Infection Basics

Lecture 12
Biology 4310
Virology
Spring 2020

Before I came here I was confused about this subject. Having listened to your lecture, I am still confused—but at a higher level.

—ENRICO FERMI
The nature of host-parasite interactions

The viral genome must establish itself in a host population to endure

In both the infected cell and the infected host, viruses must get in and they must get out
We live and prosper in a cloud of viruses

- Most virus encounters have no consequence
- Many infections are *inapparent* or *asymptomatic*
  - *Signs*: Evidence of disease that can be observed by others
  - *Symptoms*: Apparent only to the patient
  - May overlap, e.g. rashes
Example: West Nile virus infection

- WNV spread across the US in less than 4 years (‘99)
  - By October 2004 about 1 million people were infected (Ab+)
  - Febrile illness developed in 20% of infected people
  - Central nervous system illness developed in 1% of infected people
- Many people were infected with no obvious disease
  - Inability to stop an epidemic because it can't be recognized early
Incubation period

- Initial period before *symptoms* of disease are obvious
- Viral genomes are replicating
- Host is responding
- Virus may or may not be transmitted during incubation period
### Incubation periods of some viral infections

<table>
<thead>
<tr>
<th>Disease</th>
<th>Incubation period (days)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza virus</td>
<td>1–2</td>
</tr>
<tr>
<td>Rhinovirus</td>
<td>1–3</td>
</tr>
<tr>
<td>Ebola virus</td>
<td>2–21</td>
</tr>
<tr>
<td>Acute respiratory disease (adenoviruses)</td>
<td>5–7</td>
</tr>
<tr>
<td>Dengue</td>
<td>5–8</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>5–8</td>
</tr>
<tr>
<td>Coxsackievirus</td>
<td>6–12</td>
</tr>
<tr>
<td>Poliovirus</td>
<td>5–20</td>
</tr>
<tr>
<td>Human immunodeficiency virus</td>
<td>8–21</td>
</tr>
<tr>
<td>Measles</td>
<td>9–12</td>
</tr>
<tr>
<td>Smallpox</td>
<td>12–14</td>
</tr>
<tr>
<td>Varicella-zoster virus</td>
<td>13–17</td>
</tr>
<tr>
<td>Mumps</td>
<td>16–20</td>
</tr>
<tr>
<td>Rubella</td>
<td>17–20</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>30–50</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>15–40</td>
</tr>
<tr>
<td>Hepatitis B and C</td>
<td>50–150</td>
</tr>
<tr>
<td>Rabies</td>
<td>30–100</td>
</tr>
<tr>
<td>Papilloma (warts)</td>
<td>50–150</td>
</tr>
</tbody>
</table>

*Until first appearance of prodromal symptoms.

**Short** - replication at primary site produces symptoms

**Long** - Symptoms beyond primary site

**Prodrome** - Period of symptoms before those characteristic of disease

Gr *prodromos* = precursor

**SARS-CoV-2** 1–14 days
Morbidity, mortality, incidence, case fatality

- Incidence: \# people infected/\# in population
- Morbidity rate: \# people ill/\# people at risk
- Mortality rate: \# deaths/\# people at risk
- Case fatality ratio: \# deaths/\# infected
Basic reproductive number, $R_0$

$$R_0 = \tau * c * d$$

$\tau$ = probability of infection given contact  
$c$ = average duration of contact between infected and uninfected host  
$d$ = duration of infectivity

- Number of secondary infections that can arise in population of susceptible hosts from a single infected individual
- If $R_0 < 1$, epidemic cannot be sustained
- If $R_0 > 1$ epidemic is possible
- If $R_0$ is much greater than 1, epidemic is certain
- Influenced by time of contact between individuals, length of infectious period
- May be affected by interventions!
CFR and R0

SARS-CoV-2

CFR

R0

More deadly

Spreads faster

SARS-CoV-2

Influenza
- 2009 (H1N1): 1.47
- 1957, 1968 pandemics: 1.8
- 1918 pandemic: 2.4-5.4
- Ebola: 1.3–1.8

