Author(s): David Miller, M.D., Ph.D., 2009

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Respiratory Viruses

Infectious Diseases/Microbiology Sequence Course

David J. Miller, M.D., Ph.D.
Objectives

• Know the major respiratory viruses and their clinical presentation
  – influenza, rhinovirus, respiratory syncytial virus (RSV),
    coronavirus, adenovirus

• Appreciate key features of structure and replication strategies related to pathogenesis, treatment, and prevention

Reading assignment: Schaechter’s, 4th edition, chapters 32, 34, 36, and 39
30 year old generally healthy female returning from a trip to San Francisco in January sat in front of passenger on the plane who was coughing repeatedly throughout the flight. Two days later she developed fever to 39°C with shaking chills, non-productive cough, headache, and severe myalgias. Because of her severe symptoms she was bedridden for three days, but eventually fully recovered without specific treatment after a week and returned to work.
30 year old generally healthy female returning from a trip to San Francisco in January sat in front of passenger on the plane who was coughing repeatedly throughout the flight. Two days later she developed fever to 39°C with shaking chills, non-productive cough, headache, and severe myalgias. Because of her severe symptoms she was bedridden for three days, but eventually fully recovered without specific treatment after a week and returned to work.

Diagnosis?
Can this happen again?
Influenza virus

• Yearly impact for endemic/epidemic disease (CDC estimates)
  – >200,000 hospitalizations
  – Estimated 36,000 deaths (mortality rate <0.1%)
  – Greater than $1 billion (U.S.) economic loss

• Estimated impact for new pandemic disease
  – 500,000 to 700,000 hospitalizations
  – 100,000 to 200,000 deaths
  – Greater than $100 billion (U.S.) economic loss

• 2009 H1N1 pandemic (CDC estimates as of Feb. 2010)
  – U.S. - ~57 million cases, ~250,000 hospitalizations, ~11,000 deaths
  – International - 213 countries with confirmed cases
  – Economic losses ???

*Vaccine costs about $10 per person*
Influenza virus

- Family: *Orthomyxoviridae*
- Enveloped
- Negative (-) strand RNA genome, 8 (7) segments
- Three influenza types: A, B, C
# Comparison of Influenza A, B, and C Viruses

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severity of illness</strong></td>
<td>++++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Subtypes</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Animal reservoir</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Spread in humans</strong></td>
<td>Pandemic</td>
<td>Epidemic</td>
<td>Sporadic</td>
</tr>
<tr>
<td><strong>Antigenic changes</strong></td>
<td>Shift, drift</td>
<td>Drift</td>
<td>Drift</td>
</tr>
</tbody>
</table>
Influenza A Virus Structure

- **Hemagglutinin (HA)**
  - Receptor binding (sialic acid)
  - Membrane fusion
  - Neutralizing antibody target
- **Neuraminidase (NA)**
  - Remove sialic acid residues
  - Virion release
- **Ion channel (M2)**
  - H⁺-dependent uncoating
  - Influenza A only
- **Influenza A subtypes based on HA (16) and NA (9)**
  - H1N1, H3N2
  - A/Hong Kong/8/68
Influenza virus life cycle
Influenza Pathogenesis

• Direct cell lysis
  – Primary mechanism for influenza virus
  – Upper and lower respiratory tracts

• Role of immune response
  – Primarily protective rather than pathogenic
  – Induces virus- and type-specific immunity
  – Virus-mediated suppression (NS1 protein)

Why was the 1918 virus so deadly?
Influenza Epidemiology

Pneumonia and Influenza Mortality for 122 U.S. Cities
Week Ending 2/20/2010

- Pandemic: Rapid global spread
- Epidemic
- Endemic
- Winter

Source Undetermined
Influenza Antigenic Variation

- Antigenic drift

- Antigenic shift
Influenza Antigenic Variation

- Antigenic drift
  - Occurs with influenza A, B, and C
  - Small number of slowly occurring changes (mutations)
    - Error-prone viral RNA polymerase
  - HA changes most prominent, but can occur in any viral gene
  - Partially responsible for yearly vaccine changes
  - MAY result in breach of species barrier and pandemic
Health Alert Network

This is an official CDC HEALTH ADVISORY

Distributed via Health Alert Network.
Friday, December 19, 2008, 11:50 EST (11:50 AM EST)
CDCHAN-00279-2008-12-19-ADV-N

