Acute Infections

Session 16

Virology Live

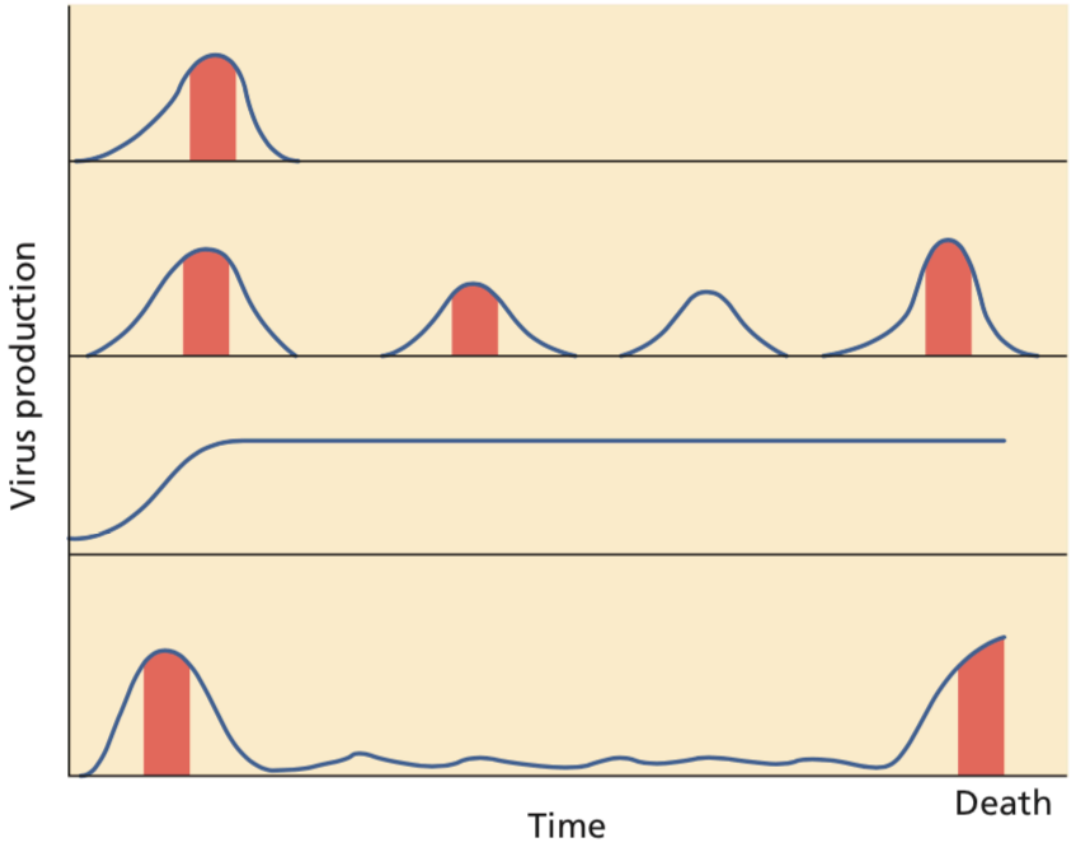
Fall 2021

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

Principles of Virology, ASM Press

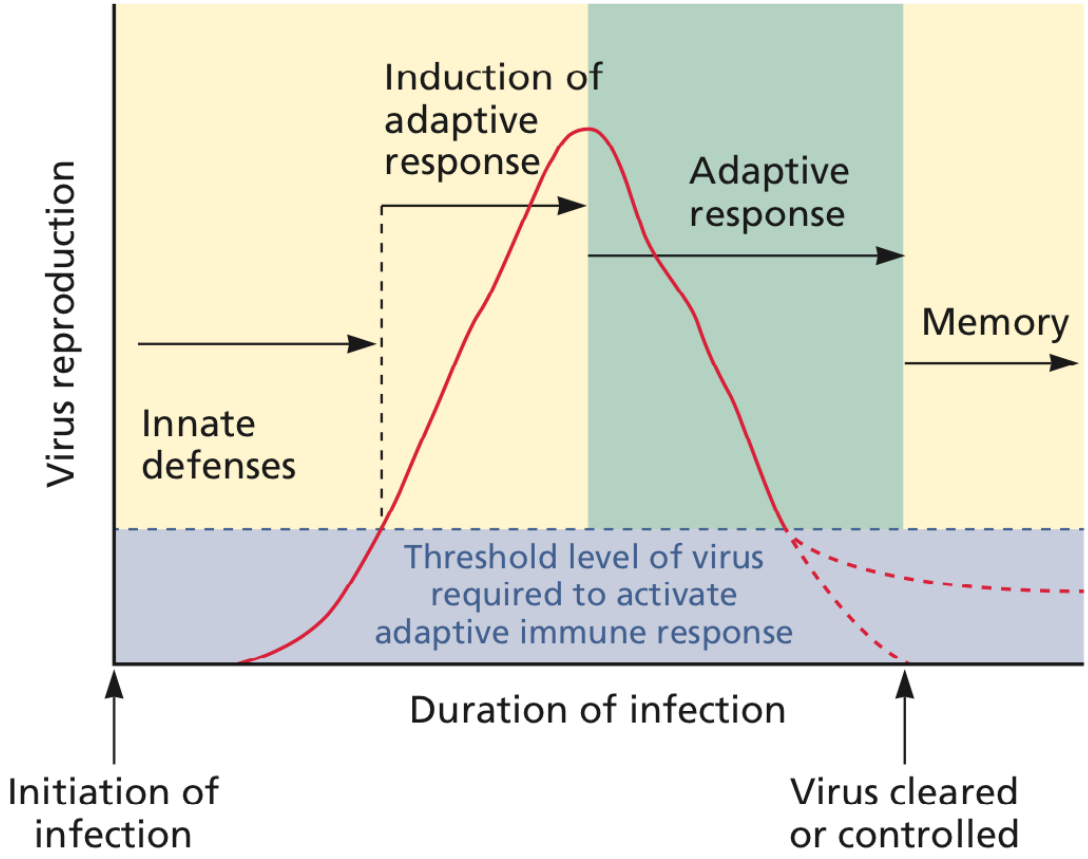
Acute infections

- Rapid onset of viral reproduction
- Limited (not necessarily short) but possibly severe course of disease
- Production of large numbers of virus particles
- Immune clearance

Principles of Virology, ASM Press

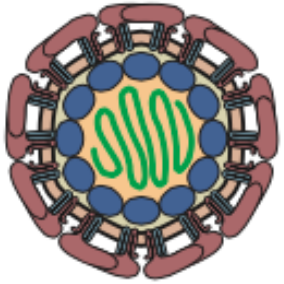
The course of a typical acute infection

Rapid and self-limiting



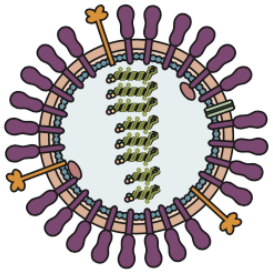
Principles of Virology, ASM Press

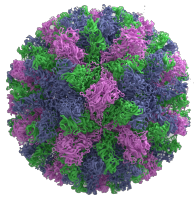
Inapparent acute infections



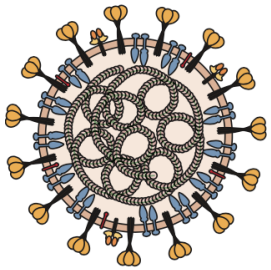
- Successful infections, no symptoms or disease
- Sufficient virus particles produced to spread in the population
- How do we know?
- Well adapted pathogens
  - >90% of poliovirus infections inapparent
- SARS-CoV-2 - 20%?

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



Principles of Virology, ASM Press

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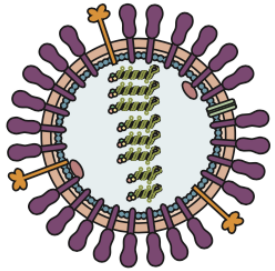
room number: virus

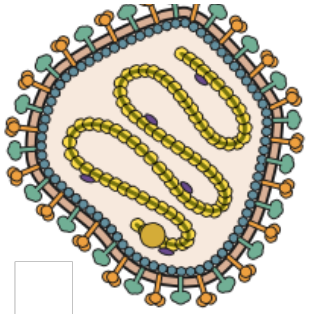
Which of the following do acute infections and incubation periods have in common?

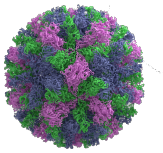
A. The virus is not replicating
B. No symptoms are visible
C. Immune defenses are engaged
D. The immune system does not respond
E. All of the above

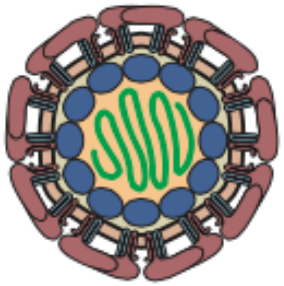
Viruses that cause acute infections

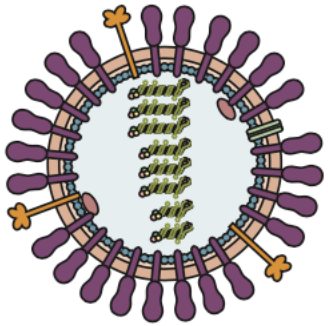
- Influenza virus
- Poliovirus
- Measles virus
- Norovirus
- West Nile virus



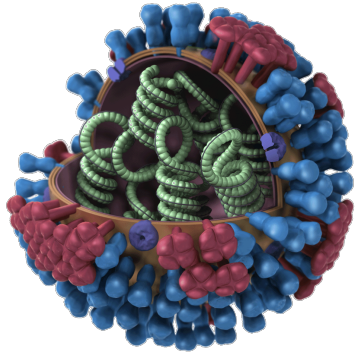






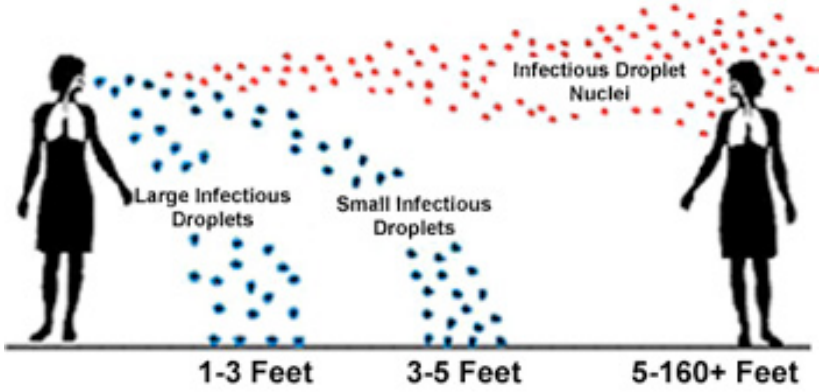


Influenza



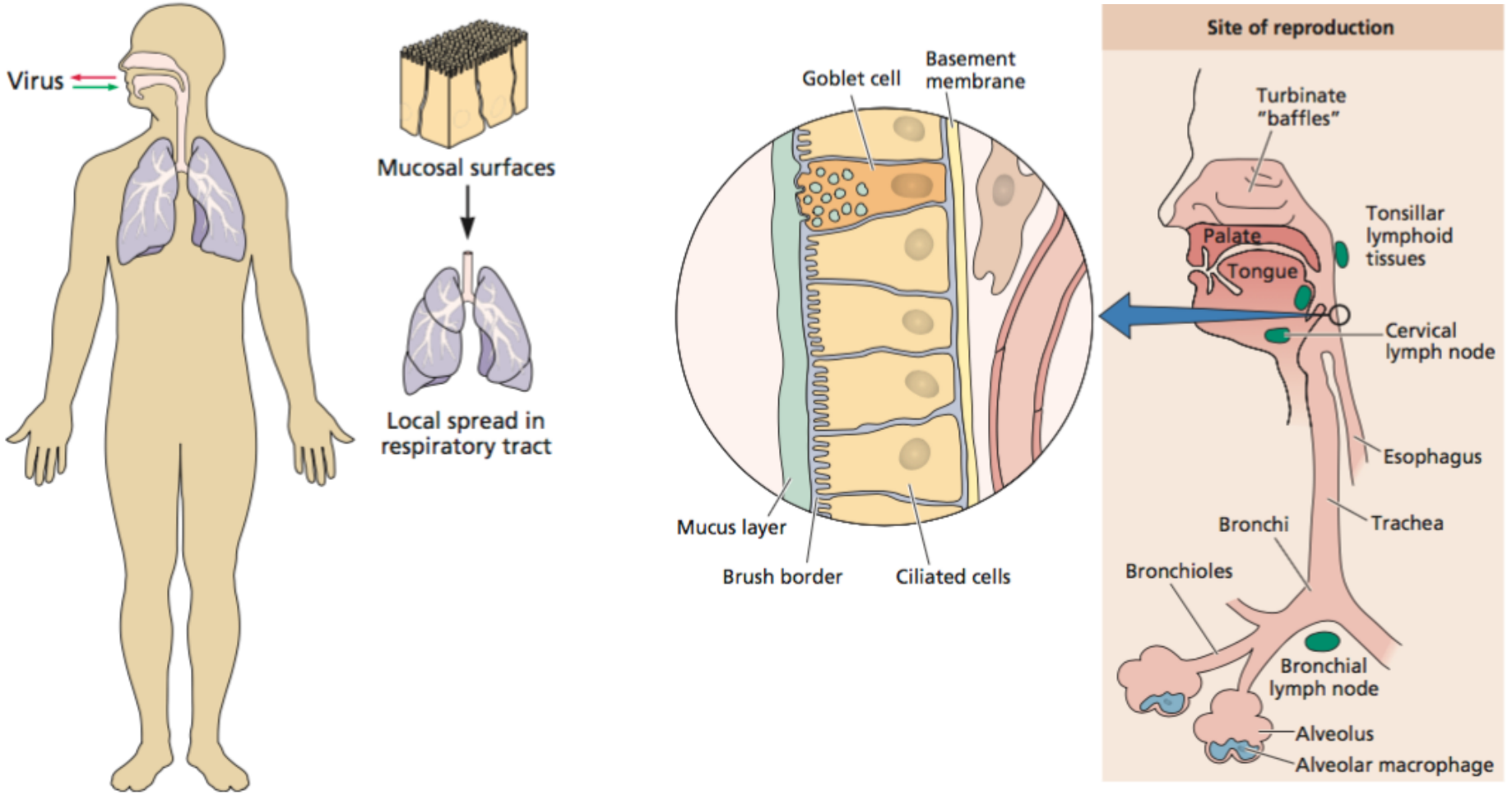
- Types: A, B, C
- A, B cause similar disease; C mostly inapparent or mild upper respiratory tract illness
- Only A cause pandemics
- Antigenic variation

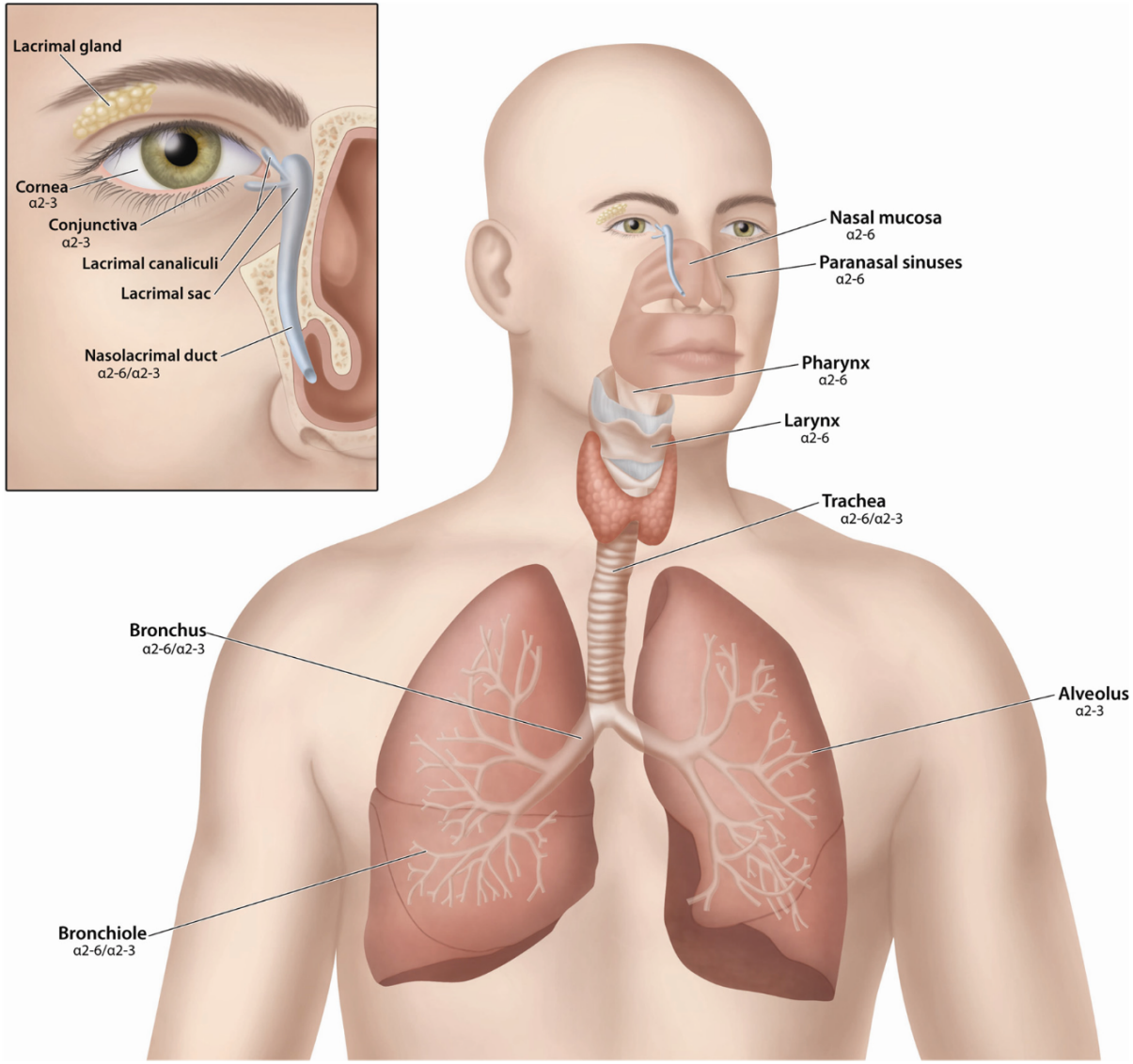
Influenza transmission



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

http://www.virology.ws/2009/04/29/influenza-virus-transmission/


Virus
Mucosal surfaces
Local spread in respiratory tract
Goblet cell
Basement membrane
Mucus layer
Brush border
Ciliated cells
Site of reproduction
Turbinate "baffles"
Tonsillar lymphoid tissues
Palate
Tongue
Cervical lymph node
Esophagus
Trachea
Bronchi
Bronchioles
Bronchial lymph node
Alveolus
Alveolar macrophage



