Influenza and Other Viral Infections

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Modes of Respiratory Infection Transmission

• Direct Contact
  – Inoculation from hands or fomites (objects)

• Large droplet
  – Particles >10μm land on mucosa of a susceptible individual in close proximity

• Airborne Transmission
  – Fine particles (droplet nuclei or residue) <5μm are inhaled & deposited in the respiratory tract, initiating infection.
Classification of Aerosol Transmission of Disease

- **Obligate**
- **Preferential**
- **Opportunistic**

Obligate Airborne Transmission

- Target cells only present in distal lung
  - Infection must initiate in alveoli and/or small airways
  - Fine particle aerosols required to reach target
- **Agents**
  - *Mycobacterium tuberculosis*
  - *(H5N1 Influenza A?)*
Preferential Airborne Transmission

• Target cells present in upper and lower airways
  – Infection can initiate anywhere in respiratory tract.
  – Fine particles, larger droplets, and fingers can reach target

• Modified or attenuated disease if not via lower airways
  – Variolation
    • Skin inoculation or nasal insufflation → milder disease ↓ mortality
  – Experimental influenza:
    • Severity: nose drops << aerosols
    • Infectious dose: nose drops >> aerosols

• Agents:
  – Influenza, measles, smallpox, varicella-zoster, adenovirus, *Bacillus anthracis*

Opportunistic Airborne Transmission

• Target cells present in upper and lower airways and/or GI tract
  – Infection can initiate anywhere in respiratory tract and/or GI tract.
  – Fine particles, larger droplets, and fingers can reach target
  – May require agent to be swallowed after deposition

• Same disease and severity regardless of route
• Often via transmitted via other routes
  – Efficiently transmitted via aerosols in certain environments.
• Agents:
  – Rhinovirus, possibly norovirus and rotavirus
The Aerobiological Pathway for Transmission of Communicable Respiratory Disease

A: Source, B: Transport and Dispersion, C: Deposition

Viral Infectious Diseases Associated with Preferential or Opportunistic Aerosol Transmission

- Influenza virus
  - Seasonal
  - Pandemic
- Corona virus
  - SARS
- Measles virus
- Varicella-zoster
- Variola major
- Rhinovirus

*New diseases are emerging at the unprecedented rate of one a year for the last two decades, and this trend seems certain to continue.*

SARS??

Amoy Gardens
Model of the Movement of the Virus-Laden Plume

Airborne Transmission: Boeing 737-300 Flight 2 from Hong Kong to Beijing
Probable cases of SARS by reported source of infection, Singapore, Feb 25 – Apr 30 (MMWR)

SARS: Toronto Emergency Room

March 16th, 22:45-23:30
Emergency SGH
SARS and Masks

- N95 and surgical mask protective in ICU
- RR = 0.5 N95 compared with mask (ns)

Loeb M et al. EID 2004;10:251
Influenza

• Influenza: viral respiratory infection characterized by upper and lower respiratory symptoms, fever, generalized malaises and myalgias.

• Complications include viral pneumonia, bacterial superinfection, cytokine storm.

• Wide range of clinical outcome of infection, from asymptomatic to fatal.

### Table 1

<table>
<thead>
<tr>
<th>Subtypes</th>
<th>Humans</th>
<th>Swine</th>
<th>Pigeons</th>
<th>Horses</th>
<th>Birds</th>
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<tbody>
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<td>Sw/1938/30</td>
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<td>H1/1808</td>
<td>Sw/Florida/73</td>
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<td>Sw/1938/30</td>
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</tbody>
</table>

*The reference strains of influenza viruses, or the first isolates from that species, are presented.*

*Current subtype designations. From ref. 53A, with permission.*

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### Influenza A virus subtypes in the human population

![Diagram showing influenza A virus subtypes](image)

**Figure 2** Influenza A viruses circulating in the human population. Viruses with three different hemagglutinin subtypes (H1, H2 or H3) and two neuraminidase subtypes (N1 or N2) have been identified in humans. Solid squares indicate the introduction of the pandemic H1N1, H2N2 and H3N2 strains in 1918, 1957 and 1968, respectively. In 1977, H1N1 viruses similar to those of 1950 were reintroduced. Broken lines indicate the absence of virus isolates and only indirect evidence for circulating strains based on serologic data.