CDC Issues Interim Recommendations for the Use of Influenza Antiviral Medications in the Setting of Oseltamivir Resistance among Circulating Influenza A (H1N1) Viruses, 2008-09 Influenza Season
Influenza Antigenic Variation

• Antigenic shift
  – Influenza A only
  – Large dramatic changes that occur rapidly
  – Primarily responsible for pandemics
  – Due to gene shuffling and reassortment
  – Requirements
    • Segmented genome
    • Multiple HA and NA subtypes
    • Animal reservoir (wild aquatic birds)
    • Susceptible species for both avian and human influenza (swine)
Influenza Pandemics

1918 “Spanish influenza”
H1N1 influenza virus
Bird-to-human transmission of H1N1 virus

• All 8 genetic segments thought to have originated from avian influenza virus

1957 “Asian influenza”
H2N2 influenza virus
H2N2 avian virus – H1N1 human virus
Reassortment

• 3 new genetic segments from avian influenza virus introduced (HA, NA, PB1):

  Contained 5 RNA segments from 1918

1968 “Hong Kong influenza”
H3N2 influenza virus
H3 avian virus – H2N2 human virus
Reassortment

• 2 new genetic segments from avian influenza introduced (HA, PB1):

  Contained 5 RNA segments from 1918

Next pandemic influenza

Avian virus
Or
Avian virus – H3N2 human virus

• All 8 genes new or further derivative of 1918 virus

Please see: http://www.lincoln.ac.uk/dbs/images/birdflu1.jpg
Pathways for generation of virulent pandemic influenza viruses

Human influenza virus

Avian influenza virus

Intraspecies transmission

Interspecies transmission

Reassortment
Sialic acid linkages determine influenza virus HA receptor binding.

Human influenza virus specificity (H1N1, H3N2) uses α2,6-linkage, allowing binding to humans and pigs.

Avian influenza virus specificity (H5N1, H7N7) uses α2,3-linkage, allowing binding to birds and pigs.

Cell surface glycoprotein or glycolipid is the site of attachment for influenza viruses.
Different human airway epithelial cells can express either $\alpha_{2,3}$- or $\alpha_{2,6}$-linked sialic acid residues.

Human influenza virus ($\alpha_{2,6}$)

Avian influenza virus ($\alpha_{2,3}$)

Matrosovich et al., PNAS 101:4620, 2004
Origin of 2009 pandemic H1N1 influenza strain “quadruple reassortant”

Trifonov et al., NEJM 361:115, 2009
Xu et al., Scienceexpress, 25 March 2010
Influenza Clinical Manifestations

• Transmission
  – Airborne droplets

• Primary symptoms
  – Acute onset fevers, chills, headache, myalgias
  – Non-productive cough
  –Potentially severe even in generally healthy patients

• Complications
  – Young and elderly most susceptible
  – Viral and secondary bacterial pneumonia
  – Encephalitis
  – Reye syndrome (aspirin use)
Influenza Diagnosis, Treatment, and Prevention

• **Diagnosis**
  – Clinical suspicion
  – Virus detection (nasal swab)
  – Culture, antigen (DFA), or genome (RT-PCR) detection

• **Treatment**
  – Symptomatic
  – M2 channel blockers
    • Amantidine and rimantadine
  – Neuraminidase inhibitors
    • Oseltamivir (oral) and zanamivir (inhaled)
    • *Peramivir (IV)* – CDC issued EAU in late fall, 2009
  – NO ANTIBIOTICS (unless concern for bacterial superinfection present)

• **Prevention**
  – Prophylaxis
  – Vaccination
TRUE or FALSE?