α(2,6) human

α(2,3) avian

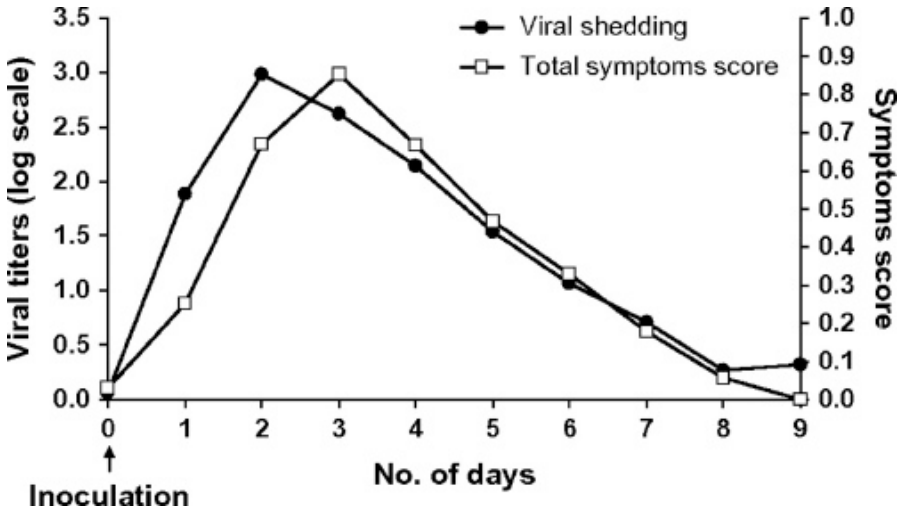
doi: 10.1128/MMBR .00058-12

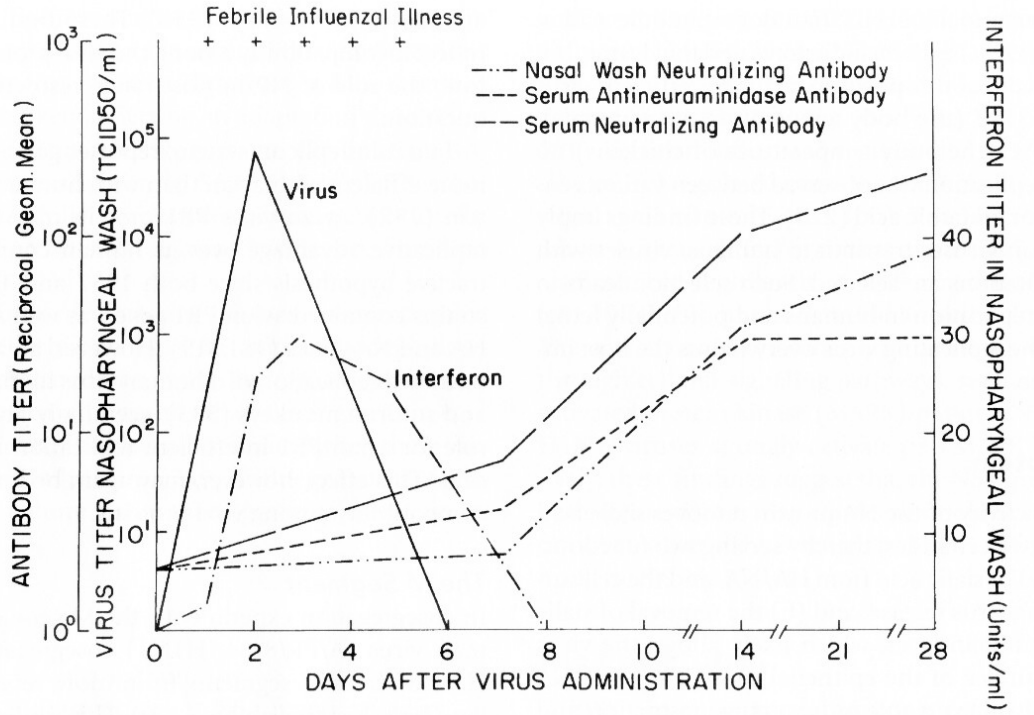
Uncomplicated influenza

- 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

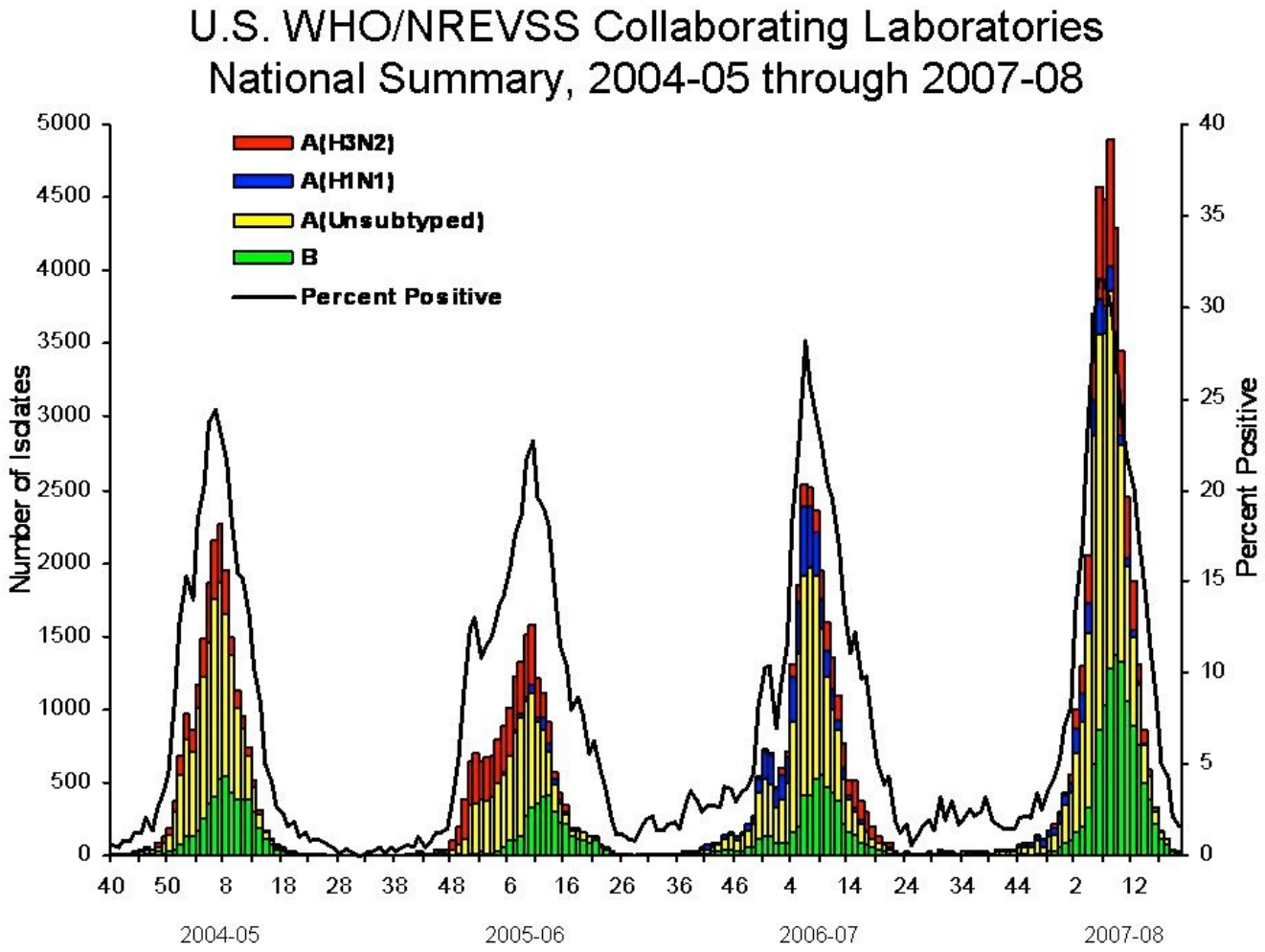
How is influenza diagnosed?

- 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


Viral shedding
Total symptoms score
Viral titers (log scale)
Symptoms score
No. of days
Inoculation

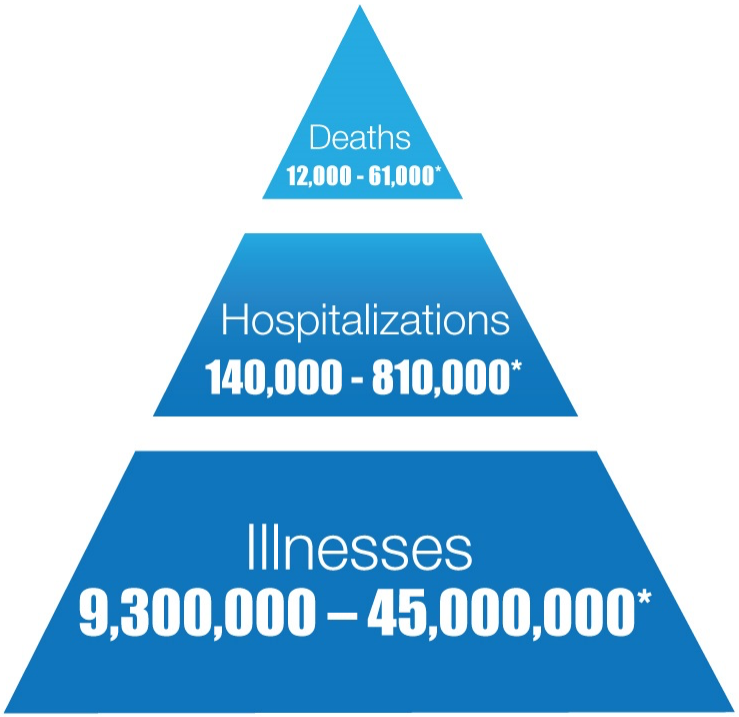

Febrile Influenzal Illness
Nasal Wash Neutralizing Antibody
Serum Antineuraminidase Antibody
Serum Neutralizing Antibody
Virus
Interferon
ANTIBODY TITER (Reciprocal Geom. Mean)
VIRUS TITER NASOPHARYNGEAL WASH (TCID50/ml)
INTERFERON TITER IN NASOPHARYNGEAL WASH (Units/ml)
DAYS AFTER VIRUS ADMINISTRATION

Seasonal influenza

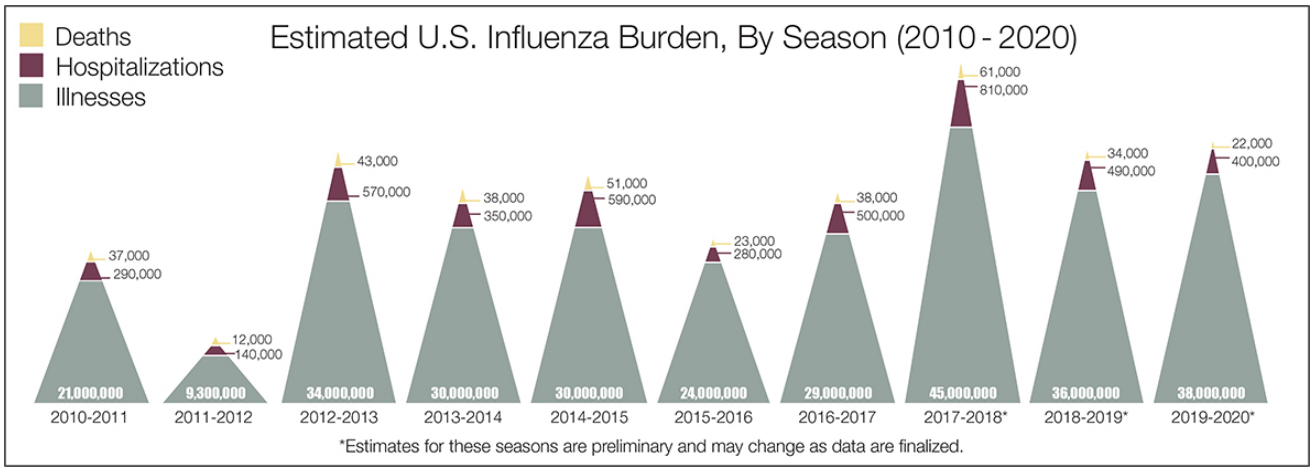


http://www.cdc.gov/flu/weekly/fluactivitysurv.htm

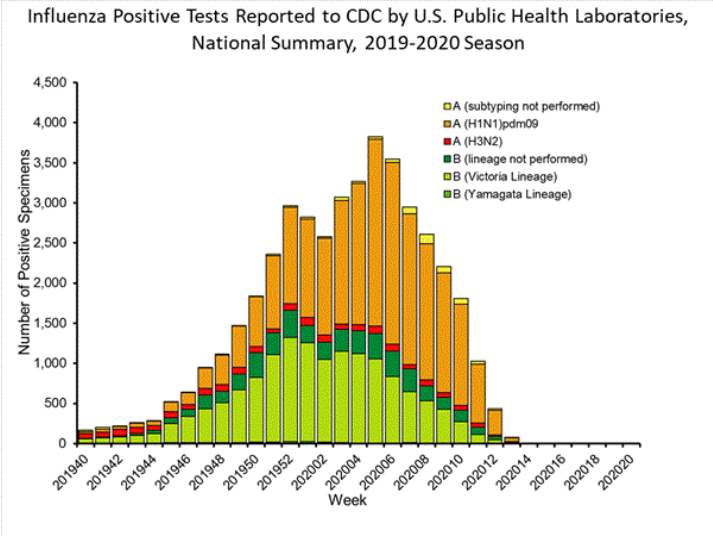
Burden of influenza, US

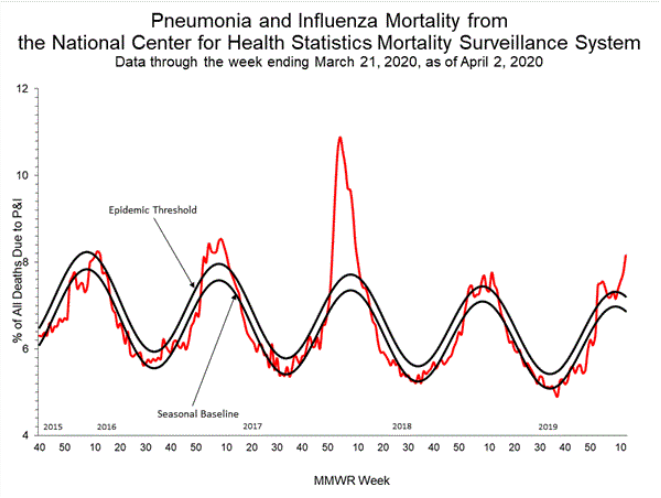


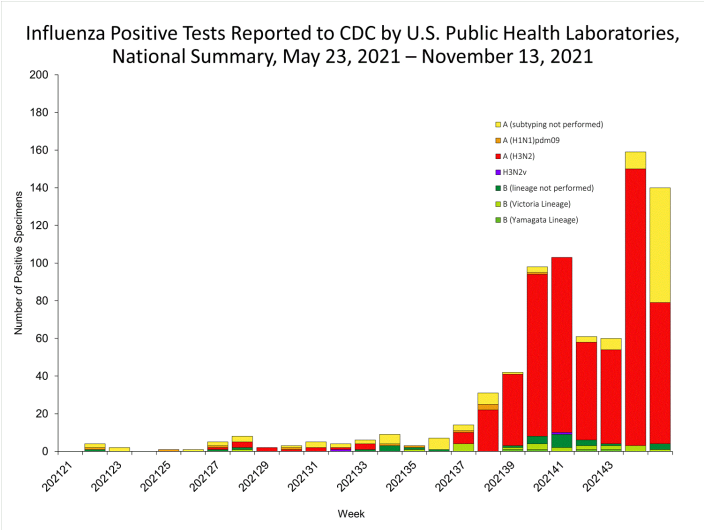
*The top range of these burden estimates are from the 2017-2018 flu season. These are preliminary and may change as data are finalized.