Bird flu
- MERS
- Ebola
- Smallpox
- SARS
- Spanish flu
- Seasonal flu
- Polio
- 2009 flu
- Common cold
- Chickenpox
- Measles
# SARS-CoV-2: One CFR does not fit all

## Table

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Confirmed Cases, N (%)</th>
<th>Deaths, N (%)</th>
<th>Case Fatality Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>44,672 (100)</td>
<td>1,023 (2.3)</td>
<td>2.3</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–9</td>
<td>416 (0.9)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>10–19</td>
<td>549 (1.2)</td>
<td>1 (0.1)</td>
<td>0.2</td>
</tr>
<tr>
<td>20–29</td>
<td>3,619 (8.1)</td>
<td>7 (0.7)</td>
<td>0.2</td>
</tr>
<tr>
<td>30–39</td>
<td>7,600 (17.0)</td>
<td>18 (1.8)</td>
<td>0.2</td>
</tr>
<tr>
<td>40–49</td>
<td>8,571 (19.2)</td>
<td>38 (3.7)</td>
<td>0.4</td>
</tr>
<tr>
<td>50–59</td>
<td>10,008 (22.4)</td>
<td>130 (12.7)</td>
<td>1.3</td>
</tr>
<tr>
<td>60–69</td>
<td>8,583 (19.2)</td>
<td>309 (30.2)</td>
<td>3.6</td>
</tr>
<tr>
<td>70–79</td>
<td>3,918 (8.8)</td>
<td>312 (30.5)</td>
<td>8.0</td>
</tr>
<tr>
<td>≥80</td>
<td>1,408 (3.2)</td>
<td>208 (20.3)</td>
<td>14.8</td>
</tr>
</tbody>
</table>

## Sex

<table>
<thead>
<tr>
<th>Gender</th>
<th>Confirmed Cases, N (%)</th>
<th>Deaths, N (%)</th>
<th>Case Fatality Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>22,981 (51.4)</td>
<td>653 (63.8)</td>
<td>2.8</td>
</tr>
<tr>
<td>Female</td>
<td>21,691 (48.6)</td>
<td>370 (36.2)</td>
<td>1.7</td>
</tr>
</tbody>
</table>

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`South Korea 28/5621 = 0.4%`

`Singapore 0/110`

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Report of the WHO-China Joint Mission on COVID-19
Viral pathogenesis

• *Pathogenesis*: the process of producing a disease

• Two components of viral disease:
  - Effects of viral replication on the host
  - Effects of host response on virus and host
Fundamental questions of viral pathogenesis

- How does a virus particle enter the host?
- What is the initial host response?
- Where does primary replication occur?
- How does the infection spread in the host?
- What organs and tissues are infected?
- Is the infection cleared from the host or is a persistent infection established?
- How is the virus transmitted to other hosts?
Three requirements for a successful infection

- Enough virus
- Cells accessible, susceptible, permissive
- Local antiviral defense absent or overcome
Gaining access: site of entry is critical

The human body presents only a limited spectrum of entry sites for viral infection
How Mosquitoes Spread Viruses
https://youtu.be/7wsk8a3ze80
Mucosal surfaces are ripe for viral infection

Lined by living cells
<table>
<thead>
<tr>
<th>Site of reproduction</th>
<th>Clinical manifestation</th>
<th>Virus</th>
</tr>
</thead>
</table>
| Turbinate “baffles”  | Rhinitis (common cold) | Rhinovirus  
Coronavirus  
Parainfluenza virus  
Respiratory syncytial virus |
| Palate, Tonsillar lymphoid tissues | Pharyngitis | Influenza virus  
Adenovirus  
Herpes simplex virus  
Epstein-Barr virus |
| Cervical lymph node | Laryngitis |  |
| Bronchi, Trachea, Bronchioles | Tracheitis  
Bronchitis  
Bronchiolitis  
Bronchopneumonia | Parainfluenza virus  
Respiratory syncytial virus  
Influenza virus  
Adenovirus  
Measles  
SARS  
MERS |
Alimentary tract

