The Respiratory Viruses

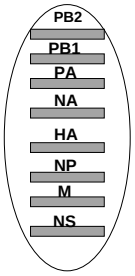
Influenza, RSV, and Rhinoviruses

The Virus

- Orthomyxovirus Family
  - Influenza A, B, and C
- Enveloped viruses with single strand, negative sense RNA genomes
- RNA is segmented
  - 8 segments in influenza A and B
  - 7 segments in influenza C

- Viruses that gain access to the body through the respiratory tract
- Some of the most common causes of symptomatic human infections
- Viral upper respiratory tract infections alone account for 26 million days of school absence and 23 million days of work absence in the US EACH YEAR!

Influenza Virus Proteins



PB1, PB2, PA: polymerase proteins

NA: neuraminidase protein- catalyzes removal of sialic acid residues and permits movement through mucous

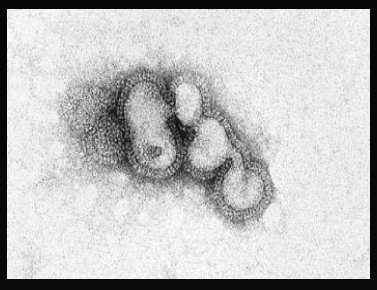
HA: hemagglutinin- binds to sialic residues allowing viral attachment, mediates fusion of viral membrane with endosome

NP: nucleocapsid protein

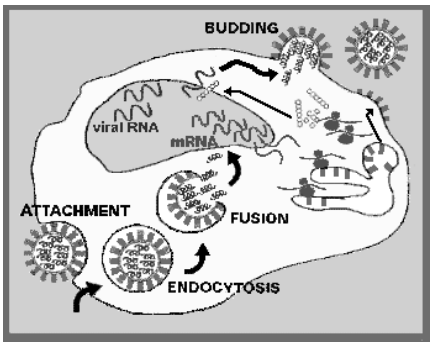
M: M1- matrix protein- provides rigidity
M2- ion channel present only in flu A

NS: nonstructural proteins

Influenza virus



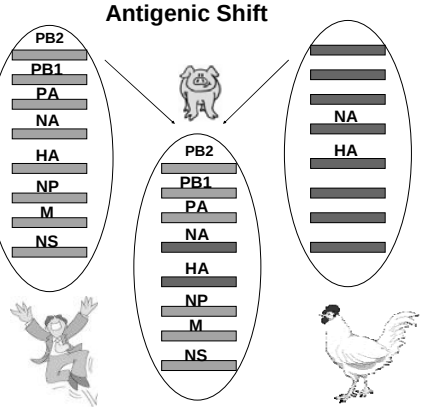
(From RDolin, AmFamPhys 14:74, 1976.)

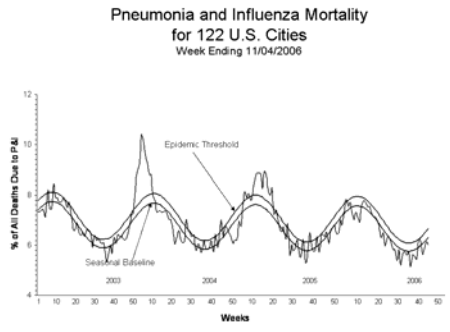


Antigenic Drift and Shift

- **Shift**
  - –Appearance of a new viral subtype with novel HA and/or NA due to reassortment of circulating human strains with strains of animal origin
  - –Occurs in nature only with influenza A

- Drift
  - – Ongoing mutations within RNA encoding HA and NA proteins resulting in amino acid changes which decrease immune recognition
  - – Seen in all types of flu, but influenza A has the greatest rate of change
  - – Drift is responsible for the year to year variations in flu outbreaks





From Shift to Pandemic

- Need a virus with HA and/or NA to which human population has little immunity
- Virus must replicate well in humans
- Virus must be transmissible from human to human

Pandemics

- 1918- "Spanish" flu H1N1; mortality 20-40 million worldwide; 500,000 US
- 1957- "Asian" flu H2N2; mortality 70,000 US
- 1968- "Hong Kong" flu H3N2; mortality 30,000 US
  - Modern circulating strain
  - Lower mortality than previous pandemics
    - Only HA changed
    - Similar strain circulated in 1890's- elderly had some protection

Will this be another 1918?