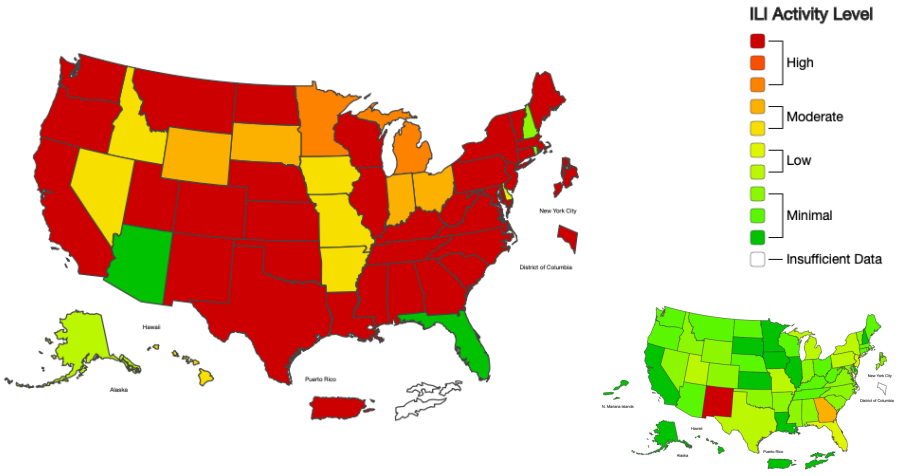


https://www.cdc.gov/flu/about/burden/index.html









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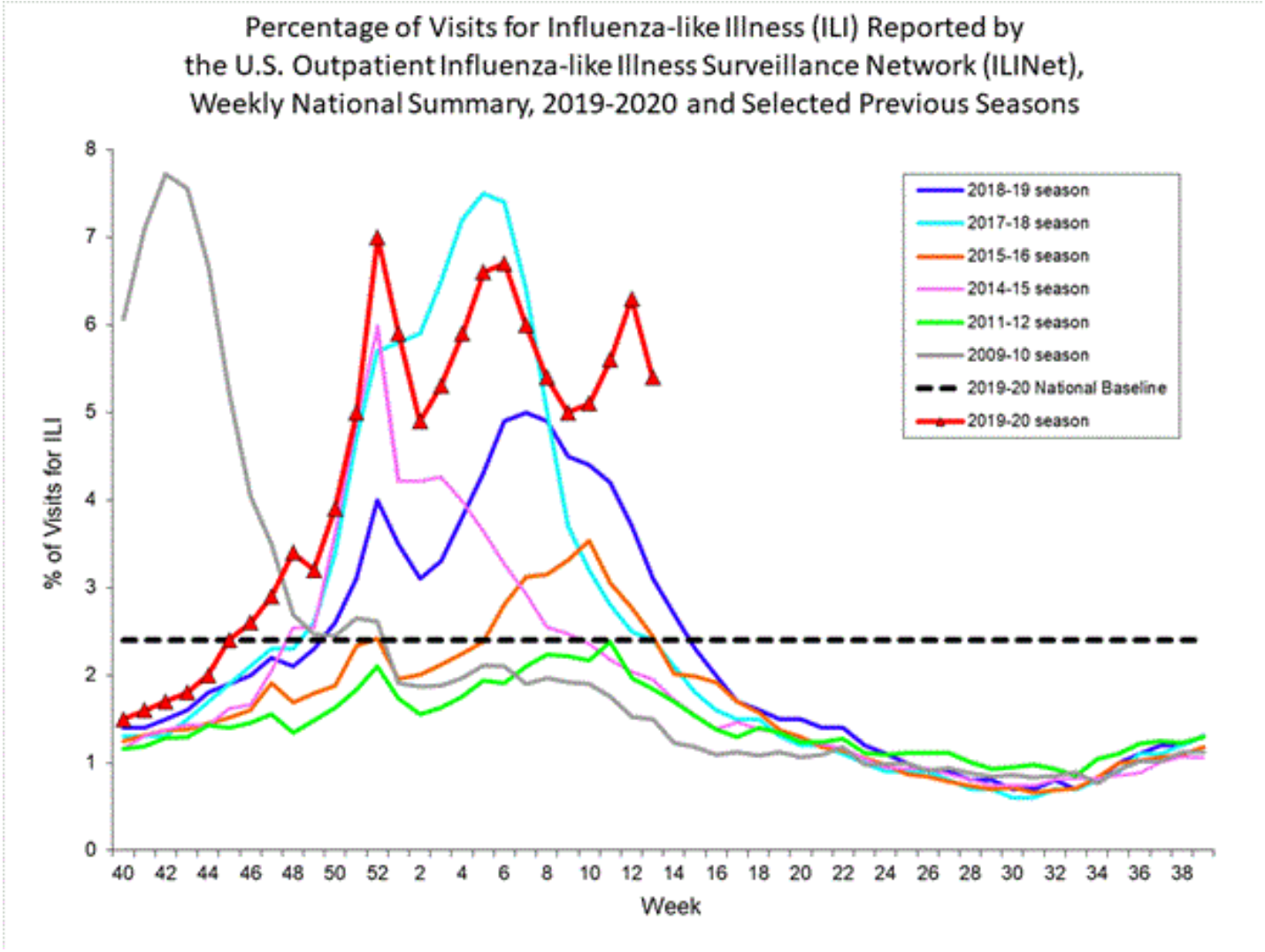
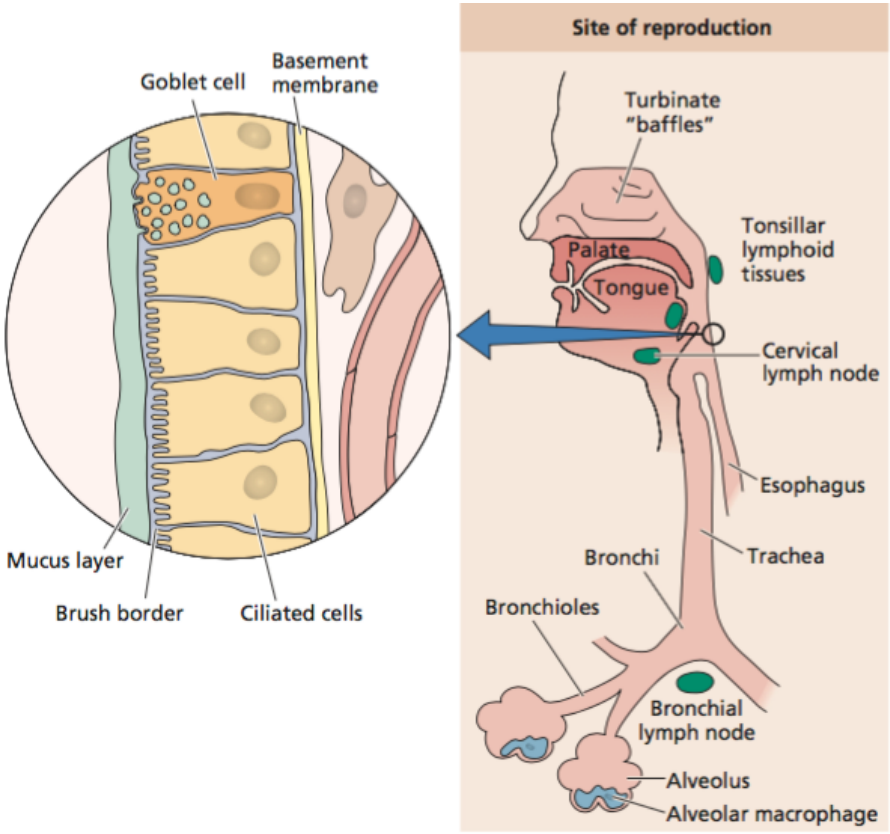


http://www.cdc.gov/flu/weekly/

Complications of influenza

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



Principles of Virology, ASM Press

Interventions for influenza

- Non-pharmaceutical
- Antiviral drugs
  - Tamiflu (oseltamivir)
  - Relenza (zanamavir)
  - Flumadine (rimantadine)
  - Xofluza (baloxavir marboxil)
- Vaccines

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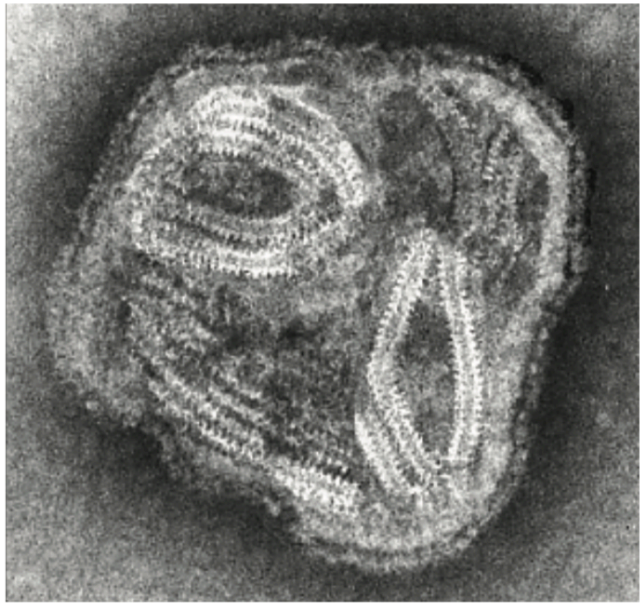
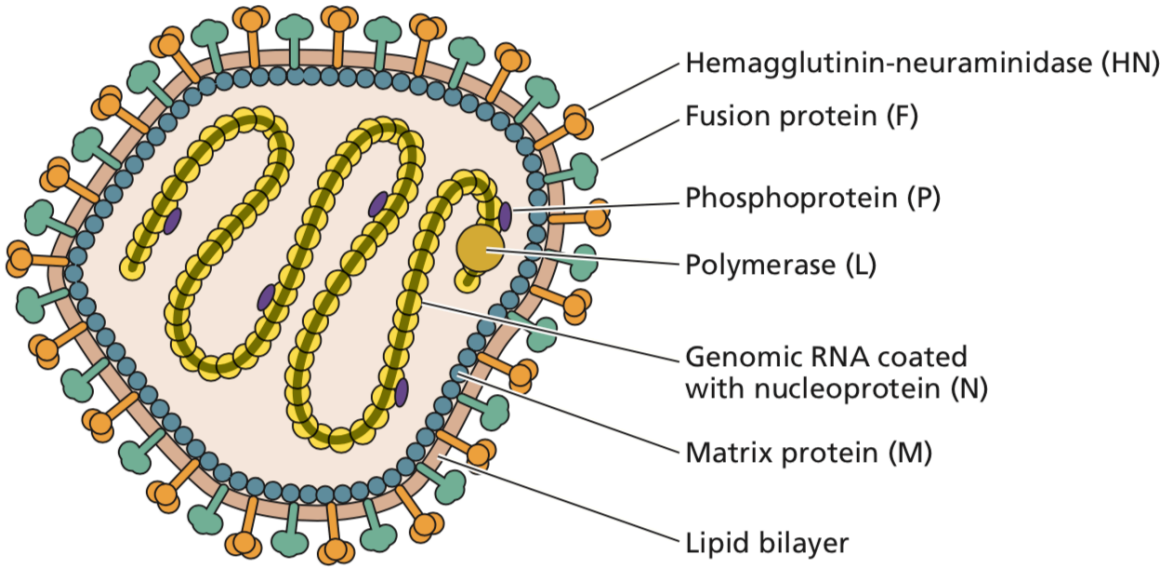
room number: virus

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

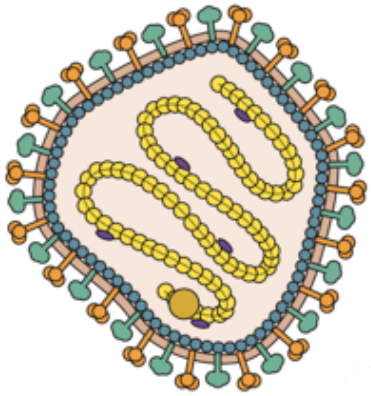
Measles





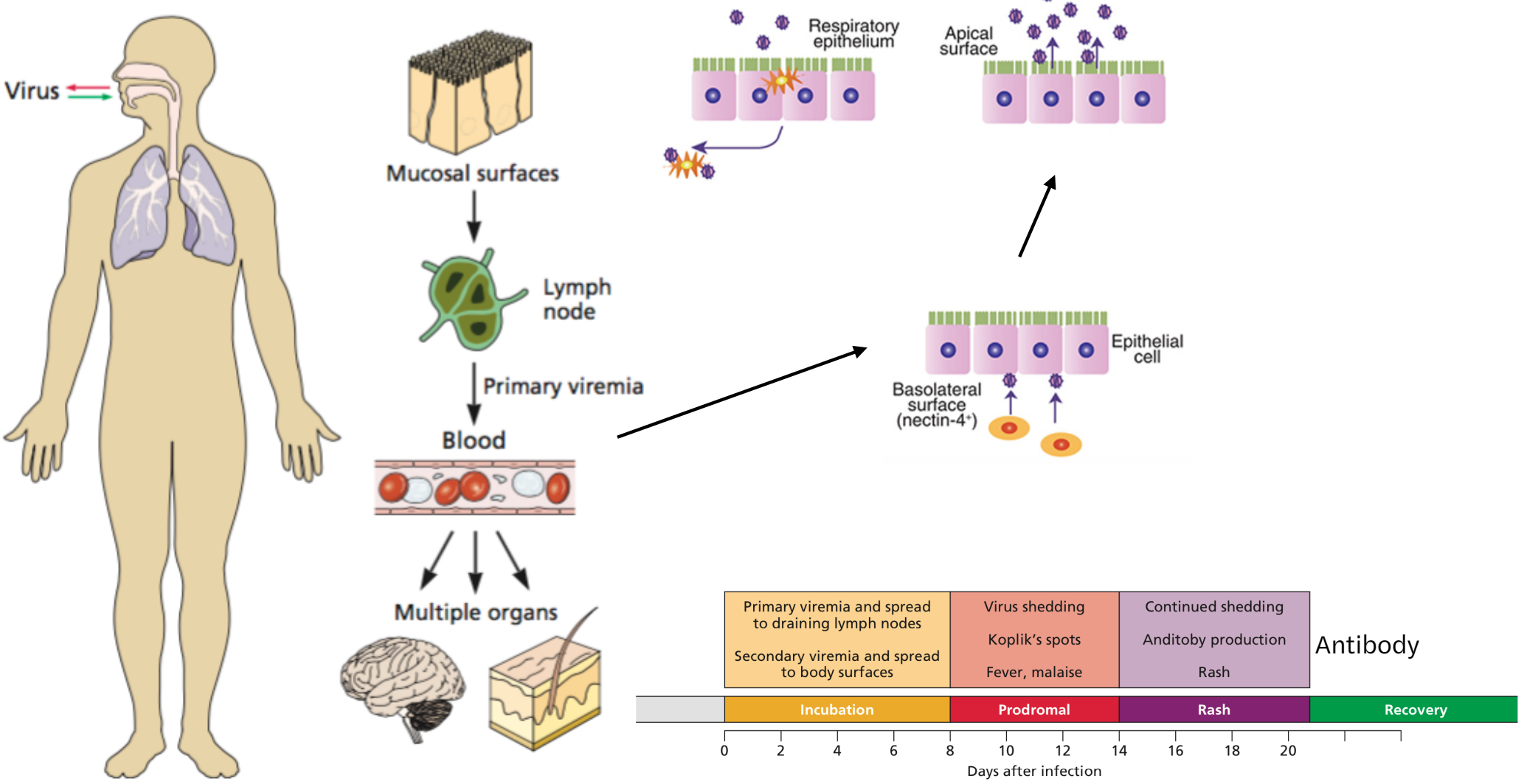
- Measles virus, *Paramyxoviridae*
- One of the most contagious human viruses (R_0 = 15)

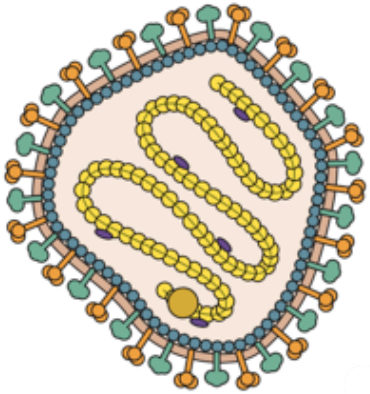
Principles of Virology, ASM Press



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

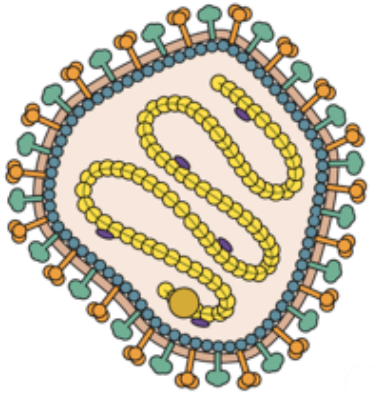

Virus
Mucosal surfaces
Lymph node
Primary viremia
Blood
Multiple organs
Respiratory epithelium
Apical surface
Epithelial cell
Basolateral surface (nectin-4+)
Primary viremia and spread to draining lymph nodes
Secondary viremia and spread to body surfaces
Virus shedding
Koplik's spots
Fever, malaise
Continued shedding
Anditoby production
Rash
Antibody
Incubation
Prodromal
Rash
Recovery
0 2 4 6 8 10 12 14 16 18 20
Days after infection



Uncomplicated measles

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

Principles of Virology, ASM Press

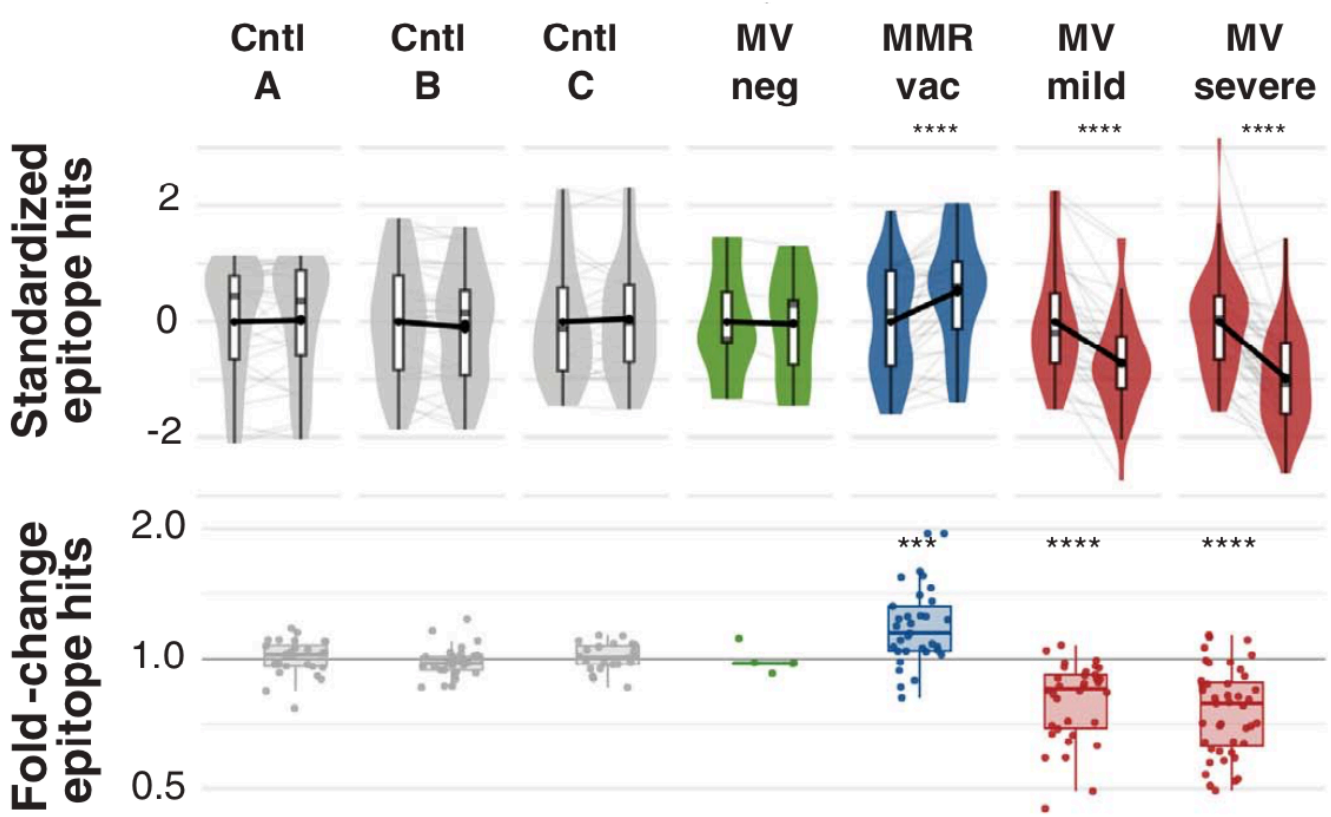


Measles complications

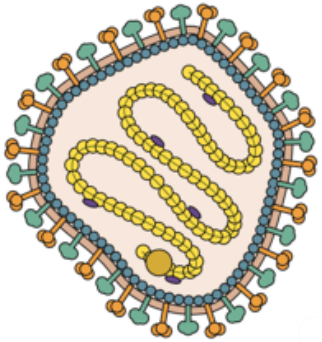
- Acute postinfectious encephalitis (1/1,000)
- Bronchitis, pneumonia, ear infection
- Fatality 1-2/1000 (28% poor nutrition)
- Subacute sclerosing panencephalitis (SSPE)
- Immunosuppression leading to secondary infections (main cause of death in Third World children)

