

## The Respiratory Viruses

Influenza, RSV, and Rhinoviruses

- 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

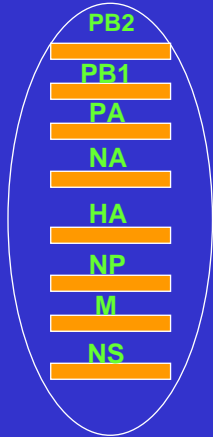


(From RDolin AmFamPhys 14:74, 136.)

## 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

## Influenza Virus Proteins



**PB1, PB2, PA:** polymerase proteins

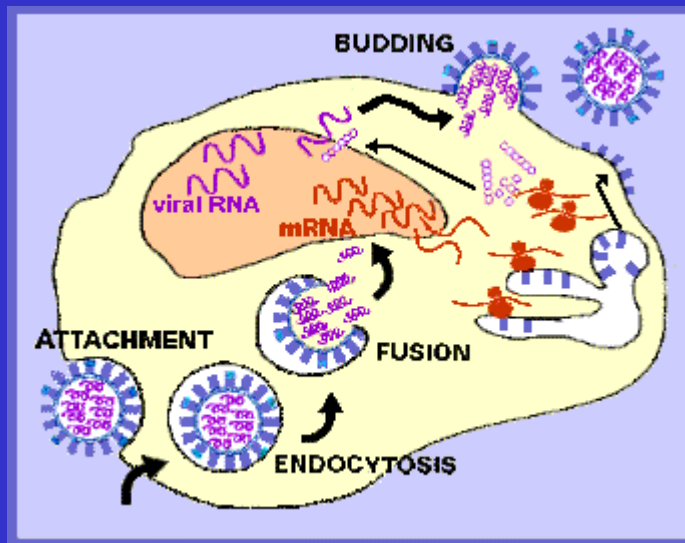
**NA:** neuraminidase protein- catalyzes removal of sialic acid residues and permits movement through mucous

**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

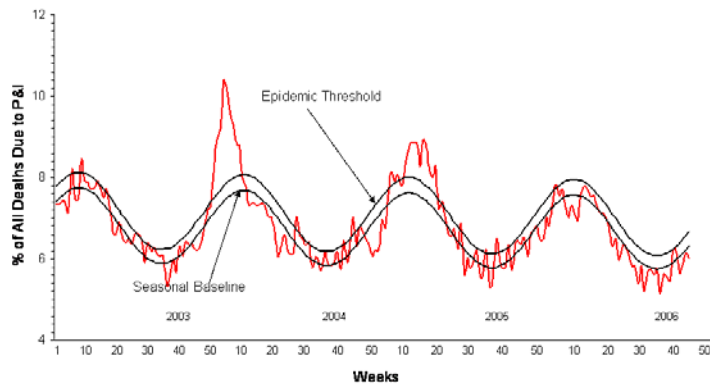
**NS:** nonstructural proteins



## Antigenic Drift and Shift

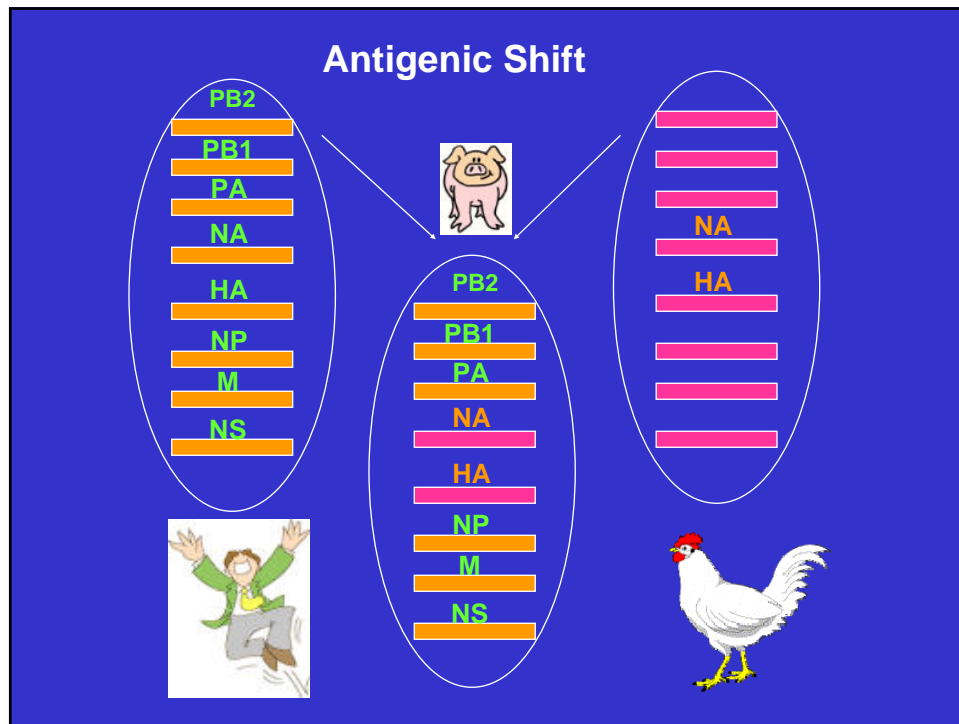
- Drift
  - Ongoing mutations within RNA encoding HA and NA proteins resulting in amino acid changes which decrease immune recognition
  - Seen in all types of flu, but influenza A has the greatest rate of change
  - Drift is responsible for the year to year variations in flu outbreaks