Palese P. Nat Med 2004; 12: S82-S87
Influenza Global Impacts

- Human influenza: 500,000 deaths /y globally in a “good” year.
- Three pandemics in 20th century
  - Deaths ranged from ~2 million (1968) to 50 -100 million (1918)
  - Another pandemic expected eventually
- Avian flu (H5N1)
  - 243 deaths / 385 cases, 16 countries, 2003-08 (19 June)
Important properties of avian influenza A(H5N1)

- High mortality/case ratio (~60%)
- No (or very few) asymptomatic case
- Death by viral pneumonia / cytokine storm
- Viremia and visceral dissemination
- No prior immunity in the population

Sources of Evidence Regarding Role of Aerosols in Transmission of Influenza A Virus

- Outbreak reports
- Experimental infection of humans
- Animal experimentation
- Zanamivir trials
- Livermore Veterans Study
- New data on exhaled breath
An Airplane Outbreak Report

- Airplane passengers: plane grounded 4 hr, 1 source case, 72% passengers became ill within 72 hours. Lower attack rate among persons who got off during delay. (Moser MR et al. 1979)

Experimental Infection of Human “Volunteers”

- Permit clear separation of aerosol route from transmission by large droplets
  - Homogeneous small particle aerosols without large droplets
  - Large droplets transmission by intranasal drops (no accompanying aerosols)
Experimental Design

- Human “volunteers”
  - Antibody levels measured
- Aim at establishing Human infectious Dose 50% (HID$_{50}$); very low doses of virus
- Aerosolized virus from culture;
  - 1-3 μm, RH 45-55%
- 10 liters of aerosol administered by mask

Alford et al
Results

• Neutralizing antibodies are protective
• 1 HID<sub>50</sub> = 0.6 - 3 TCID<sub>50</sub>

Comparison of Human Infectious Dose of Influenza A Virus by Aerosol or Intranasal Route

• Aerosol (airborne):
  HID<sub>50</sub> = 0.6 to 3 TCID<sub>50</sub>
• Intranasal (large droplet)
  HID<sub>50</sub> = 127 to 320 TCID<sub>50</sub>

Couch et al J Infect Dis 1971; 124: 473-80
Couch et al J Infect Dis 1974; 129: 411-420
Douglas R.G. Influenza in Man. Pp 375-447 in
The Influenza Viruses and Influenza, Kilbourne E.D. ed,
Academic Press, New York 1975.)
“When the infectious dose deposited by aerosol in the nose is smaller than the infectious dose by nasal drops, it is probable that the lower respiratory tract is the site of initiation of infection” (V. Knight)

Animal Models

- Ferrets: transmission of influenza A from sick to healthy ferrets through straight, S or U-shaped ducts (Andrewes and Glover 1941)
- Mice: infected via influenza aerosol generator (Edward D et al., 1943)
- Mice: inverse correlation between air exchange and infection rate regardless of mice proximity, infectious particles found in air (Schulman JL, 1967; Schulman JL, 1968)
- Guinea pig: transmission over distance of 91 cm only in direction of airflow and affected by RH and temperature (Lowen et al, 2006, 2007)
“Droplet” transmission of Pan/99 virus among guinea pigs

Inhibition of Influenza A Virus Aerosol Transmission by High RH

Lowen A. C. et al. PNAS 2006; 103:9988-9992

Lowen AC et al PLOS Pathogens 2007; 3: 1470-1476
Hemmes et al 1962; Antonie Van Leeuwenhoek 1962; 28: 221-233

**Median diameter:**

5-6 μm

**RH Effect on Survival of Virus Aerosols**

Fig. 6. Survival curves of poliomyelitis (PoLV) and influenza (FluV) virus aerosolized in mixed suspensions at 20°C.

**Inhibition of Influenza A Virus Aerosol Transmission by High Temperature**

Lowen AC et al PLOS Pathogens 2007; 3: 1470-1476
Absence of Effect of Temperature on Contact Transmission of Influenza A Virus


Hong Kong

CM Wong et al. PLoS Medicine 2006
Short-Term Treatment with Zanamivir to Prevent Influenza: Results of a Placebo-Controlled Study

Lauren Kaiser, Dan Henry, Nancy P. Flack, Oliver Kearns, and Frederick G. Hayden

From the Division of Epidemiology and Virology, Department of Internal Medicine, University of Virginia School of Medicine, Charlottesville; Brookhaven Clinic, Salt Lake City, Utah; VHA
Veterans Research Triangle Park, North Carolina; and VHA
Wellcome Research and Development, Greensford, Middlesex, United Kingdom

Table 2. Incidence of symptomatic influenza (S) or asymptomatic influenza (AS) after initiation of prophylaxis, by treatment group.