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

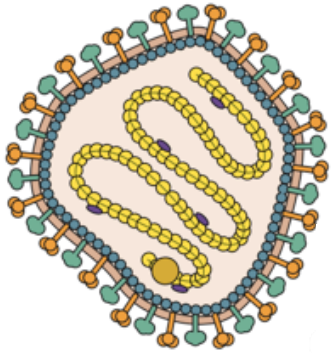


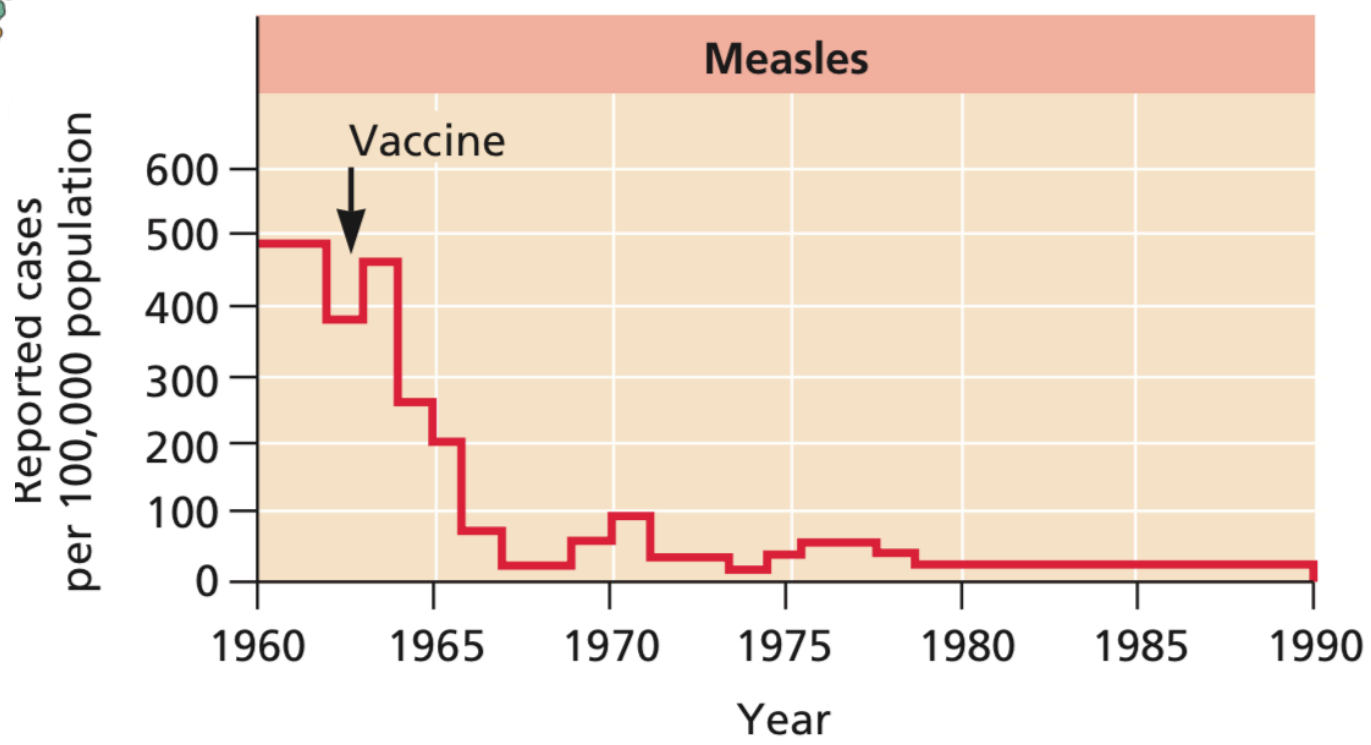
Mina et al., Science 366, 599–606 (2019)

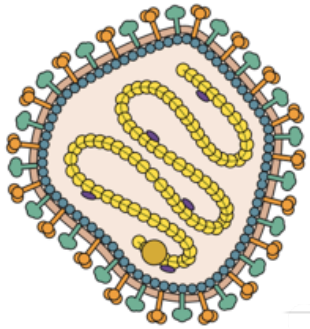


Measles prevention

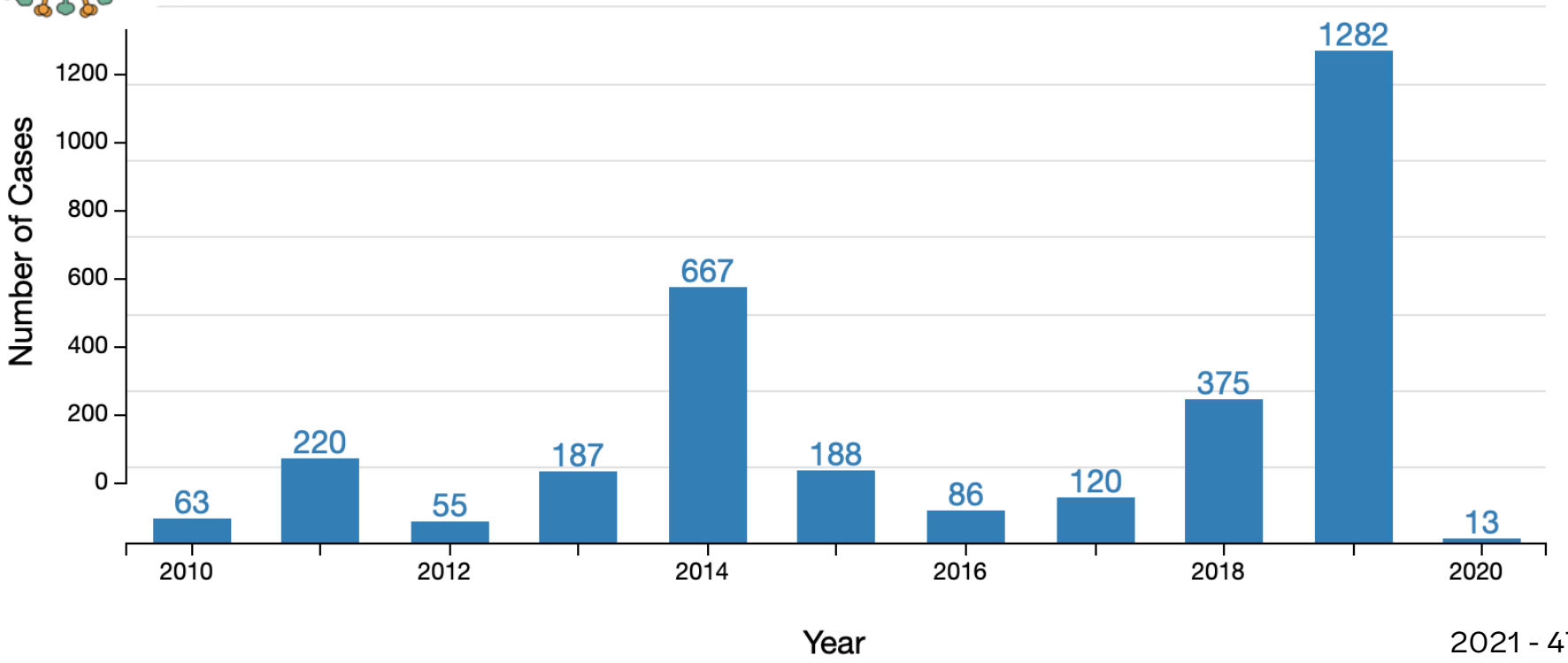
- Pre-vaccine in the US: 3-4 million/yr, 400-500 deaths, 48,000 hospitalizations, 1,000 chronic disability from encephalitis
- Endemic transmission stopped 2000 by vaccine
- MMR: measles, mumps, rubella vaccine
- Wakefield 1998 report lead to decreased MMR immunization, outbreaks in UK, Ireland
- US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




Measles
Vaccine
Reported cases per 100,000 population
600
500
400
300
200
100
0
1960
1965
1970
1975
1980
1985
1990
Year



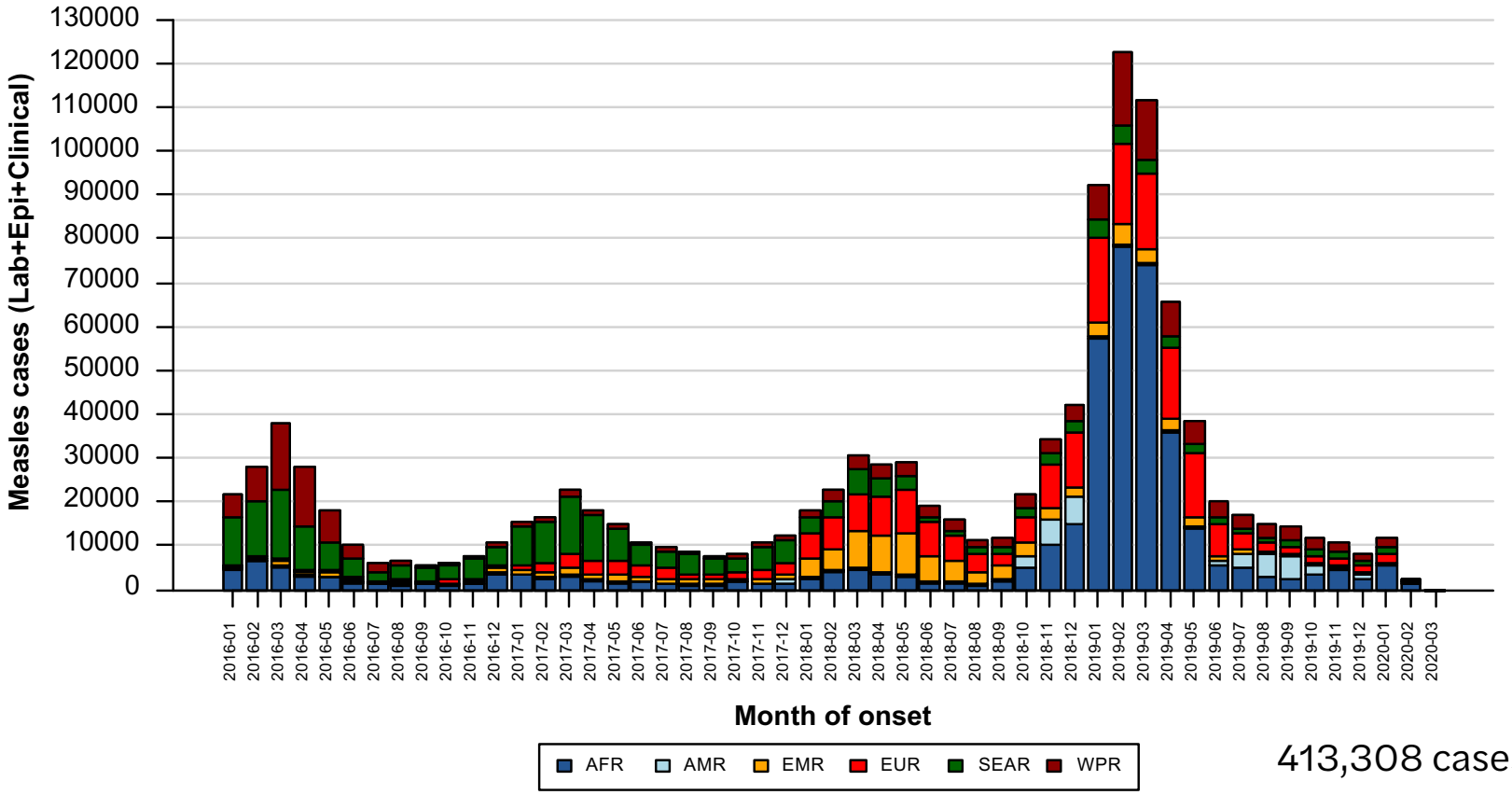
Measles cases by year, US



2021 - 47 cases

https://www.cdc.gov/measles/cases-outbreaks.html

Measles case distribution by month and WHO Region (2016-2020)



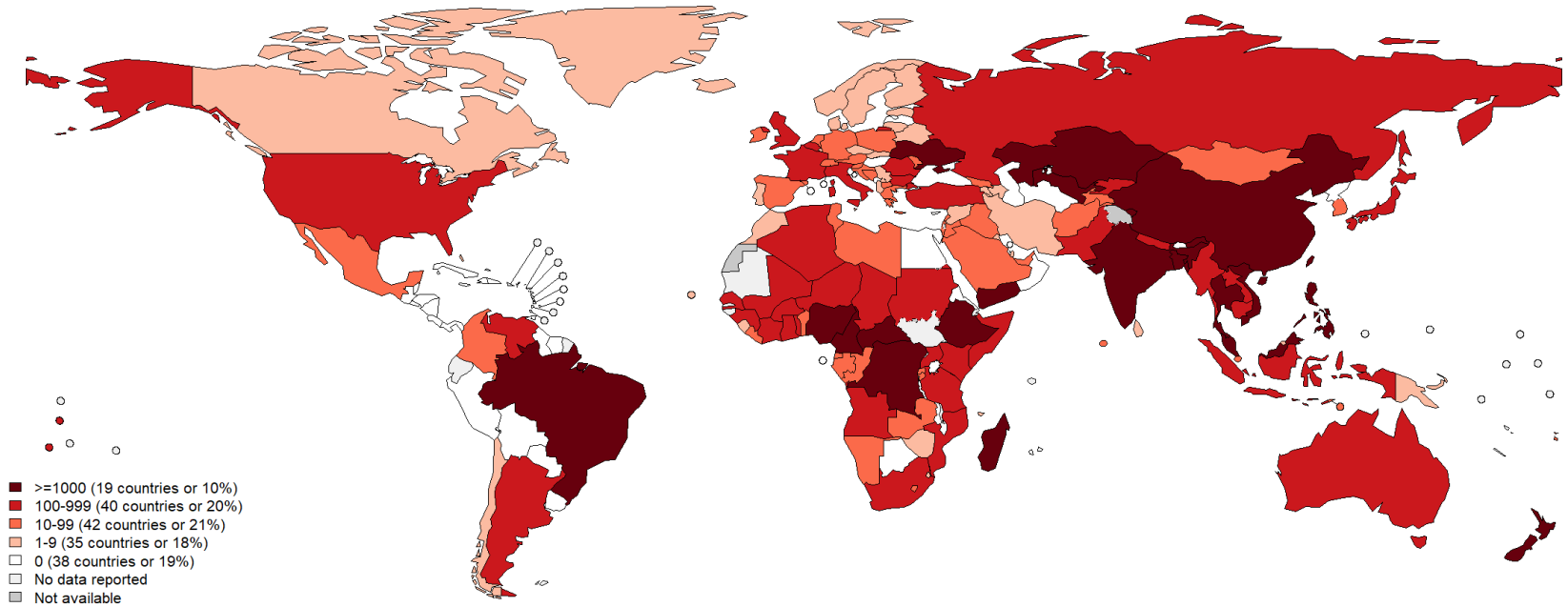
413,308 cases in 2019

Source: WHO

Number of reported measles cases (6M period)

Top 10 countries with measles outbreaks

Rank	Country	Number of Cases
1	Yemen	1,896
2	United Republic of Tanzania	1,042
3	India	893
4	Nigeria	798
5	Pakistan	557
6	Burundi	472
7	China	470
8	Brazil	468
9	Democratic Republic of the Congo	415
10	Kenya	291



World Health Organization

Map production: World Health Organization, WHO, 2020. All rights reserved
Data source: IVB Database

Disclaimer:
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Almost 41 countries have already put off, or may put off, their measles campaigns for 2020 or 2021 due to the COVID-19 pandemic.

