Viruses causing Respiratory Disease
Mechanisms of Human Disease

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INFLUENZA VIRUS: A threatening respiratory virus that can cause pandemic disease

For more information about 1918 influenza, see the links within the lecture handout.

CONTRACTING INFLUENZA VIRUS INFECTION:
Inhalation is the most common route of virus infections

One sneeze = ~ 20,000 "droplets"
Many viruses in each ~ 10 micron droplet
Viruses are in secretions when symptomatic

Mucociliary motor and alveolar macrophages protect against infection
ONCE CONTRACTED, SYMPTOMS FOLLOW VIRUS REPLICATION:

Influenza replication begins to be detectable at ~3 days (slower than common cold picornavirus, but far faster than HIV retrovirus).

This particular graph shows remarkably rapid increase in virus levels (at 1 to 2 days). The main point here is that virus shedding precedes symptoms by about 1 day.

Symptoms of Influenza:

- Central
  - Headache
- Systemic
  - Fever (usually high)
- Muscular
  - (Extreme) tiredness
- Joints
  - Aches
- Nasopharynx
  - Runny or stuffy nose
  - Sore throat
  - Aches
- Respiratory
  - Coughing
- Gastric
  - Vomiting

SYMPTOMS OF INFLUENZA: Lung Consolidation

H5N1 avian influenza virus.

Chest x-rays of patients infected with the virus may demonstrate focal consolidation, reticulonodular shadowing, pleural effusion and/or thickening, pneumothorax, lobar collapse, and lymphadenopathy.

All images courtesy of Dr. Nagmi Qureshi.
Influenza virus infects the epithelial cells of the respiratory tract. The cells die, due to the direct effects of the virus on the cell, and also due to interferon. The efficiency of ciliary clearance is reduced, impairing the mucus elevator. Gaps in the protective epithelium provide other pathogens with access to other cells. Bacterial pneumonia can develop. Acute Respiratory Distress Syndrome (ARDS) can rarely develop. Viremia, however, is almost never observed.

**SYMPTOMS OF INFLUENZA: Exuberant Host Responses**

![Exuberant Host Responses](image)

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**SYMPTOMS OF INFLUENZA: Severe Cases**

Can be severe when co-morbidities are present:
- Asthma
- COPD (also congestive cardiac failure)
- Obesity (BMI > 40)
- Bacterial pneumonia
- Immunosuppression and cytokine dysregulation

Can be severe in selected patient populations:
- Infants (smaller airway passages)
- Pregnant or postpartum (< 2 weeks)
- Age < 5 and > 65 (less developed or waning immunity)

*Consider antiviral therapies for at-risk populations*
THE INFLUENZA VIRUS AND ITS REPLICATION

INFLUENZA VIRIONS

Pleomorphic enveloped virions exist in droplet nuclei and in nasal secretions.

Enveloped virions are destroyed by common hand soaps. (So called “antibacterial” soaps are no better than ordinary soaps.)

Schematic of the influenza virion

PM2, PA, PA (RNA polymerase)

M (matrix protein)

HA (hemagglutinin)

NP (nucleocapsid protein)

N1 (neuraminidase)

Lipid bilayer

Segmented (-) strand RNA genome
Influenza virus infection cycle

Apical entry

Apical egress

Infection normally stays restricted to the lungs and airways

INFLUENZA VIRUS EPIDEMIOLOGY

Epidemiology: Epidemics

Hemagglutinin (HA) is featured
Epidemiology: Epidemics

1. Influenza viruses replicate through RNA intermediates.
2. RNA-dependent RNA replication is error-prone.
3. RNAs with errors in them are translated.
4. Some flu particles therefore have proteins with altered structure.
5. Altered structures can be antigenically distinct, that is, “drifted”;

ANTIGENIC DRIFT, PARTICULARLY IN THE HEMAGGLUTININ SPIKES, CREATES EPIDEMIC VIRUS

Epidemiology: Pandemics

Remember:

Influenza is widespread, infecting humans, animals and birds.
Influenza has a segmented genome, with 8 RNAs in its core.
RNA segment reassortments create antigenic shifts. Viruses with dramatically altered antigenicities create PANDEMICS

Influenza A antigenic types reappear on a time scale that is roughly equivalent to one human generation

Epidemiology of Human Influenza Viruses

Current 21st century is witnessing intrusions of novel bird and swine influenza types into the human population
MAKING INFLUENZA VIRUS VACCINES

Influenza virus vaccine strains are grown in chicken eggs, then purified from allantoic fluids, inactivated, quality-controlled, and injected intramuscularly. A live-attenuated influenza vaccine is also available for intranasal Delivery (“Flu-Mist”). Protective antibodies typically arise within ~2 - 4 weeks after vaccination.