- Pandemic preparedness
- Better health care
- Vaccines
  - Standard H5N1 vaccine disappointing
  - Much better when given with adjuvants
  - New "pan-influenza" vaccines

The Next Pandemic: H5N1?

- Why is this one different?
  - Kills birds and humans
    - Highly cleavable hemagglutinin
    - Enhanced replication
    - Increased resistance to IFN and TNF-α
    - Causes macrophages to produce more cytokines
  - Little innate human immunity
- Other possibilities
  - H9N1
  - H2N2

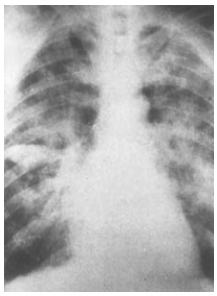
Clinical Manifestations

- Classical
  - fever- up to 106!
  - chills
  - headache
  - myalgia
  - arthralgia
  - dry cough
  - nasal discharge
- Acute phase usually 4-8 days followed by convalescence of 1-2 weeks
- Many people are asymptomatic

Nations With Confirmed Cases H5N1 Avian Influenza (July 7, 2006)

Complications

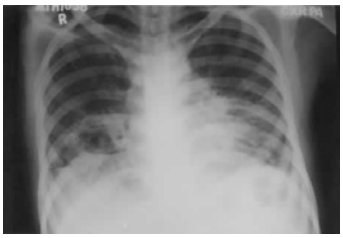
- Primary- viral (influenza) pneumonia
  - otherwise healthy adults
  - rapid progression of fever, cough, cyanosis following onset of flu sx's
  - CXR with bilateral ISIF, ABG with hypoxia



Secondary- bacterial

•Classic flu followed by improvement then sx's of pneumonia

•Pneumococcus most common; also see staph aureus and H.flu



Influenza vaccine

- Major public health intervention for preventing spread of influenza
- Currently use inactivated viruses circulating during the previous influenza season
- This year includes
  A/New Caledonia/20/1999 (H1N1)-like
  A/Wisconsin/67/2005 (H3N2)-like, and
  B/Malaysia/2506/2004-like viruses.
- Generally 50-80% protective
  – Less efficacious in the elderly but decreases hospitalization by 70% and death by 80%

Complications (cont.)

- Myositis
  – Most common in children after flu B infection
  – Can prevent walking: affects gastrocs and soleus
- Neurologic
  – GBS (controversial)
  – transverse myelitis and encephalitis
- Reye syndrome

Flumist

- Live attenuated flu vaccine licensed for use in healthy individuals aged 5-49
- Efficacious, some concern about viral shedding, useful for contacts of at-risk individuals (as long as they're not very immunocompromised)
- Trials underway in children 6-23 months

Diagnosis

- Virus isolation and culture
- Antigen Tests
  –Performed directly on patient samples
  –Rapid
  –EIA for flu A
  –DFA for flu B
- Hexaplex
  -RT PCR for flu A and B, RSV, parainfluenza
  -Sens 100%; spec 98%

Vaccine: who should get it

- Any individual > 6mos who is at risk for complications of influenza
  – chronic cardiac, pulmonary (including asthma), renal disease, diabetes, hemoglobinopathies, immunosuppression
  – Children aged 6 mos to 59 months
- Residents of nursing homes
- Household contacts of infants < 6 mos
- Individuals who care for high-risk patients
- Healthy people over age 50*

*** New ACIP recommendation**

Most important groups to vaccinate

- all children aged 6–23 months;
- adults aged 65 years and older;
- persons aged 2–64 years with underlying chronic medical conditions;
- all women who will be pregnant during the influenza season;
- residents of nursing homes and long-term care facilities;
- children aged 6 months–18 years on chronic aspirin therapy;
- health-care workers involved in direct patient care; and
- out-of-home caregivers and household contacts of children aged <6 months

Respiratory Syncytial Virus

Treatment

- Amantidine/rimantidine
  - Symmetric amines
  - Inhibit viral uncoating by interfering with M2 protein
  - Approved for both treatment and prevention
  - If given within 48 hours of onset of symptoms, will decrease duration of illness by one day

