Viral respiratory illness

- Exceedingly common causes of disease throughout life
  - Frequently seasonal
  - Often mild/self limited
  - Tremendous economic cost
  - Contribute to burden of antibiotic resistance (inappropriate prescribing)

- Covering two of the most important here:
  - Influenza (seasonal and pandemic)
  - Respiratory syncytial virus (RSV)

- Many other causes of viral respiratory disease
  - Parainfluenza
  - Rhinoviruses
  - Human metapneumovirus
  - Coronaviruses (including SARS coronavirus)
  - Adenoviruses
  - Enteroviruses

Childhood respiratory infection deaths

Poverty

Respiratory syncytial virus (RSV)

- Ubiquitous infectious disease
  - essentially all children infected by age 2
  - world-wide epidemics
  - marked seasonality
  - risk for severe disease in:
    1. very young infants
    2. prematurity
    3. immunocompromised states
    4. congenital heart or lung diseases

- 1-2% of healthy infants are hospitalized for RSV
  - >50,000 childhood hospitalizations/yr (U.S.)
  - most common cause of viral respiratory infection in childhood
RSV: Pathogenesis

- Member of Paramyxoviridae
  - other members include metapneumovirus, parainfluenza, measles, mumps
- ssRNA, negative-sense, enveloped viruses
- Viral genome encodes 11 proteins
  - N = nucleoprotein
  - P = phosphoprotein
  - L = large polymerase protein
  - M = matrix protein
  - M2-1, M2-2 = regulatory proteins
  - F, G = surface glycoproteins

Glycoproteins F and G mediate attachment and are the main targets of immune response.

RSV life cycle

- Replicates in cells of nasopharynx
- Transmission by respiratory secretions
  - survival on fomites (tabletops, toys, your stethoscope)
  - Very, very common cause of hospital-acquired infections
- May spread to lower airways (bronchioles, alveoli)
  - Most damage in small airways
  - Clinical syndrome: RSV bronchiolitis
  - May spread to lower airways: RSV pneumonia

Clinical signs of RSV

- Incubation period = 3-6 days
- Duration of uncomplicated RSV = 1-3 weeks
- Progression of clinical syndromes
  - Upper respiratory tract disease
    - Rhinorrhea and congestion, fever
  - Croup (laryngotracheobronchitis)
  - Cough, stridor
  - Bronchiolitis (about 50% of cases)
    - Cough, wheeze, air trapping
    - Crackles, wheezes on examination
  - Pneumonia
    - More severe respiratory distress, hypoxia
  - Otitis media
  - Apnea (infants)
- No viremic phase, risk of invasive disease is very low
**Immune response to RSV**

- Single serotype but two “subgroups” (A and B) exist – unclear significance
- Immunity is incomplete – reinfection is common
- Innate recognition of RSV – surfactant proteins, toll-like receptors
- Cell-mediated immunity seems to be important for clearance/resolution – prolonged in compromised patients
- Antibody-mediated immunity is directed at F and G glycoproteins – reinfection possible even with high antibody titers
- In general, viral replication is low to undetectable during the symptomatic phase of illness. Much of the pathology is due to the immune response.

**Diagnosis of RSV**

- Clinical diagnosis
  - Viral culture: Specimens produce cytopathic effect (syncytia formation) within 3-7 days.
  - Rapid antigen detection: Very useful in ER, hospital for infection control
  - RT-PCR: Higher sensitivity than rapid antigen detection but not widely available

**Treatment of RSV**

- Treatment is largely supportive: supplemental O2, secretion management, monitoring for apnea, intubation/ventilation if needed
- Bronchodilators in RSV bronchiolitis: controversial
- Steroids in RSV bronchiolitis: no benefit
- Ribavirin: only in severe cases in immunocompromised. Unclear benefit.

**Prevention of RSV**

- Infection control
  - Handwashing
  - Cleaning of potential fomites
  - Isolation of cases
- Antibody-based prophylaxis in high-risk infants
  - Hyper-immune globulin (RSV-IGIV)
  - Monoclonal antibody (palivizumab) targets F glycoprotein – monthly doses to highest risk population during RSV season
- Vaccine prospects
  - Traditional approaches have failed: inactivated vaccine gave incomplete immunity (insufficient TLR activation) and led to more severe disease
  - Live-attenuated vaccine?
  - Maternal vaccination?

