You know something's happening, but you don't know what it is, do you, Mr. Jones?
—Bob Dylan

Ballad of a thin man
General patterns of infection

- **Acute**
  - Rhinovirus
  - Rotavirus
  - Influenza virus

- **Latent**
  - Herpes simplex virus types 1 and 2

- **Persistent: asymptomatic**
  - Lymphocytic choriomeningitis virus
  - JC virus

- **Persistent: pathogenic**
  - Human immunodeficiency virus type 1
  - Human T-lymphotropic virus
  - Measles virus SSPE
Acute infections

- Rapid onset of viral reproduction
- Short but possibly severe course of disease
- Production of large numbers of virus particles
- Immune clearance
The course of a typical acute infection

Rapid and self-limiting

- Induction of adaptive response
- Adaptive response
- Memory
- Threshold level of virus required to activate adaptive immune response

Virology Lectures 2021 • Prof. Vincent Racaniello • Columbia University
Inapparent acute infections

- Successful infections, no symptoms or disease
- Sufficient virus particles produced to spread in the population
- How do we know?
- Well adapted pathogens
  - >90% of poliovirus infections inapparent
- SARS-CoV-2 - 20%?
Acute infections are common public health problems

- Serious epidemics affecting millions each year (influenza, norovirus)
- Acute infections are difficult problems: by the time you feel ill, the infection may be over and has spread
Which of the following do acute infections and incubation periods have in common?

A. The virus is not replicating
B. No symptoms are visible
C. Immune defenses are engaged
D. The immune system does not respond
E. All of the above
Viruses that cause acute infections

- Influenza virus
- Poliovirus
- Measles virus
- Norovirus
- West Nile virus
- Types: A, B, C
- A, B cause similar disease; C mostly inapparent or mild upper respiratory tract illness
- Only A cause pandemics
- Antigenic variation
Influenza transmission

- Droplets produced by coughing, sneezing, talking
- Direct contact with infected individuals
- Contact with contaminated surface, touch mouth, eyes, nose

α(2,6) human
α(2,3) avian
Uncomplicated influenza

- Incubation period 1-5 days, depending on dose, immune status of host
- Abrupt onset: headache, chills, dry cough
- High fever, myalgias, malaise, anorexia
- Fever peaks within 24 hr, 38° - 40°C
- Fever declines day 2-3, gone by day 6
- As fever declines, respiratory signs intensify
- Cough changes from dry to productive
- Cough, weakness can persist 1-2 weeks
How is influenza diagnosed?

- Influenza-like illness, ILI
- Fever at least 100°F
- Cough OR sore throat
- No other known cause
- Rapid lab tests: 50-70% accuracy
- PCR, viral culture, serology
Seasonal influenza

U.S. WHO/NREVSS Collaborating Laboratories
National Summary, 2004-05 through 2007-08

http://www.cdc.gov/flu/weekly/fluactivitysurv.htm
Preliminary burden estimates, 2019-2020 influenza season

CDC estimates* that, from October 1, 2019, through April 4, 2020, there have been:

- 39,000,000 – 56,000,000 flu illnesses
- 18,000,000 – 26,000,000 flu medical visits
- 410,000 – 740,000 flu hospitalizations
- 24,000 – 62,000 flu deaths

*Because influenza surveillance does not capture all cases of flu that occur in the U.S., CDC provides these estimated ranges to better reflect the larger burden of influenza. These estimates are calculated based on CDC’s weekly influenza surveillance data.
Percentage of Visits for Influenza-like Illness (ILI) Reported by the U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet), Weekly National Summary, 2019-2020 and Selected Previous Seasons.
Complications of influenza

- Primary viral pneumonia
- Secondary bacterial pneumonia
- Myositis - generalized muscle pain
- Cardiac involvement
- Reye syndrome (encephalopathy, liver damage)
Interventions for influenza

- Non-pharmaceutical
- Antiviral drugs
  - Tamiflu (oseltamivir)
  - Relenza (zanamavir)
  - Flumadine (rimantadine)
  - Xofluza (baloxavir marboxil)
- Vaccines
Which of the following is characteristic of uncomplicated influenza?