- Conjunctiva
- Mouth/nose
- Respiratory tract
- Capillary
- Skin
- Anus
- Urogenital tract
- Arthropod
- Scratch, injury
The small intestine

- A selectively permeable barrier
- Polarized epithelial cells
- Direct contact with outside world
- Direct contact with the immune system and the nervous system
Urogenital tract

- Protected by mucus, low pH
- Minute abrasions from sexual activity may allow viruses to enter
- Some viruses produce local lesions (HPV)
- Some viruses spread from urogenital tract (HIV, HSV)
Eye

- Corneal epithelial cells
  - Adenovirus
  - Influenza virus
  - Respiratory syncytial virus

- Corneal stromal fibroblasts
  - Adenovirus

- Iris

- Lens

- Trabecular meshwork cells
  - Influenza virus

- Conjunctival epithelial cells
  - Adenovirus
  - Influenza virus
  - Respiratory syncytial virus

- Vitreous cavity

- Choroid

- Optic nerve

- Retinal pigment epithelial cells
  - Influenza virus

- Sclera
The fetus

- Transplacental vs perinatal infection
- TORCH pathogens: Toxoplasma, rubella, cytomegalovirus, HIV, other
- Zika virus
The outer layer of which of the following is dead but can still serve as a portal of virus entry?

A. Respiratory tract  
B. Alimentary tract  
C. Eye  
D. Skin  
E. Urogenital tract
Viral spread

- After replication at the site of entry, viruses may remain **localized**: virus spreads within the epithelium and is contained by tissue structure and immune system.
- Some viruses spread beyond the primary site: **disseminated**; if many organs are infected, **systemic**.
- Physical and immune barriers must be breached.
Viral spread

Apical side

Microvillus

Tight junction

M cell pocket

Nucleus

Basement membrane

Macrophage

Enterocyte

Lymphocyte
Viral spread

- Apical release facilitates virus dispersal (poliovirus)
- Basolateral release provides access to underlying tissues, may facilitate systemic spread
- Sendai virus
Hematogenous spread
Viremia

The graph illustrates the pattern of viremia over time following infection. It shows three phases:
- **Primary viremia** occurs immediately after infection and peaks around 2-4 days.
- **Secondary viremia** appears later, typically around 8-10 days after infection, and peaks higher than primary viremia.
- The graph also notes a **Passive viremia** period, indicating the presence of virus in the blood during the immune response.

The x-axis represents days after infection, while the y-axis shows the relative virus titer.
Pathogenesis of mousepox
<table>
<thead>
<tr>
<th>Virus</th>
<th>Disease</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coxsackievirus A16</td>
<td>Hand-foot-and-mouth disease</td>
<td>Maculopapular rash</td>
</tr>
<tr>
<td>Measles virus</td>
<td>Measles</td>
<td>Maculopapular rash</td>
</tr>
<tr>
<td>Parvovirus</td>
<td>Erythema infectiosum</td>
<td>Maculopapular rash</td>
</tr>
<tr>
<td>Rubella virus</td>
<td>German measles</td>
<td>Maculopapular rash</td>
</tr>
<tr>
<td>Varicella-zoster virus</td>
<td>Chickenpox, shingles</td>
<td>Vesicular rash</td>
</tr>
<tr>
<td>Zika virus</td>
<td>ZIKV illness</td>
<td>Maculopapular rash</td>
</tr>
</tbody>
</table>
Go to:

b.socrative.com/login/student
room number: virus

Which of the following assist in viral dissemination in the infected animal?