**Pandemic Influenza 2009**

- *Pandemic Influenza 2009* [link](http://www.who.int/csr/disease/swineflu/en/)

**Influenza**

- *NEW YORK POST* Page Six
  - HOG WILD
  - 150 NY kids ill amid swine flu crisis
Influenza

- Most important viral respiratory disease worldwide
- Annual seasonal epidemics despite effective vaccine
- >36,000 annual deaths, 200,000 hospitalizations in U.S.
- Severe illness in children, elderly, pregnancy, immunocompromised
- Pandemic potential

Clinical signs of influenza

- Fever (may be very high)
- Chills
- Headache
- Myalgias
- Arthralgias
- Dry cough
- Nasal discharge

- Young children may have atypical course
  "sepsis-like" syndrome, GI symptoms, croup/bronchiolitis, otitis media
- Complications: pneumonia, bacterial superinfection common
  myocardiitis, encephalitis, myositis, Reye syndrome rare
- Incubation period = 1-5 days
- Duration of illness = 4-8 days of acute illness, 1-2 weeks convalescence

Influenza: Pathogenesis

- Member of Orthomyxoviridae
  - ssRNA, negative-sense, enveloped virus
  - Viral genome in 8 segments (7 for influenza C)
    HA = hemagglutinin
    NA = neuraminidase (influenza A, B)
    PB1, PB2, PA = polymerases
    L = large polymerase protein
    M1 = associated with NP
    M2 = ion channel (influenza A only)
    NS = non-structural proteins

- HA, NA are the immunodominant antigens and are the major determinants of the viral serotype (e.g. H1N1 vs. H3N2).
- Nomenclature: Type/host species (human default)/location/year (HA/NA type)
  Influenza A/California/2009 (H1N1)

Influenza virus life cycle

- HA promotes binding & entry
- Neuraminidase (NA) allows budding & release

Influenza virus life cycle

- Influenza virus infects columnar epithelial cells of respiratory tract.
- Replication early (1-3 days), shedding for ~7 days
- Destruction of epithelial cells, increased mucus production, ciliary stasis
- Local cytokine production
- Induces innate and adaptive immune response – both important to clearance. Antibody responses to HA, NA important for future immunity.
Influenza: antigenic shift and drift

Antigenic drift (due to ongoing accumulation of mutations) leads to changes in HA and NA that limit the efficacy of antibody developed in response to prior year's influenza strains.

Antigenic shift (due to reassortment of influenza genes during simultaneous infection of a single cell with multiple viruses) leads to large changes in the viral genome and may result in novel strains.

From antigenic shift to pandemic

Novel viruses must replicate in human cells, be transmissible between humans, and be associated with little pre-existing immunity in populations in order to have pandemic potential.
1918 influenza pandemic

The Influenza Pandemic in the American Army Corps during September and October, 1918

Bacterial pneumonia following influenza

MRSA pneumonia following influenza

Synergy between influenza and S. pneumoniae

New thoughts about the 1918 flu
Diagnosis of influenza

- Clinical diagnosis
  Useful during epidemic, but important to remember that other respiratory viruses may circulate simultaneously.

- Viral culture
  Sample respiratory secretions, look for cytopathic effect on tissue culture cells.

- Rapid antigen testing (solid-phase)
  - Rapid tests for influenza A and B (~15 min)
  - Very useful in ER, office settings
  - Sensitivity may only be 50-70%

- PCR testing
  - Useful for novel H1N1 strain
  - Not universally available

Treatment of influenza

- Adamantanes (amantidine, rimantidine)
  - Effective for influenza A only
  - Target M2 ion channel, interfere with uncoating
  - Resistance common, may develop on therapy
  - Prophylaxis (both) and treatment (amantidine only)

- Neuraminidase inhibitors (zanamivir, oseltamivir)
  - Effective for influenza A and B
  - Resistance emerging, including among novel H1N1 strains
  - Prophylaxis and treatment
  - Early initiation of therapy (<72 hrs) most important for efficacy