A. Transmission may occur via respiratory droplets
B. Incubation period is 1-5 days
C. Fever peaks within 24 hr
D. Coughing and weakness can last for 2 weeks
E. All of the above
- Measles virus, *Paramyxoviridae*

- One of the most contagious human viruses ($R_0 = 15$)
Measles pathogenesis

- One viral serotype, infection confers life-long protection
- Transmitted by inhalation of respiratory droplets/aerosols
- Period of maximum contagiousness 2-3 days before rash
- Nearly all infected individuals show signs of disease
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Antibody

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Principles of Virology, ASM Press
Uncomplicated measles

- Fever, 38.3°C or above
- Respiratory symptoms: coryza, cough
- Conjunctivitis
- Koplik spots
- Rash from face to extremities
Measles complications

- Acute postinfectious encephalitis (1/1,000)
- Bronchitis, pneumonia, ear infection
- Fatality 1-2/1000 (28% poor nutrition)
- Subacute sclerosing panencephalitis (SSPE)
- Immunosuppression leading to secondary infections (main cause of death in Third World children)
Measles erases immune memory - immune amnesia

- VirScan used to track antibodies to thousands of pathogen epitopes in 77 unvaccinated children before and 2 months after measles infection
- Measles caused elimination of 11-73% of antibody repertoire
- Caused by measles virus infection of B and T memory cells and plasma cells

Measles prevention

- Pre-vaccine in the US: 3-4 million/yr, 400-500 deaths, 48,000 hospitalizations, 1,000 chronic disability from encephalitis
- Endemic transmission stopped 2000 by vaccine
- MMR: measles, mumps, rubella vaccine
- Wakefield 1998 report lead to decreased MMR immunization, outbreaks in UK, Ireland
- US outbreaks, imported - e.g. Rockland County, NY
Measles cases by year, US

Year:
- 2010: 63 cases
- 2012: 55 cases
- 2014: 667 cases
- 2016: 86 cases
- 2018: 375 cases
- 2020: 13 cases

Number of Cases:
- 0
- 200
- 400
- 600
- 800
- 1000
- 1200

Source: https://www.cdc.gov/measles/cases-outbreaks.html
Measles case distribution by month and WHO Region (2016-2020)

413,308 cases in 2019

Source: WHO
Almost 41 countries have already put off, or may put off, their measles campaigns for 2020 or 2021 due to the COVID-19 pandemic.
Which of the following is a good reason to get measles vaccine?

A. There is a 1/1000 chance of acute post-infection encephalitis
B. There is a 1-2/1000 chance of death from measles
C. Each infected person spreads measles virus to 15 others
D. Immunosuppression can lead to secondary infections
E. All of the above
Poliomyelitis - poliovirus
Poliovirus pathogenesis
### Chronology of an Acute Infection

<table>
<thead>
<tr>
<th>Time</th>
<th>Incubation</th>
<th>Systemic</th>
<th>Neural</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td>Headache</td>
<td>Sore Throat</td>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td>Temp.</td>
<td>100 F.</td>
<td>101 F.</td>
<td>102 F.</td>
<td>103 F.</td>
</tr>
<tr>
<td><strong>Alimentary Tract</strong></td>
<td>10,000</td>
<td>Virus in Throat Secretions</td>
<td>Antibody in Throat Secretions</td>
<td></td>
</tr>
<tr>
<td><strong>Lymphatic and Blood</strong></td>
<td>100</td>
<td>Virus in Blood</td>
<td>Serum Antibody</td>
<td></td>
</tr>
<tr>
<td><strong>Central Nervous System</strong></td>
<td>10,000</td>
<td>Virus in CNS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Exposure to Paralysis: Days 5-15

Pathogenesis of poliomyelitis

- Humans are only known reservoir
- Spread by fecal-oral transmission
- Peaks during warm months in temperate climates
- Complication: post-polio syndrome
  - 30-40 year interval
  - 25-40%
  - Not an infectious process
Poliomyelitis—United States, 1940-1990
In a 24 hour period...

- About 200,000,000 people have gastroenteritis
- The amount of diarrheal water passed equals the volume of water passing over Victoria Falls in 1 minute

65,280,000 liters/min
Norovirus

- **Caliciviridae**
- **(+) strand RNA virus**
- **Cause 50% of all food-borne outbreaks of gastroenteritis (48 million/yr US)**
How contagious is norovirus?

Just a very small amount - as few as 18 viral particles - of norovirus on your food or your hands can make you sick.