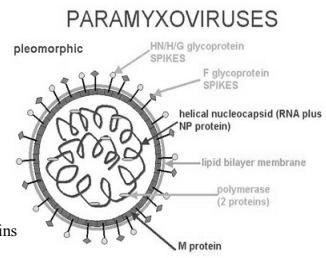
Respiratory Syncytial Virus

- **Paramyxovirus**
  - Genome encodes 10 viral proteins
    - F, G, SH- glycosylated surface proteins that mediate attachment of the virus to the host cell and fusion of the viral and cell membranes
    - N, L, and P- associate with RNA genome and form nucleocapsid and polymerase complex
    - M and M2- matrix proteins
    - NS1 and NS2 are non-structural proteins
  - Grows well in human cell lines and forms characteristic syncytia
  - Two groups of isolates have been identified and are designated A and B- circulate simultaneously during outbreaks

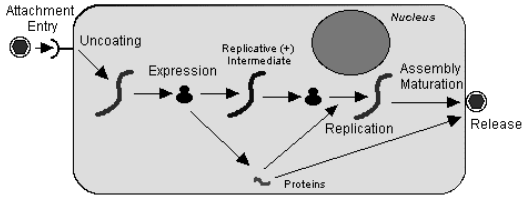
- Neuraminidase inhibitors
  - zanamivir and oseltamivir
  - Mimic sialic acid residues blocking neuraminidase
  - Efficacious against both influenza A and B

General Features of Paramyxoviruses

- Enveloped- lipid bilayer obtained from host cell
- Genome- single-stranded negative sense RNA
- Viral proteins
  - HN/H/G- attachment proteins
  - F- fusion protein
  - M- matrix protein
  - N- nucleoprotein
  - P/L- polymerase proteins



Paramyxovirus Replication



- **Epidemiology**
  - Ubiquitous
  - Virtually all children infected by age 2
  - Severe illness most common in young infants
    - Boys are more likely to have serious illness than girls
    - Lower socioeconomic background correlates with worse disease

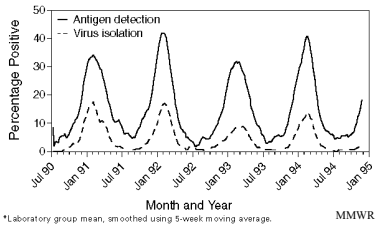
- **Pathogenesis**
  - Inoculation occurs through the nose or eyes and spreads through respiratory epithelium
  - Viral replication in the peribronchiolar tissues leads to edema, proliferation and necrosis of the bronchioles. Collections of sloughed epithelial cells leads to obstruction of small bronchioles and air trapping.
  - Pneumonia, either primary RSV or secondary bacterial may also develop. Pathology of RSV pneumonia shows multinucleated giant cells.

Striking seasonality in temperate climates

•Peaks in January

•Summer respite

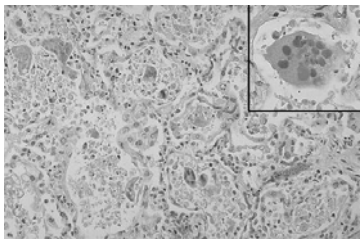
FIGURE 1. Percentage* of specimens positive for respiratory syncytial virus, by method of confirmation and week — United States, July 1, 1990-December 9, 1994



*Laboratory group mean, smoothed using 5-week moving average.

MMWR

Multinucleated giant cell formation in RSV pneumonia



- Clinical Features
  - Primary infection is usually symptomatic and lasts 7-21 days
    - Starts as URI with congestion, sore throat, fever
    - Cough deepens and becomes more prominent
    - LRT involvement heralded by increased respiratory rate and intercostal muscle retraction
    - Hospitalization rates can approach 40% in young infants
  - Reinfection in adults and older children
    - Rarely asymptomatic
    - Generally resembles a severe cold

- **Immunity**
  - Incomplete, reinfections are common
  - Cell-mediated immunity, as opposed to humoral, is important in protecting against severe disease.
  - Humoral immunity, in the absence of cell-mediated immunity, may predispose to more serious disease.