Source: WHO

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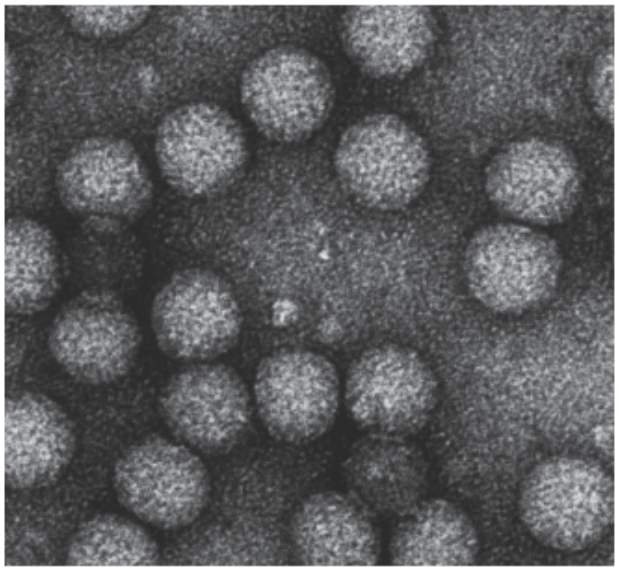
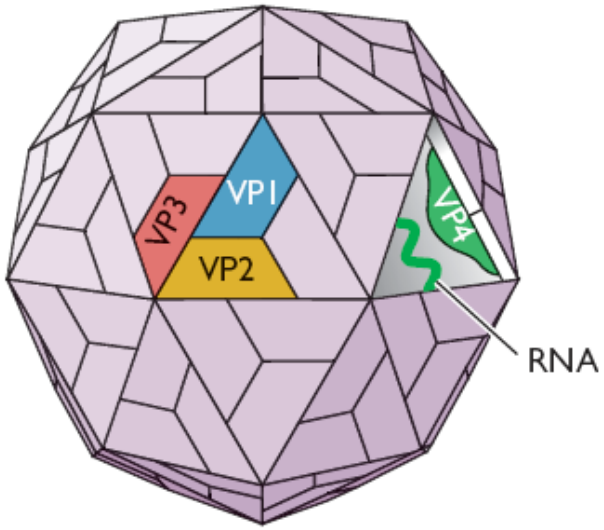
room number: virus

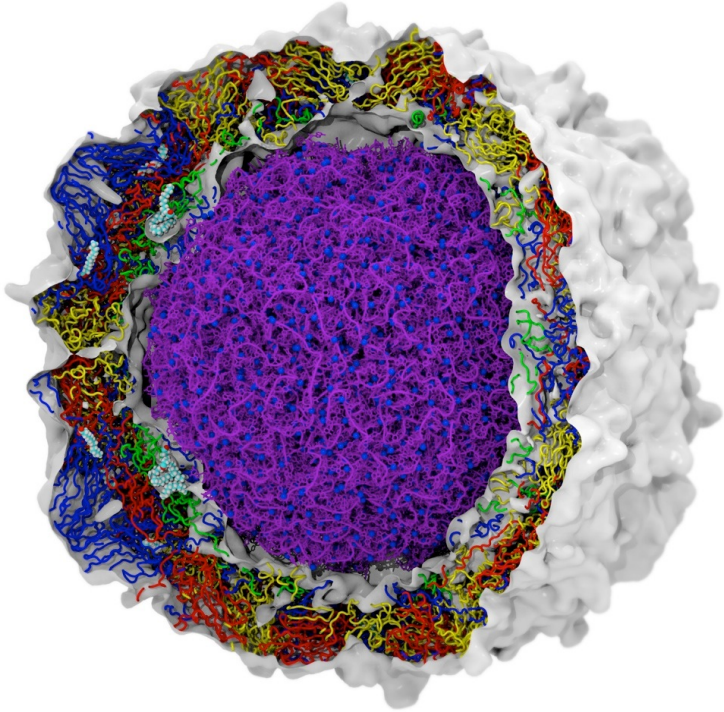
Which of the following is a good reason to get measles vaccine?

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







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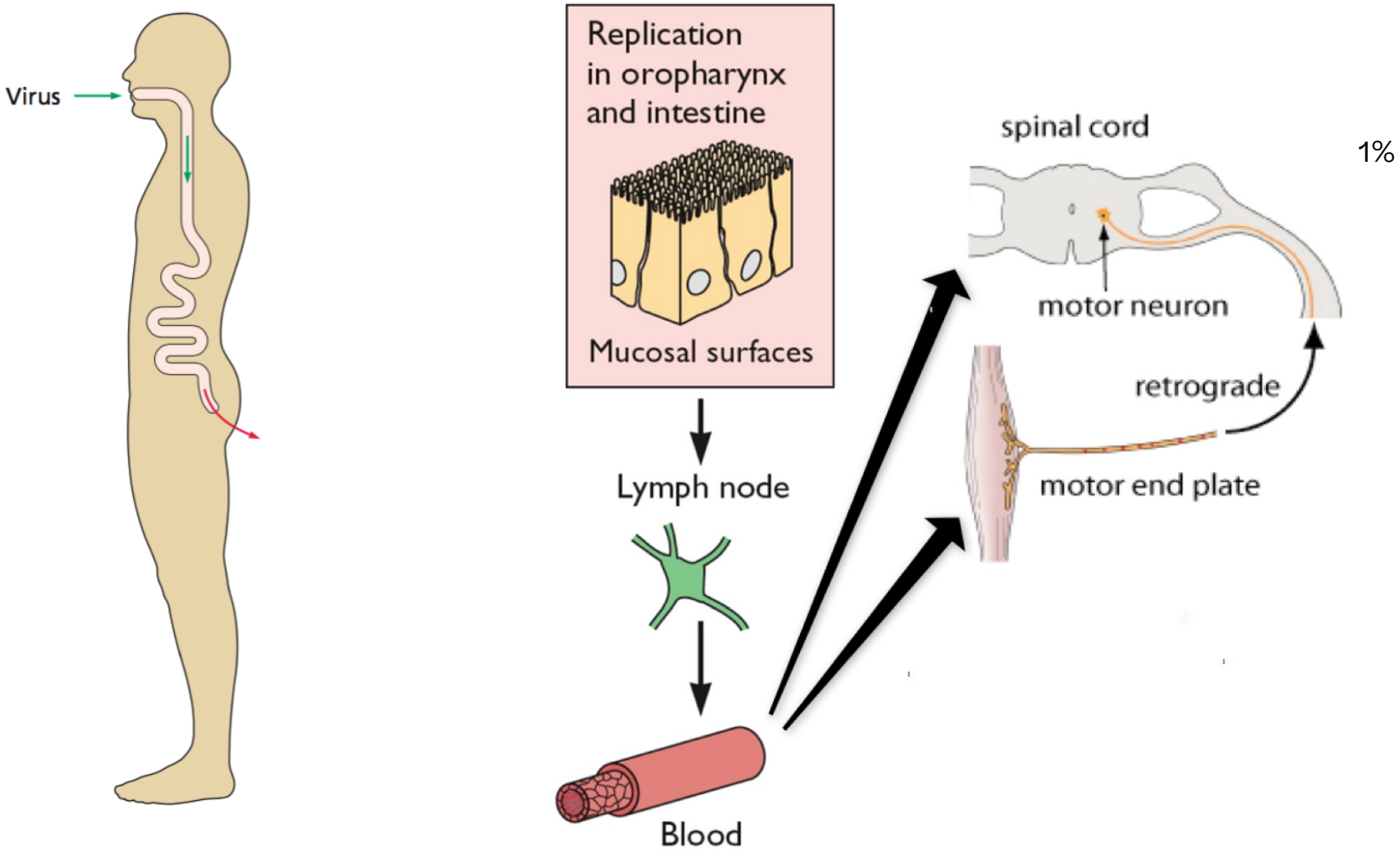
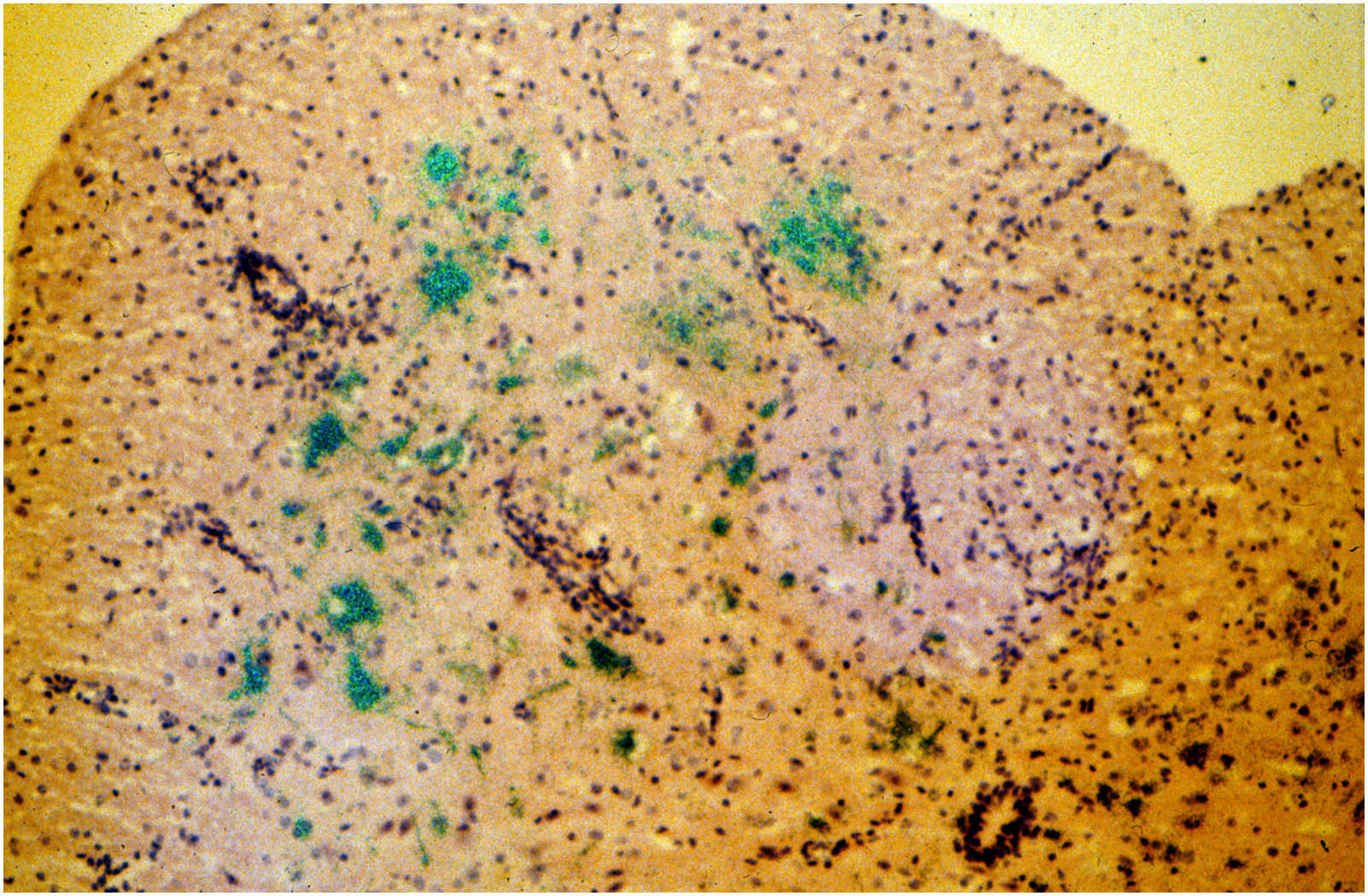
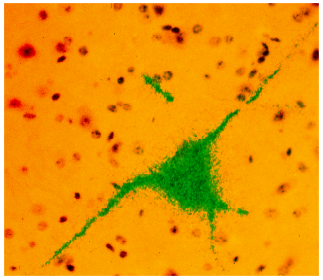
Poliovirus pathogenesis



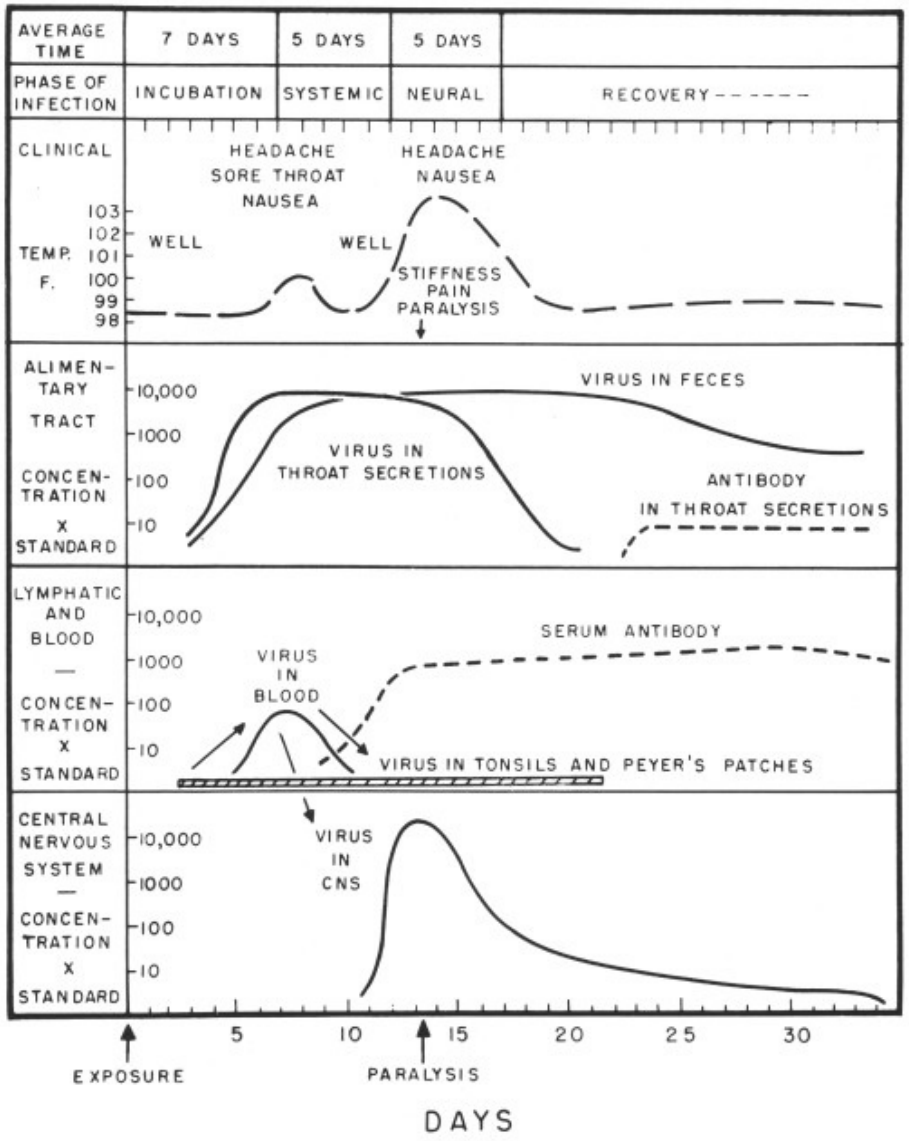
Principles of Virology, ASM Press





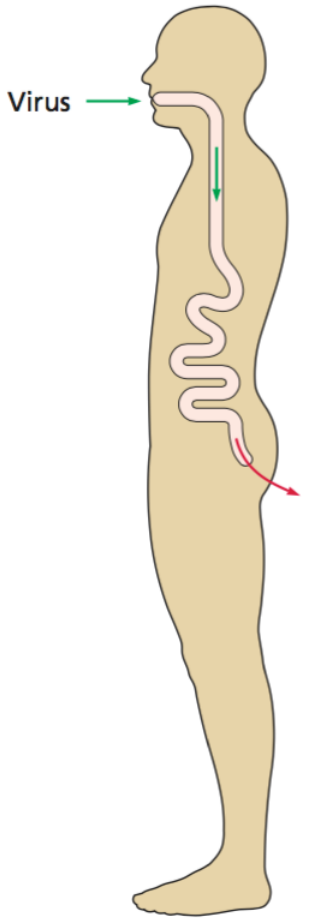
Virology Live 2021 • Vincent Racaniello

http://www.virology.ws/2009/03/11/chronology-of-an-acute-infection/



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



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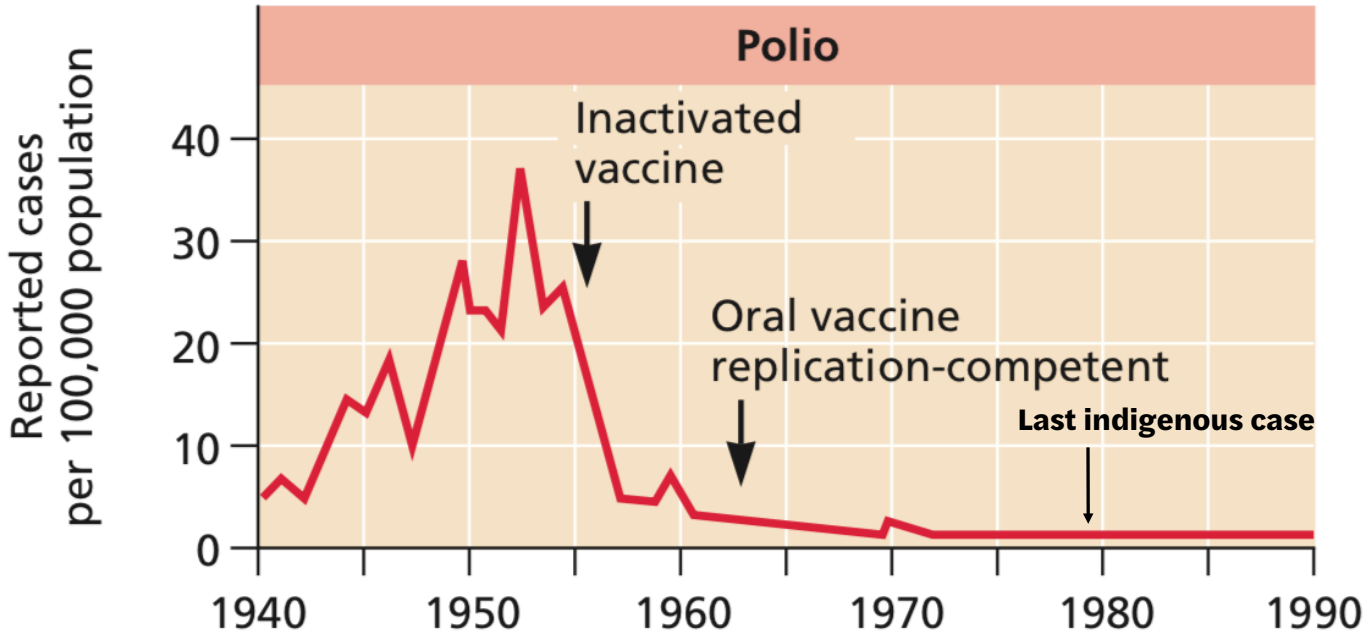
Poliomyelitis—United States, 1940-1990



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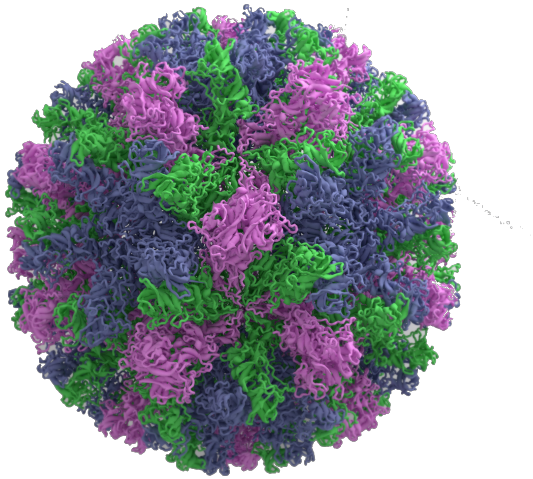
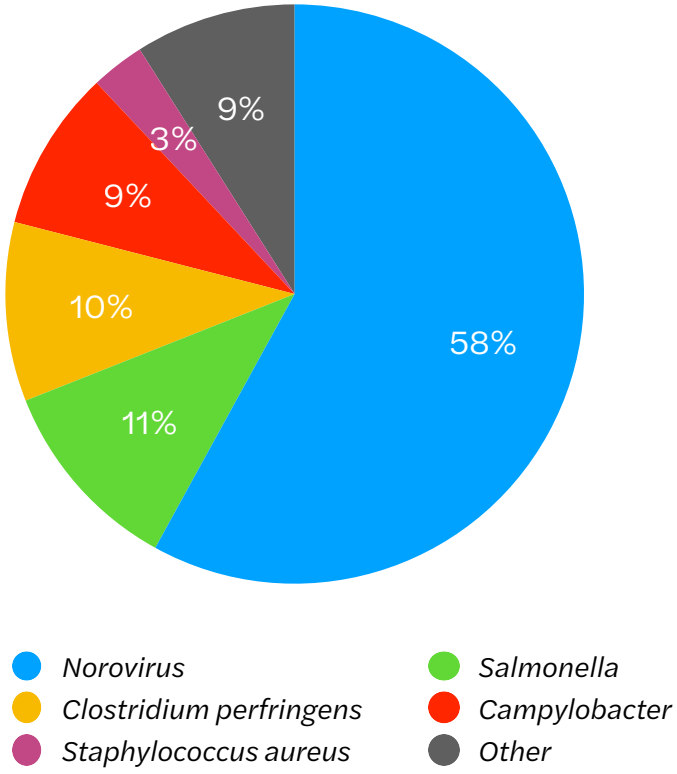
In a 24 hour period...