<table>
<thead>
<tr>
<th>Proven influenza</th>
<th>Placebo (n = 144)</th>
<th>Inhaled (n = 144)</th>
<th>Inhaled and Inhaled</th>
<th>Total no. of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>S or AS during 21 d after initiation</td>
<td>27 (19)</td>
<td>28 (21)</td>
<td>16 (11)</td>
<td>21 (14)</td>
</tr>
<tr>
<td>S during 10 d after initiation</td>
<td>11 (10)</td>
<td>11 (10)</td>
<td>6 (4)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>0.9 (0.39, 2.2)</td>
<td>0.6 (0.3, 1.2)</td>
<td>0.51 (0.17, 1.49)</td>
<td>0.52 (0.17, 1.58)</td>
</tr>
<tr>
<td>S during 5 d of prophylaxis</td>
<td>9 (6)</td>
<td>6 (4)</td>
<td>3 (2)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>0.9 (0.30, 2.72)</td>
<td>0.27 (0.1, 0.75)</td>
<td>0.52 (0.17, 1.58)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Data are no. (%) of subjects, except as indicated. ORs and 95% CIs stratified by center were calculated by use of Mantel-Haenszel estimates with test-based CIs.


The 1957-58 Livermore Veterans Pandemic Influenza Study

- Livermore, CA
- Veterans Hospital
- July 1957 – March 1958
  - Upper Room UVC
    - Used in Building 62 but not Building 2
    - Long-term TB patients
    - Patients restricted to assigned building
    - Serology July, November, March

The 1957-58 Livermore Study Results

- Health Care Workers
  - 18% attack rate
  - Equivalent exposure to patients in both buildings
- **UV was 90% effective in patients**
  - \((95\% \text{ CI: 73\% to 96\%})\)

<table>
<thead>
<tr>
<th>Pandemic Influenza Serologically Confirmed Attack Rate Among Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Risk</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td><strong>UV</strong></td>
</tr>
<tr>
<td><strong>No UV</strong></td>
</tr>
</tbody>
</table>

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The 1957-58 Livermore Study Weaknesses

- **Publication**
  - Discussion in proceedings of a conference on the 1957 pandemic
  - Mention in Riley’s 1961 book
  - Never published in a peer reviewed journal article.

- **Repetition**
  - Not attempted
Influenza Virus in Human Exhaled Breath: An Observational Study

- Recruited subjects from 3 clinics in HK
  - Rapid test positive for influenza virus A or B
  - Within 3 days of disease onset
- Answered health questionnaire
- Collected a 3 minute exhaled breath sample for particle counts
- Collected a 15 minute exhaled breath sample for influenza virus


Exhalair Breath Sampler

- Tidal Breathing into CPAP Mask
- Records:
  - Airflow
  - Particle counts 0.3- >5μm (optical)
- Collects filter sample

Manufacturer: Pulmatrix, Inc, Lexington, MA & PMS, Inc, Boulder, CO
Recruitment

- Collected 68 nasal swabs from suspected influenza cases for rapid test
- Confirmed 13 influenza cases
- Collected:
  - 12 exhaled breath filters
  - 10 particle counts (2 failed attempts)
  - 1 declined to participate due to fatigue

Virus Detection by qPCR

- Influenza virus detection:
  - Four (33%) of the 12 studied patients.
    - Three of five (60%) subjects with influenza virus A infection
    - One of seven (14%) subjects with influenza virus B infection
  - No age, gender, vaccination, or symptom differences between + and – cases.
Influenza virus type, results for each qPCR replicate, and exhalation rate

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Influenza virus type (sub-type)</th>
<th>Replicate 1</th>
<th>Replicate 2</th>
<th>Replicate 3</th>
<th>Exhalation rate (copies/minute)</th>
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</thead>
<tbody>
<tr>
<td>A-06</td>
<td>A (H3)</td>
<td>47</td>
<td>21</td>
<td>44</td>
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<td>A-07</td>
<td>A (H3)</td>
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<td>&lt;6</td>
<td>&lt;3.2</td>
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<tr>
<td>A-08</td>
<td>B</td>
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</table>

*Number of influenza RNA copies detected per well (5 µl cDNA per well).

Exhaled breath particle size distribution averaged from 10 influenza infected subjects
Summary

• Influenza probably preferentially aerosol transmitted:
  – Lower infectious dose via aerosol
  – More severe symptoms after aerosol dose
  – Protection by inhaled but not nasal prophylaxis
  – Evidence for protection by upper-room UVC
  – Evidence for presence in exhaled fine particles

• Still controversial