There is very small yet scientifically validated link between childhood vaccination and autism.
<table>
<thead>
<tr>
<th>Vaccine-Preventable Diseases, 2009a</th>
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</thead>
<tbody>
<tr>
<td><strong>Adult</strong></td>
</tr>
<tr>
<td>Tetanus</td>
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<tr>
<td>Diphtheria</td>
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<tr>
<td>Pertussis (whooping cough)</td>
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<tr>
<td>Measles</td>
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<tr>
<td>Mumps</td>
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<tr>
<td>Rubella</td>
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<tr>
<td>Varicella (chickenpox)</td>
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<tr>
<td>Influenza</td>
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<tr>
<td>Pneumococcal diseases</td>
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<tr>
<td>Hepatitis A</td>
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<tr>
<td>Hepatitis B</td>
</tr>
<tr>
<td>Meningococcal diseases</td>
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<tr>
<td>Herpes zoster (shingles)</td>
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<tr>
<td>HPV (cervical cancer)</td>
</tr>
</tbody>
</table>

*For specific dosing criteria based on age, medical condition, and other conditions, refer to the ACIP recommended immunization schedules.*

ACIP: Advisory Committee on Immunization Practices; HIB: Haemophilus influenzae type b; HPV: human papillomavirus.

Source: References 3, 4.

Pre-vaccine annual U.S. cases/deaths
- 150,000/15,000
- 200,000/10,000
- 3,500,000/500
- 200,000/100
- 60,000/rare
- 4,000,000/100
- 25,000/2,000
- 20,000/1,000

(500,000 deaths worldwide)

Smallpox (total 300-500 million deaths during 20th century worldwide)
Influenza Vaccines

• Three general types
  – Killed virus (TIV – trivalent inactivated influenza vaccine)
  – Live virus (LAIV – live attenuated influenza vaccine)
  – Genetically engineered, subunit (in development)

• Very effective (70-80%)
  – Dependent on virus match (only 40% in 2007-2008)

• Contain three different viruses
  – 2 influenza A subtypes, 1 influenza B strain
  – 2009-2010 vaccine: A/Brisbane/59/2007 (H1N1), and A/Brisbane/10/2007 (H3N2), B/Brisbane/60/2008
  – 2010-2011 vaccine: A/California/7/2009 (pandemic H1N1), A/Perth/16/2009-like (H3N2), and B/Brisbane/60/2008

• Changes (possible) every year

• Should be administered yearly
Influenza Vaccine Recommendations – Children (prior to 2010)

- All children aged 6 months to 18 years (new recommendation for 2008-2009 season)

- High priority populations
  1. Very young (age 6 months to 4 years)
  2. Chronic pulmonary, cardiovascular, renal, hepatic, hematologic, or metabolic disorders
     Includes children with asthma and diabetes
  3. Immunosuppression
  4. Aspiration risk (e.g. seizure disorder, spinal cord injury)
  5. Long-term aspirin therapy
  6. Chronic care facility residents
  7. Anticipated pregnancy during influenza season

Influenza Vaccine Recommendations – Adults (prior to 2010)

- **Anyone who wants it**
  - **Exceptions:** egg allergies and previous adverse reactions to vaccine

- **High risk populations**
  1. Persons aged $\geq 50$ years
  2. Chronic pulmonary, cardiovascular, renal, hepatic, hematologic, or metabolic disorders
     - Includes children with asthma and diabetes
  3. Immunosuppression
  4. Aspiration risk (e.g. seizure disorder, spinal cord injury)
  5. Chronic care facility residents
  6. Anticipated pregnancy during influenza season
  7. Health care workers
  8. Close contacts/caregivers of children $< 5$ years and adults $\geq 50$ years and patients with high risk medical conditions

Influenza Vaccine Options

- TIV (inactivated) approved for ALL patients

- LAIV (attenuated) exceptions
  - Persons age <2 or ≥ 50 years
  - Children 2-4 years old with history of possible reactive airway disease
  - High risk for influenza-related complications
  - Caregivers of severely immunosuppressed patients (e.g. BMT)
  - Pregnancy

A panel of immunization experts voted today (February 24, 2010) to expand the recommendation for annual influenza vaccination to include all people aged 6 months and older. The expanded recommendation is to take effect in the 2010-2011 influenza season. The new recommendation seeks to remove barriers to influenza immunization and signals the importance of preventing influenza across the entire population.

The Advisory Committee on Immunization Practices (ACIP) (http://www.cdc.gov/vaccines/recs/acip/), which advises the Centers for Disease Control and Prevention (CDC) (http://www.cdc.gov) on vaccine issues, voted on the new recommendation during its February 24, 2010 meeting in Atlanta. The vote took place against a backdrop of incremental increases in the numbers and groups of people recommended for influenza vaccination in years past, and lessons learned from the world’s still ongoing first flu pandemic in 40 years.