- Ribavirin (rarely used)
  - Severe disease with virus resistant to other agents
  - Combination therapy in immune compromised with prolonged shedding

Treatment of influenza

Prevention of influenza: vaccination

- Vaccine formulations change annually
  - Includes 2 A strains, 1 B strain – prediction based on circulating viruses
  - Efficacy 60-90%
  - Changes based on age of patient, match of vaccine to actual virus

- Trivalent, inactivated vaccine (TIV) – intramuscular
  - Whole influenza virus grown in eggs
  - Formally-fixed whole virus or "split-virus" formulations
  - 1 dose/year except for children under age 9 getting first vaccination (2 doses)
  - Immunity in ~1-2 weeks, lasts ~6 months

- Live, attenuated vaccine (LAIV) – intranasal ("the squirt!")
  - 6 genes from cold-adapted virus reassorted with known HA, NA genes
  - For healthy people 5-49 years old
  - Better acceptability
  - Mild increase in risk of airway reactivity (wheezing) following vaccination
  - Small but finite risk of transmission

Who gets influenza vaccine?

- You! (health care workers)
- Children 6 months – 18 years; adults > age 50
- Contacts of children < 6 months or other high risk people
- Pregnant women
- Chronic medical conditions
- Aspirin therapy
- Chronic care facilities
- Anyone who wants it!

Who shouldn’t get influenza vaccine?

- Inactivated vaccine (TIV)
  - Children under 6 months
  - Anaphylactic reaction to eggs or other vaccine components

- Live-attenuated vaccine (LAIV)
  - Children less than 5 years or adults > 50 years
  - Anaphylactic reaction to eggs or other vaccine components
  - Immunosuppressed or other high risk for severe influenza
  - Currently receiving salicylates (aspirin)
  - History of Guillain-Barré syndrome
  - Asthma
  - Pregnant women

Encourage your patients, colleagues, friends, and family to be vaccinated!
Prevention of influenza: chemoprophylaxis

• People at high risk of complications who are close contacts of confirmed cases of influenza.
• Health care workers who had unprotected close contact exposure to a confirmed case of influenza.
• Because novel H1N1 is resistant to the adamantanes, neuraminidase inhibitors are the only current option for prophylaxis.

<table>
<thead>
<tr>
<th>Agent group</th>
<th>Treatment</th>
<th>Chemoprophylaxis</th>
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<tbody>
<tr>
<td>Oseltamivir</td>
<td>75 mg oral</td>
<td>2 doses spaced one day apart</td>
</tr>
<tr>
<td>Oseltamivir</td>
<td>75 mg oral</td>
<td>1 dose spaced 12 hours later</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>Nasally 10 mg</td>
<td>1 dose spaced 12 hours later</td>
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</tbody>
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Public health measures: 1918

Influenza and Pneumonia—Notification of Cases. Measures to Prevent Spread of Influenza. (Reg. No. of H. Dec. 2, 1918.)

1. That from and after this date, all schools of the city, all churches, all pool halls, card rooms, theaters, moving picture shows, houses of amusement and amusement, district court, except for the hearing of equity cases and matters triable to the court without witnesses, demes, lodges, banquet, social and religious gatherings, and all other public gatherings of every kind and description whatsoever, be closed and prohibited.

2. That all inns, hotels, and other places of business of the city. Including five and ten-cent stores, shall not permit more than 12 patrons or guests to any dinner or dinner of board at any time there, be exhibitions for the regular employees, and no place of business shall remain open between the hours of 5 p.m. and 7 a.m. on any day, excepting only eating houses, hotels, restaurants and the prescription departments of drug stores, and no healing shall be permitted therein.

3. That all inns shall be private and that no public functions shall be held.

4. That no special rates of any kind shall be advertised or held by any of the inns, hotels, or ten-cent stores.

5. That all physicians practicing medicine within the corporate limits of said city shall within 12 hours from the service of notice of these regulations upon him, report to the mayor of said city, or to the clerk thereof, all existing cases of cold, gripes, in gripes, influenza, Spanish influenza, pneumonia, and all similar diseases or ailments within the knowledge or such physicians.