Pneumonia and Influenza Mortality  
for 122 U.S. Cities  
Week Ending 11/04/2006



- 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



## From Shift to Pandemic

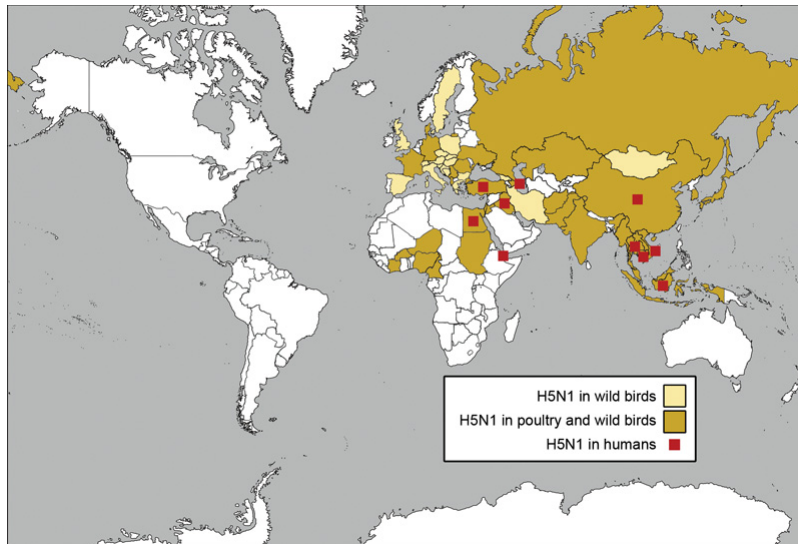
- Need a virus with HA and/or NA to which human population has little immunity
- Virus must replicate well in humans
- Virus must be transmissible from human to human

## 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

## The Next Pandemic: H5N1?

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



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

## 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

## Clinical Manifestations

- Classical

- fever- up to 106!

- chills

- headache

- myalgia

- arthralgia

- dry cough

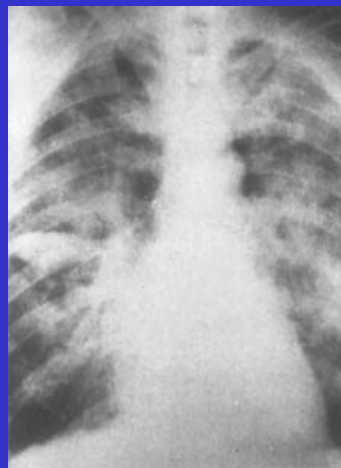
- nasal discharge

- Acute phase usually 4-8 days followed by convalescence of 1-2 weeks
- Many people are asymptomatic