- 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

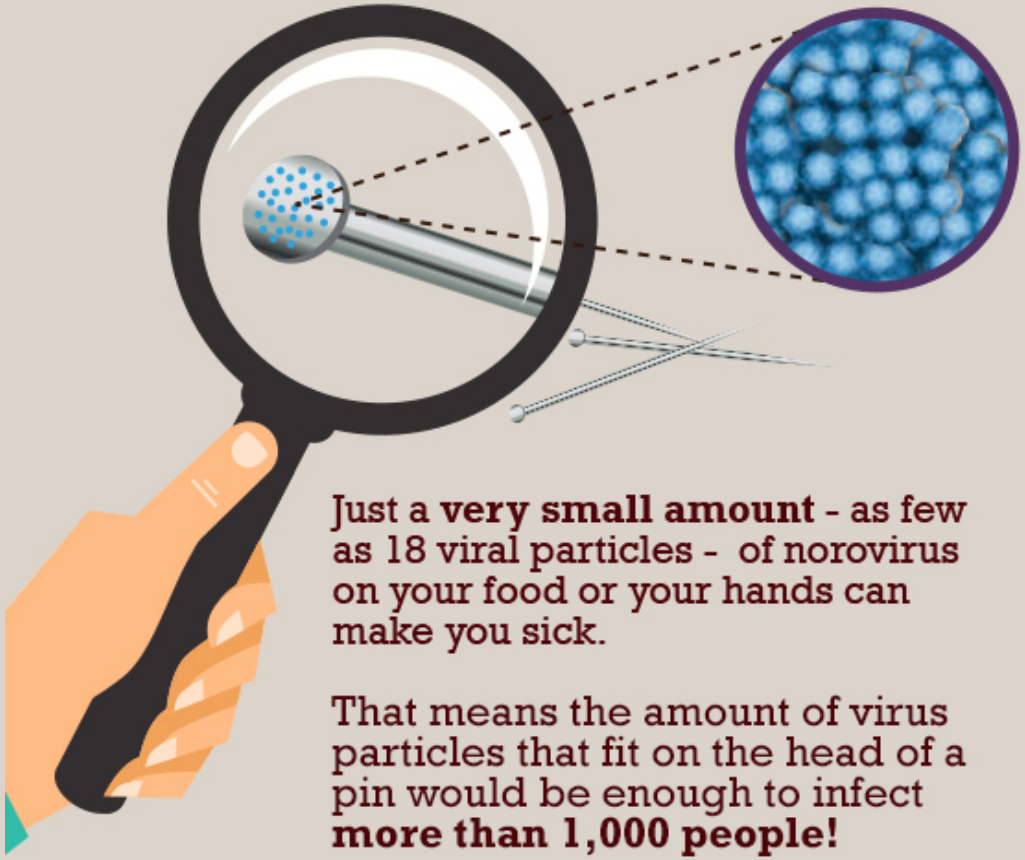


Norovirus



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

How contagious is norovirus?

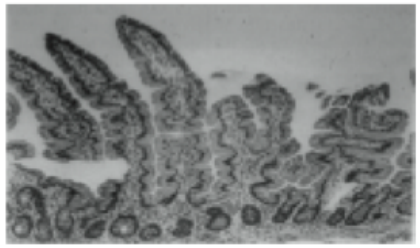


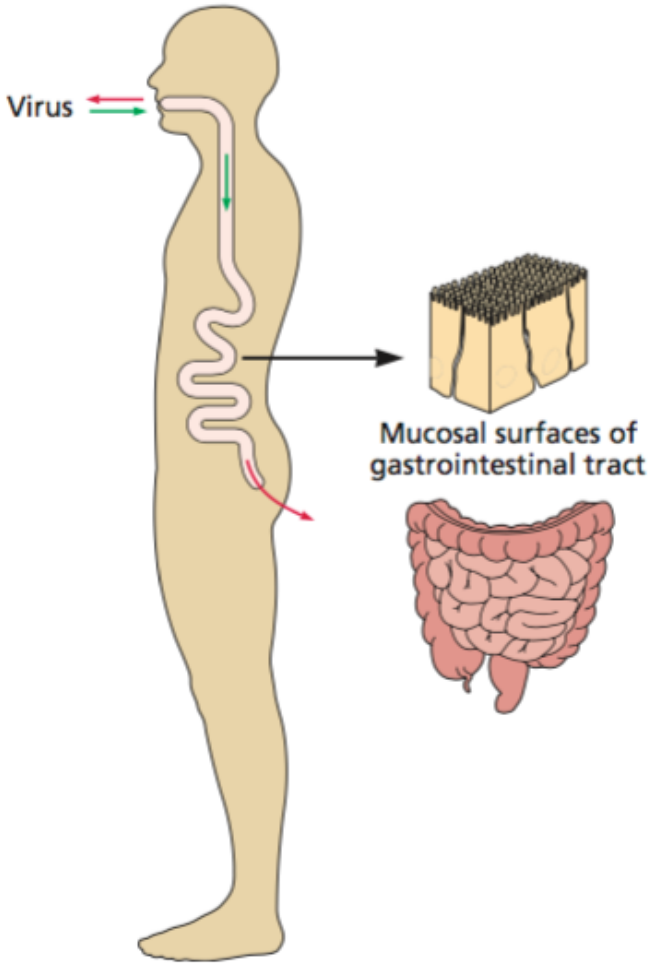
Just a **very small amount** - as few as 18 viral particles - of norovirus on your food or your hands can make you sick.

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

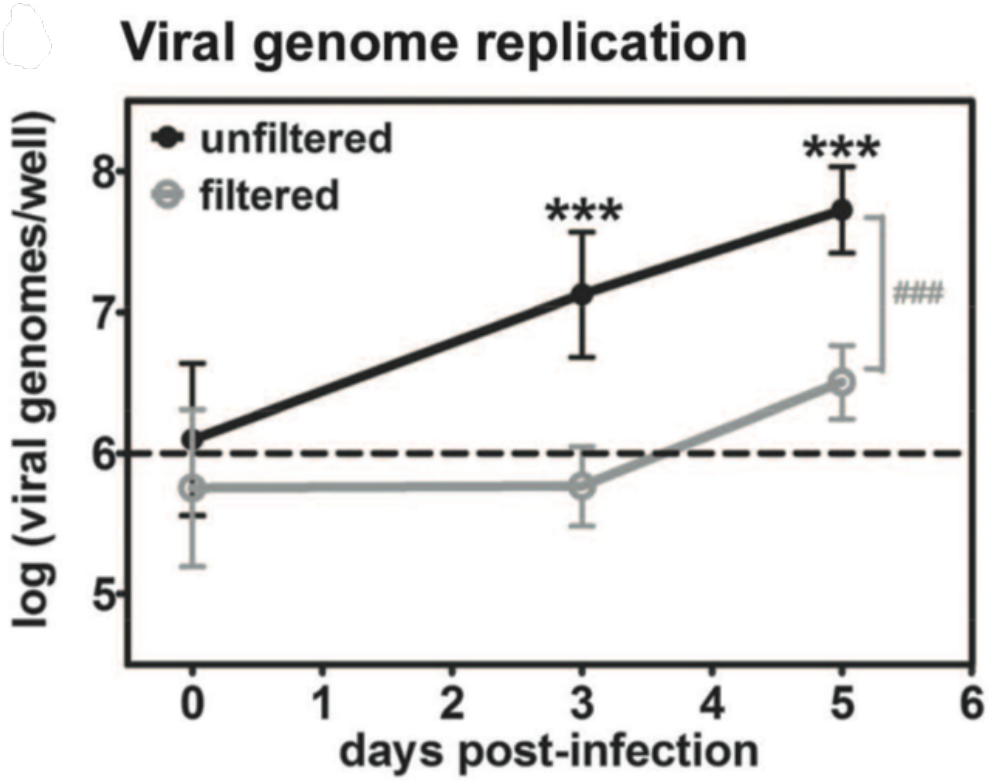
- Fecal-oral spread
- Virus particles retain infectivity passing through stomach
- Blunting of villi in proximal jejunum
- Basis for vomiting, diarrhea not known





Principles of Virology, ASM Press

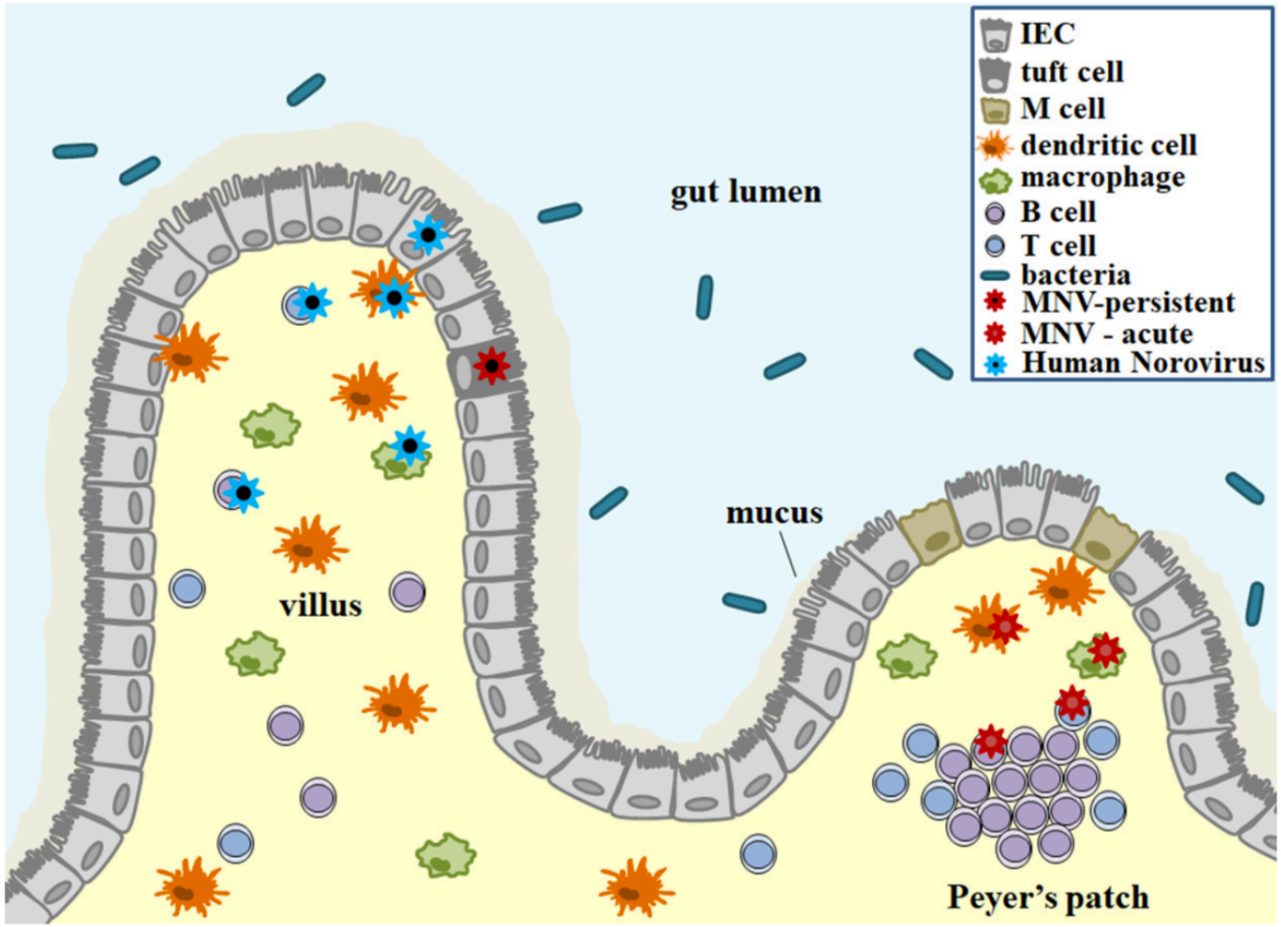
Enteric bacteria promote human and mouse norovirus infection of B cells



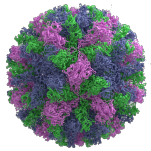
Science 346:6210 (2014)

Norovirus pathogenesis

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

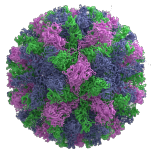


https://doi.org/10.1128/JVI.01010-17



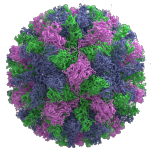
Clinical and epidemiological features

- 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



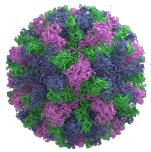
Clinical and epidemiological features

- 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

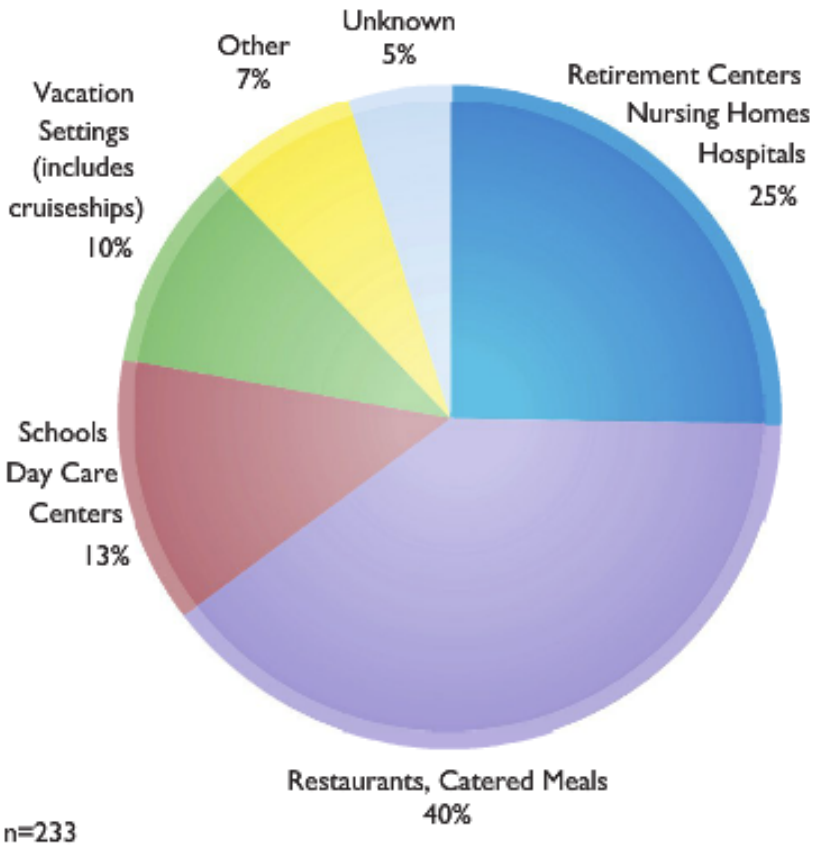
- Reservoir: Humans, might be able to infect non-human animals
- Affects all ages
- Year round, peaks in cold weather
- Outbreaks often occur in semi-closed environments (nursing homes, hospitals, cruise ships), military, schools, recreational activities (sports events, camping trips, travel) that favor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



Clinical and epidemiological features

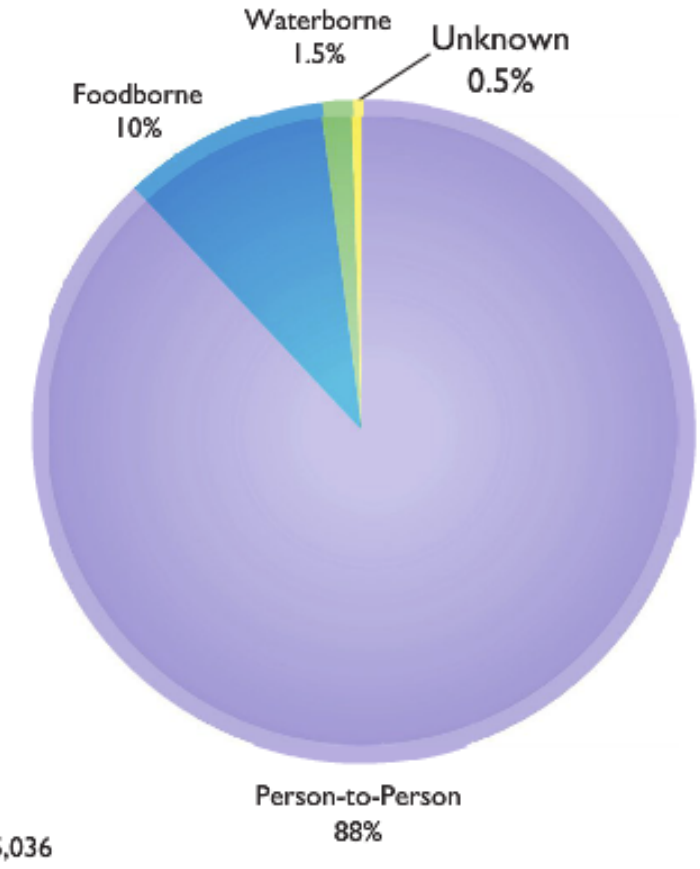
- Treatment: Supportive to prevent dehydration
- Vaccine in development
- 200,000 deaths/yr mainly in children

A Settings



n=233

B Modes of Transmission



n=5,036

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.