That means the amount of virus particles that fit on the head of a pin would be enough to infect more than 1,000 people!

SOURCE: Journal of Medical Virology, August, 2008
- Fecal-oral spread
- Virus particles retain infectivity passing through stomach
- Blunting of villi in proximal jejunum
- Basis for vomiting, diarrhea not known
Enteric bacteria promote human and mouse norovirus infection of B cells

![Graph showing viral genome replication](image)
Human noroviruses infect intestinal epithelial cells (IEC), macrophages, dendritic cells, and T cells in immunocompromised hosts in vivo and IEC and B cells in vitro.
Clinical and epidemiological features

- Transmission: Fecal–oral; aerosol–vomitus; contact with fomites; food, water, or environmental contamination; foods can be contaminated at the source (oysters, raspberries) or during preparation by food handlers
- Incubation period 10-51 hr
- Symptoms: Sudden onset of vomiting (more common in children), diarrhea (more common in adults), stomach pain
- Duration of illness: 28-60 hr; longer in immunocompromised or with underlying illness
- 30% asymptomatic infections
Clinical and epidemiological features

- Viral shedding peaks 1-3 days after illness onset, may persist for 56 days
- Immunity: short term homologous only; reinfection with other strains may occur, or later in life
Clinical and epidemiological features

- Reservoir: Humans, might be able to infect non-human animals
- Affects all ages
- Year round, peaks in cold weather
- Outbreaks often occur in semi-closed environments (nursing homes, hospitals, cruise ships), military, schools, recreational activities (sports events, camping trips, travel) that favor person-to-person spread
Clinical and epidemiological features

- Treatment: Supportive to prevent dehydration
- Vaccine in development
- 200,000 deaths/yr mainly in children
Real life ‘Airplane!’ Entire flight sickened by norovirus

Wednesday, December 28, 2011

Holiday travel can not only be a hassle but can you get sick -- and in a recent case among Air New Zealand crew members, seriously ill. According to a report last week in Scientific American, recent studies have shown just how easily the cruise ship gastrointestinal bug, norovirus, can be transmitted to travelers on planes.

On a recent Air New Zealand flight, a sick passenger passed norovirus along to the crew. "Not only did the crew that cleaned up the mess get sick, but on every successive flight at least one or more crew members got sick with typical symptoms of norovirus," said David Freedman, of the University of Alabama at Birmingham, at a meeting of the American Society of Tropical Medicine and Hygiene held earlier this month.
## The happiest place on Earth™?

### 2010

<table>
<thead>
<tr>
<th>Cruise Line</th>
<th>Cruise Ship</th>
<th>Sailing Dates</th>
<th>Causative Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystal Cruises</td>
<td>Crystal Symphony</td>
<td>11/02 - 11/21</td>
<td>Unknown</td>
</tr>
<tr>
<td>Holland America Line</td>
<td>Nieuw Amsterdam</td>
<td>10/18 - 11/07</td>
<td>Norovirus</td>
</tr>
<tr>
<td>Carnival Cruise Lines</td>
<td>Carnival Glory</td>
<td>10/09 - 10/16</td>
<td>Norovirus</td>
</tr>
<tr>
<td>Holland America Line</td>
<td>Zuiderdam</td>
<td>04/20 - 05/08</td>
<td>Unknown</td>
</tr>
<tr>
<td>Celebrity Cruises</td>
<td>Mercury</td>
<td>03/08 - 03/19</td>
<td>Norovirus</td>
</tr>
<tr>
<td>Celebrity Cruises</td>
<td>Mercury</td>
<td>02/26 - 03/08</td>
<td>Norovirus</td>
</tr>
<tr>
<td>Royal Caribbean International</td>
<td>Jewel of the Seas</td>
<td>02/22 - 03/05</td>
<td>Unknown</td>
</tr>
<tr>
<td>Celebrity Cruises</td>
<td>Millennium</td>
<td>02/22 - 03/05</td>
<td>Norovirus</td>
</tr>
<tr>
<td>Holland America Line</td>
<td>Maasdam</td>
<td>02/19 - 03/05</td>
<td>Norovirus</td>
</tr>
<tr>
<td>Celebrity Cruises</td>
<td>Mercury</td>
<td>02/15 - 02/26</td>
<td>Norovirus</td>
</tr>
<tr>
<td>Fred Olsen Cruise Lines</td>
<td>Balmoral</td>
<td>01/05 - 02/04</td>
<td>Unknown</td>
</tr>
<tr>
<td>Cunard Cruise Line</td>
<td>Queen Victoria</td>
<td>01/12 - 01/27</td>
<td>Unknown</td>
</tr>
<tr>
<td>Cunard Cruise Line</td>
<td>Queen Victoria</td>
<td>01/04 - 01/12</td>
<td>Norovirus</td>
</tr>
</tbody>
</table>
Why are noroviruses associated with cruise ships?