A. Viremia
B. Basolateral release from epithelial cells
C. Movement through the lymphatic system
D. Inflammation at the basement membrane
E. All of the above
Neural spread

Diagram showing the neural spread of viruses including:
- Dorsal root ganglion
- Sensory pseudounipolar neuron
- Motor neuron
- Motor end plate
- Anterograde
- Perineural lymphatics
- Endoneural space
- Schwann cell
- Net anterograde
- Synaptic vesicle
- PRV particle
- Us9
- Kinesin
- Microtubules
- Dynein
- Infecting HSV-I
- Net retrograde
- Terminal

Image of neural network showing neuroanatomy.
Infections of the CNS

- **Neurotropic** virus can infect neural cells; infection may occur by neural or hematogenous spread from a peripheral site.
- **Neuroinvasive** virus can enter the CNS after infection of a peripheral site.
- **Neurovirulent** virus can cause disease of nervous tissue.
- HSV: low neuroinvasiveness, high neurovirulence.
- Mumps: high neuroinvasiveness, low neurovirulence.
- Rabies: high neuroinvasiveness, high neurovirulence.
Tissue invasion

- Liver, spleen, bone marrow, adrenal glands
- Renal glomerulus, pancreas, ileum, colon
- CNS, connective tissue, skeletal & cardiac muscle

Pericyte (glial cell in CNS) → Neuron → Pore → Basement membrane → Capillary, Venules, Sinusoids
Transmission of infection

- Spread of infection from one susceptible host to another; required to maintain chain of infection
- Two general patterns
Transmission terms

- **Horizontal transmission** - between members of same species (zoonotic - different species)
- **Vertical transmission** - transfer of infection between mother and child
- **Iatrogenic** - activity of health care worker leads to infection of patient
- **Nosocomial** - when an individual is infected while in hospital or health care facility
- **Germ line transmission** - agent is transmitted as part of the genome (e.g. proviral DNA)
**Virus shedding**

- Respiratory secretions
  - Feces
  - Skin lesions
- Mucosal shedding
  - Blood
  - Blood supply
- Urine
- Semen
- Feces
- Insect vectors
- Germline
- Vertical (Mother to baby)
Virus shedding

- Respiratory secretions - aerosols produced by coughing, sneezing, speaking
- Nasal secretions contaminating hands, tissues, subway poles, etc.

http://www.virology.ws/2013/01/23/slow-motion-sneezing/
Gesundheit-II

TWiV 480: The PFU in your achoo
http://www.microbe.tv/twiv/twiv-480/

- 156 individuals in college community with confirmed influenza
- Infectious virus shedding in fine aerosols produced by breathing, speaking
- Sneezing does not make important contribution to virus shedding in aerosols
- Coughing not necessary for infectious aerosol generation
Which statement about viral transmission is not correct?

A. All virus infections are transmitted by shedding
B. The route is determined by the site of virus shedding
C. Transmission is required to maintain a chain of infection
D. Speaking can produce an aerosol that can transmit infection
E. Horizontal transmission is among members of one species
Influence of geography

- Geography may restrict presence of virus - requirement for specific vector or animal reservoir

- Chikungunya virus - how vector can affect localization of viral infection
Chikungunya virus

- Togavirus, alphavirus genus
- Spread by *Aedes aegypti*
- Rash, fever, joint pains
Chikungunya virus

- Asia, Africa, never Europe or US
- 2004 - outbreaks spread from Kenya to India
- 2007 - outbreak in Italy, first in Europe
Chikungunya virus

- Recent outbreaks associated with *Aedes albopictus*
- One amino acid change in viral E1 glycoprotein
Aedes albopictus

Chikungunya virus infections, US 2017

114 cases, no local transmission
(rare before 2006)

A. albopictus range
Seasonality of virus infections

A Rubella, 1963–1968

B Influenza, 1994–1999

C Poliomyelitis, 1956–1957

Latitude

35–70°N (Anchorage, Alaska; 61°N)

10–35°N (Tel Aviv, Israel; 32°N)

10°N–10°S (Bogota, Colombia; 4°N)

10–25°S (Rio de Janeiro, Brazil; 22°S)

25–55°S (Perth, Australia; 31°S)
Temperature and humidity influence influenza virus transmission

Virus particles are stable; droplet nuclei form

Virus particles are unstable

Droplet nuclei take on water and are no longer airborne

Temperature: 5°C, 20°C

Relative humidity: 0%, 100%
Next time: Intrinsic and innate defenses