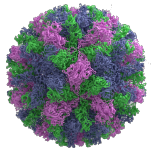
On a recent Air New Zealand flight, a sick passenger passed norovirus along to the crew. "Not only did the crew that cleaned up the mess get sick, but on every successive flight at least one or more crew members got sick with typical symptoms of norovirus," said David Freedman, of the University of Alabama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

On a recent Air New Zealand flight, a sick passenger passed norovirus along...

The happiest place on Earth™?

2010

Cruise Line	Cruise Ship	Sailing Dates	Causative Agent
Crystal Cruises	*Crystal Symphony*	11/02 - 11/21	Unknown
Holland America Line	*Nieuw Amsterdam*	10/18 - 11/07	Norovirus
Carnival Cruise Lines	*Carnival Glory*	10/09 - 10/16	Norovirus
Holland America Line	*Zuiderdam*	04/20 - 05/08	Unknown
Celebrity Cruises	*Mercury*	03/08 - 03/19	Norovirus
Celebrity Cruises	*Mercury*	02/26 - 03/08	Norovirus
Royal Caribbean International	*Jewel of the Seas*	02/22 - 03/05	Unknown
Celebrity Cruises	*Millennium*	02/22 - 03/05	Norovirus
Holland America Line	*Maasdam*	02/19 - 03/05	Norovirus
Celebrity Cruises	*Mercury*	02/15 - 02/26	Norovirus
Fred Olsen Cruise Lines	*Balmoral*	01/05 - 02/04	Unknown
Cunard Cruise Line	*Queen Victoria*	01/12 - 01/27	Unknown
Cunard Cruise Line	*Queen Victoria*	01/04 - 01/12	Norovirus

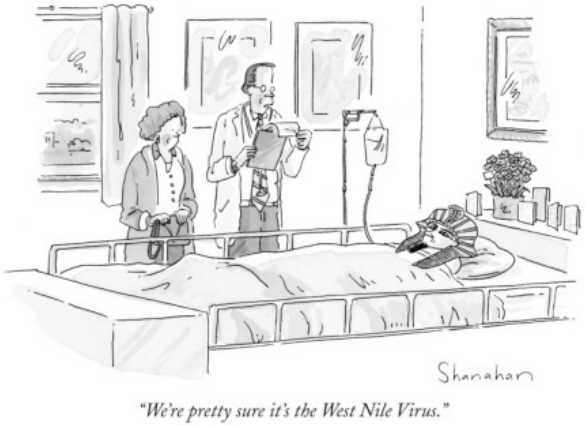


Why are noroviruses associated with cruise ships?

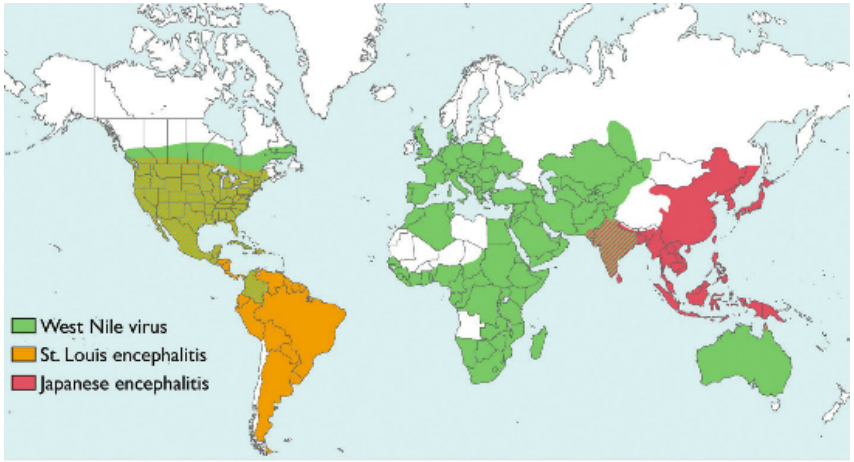
- Health officials track illness on cruise ships, so outbreaks are found and reported more quickly on a cruise ship than on land
- Close living quarters may increase the amount of group contact
- New passenger arrivals may bring the virus to other passengers and crew


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
CDC

West Nile virus

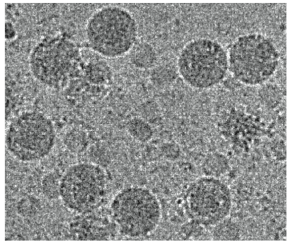


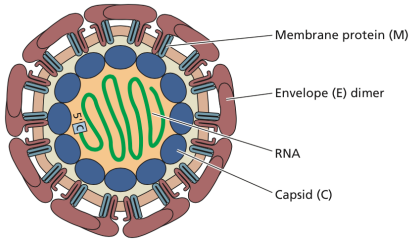
"We're pretty sure it's the West Nile Virus."

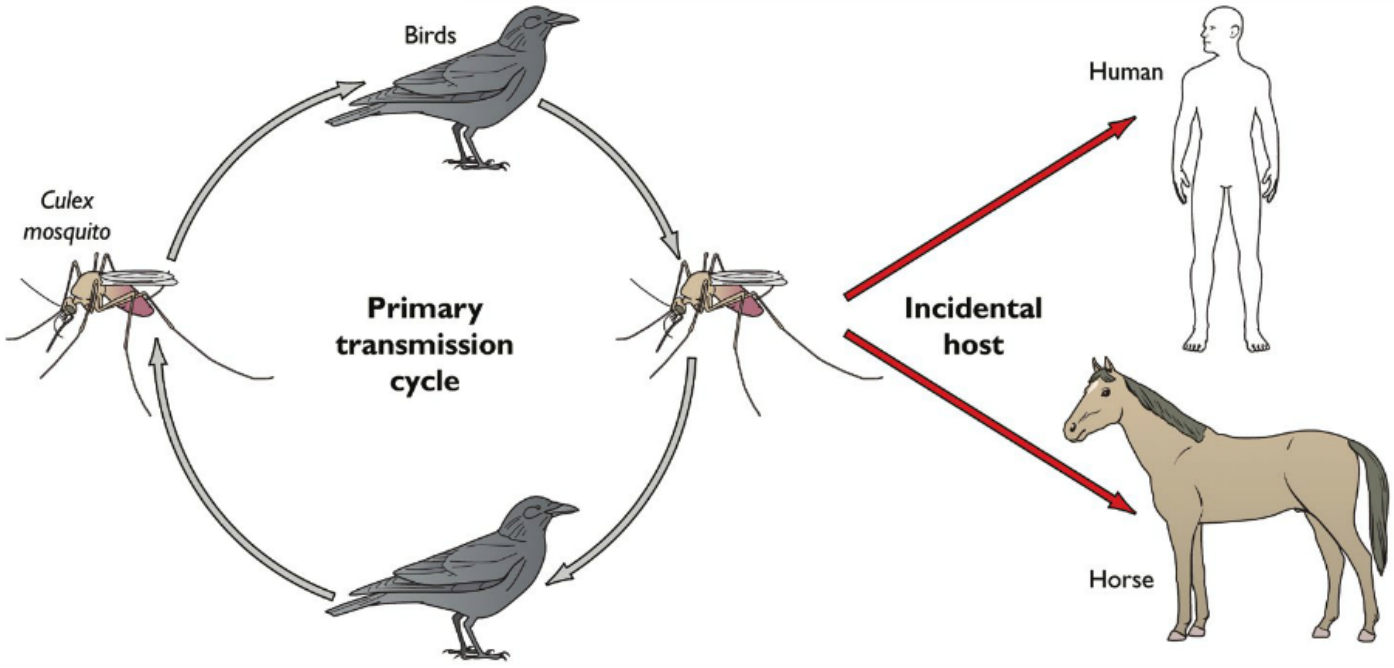


- *Flaviviridae*, isolated 1937, West Nile district of Uganda
- Absent from Western Hemisphere until 1999
- New York isolate identical to virus from Israeli goose
- Virus infects hundreds of birds, 37 kinds of mosquitoes, 18 other vertebrates

WNV transmission cycle



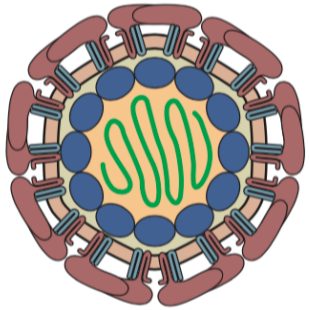




Principles of Virology, ASM Press

WNV pathogenesis

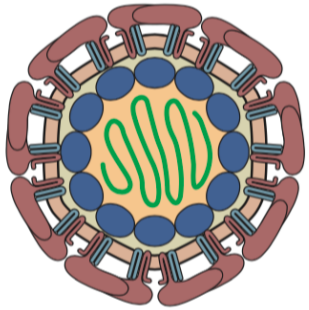
- Transmitted to humans by *Culex* mosquito bite
- Incubation period 3-14 days
- 20-30% develop flu-like illness called WNV fever
- 80%: no symptoms

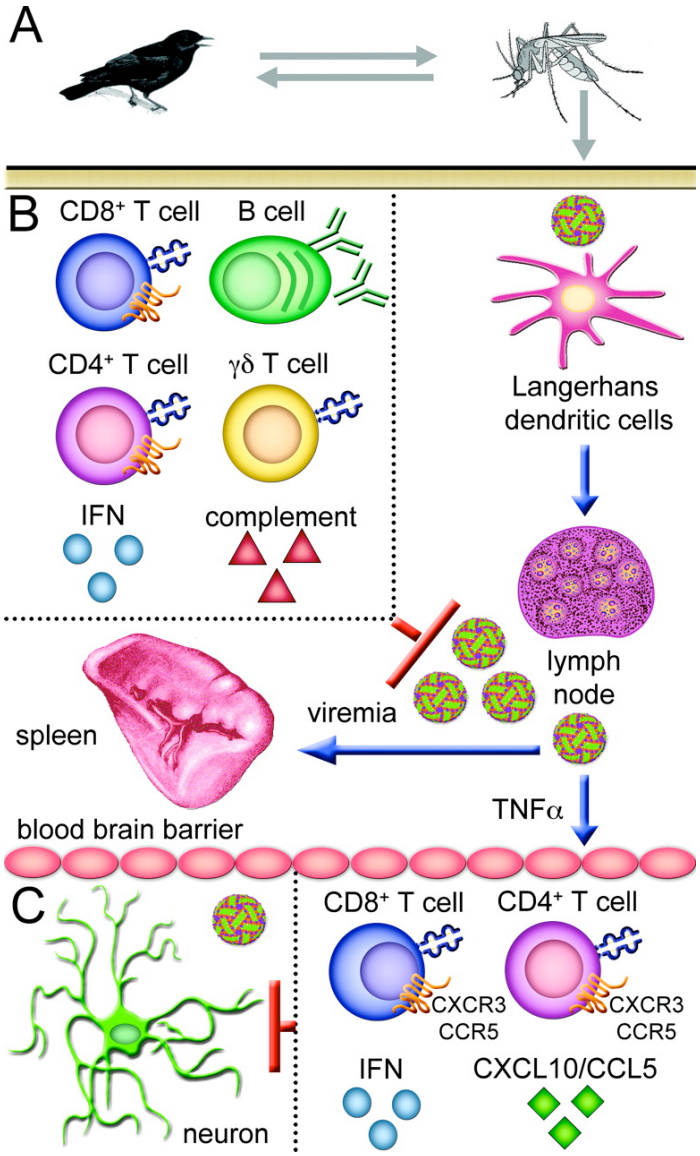


WNV pathogenesis

1/150 individuals develop neuroinvasive disease

- Headache
- Ocular manifestations
- Muscle weakness
- Cognitive impairment
- Polio-like flaccid paralysis
- 10% mortality
- >50% long term neurological sequelae

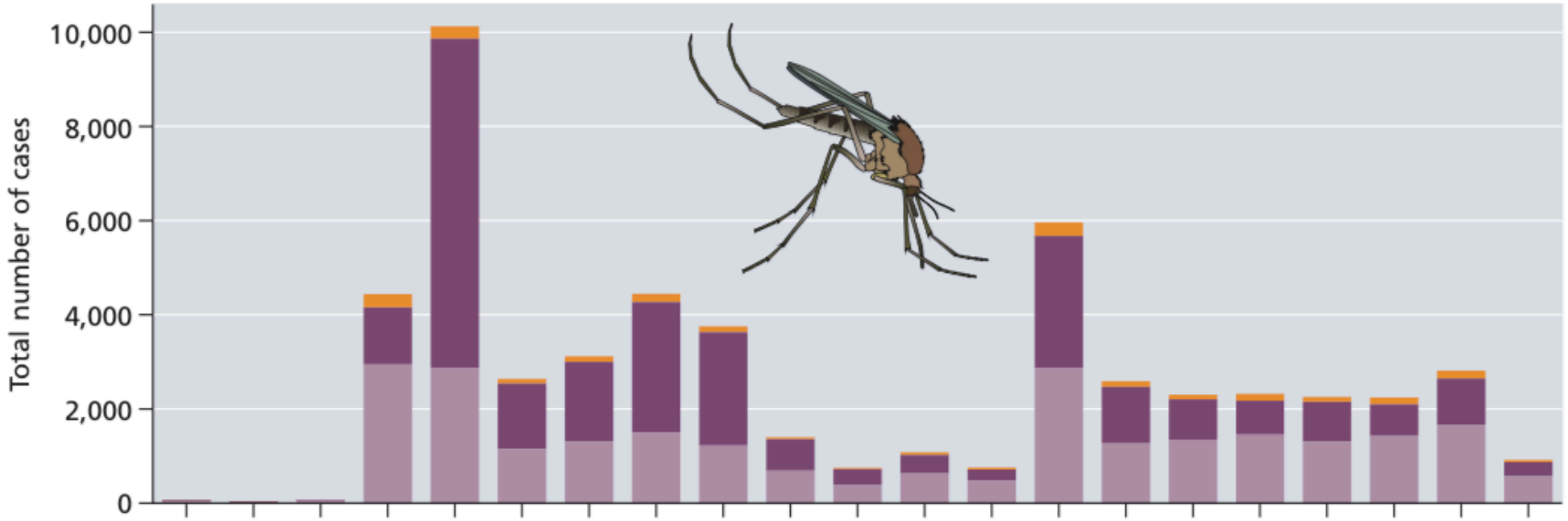




TLR3

doi:10.1128/JVI.01122-06

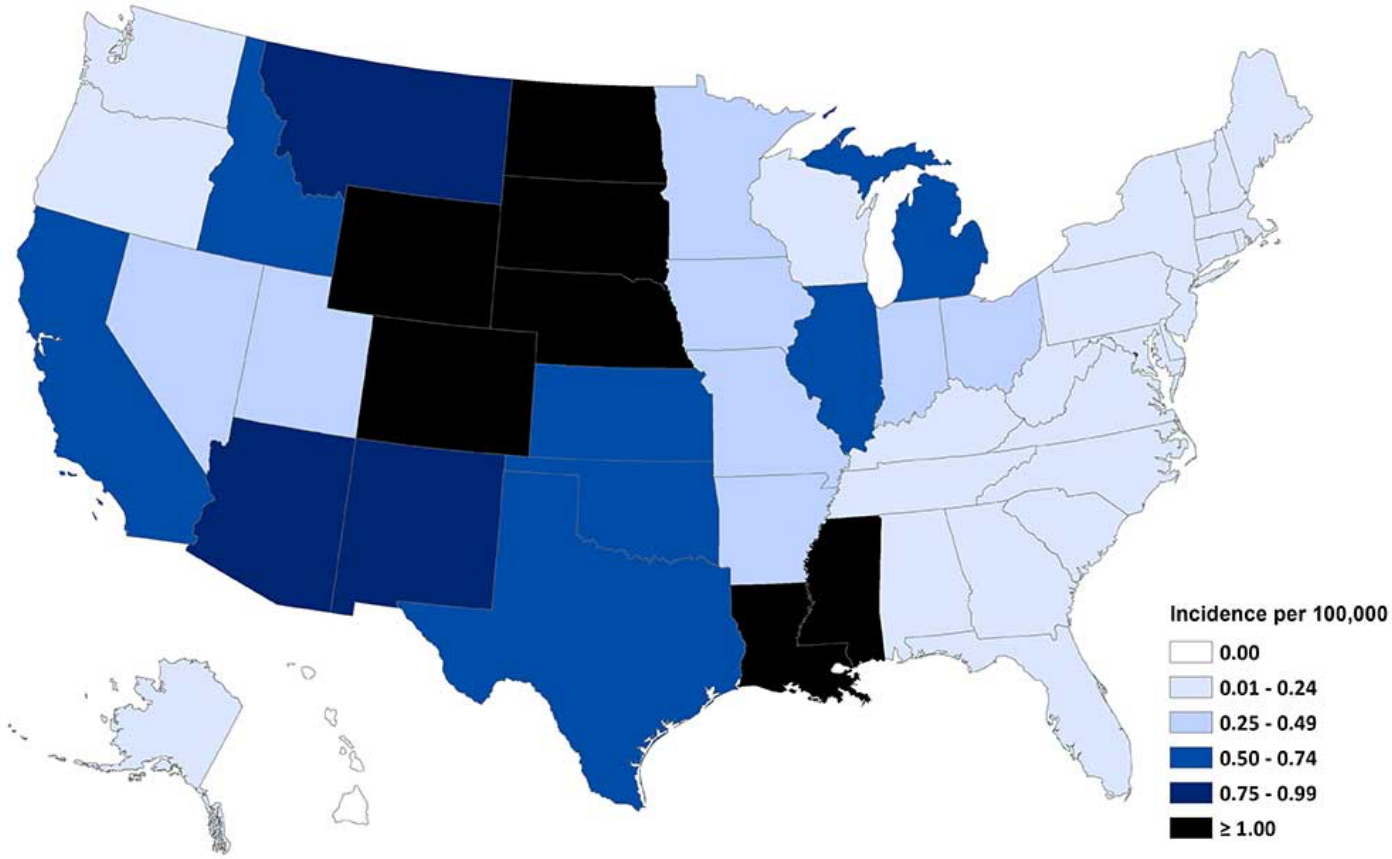
West Nile Virus USA



Disease cases	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Neuroinvasive	59	19	64	2,946	2,866	1,148	1,309	1,495	1,227	689	386	629	486	2,873	1,267	1,347	1,455	1,309	1,425	1,658	570
Non-neuroinvasive	3	2	2	1,210	6,996	1,391	1,691	2,774	2,403	667	334	392	226	2,801	1,202	858	720	840	672	989	302
Total cases	62	21	66	4,156	9,862	2,539	3,000	4,269	3,630	1,356	720	1,021	712	5,674	2,469	2,205	2,175	2,149	2,097	2,647	872
Deaths	7	2	10	284	261	100	119	177	124	44	32	57	43	286	119	97	146	106	146	167	46

