Overview of the Influenza Virus

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General Features of Influenza Virus Infections
Clinical Features of Influenza

- Sudden onset of symptoms
- Incubation period: 1 - 4 days
- Infectious period
  - Adults: 6 days, from 1 day before symptoms
  - Children: ≥10 days, from ≤6 days before symptoms
- Varying symptomatology
  - Fever, cough, sore throat, runny or stuffy nose, body aches, headache, chills, fatigue
  - Sometimes can have diarrhea and vomiting

Influenza Virus Illness

Characteristics

- high infectivity
  ♦ shortly before symptoms
  ♦ ends shortly after pyrexia

Mandal BK et al. Lecture Notes on Infectious Diseases. 1996.
Influenza Virus Illness

Characteristics

- high infectivity
- attack rates up to 5-20%


Influenza Virus Illness

Characteristics

- high infectivity
- attack rates up to 5-20%
- subclinical infection common


Influenza Virus Illness

Characteristics

– high infectivity
– attack rates up to 5-20%
– subclinical infection common
– transmission
  ♦ infected droplets
  ♦ contact with contaminant

Mandal BK et al. Lecture Notes on Infectious Diseases. 1996.
Influenza Virus Illness

Characteristics

- high infectivity
- attack rates up to 5-20%
- subclinical infection common
- transmission
- cytopathic to respiratory tract
  - Primary influenza pneumonia
  - Secondary bacterial infections

Mandal BK et al. Lecture Notes on Infectious Diseases. 1996.
Influenza Virus

Characteristics

- high infectivity
- attack rates up to 5-20%
- subclinical infection common
- transmission
- cytopathic to respiratory tract
- viral characteristics
  - genome: 8 RNA fragments
  - nucleocapsid, lipid envelope
  - two surface antigen proteins
    - Hemagglutinin (HA)
    - Neuraminidase (NA)

Influenza Virus Health Risk

Characteristics

– influenza A
  ♦ affects all age groups

– moderate to severe illness
– groups with increased risk for complications include:
  • Children < 5, especially those <2
  • Individuals over 65
  • Pregnant women
  • People with underlying conditions, including immunocompromise

Influenza Virus
Influenza Virus
Orthomyxoviridae

Non-structural proteins
- NS1
- NEP
- PB1-F2

RNP Complex
- NP (nucleoprotein)
- RNA (negative sense)
- Polymerase complex (PA, PB1, PB2)

11 proteins on 8 (-) strand RNA gene segments (~ 14 kb)
Influenza Virus Infection Cycle

Laver et al. Scientific American (1999)
Influenza A Viruses in Nature
The Ecology of Influenza A Viruses (HA)
The Ecology of Influenza A Viruses (HA)

Bird Flu (H5N1)
Influenza Viruses: Pandemics and Epidemics
The Ecology of Influenza Viruses

• Wild aquatic birds are the natural reservoirs of all influenza A viruses in other species

• In wild aquatic birds, influenza viruses replicate predominantly in the intestinal tract and are shed by fecal oral transmission often through water
Influenza Virus Pandemic: Antigenic Shift

- pandemics
  - every 1-2 decades
- influenza A virus changes
  - antigenic shift
    - major sudden change
    - exchange of genes in animal reservoir

The Ecology of Influenza Viruses

Direct transmission from birds to humans
H5N1, H7N9
Uncommon

Avian Species
- HA: NA
- H1: N1
- H2: N2
- H3: N3
- H4: N4
- H5: N5
- H6: N6
- H7: N7
- H8: N8
- H9: N9
- H10
- H11
- H12
- H13
- H14
- H15
- H16

Humans
- HA: NA
- H1: N1
- H2: N2
- H3

Pigs
- HA: NA
- H1: N1
- H3: N2

Dominant subtypes
- H1N1: 1918-1956
- H2N2: 1957-1967
- H3N2: 1968-Present
- H1N1: 1977-Present

Dominant subtypes
- H1N1, H1N2, H3N2
The Ecology of Influenza Viruses

• Influenza viruses in their natural reservoirs tend to be in evolutionary stasis

• Rapid evolution can occur after transfer to new hosts (antigenic drift)
  • Pandemic influenza viruses often become epidemic influenza

• Most interspecies transmissions are transitory and do not result in stable lineages
Influenza Virus Epidemic: Antigenic Drift

- epidemics
  - every 1-3 years
- influenza A mutation
  - antigenic drift
    - small continuous change
    - RNA point mutations

Influenza Virus: Antigenic Sites

Antigenic Drift

- Small, continuous change:
  - H3 remains H3, but escapes host immunity
  - Major antigenic changes lead to epidemics and vaccine updates