The best antibodies block influenza HA protein activity. This prevents virus entry / membrane fusion.
**INFLUENZA VIRUS VACCINES**

INFLUENZA VIRUS VACCINES REPRESENT THE CURRENTLY CIRCULATING VIRUS STRAINS, AND ARE CLASSIFIED BY:

1. Serotype (A, B or C)
2. The geographic location of the isolate
3. The host of origin
4. Strain number and year of isolation
5. HA and NA subtypes

The 2014-2015 trivalent vaccines:

A/California/7/2009 (H1N1)-like
A/Texas/50/2012 (H3N2)-like
B/Massachusetts/2/2012-like (Yamagata lineage)

**INFLUENZA VIRUS DIAGNOSIS AND ANTIVIRAL TREATMENTS**

Rapid laboratory tests are needed in severe cases:

<table>
<thead>
<tr>
<th>Technique</th>
<th>Advantages</th>
<th>Disadvantages</th>
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</thead>
<tbody>
<tr>
<td>Immunofluorescence</td>
<td>Rapid and Specific</td>
<td>Labor-intensive and requires quality reagents</td>
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<tr>
<td>Enzyme immunoassay</td>
<td>Rapid, can be automated</td>
<td>Expensive, can be insensitive</td>
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<tr>
<td>Culture</td>
<td>Confirms infective virus</td>
<td>Slow process, Some viruses cannot be cultivated</td>
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<tr>
<td>PCR</td>
<td>Fast, sensitive, specific</td>
<td>Expensive, Some false-positives</td>
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</table>
INFLUENZA DIAGNOSIS AND TREATMENT:

Two classes of anti-influenza virus drugs:

Block M2 proteins

Block neuraminidase

Block M2 with amantadine:
RNAs will not release from virion proteins.
Infection blocked at entry stage.

Block neuraminidase (NA) with inhibitors ("Tamiflu"):  
NEURAMINIDASE INHIBITORS RETARD VIRUS DISSEMINATION
Influenza virus binds to sialic acids on lung epithelial cells

Neuraminidase cleaves sialic acids from infected cells and from virions: NEURAMINIDASE INHIBITORS RETARD VIRUS DISSEMINATION

ADDITIONAL RESPIRATORY VIRUSES

The Most Common Upper and Lower Respiratory Tract Viruses
ADDITIONAL RESPIRATORY VIRUSES CAUSE COMMON SYNDROMES

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<thead>
<tr>
<th>SYNDROME</th>
<th>COMMON CAUSES</th>
<th>LESS COMMON CAUSES</th>
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<tbody>
<tr>
<td>Bronchiolitis</td>
<td>Respiratory Syncytial Virus (RSV)</td>
<td>Influenza viruses</td>
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<td>Parainfluenza viruses</td>
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<td>Adenoviruses</td>
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<td>Rhinoviruses</td>
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<td>Common cold</td>
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<td>Adenoviruses</td>
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<td>Human metapneumoviruses</td>
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RHINOVIRUSES, ADENOVIRUSES, CORONAVIRUSES

RHINOVIRUSES – “Common Cold”
- Acute infections in respiratory tract (30% of all resp virus)
- Diversity of serotypes limits utility of vaccines
- Antiviral drugs will be required to eliminate disease

ADENOVIRUSES – “Common Cold”
- Infections in respiratory tract
- Conjunctivitis, “pink eye”
- > 47 human adenovirus serotypes
- Live-attenuated vaccine to some serotypes
- No antiviral drugs yet available

CORONAVIRUSES – “Common Cold”
- Both respiratory and gastrointestinal infections
- Common in children
- Often the cause of “croup”
- Some strains, i.e., SARS-coronavirus, exceedingly virulent

USMLE Q-Bank Question (not an easy one)
Question 126
Marks: 1/1
A cautious 43-year-old office worker decided to get vaccinated before the pending (2002-2003) flu season. Her physician vaccinated her with an intramuscular dose containing: A/Panama (H3N2) and A/New Caledonia/20/99 (H1N1) and B/Yamanashi. Four weeks after receiving the vaccine, the woman developed a high fever, myalgia, headaches, chills, and a dry, unproductive cough. The cough became progressive with the general symptoms lasting 3 weeks. Her doctor told her that she had the flu even though serological tests showed that the woman seroconverted and had a high vaccine antibody titer. Small changes in the surface glycosylation of the influenza virus are called which of the following?
A. Genetic shift
B. Genetic drift
C. Camouflage
D. Genetic reassortment
E. Point mutations
Answer is “C”