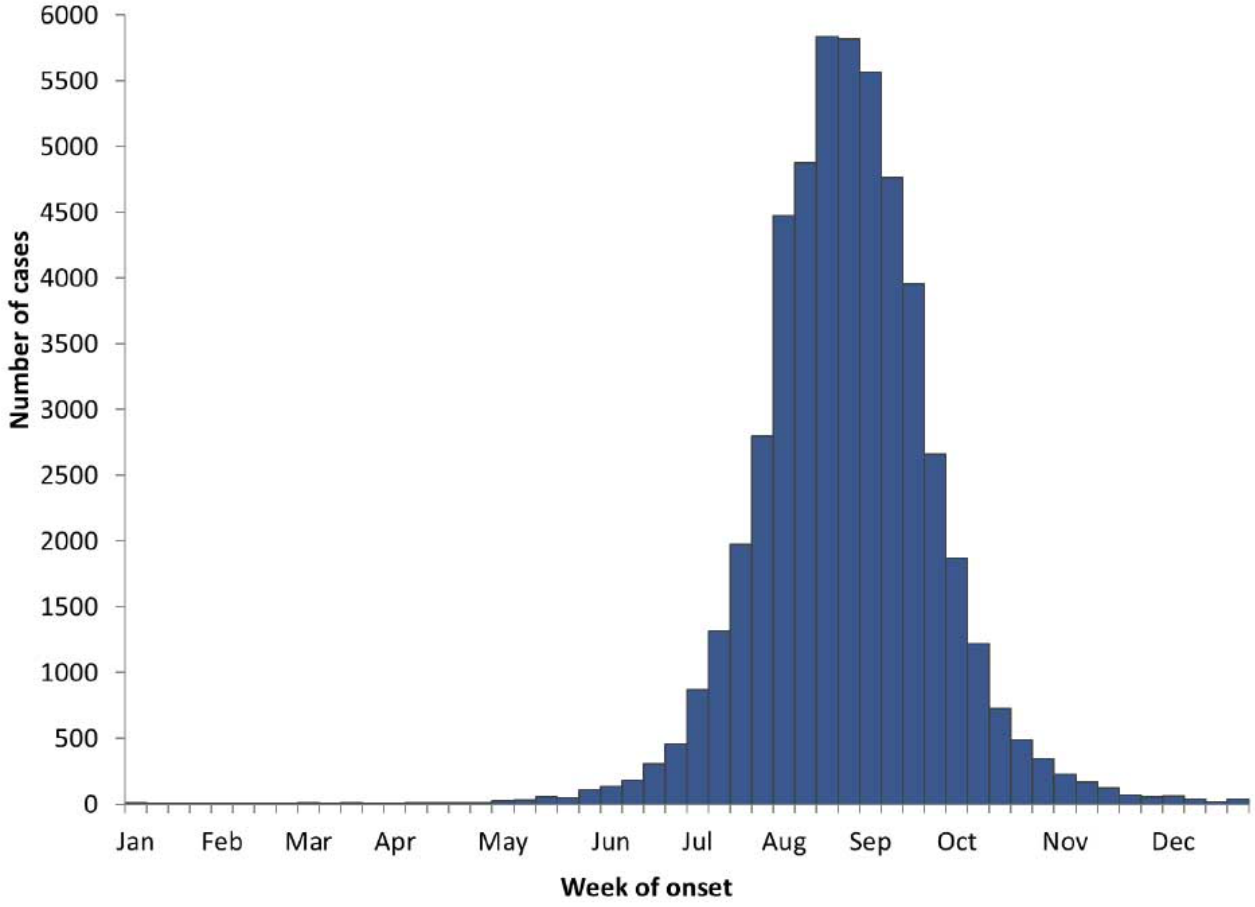
Principles of Virology, ASM Press

Average annual incidence of WNV neuroinvasive disease by state 1999-2019



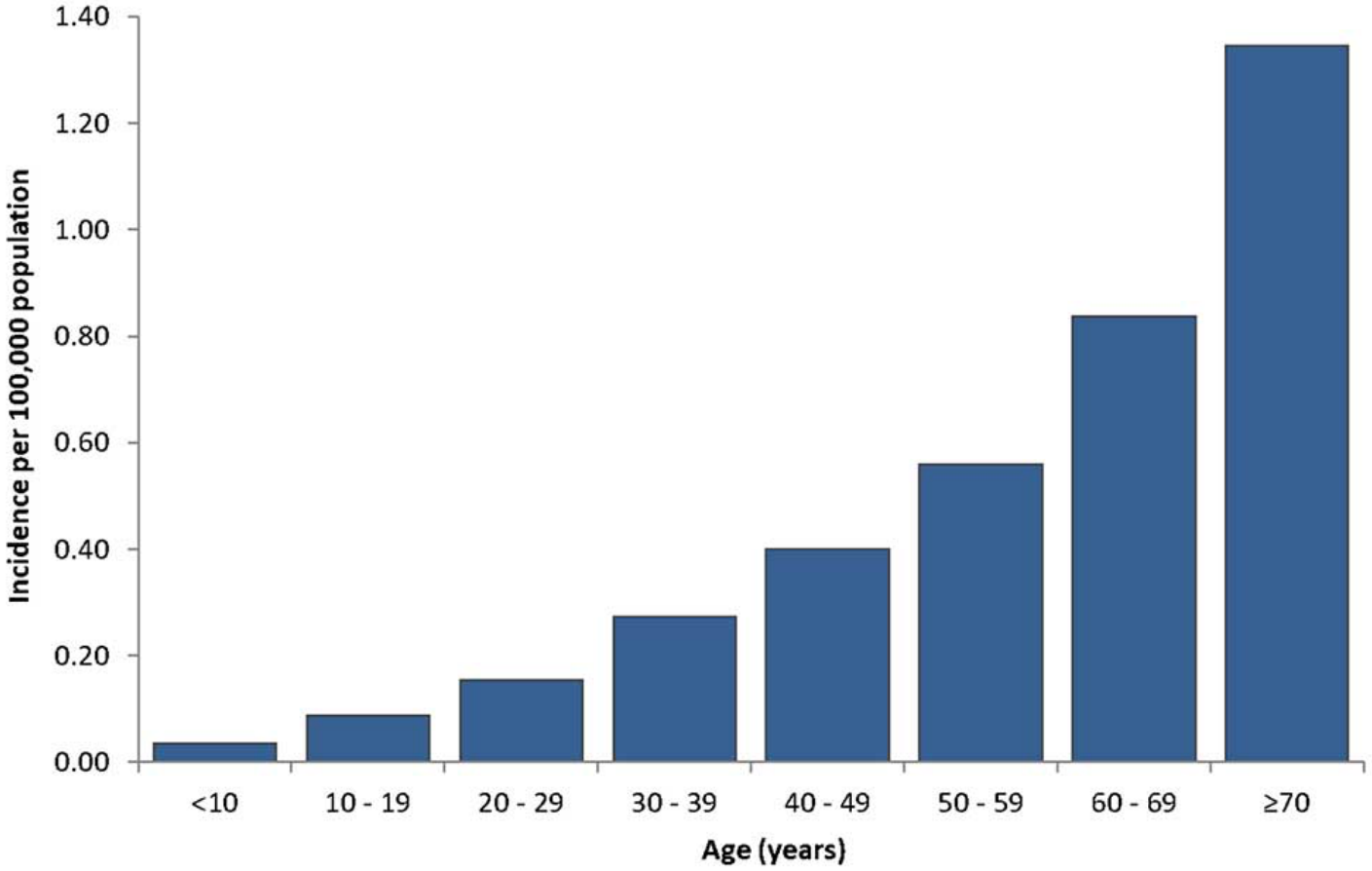
http://www.cdc.gov/westnile/

West Nile virus disease cases reported to CDC by week of illness onset, 1999-2019



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

WNV neuroinvasive disease by age group, 1999-2019



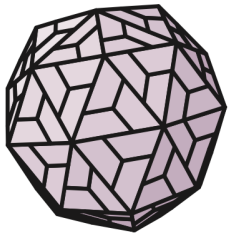
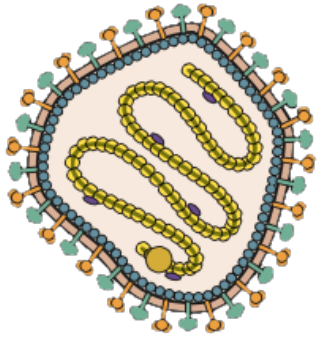
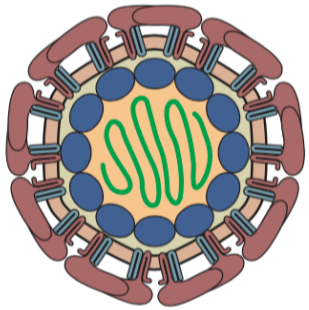
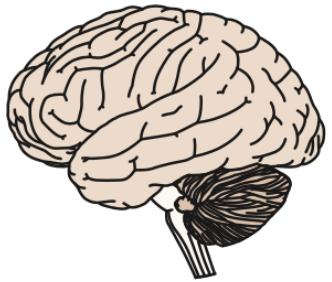
http://www.cdc.gov/westnile/

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

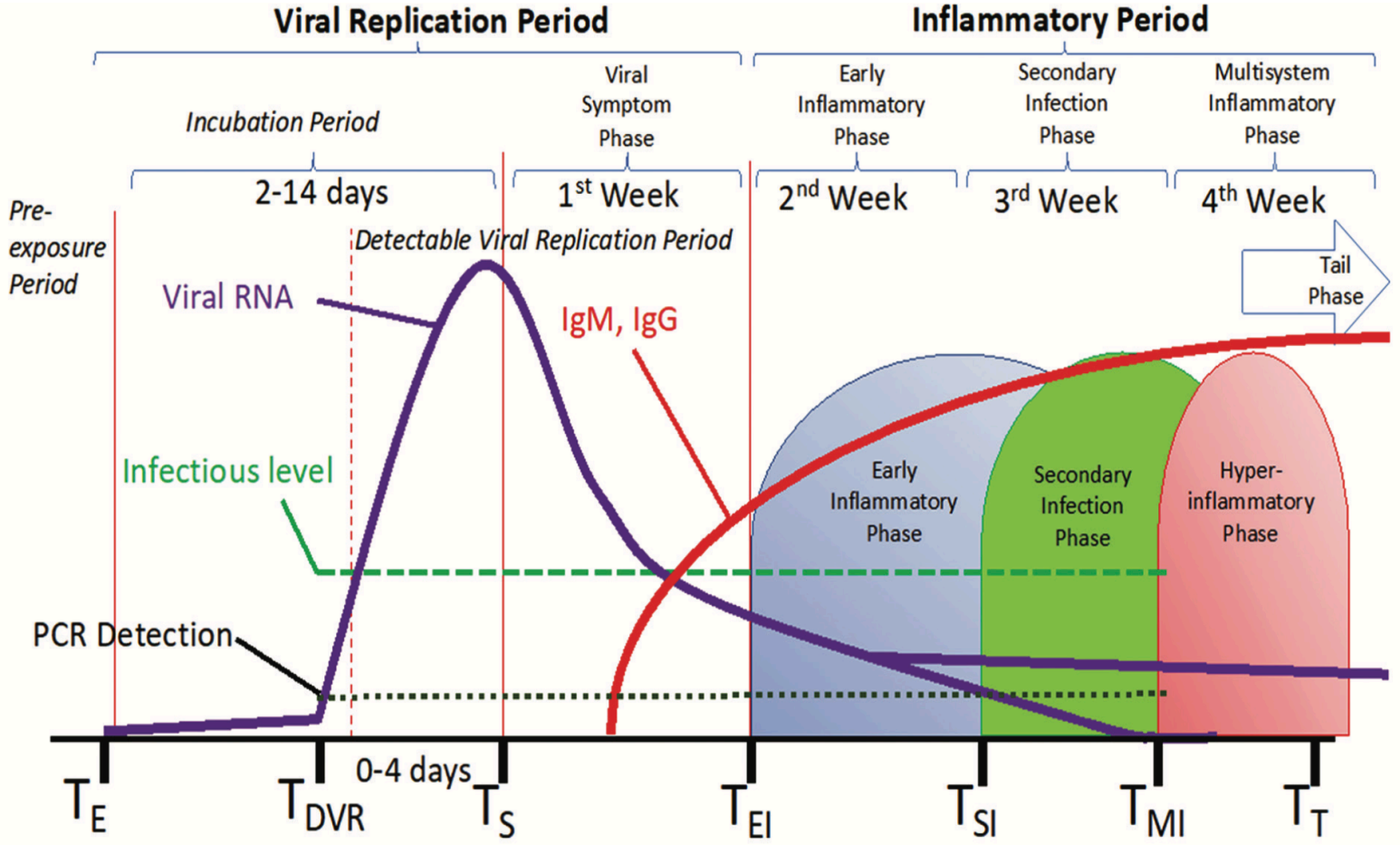
Viruses and the central nervous system

- 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

Principles of Virology, ASM Press

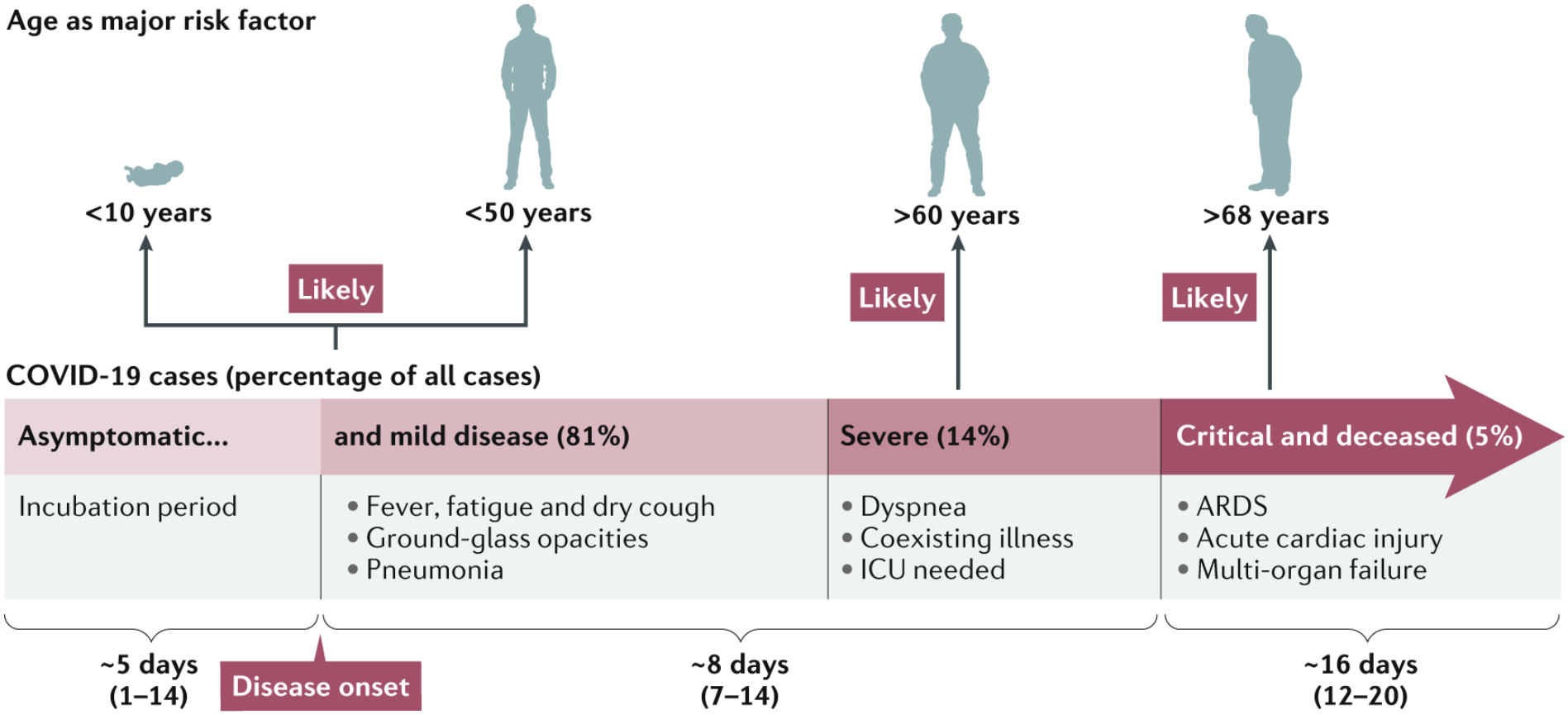
COVID-19 is an acute infection



Long COVID

Courtesy Daniel Griffin, MD PhD

COVID-19, an acute infection



Don't forget long COVID

https://doi.org/10.1038/s41579-020-00459-7

Next time: Persistent Infections