- Health officials track illness on cruise ships, so outbreaks are found and reported more quickly on a cruise ship than on land
- Close living quarters may increase the amount of group contact
- New passenger arrivals may bring the virus to other passengers and crew
Protect Yourself from Norovirus!

- Wash your hands often
- Rinse fruits & vegetables
- Cook shellfish thoroughly
- Clean surfaces & wash laundry
- When you're sick, don't prepare food or care for others

Share this widget | More info
www.cdc.gov/Norovirus
West Nile virus

- *Flaviviridae*, isolated 1937, West Nile district of Uganda
- Absent from Western Hemisphere until 1999
- New York isolate identical to virus from Israeli goose
- Virus infects hundreds of birds, 37 kinds of mosquitoes, 18 other vertebrates
WNV transmission cycle
WNV pathogenesis

- Transmitted to humans by *Culex* mosquito bite
- Incubation period 3-14 days
- 20-30% develop flu-like illness called WNV fever
- 80%: no symptoms
WNV pathogenesis

1/150 individuals develop neuroinvasive disease
- Headache
- Ocular manifestations
- Muscle weakness
- Cognitive impairment
- Polio-like flaccid paralysis
- 10% mortality
- >50% long term neurological sequelae
Average annual incidence of WNV neuroinvasive disease by state 1999-2019

http://www.cdc.gov/westnile/
West Nile virus disease cases reported to CDC by week of illness onset, 1999-2019
WNV neuroinvasive disease by age group, 1999-2019

http://www.cdc.gov/westnile/
WNV prevention

- *Culex* species bite evening to morning
- Repellants, screens, clothing
- Human vaccines in development - horse vaccines available (WNV infection has 30% fatality in horses)

https://www.cdc.gov/chikungunya/pdfs/fs_mosquito_bite_prevention_us.pdf
Viruses and the central nervous system

- Poliovirus, measles virus, West Nile virus invade the CNS
- These viruses are effectively transmitted by shedding elsewhere (gut, respiratory tract) or by mosquitoes (WNV)
- In general viral CNS invasion is a dead end in humans
COVID-19 is an acute infection 

Viral Replication Period

- Incubation Period: 2-14 days
- Detectable Viral Replication Period

Inflammatory Period

- Early Inflammatory Phase
- Secondary Infection Phase
- Multisystem Inflammatory Phase

Pre-exposure Period

Viral RNA

Infectious level

PCR Detection

Detectable Viral Replication Period

IgM, IgG

Courtesy Daniel Griffin, MD PhD
COVID-19, an acute infection

Age as major risk factor

<10 years
<50 years
>60 years
>68 years

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>
<tbody>
<tr>
<td>Incubation period</td>
<td>• Fever, fatigue and dry cough&lt;br&gt;• Ground-glass opacities&lt;br&gt;• Pneumonia</td>
<td>• Dyspnea&lt;br&gt;• Coexisting illness&lt;br&gt;• ICU needed</td>
<td>• ARDS&lt;br&gt;• Acute cardiac injury&lt;br&gt;• Multi-organ failure</td>
</tr>
</tbody>
</table>

~5 days (1–14) **Disease onset**
~8 days (7–14)
~16 days (12–20)

Don’t forget long COVID
Virus shedding and transmissibility

SARS-CoV-2

Estimated incubation period: 14 days (5.2 avg)

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

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

Seasonal influenza

Estimated incubation period: 2 days

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

Days from symptom onset of primary case

Viral shedding (infectiousness)

Primary case

Days from symptom onset of primary case

Viral shedding (infectiousness)

Primary case

SARS 2003

Estimated incubation period: 4–5 days

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

https://doi.org/10.1038/s41591-020-0869-5
Next time: Persistent Infections