Prior to today’s vote, ACIP recommendations for seasonal influenza vaccination—which focused on vaccination of higher risk persons, children 6 months through 18 years of age and close contacts of higher risk persons—already applied to about 55 percent of the U.S. population.

Discussion at the ACIP meeting focused on the value of protecting all people 19 to 49 years of age, who have been hard hit by the 2009 H1N1 pandemic virus, which is likely to continue circulating into next season and beyond. Another reason cited in favor of a universal recommendation for vaccination is that many people in currently recommended “higher risk” groups are unaware of their risk factor or that they are recommended for vaccination. The ACIP discussion also recognized the practicality and value of issuing a simple and clear message regarding the importance of influenza vaccination in the hopes that this would remove impediments to vaccination and expand coverage. Finally, new data collected over the course of the 2009 H1N1 pandemic indicates that some people who do not currently have a specific recommendation for vaccination may also be at higher risk of serious flu-related complications, including those people who are obese, post-partum women and people in certain racial/ethnic groups.
42 year old generally healthy male student returned from Christmas break and developed acute onset of clear rhinorrhea, mild sore throat, and low grade fevers. He had very minimal cough and no myalgias, and felt well enough to return to classes. Symptoms spontaneously resolved within a week.
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Diagnosis?
Rhinovirus

- **Family:** *Picornaviridae*
  - Other members: coxsackie viruses, poliovirus, hepatitis A virus
- Non-enveloped
- Non-segmented positive (+) strand RNA genome
- > 100 serotypes known
Rhinovirus life cycle

- Cellular receptor (species barrier)
  - ICAM-1 (90%)
  - VLDL receptor (10%)

- Entirely cytoplasmic

- Replication most efficient at 33°C

* Antiviral drug targets

Source Undetermined
Rhinovirus Pathogenesis

• Minimal direct virus-induced cell damage
  – Primarily upper respiratory tract

• Role of immune response
  – Inflammatory response correlates with symptoms
  – Responsible for COPD and asthma exacerbations
  – Induces serotype-specific immunity
Rhinovirus Clinical Manifestations

- **Transmission**
  - Aerosol (sneezing)
  - Direct transmission (fomites)

- **Primary symptoms**
  - Rhinorrhea, sore throat, minimal cough, low grade fever
  - Generally mild

- **Complications**
  - Asthma/COPD exacerbations
Rhinovirus Diagnosis, Treatment, and Prevention

• **Diagnosis**
  – Clinical suspicion

• **Treatment**
  – Symptomatic
  – Enormous market for “alternative” medications
  – NO ANTIBIOTICS

• **Prevention**
  – Vaccine development unlikely (mild disease, serotypes)

  “Wash your hands!”
83 year old male nursing home resident with history of coronary artery disease, hypertension, and emphysema in April developed low grade fever, nasal congestion, and a non-productive cough. There were numerous other residents with similar symptoms over the past month. His cough progressed over two weeks and was keeping his roommate awake at night. He was eventually taken to the hospital when he began having trouble breathing, and despite being given numerous antibiotics he died within a week due to respiratory failure.
83 year old male nursing home resident with history of coronary artery disease, hypertension, and emphysema in April developed low grade fever, nasal congestion, and a non-productive cough. There were numerous other residents with similar symptoms over the past month. His cough progressed over two weeks and was keeping his roommate awake at night. He was eventually taken to the hospital when he began having trouble breathing, and despite being given numerous antibiotics he died within a week due to respiratory failure.

Diagnosis?
Respiratory syncytial virus (RSV)

- **Family: *Paramyxoviridae***
  - Parainfluenza virus, human metapneumovirus
  - Measles (rubeola) and mumps viruses

- **Enveloped**

- **Non-segmented negative (-) strand RNA genome**
  - No reassortment

- **Two major groups (A and B)**
RSV Structure

- **G protein (HN)**
  - Hemagglutinin and neuraminidase
  - Receptor binding (target unknown)
  - Group determinant

- **F protein**
  - Promotes virus-cell and cell-cell fusion
  - Candidate vaccine target
  - Target for palivizumab (preventive monoclonal antibody)
RSV Pathogenesis

- **Extensive direct virus-induced damage**
  - Primarily epithelial cells in lower respiratory tract