- Treatment
  - Supportive care
  - Bronchodilators
    - Studies suggest inhaled epinephrine more efficacious than inhaled ß-agonists
  - Ribavirin
    - Aerosol
    - High-risk individuals only

- High risk groups
  - Very young infants (<6 weeks) especially preemies
  - Older adults
    - Mortality from RSV pneumonia can approach 20% in this group
  - Children with bronchopulmonary dysplasia and congenital heart disease
  - Immunocompromised individuals
    - SCID
    - Transplant recipients
    - Hematologic malignancies

- Prevention
  - Gown and glove isolation in hospital
  - RSV immune globulin (RespiGam®) and palivizumab (Synagis®)- AAP recommendations
    - Children < 2 years with bronchopulmonary dysplasia and oxygen therapy in the 6 months prior to RSV season
    - Infants with gestational age < 32 weeks
    - Not approved for children with congenital heart disease
    - Being used anecdotally in immunocompromised individuals
  - No vaccine yet

- Diagnosis
  - Clinical, during outbreak
  - Virus isolation and growth
  - Rapid diagnostic techniques
    - Immunofluoresence
    - EIA/RIA
    - PCR
  - Serology

Rhinoviruses

- Most common cause of the common cold
- Cause 30% of all upper respiratory infections
- Over 110 different serotypes- prospects for a vaccine are pretty dismal

Viruses associated with the common cold		
Virus Group	**Antigenic Types**	**Percentage of cases**
Rhinoviruses	100 types and 2 subtypes	30-40%
Coronaviruses	3 or more	≥ 10
Parainfluenza viruses	4 types	
Respiratory syncytial virus	2 types	
Influenza virus	3 types	
Adenovirus	47 types	10-15
Other viruses		30-35

Adapted from Mandell, 5th edition

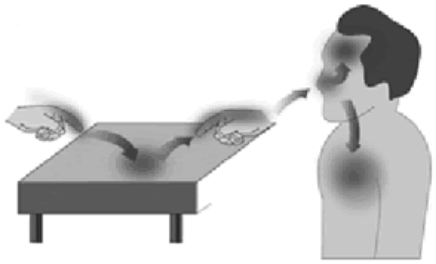
Epidemiology

- Kids are the reservoir for rhinoviruses and have the most symptomatic infections
- Worldwide distribution
- Seasonal pattern in temperate climates
  - Seen in early fall and spring
  - Less common in winter and summer

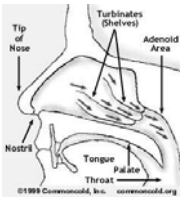
Molecular Biology

- Members of the picornavirus family
- Also includes enteroviruses and hepatitis A
- Small, non-enveloped, single stranded RNA viruses
- Grow best at 33°C- temperature of the nose
- Most use ICAM-1 as receptor

Transmission



- Enter through the nasal or ophthalmic mucosa
- Infect a small number of epithelial cells
- NO viremia; not cytolytic
- Symptoms most likely due to host immune response- especially IL-8



Clinical Manifestations

- You all know the symptoms
- Rhinovirus colds rarely have fever associated with them
- Most colds last about a week
- A non-productive cough following a cold can last up to 3 weeks- this is NOT bacterial bronchitis

Complications

- Sinusitis
  - 87% of individuals with colds will have CT evidence of sinusitis- this is mostly viral!
- Exacerbation of chronic bronchitis and asthma
- Distinguishing normal post-cold symptoms from true bacterial superinfection is tough

Lifelong Lessons

- You can't get flu from the flu vaccine
- You can't get worse flu because you were vaccinated
- You don't get a cold because you're cold/not wearing a hat/wet
- There is no moral or immunologic superiority associated with not getting colds
- Stand firm- Don't give out antibiotics for colds (or any other viral infections)

Treatment

- Tincture of time
- Symptomatic relief
  - Decongestants
  - Antihistamines
  - NSAIDs
- Randomized, controlled clinical trials have failed to show a benefit from vitamin C or Echinacea
- Virus specific therapies not practically useful

DO NOT GIVE ANTIBIOTICS FOR THE COMMON COLD

Myths of the Common Cold

- **susceptibility to colds requires a weakened immune system.**
- **Central heating dries the mucus membranes of the nose and makes a person more susceptible to catching a cold.**
- **Becoming cold or chilled leads to catching a cold.**
- **Having cold symptoms is good for you because they help you get over a cold, therefore you should not treat a cold.**
- **Drinking milk causes increased nasal mucus during a cold.**
- **You should feed a cold (and starve a fever).**

* From J. Gwaltney and F. Hayden's common cold website