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
Example: West Nile virus

- 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
## Example: SARS-CoV-2

### COVID-19 cases (percentage of all cases)

<table>
<thead>
<tr>
<th>Asymptomatic...</th>
<th>and mild disease (81%)</th>
<th>Severe (14%)</th>
<th>Critical and deceased (5%)</th>
</tr>
</thead>
</table>
| ~20%            | • Fever, fatigue and dry cough  
• Ground-glass opacities  
• Pneumonia         | • Dyspnea  
• Coexisting illness  
• ICU needed      | • ARDS  
• Acute cardiac injury  
• Multi-organ failure |
Incubation period

- Initial period before *symptoms* of disease are obvious

- *Signs* are present:
  - 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.*

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

**SARS-CoV-2** 1–14 days

**Gr prodromos** = precursor

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

**Long** - Symptoms beyond primary site
Morbidity, mortality, incidence, fatality

- Incidence: # people infected/# in population/time
- Morbidity rate: # people ill/# in population
- Mortality rate: # deaths/# in population
- Case fatality rate: # deaths/# confirmed infected
- Infection fatality rate: # deaths/# actual infections

Each icon = 10,000

- Infected (PCR+)
- Signs/symptoms (PCR+)

Incidence 25%
Morbidity 10%
Mortality 5%

CFR
10,000/50,000
25%
Basic reproductive number, $R_0$

$$R_0 = \tau \cdot c \cdot d$$

$\tau =$ 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

CFR

SARS-CoV-2

SARS

Smallpox

MERS

Bird flu

Ebola

Spanish flu

Influenza

2009 (H1N1)

1.47

1957, 1968 pandemics

1.8

1918 pandemic

2.4-5.4

Ebola

1.3–1.8

Spreads faster

More deadly

Seasonal flu

2009 flu

Common cold

Polio

Chickenpox

Measles
## SARS-CoV-2: One CFR does not fit all

<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><strong>Overall</strong></td>
<td>44,672</td>
<td>1,023</td>
<td>2.3</td>
</tr>
<tr>
<td><strong>Age, years</strong></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**

- **Male**: 22,981 (51.4) | 653 (63.8) | 2.8
- **Female**: 21,691 (48.6) | 370 (36.2) | 1.7

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*China CDC Weekly*

**Report of the WHO-China Joint Mission on COVID-19**
Overdispersion parameter $k$

- In some countries importation of SARS-CoV-2 was associated with fewer secondary cases than would be expected with $R_0=2-3$
- Suggests that not all symptomatic cases cause secondary transmission, observed with SARS-CoV
- Overdispersion - high-level individual variation in distribution of number of secondary transmissions
- For SARS-CoV-2, $k=0.1$, meaning that 80% of transmissions are caused by 10% of infectious individuals
Clustering and superspreading potential of SARS-CoV-2 infections in Hong Kong

Dillon C. Adam\textsuperscript{1,2}, Peng Wu\textsuperscript{1,5}, Jessica Y. Wong\textsuperscript{1}, Eric H. Y. Lau\textsuperscript{1}, Tim K. Tsang\textsuperscript{1}, Simon Cauchemez\textsuperscript{2}, Gabriel M. Leung\textsuperscript{1,4} and Benjamin J. Cowling\textsuperscript{1,4}
Go to:

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

Which of the following parameters is not influenced by human interventions?

A. Mortality rate
B. Case fatality ratio
C. Reproductive index
D. Incidence
E. Incubation period
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?
- How does the host respond? (IFN, antibodies, T cells, etc)
- 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
Alimentary tract
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
- 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)
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

Go to:

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

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

Vein
Postcapillary venule
Epithelium at body surface
Lymph node
Afferent lymphatic
Lymphatic capillary
Basement membrane

Great vein
Thoracic lymph duct
Efferent lymphatic
Germinal center
Pathogenesis of mousepox
## Viruses that cause skin rashes in humans

<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>

![Measles image](image1.png)

![Smallpox image](image2.png)

![Chickenpox image](image3.png)
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
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 neuroinvasivness, low neurovirulence
- Rabies: high neuroinvasiveness, high neurovirulence
Tissue invasion

Sinusoid
Liver
Spleen
Bone marrow

CNS, connective tissue, skeletal & cardiac muscle

Venule
Intestine
Pancreas
Endocrine gland

Renal glomerulus, pancreas, ileum, colon

Capillary
CNS
Skeletal muscle
Lungs

Liver, spleen, bone marrow, adrenal glands
Tissue invasion: Traversing the basement membrane
Virus entry into the central nervous system

- Blood vessel in choroid plexus
- Cerebral blood vessels
- Meningeal blood vessel
- Meninges
- Ventricles
- Pia
- Brain parenchyma
- CSF
- Nerve
- From peripheral nerve ending or nasal mucosa
- Astrocyte foot processes
- Capillary endothelial cell
- Capillary lumen
- Red blood cell
- Basement membrane
- Tight junction
- Astrocyte
Transmission of infection

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

**Animal to animal**

**Animal vector animal**
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
Mucosal shedding
  Conjugeta
  Mouth/nose
  Respiratory tract
  Alimentary tract
  Urogenital tract
Urine
Semen
Feces

Skin lesions
Blood

Blood supply
Insect vectors
Germline
Vertical* (Mother to baby)

Shedding is not always needed for transmission!
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/
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

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

http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1003205
Viral shedding and transmissibility

SARS 2003

Estimated incubation period: 4–5 days

Start: after symptom onset
Peak: ~10 days after onset
End: weeks after onset

Seasonal influenza

Estimated incubation period: 2 days

Start: ~2 days before onset
Peak: ~1 day after onset
End: 6–8 days after onset

SARS-CoV-2 is transmitted during incubation period and from asymptomatically infected persons

Start: 2.3 days before symptom onset
Peak: At or 1 day after symptom onset

https://doi.org/10.1038/s41591-020-0869-5
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
Recent outbreaks associated with *Aedes albopictus*

One amino acid change in viral E1 glycoprotein
Chikungunya virus infections, US 2017

192 imported cases
2 local transmission PR (rare before 2006)

A. albopictus range
Seasonality of virus infections

A Rubella, 1963–1968

B Influenza, 1994–1999

C Poliomyelitis, 1956–1957

© Principles of Virology, ASM Press
Temperature and humidity influence influenza virus transmission

![Diagram showing the influence of temperature and humidity on influenza virus transmission.](image)

- **Mucus droplet**
- **Evaporation**
- **Droplet nuclei**

**Graph:***

- **% Transmission**
- **% Relative humidity**

- **Virus particles are stable; droplet nuclei form** at 5°C
- **Virus particles are unstable**
- **Droplet nuclei take on water and are no longer airborne** at 20°C
Next time: Host defenses