approximately 1 day in about 70-90% of adults) if taken within two days of the onset of illness. However, oseltamivir resistance has been seen in some circulating strains recently (the 2009 H1N1 strain is sensitive).

To date there are only a few studies of how effective these drugs are in reducing serious complications in high risk groups when used to treat influenza (as contrasted with when used prophylactically). Some limited data suggest they may be beneficial. However, both are approved for prophylaxis as well as treatment.

• **Rimantadine and amantadine**

Rimantadine and amantadine block virus entry across the endosome and also interfere with virus release (see [Anti-viral chemotherapy](#)). They may be given as protective agents during an outbreak, especially to those at severe risk and key personnel.

These drugs were widely used. However, in the 2005-2006 influenza season 92% of the H3N2 strains examined had a mutation which would confer resistance to these drugs, as did 25% of the H1N1 strains tested - similar problems have been seen in seasons since then so these drugs are not recommended until the level of resistance in the major circulating strains drops. In the absence of the resistant mutations they were good prophylactic agents for influenza A (but not for influenza B), although there are some problems in taking them on a long term basis. They could be given to protect during an outbreak - especially those at severe risk and key personnel. They could also be given at the time of vaccination for a few weeks - until the humoral response had time to develop. There is some evidence that rimantadine and amantadine can reduce the duration of non-resistant influenza A if given early in infection.

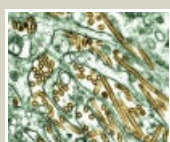
You should check with the CDC MMWR Recommendations and Reports for Influenza for concerns such as dosage, side effects, and the annual update of recommendations.

Why does amantadine not affect influenza B?	Resistance to Zanamivir and oseltamivir
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Other treatment

The best treatments are rest, liquids, anti-febrile agents (not aspirin in the young or adolescent, since Reye's syndrome is a potential problem). Be aware of and treat complications appropriately.

COMPARISON OF INFLUENZA A, B AND C			
	TYPE A	TYPE B	TYPE C
Severity of illness	++++	++	+
Animal reservoir	yes	no	no
Human pandemics	yes	no	no
Human epidemics	yes	yes	no (sporadic)



Influenza
 H5N1 (seen in gold) grown
 in MDCK cells (seen in
 green) CDC/C. Goldsmith, J. Katz,
 and S. Zaki

MOLECULAR
 STRUCTURE
 Rimantadine
 Relenza

WEB RESOURCES

Information for health care
 professionals
 CDC Information

CASE REPORT
Swine Influenza A
(H1N1) Infection in
Two Children ---
Southern California,
March--April 2009

MMWR-CDC

Antigenic changes	shift, drift	drift	drift
Segmented genome	yes	yes	yes
Amantadine, rimantidine	sensitive	no effect	no effect
Zanamivir (Relenza)	sensitive	sensitive	
Surface glycoproteins	2	2	(1)


COMPARISON OF SEASONAL AND PANDEMIC FLU	
SEASONAL	PANDEMIC
<ul style="list-style-type: none"> • Outbreaks follow predictable seasonal patterns; occurs annually, usually in winter, in temperate climates • Usually some immunity built up from previous exposure • Healthy adults usually not at risk for serious complications; the very young, the elderly and those with certain underlying health conditions at increased risk for serious complications • Health systems can usually meet public and patient needs • Vaccine developed based on known flu strains and available for annual flu season • Adequate supplies of anti-virals are usually available • Average U.S. deaths approximately 36,000/yr • Symptoms: fever, cough, runny nose, muscle pain. Deaths often caused by complications, such as pneumonia. • Generally causes modest impact on society (e.g., some school closing, encouragement of people who are sick to stay home) • Manageable impact on domestic and world economy 	<ul style="list-style-type: none"> • Occurs rarely (a few times a century) • No previous exposure; little or no pre-existing immunity • Healthy people may be at increased risk for serious complications • Health systems may be overwhelmed • Vaccine probably would not be available in the early stages of a pandemic • Effective anti-virals may be in limited supply • Number of deaths could be quite high (e.g., U.S. 1918 death toll approximately 675,000) • Symptoms may be more severe and complications more frequent • May cause major impact on society (e.g. widespread restrictions on travel, closings of schools and businesses, cancellation of large public gatherings) • Potential for severe impact on domestic and world economy
From CDC	



Return to the Virology section
of Microbiology and Immunology
On-line



Return to the Home Page of



Microbiology and Immunology On-
line

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