## 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



## 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

## 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%

## 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%

## 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

## 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

## 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

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

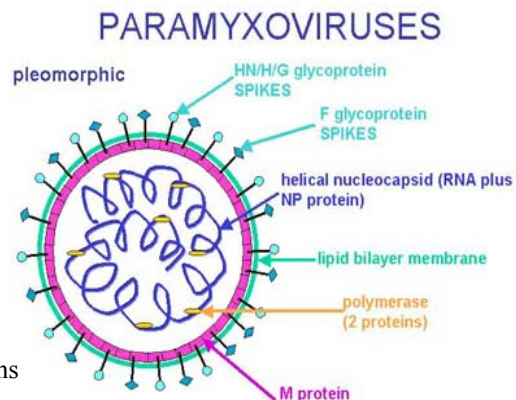
## Respiratory Syncytial Virus

# Respiratory Syncytial Virus

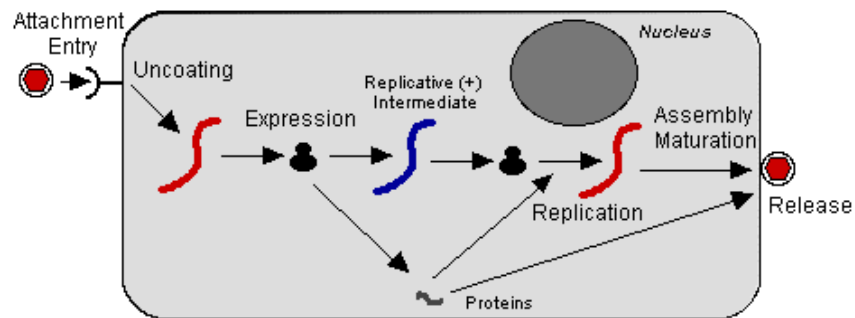
- **Paramyxovirus**
  - Genome encodes 10 viral proteins
    - F, G, SH- glycosylated surface proteins that mediate attachment of the virus to the host cell and fusion of the viral and cell membranes
    - N, L, and P- associate with RNA genome and form nucleocapsid and polymerase complex
    - M and 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

## 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



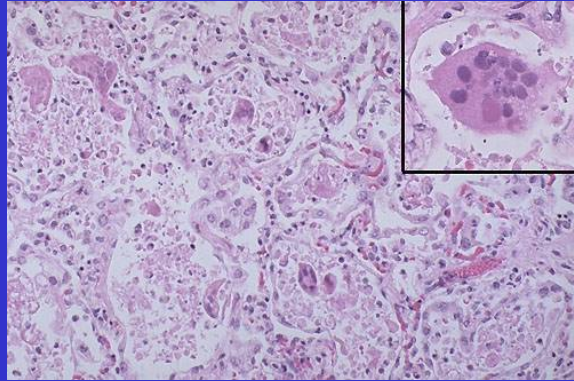
## Paramyxovirus Replication



### • 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.

## Multinucleated giant cell formation in RSV pneumonia



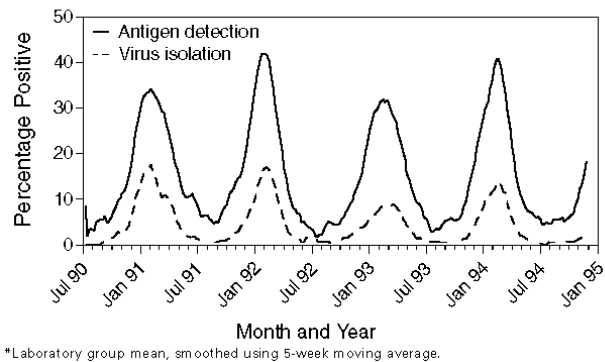
- **Epidemiology**

- 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

## 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



- 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.

- **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

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

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



- 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

## 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

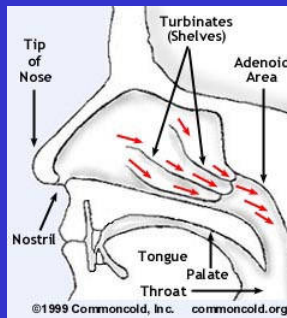
Virus Group	Antigenic Types	Percentage of cases
Rhinoviruses	100 types and 2 subtypes	30-40%
Coronaviruses	3 or more	≥ 10
Parainfluenza viruses	4 types	
Respiratory syncytial virus	2 types	
Influenza virus	3 types	
Adenovirus	47 types	10-15
Other viruses		30-35

Adapted from Mandell, 5<sup>th</sup> edition

## 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

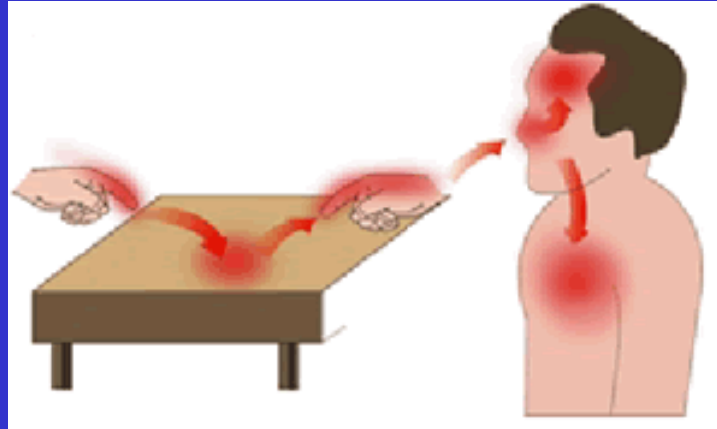
- Enter through the nasal or ophthalmic mucosa
- Infect a small number of epithelial cells
- NO viremia; not cytolytic
- Symptoms most likely due to host immune response- especially IL-8



## 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

## Transmission



## 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

## 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

## 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

## 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)

**DO NOT GIVE ANTIBIOTICS  
FOR THE COMMON COLD**