Smith et al., Science 305:371, 2004
Recent History of Influenza Pandemics

- Influenza pandemic 1918
  - Influenza A virus isolated (H1N1)
  - 40 million deaths worldwide
- 1933
- 1940
- 1945
- 1952
- Emergence of H2N2 (antigenic shift)
- WHO global influenza surveillance network established
- 1957
- Emergence of H3N2 (antigenic shift)
- 1968
- 1977
- Re-emergence of seasonal H1N1
- 1997
- 2009
- H5N1 (avian) Infections in humans
- Swine-Origin Influenza Virus (H1N1) Pandemic
- Vaccine does not protect against H1N1 (antigenic drift)
Recent History of Influenza Pandemics

- **1918**: H1N1
- **1933**: H1N1
- **1940**: H2N2
- **1945**: S-OIV (H1N1)
- **1952**: H3N2
- **1960s**: B
- **1968**: B
- **1977**: B
- **1997**: B
- **2009**: S-OIV (H1N1)
Other Human Influenza Viruses
Influenza Virus

Characteristics

– influenza B

– causes relatively few cases
  ♦ sporadic infections

Influenza Virus

Characteristics

- influenza B
- causes relatively few cases
- local epidemics
  ♦ about every 2 years

Influenza Virus

Characteristics

- influenza B

- causes relatively few cases
- local epidemics
  - about every 2 years
- especially children

Influenza Virus

Characteristics

- influenza B
- causes relatively few cases
- local epidemics
  - about every 2 years
- especially children
- influenza B mutation
  - antigenic drift
    - small continuous change
    - RNA point mutations

Influenza Virus

Characteristics

- influenza B
  - antigenic drift

- causes relatively few cases
- local epidemics
  - about every 2 years
- especially children
- influenza B mutation
  - antigenic drift
    - small continuous change
    - error prone RNA polymerase
  - antigenic shift
    - no antigenic shift

Influenza Virus

Characteristics

– influenza C

– rarely causes human disease


Secondary Bacterial Infections
Influenza A Virus

- Acute respiratory illness
- Annual influenza virus burden in US
  - 41,000 deaths (primarily in elderly)
  - 114,000 hospitalizations
  - 25 million physician visits
  - 95 million infections/illnesses
  - $3-15 billion (seasonal estimate)
Secondary bacterial infections

- R.T.H. Laennec was the first to describe secondary bacterial infections following influenza.

- He noted that the prevalence of pneumonia increased during an epidemic of “la grippe” in 1803 in Paris.

- Today it is well-appreciated that many influenza-related deaths are due to secondary invaders such as Streptococcus pneumoniae, Staphylococcus aureus (including MRSA), and Streptococcus pyogenes (Group A Strep).

Influenza virus and GAS

- GAS shares a common seasonality with influenza viruses\textsuperscript{1,2}.

- 28% of lungs in 1918 pandemic contained GAS\textsuperscript{3}.

- In the 2009-10 pandemic (H1N1), bacterial secondary infections were responsible for approximately 29% of the total fatalities, and of these ~27% were attributed to GAS\textsuperscript{4}.

- GAS and \textit{S. pneumoniae} were the major cause of parapneumonic empyema in Utah during 2009 pandemic\textsuperscript{5}, and GAS association with influenza has continued to increase since 2009\textsuperscript{6-8}.

\textsuperscript{1}Peltola and McCullers, \textit{Pediatr Infect Dis J.}, 2004; 23:S87
\textsuperscript{2}Lee et al., \textit{Vaccine}. 2008; 26:3383
\textsuperscript{3}Chien et al., \textit{N. Engl. J. Med.}, 2009; 361:2582
\textsuperscript{5}Ampofo et al., \textit{Pediatr. Infect. Dis.}, 2009; 29:905
\textsuperscript{6}Scaber et al., \textit{Euro. Surveill.}, 2011, 16:19780
\textsuperscript{7}Tasher et al., \textit{Clin. Infect. Dis.}, 2011, 53:1199
\textsuperscript{8}Zakikhany et al., \textit{Euro. Surveill.}, 2011, 16:19785
1918 Pandemic Influenza

Morbidity and Mortality

- United States
  - 25 million infected
  - 500,000 died
- England & Wales
  - 200,000 died
- Worldwide
  - 500 million stricken
  - mortality
    ♦ low: 20 Million
    ♦ high: 100 Million

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Impact Of 1918 Influenza
On Life Expectancy

Both sexes: Life expectancy in the United States, 1900–2001

Pandemic Influenza: Age-Related Mortality

Data for 1892 for Massachusetts only.
Dowdle WR. *Bull World Health Org.* 1999;77:820-828
Summary

• Influenza viruses infect humans and other animal species
• Their genetic makeup and infection cycle allow them to transmit between species
• Antigenic shift can lead to a pandemic
• Antigenic drift causes epidemics
• Influenza mortalities are typically due to complications from secondary bacterial infections
What does the future hold?

- H5N1
- H7N9
- H9N2
- H10N8

2009 pandemic was caused by H1N1 virus