- **Intense inflammatory response**
  - Skewed inflammatory response ($T_H^2$-like) may contribute to severe disease
  - Induces only partially effective immunity

Hallmark of RSV pathology is “bronchiolitis”

- Bronchiole obstruction with mucus and necrotic cells
- Peribronchiole inflammation
RSV Clinical Manifestations

• Transmission
  – Aerosol (sneezing)
  – Direct transmission (fomites, contagious secretions)
  – Highly infectious and ubiquitous (~100% children infected by 2 yo)

• Primary symptoms (mild to severe)
  – URI (rhinorrhea, sore throat, minimal cough, low grade fever)
  – Bronchitis (cough)
  – Bronchiolitis (wheezing, dyspnea)
  – Pneumonia (severe dyspnea, tachypnea, hypoxemia)

• High risk groups for complications
  – Premature infants
  – Cardiopulmonary disease
  – Immunocompromised patients
RSV Diagnosis, Treatment, and Prevention

• **Diagnosis**
  – Clinical suspicion
  – Culture, antigen (DFA), or genome (RT-PCR) detection

• **Treatment**
  – Symptomatic
  – Ribavirin of questionable utility
  – NO ANTIBIOTICS

• **Prevention**
  – Passive immunization (Palivizumab)
    • EXPENSIVE (~$77,000 to prevent one hospitalization annually)
  – Live attenuated vaccine development underway
    • Deaths associated with inactivated vaccine in 1960’s
Other respiratory viruses

• **Coronaviruses (e.g. SARS)**
  – Enveloped, positive (+) strand RNA viruses
  – Typically cause mild respiratory tract symptoms

• **Adenoviruses**
  – Non-enveloped DNA viruses
  – Many (~50) serotypes
  – Associated with mild URI symptoms, pharyngoconjunctivitis, and GI disease
  – Can cause severe pneumonia
<table>
<thead>
<tr>
<th>Commandment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>I am the Lord of Antimicrobial Agents. Do not holdeth Antipyretics before me. Antimicrobial agents are not antipyretics. If you wish to treat a fever do so, but not with antimicrobials.</td>
</tr>
<tr>
<td>II</td>
<td>Thou shalt remember the history and physical and keep it Holy. A good history and physical examination will be very useful in the diagnosis of infection.</td>
</tr>
<tr>
<td>III</td>
<td>Thou shalt not bear false witness upon the location of the host. You need to distinguish between community- and hospital-acquired infections.</td>
</tr>
<tr>
<td>IV</td>
<td>Thou shalt not forget the little things. Ask about travel, jobs, pets, immunizations, other people with the same symptoms, etc.</td>
</tr>
<tr>
<td>V</td>
<td>Thou shalt knoweth thy neighbors. Certain organisms cause infections in certain organ systems.</td>
</tr>
<tr>
<td>VI</td>
<td>Thou shalt useth what worketh, and thou shalt not covet thy apothecary’s new agents without a good reason. Use antimicrobial agents with proven efficacy for the suspected or known infection.</td>
</tr>
<tr>
<td>VII</td>
<td>Thou shalt remembereth primum non nocerum. When given a choice, avoid toxicity.</td>
</tr>
<tr>
<td>VIII</td>
<td>Thou shalt treateth what thou findeth. When the infection is established and sensitivities known, try to use the narrowest spectrum agents.</td>
</tr>
<tr>
<td>IX</td>
<td>Thou shalt not killeth thy own pharmacy budget. After choosing for high efficacy and lowest toxicity, consider cost as a variable and try to aim low.</td>
</tr>
<tr>
<td>X</td>
<td>Thou shalt study thy adversary. Learn about the natural history of what you are treating and how it responds to therapy.</td>
</tr>
</tbody>
</table>
Slide 6: Source Undetermined
Slide 9: Source Undetermined
Slide 11: Source Undetermined
Slide 12: David Miller
Slide 16: Source Undetermined
Slide 19: Centers for Disease Control and Prevention, http://www.cdc.gov/
Slide 23: Source Undetermined
Slide 24: Matrosovich et al., PNAS 101:4620, 2004
Slide 26: James Gathany, CDC Public Health Image Library #11162
Slide 34: Centers for Disease Control and Prevention, http://www.cdc.gov/
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