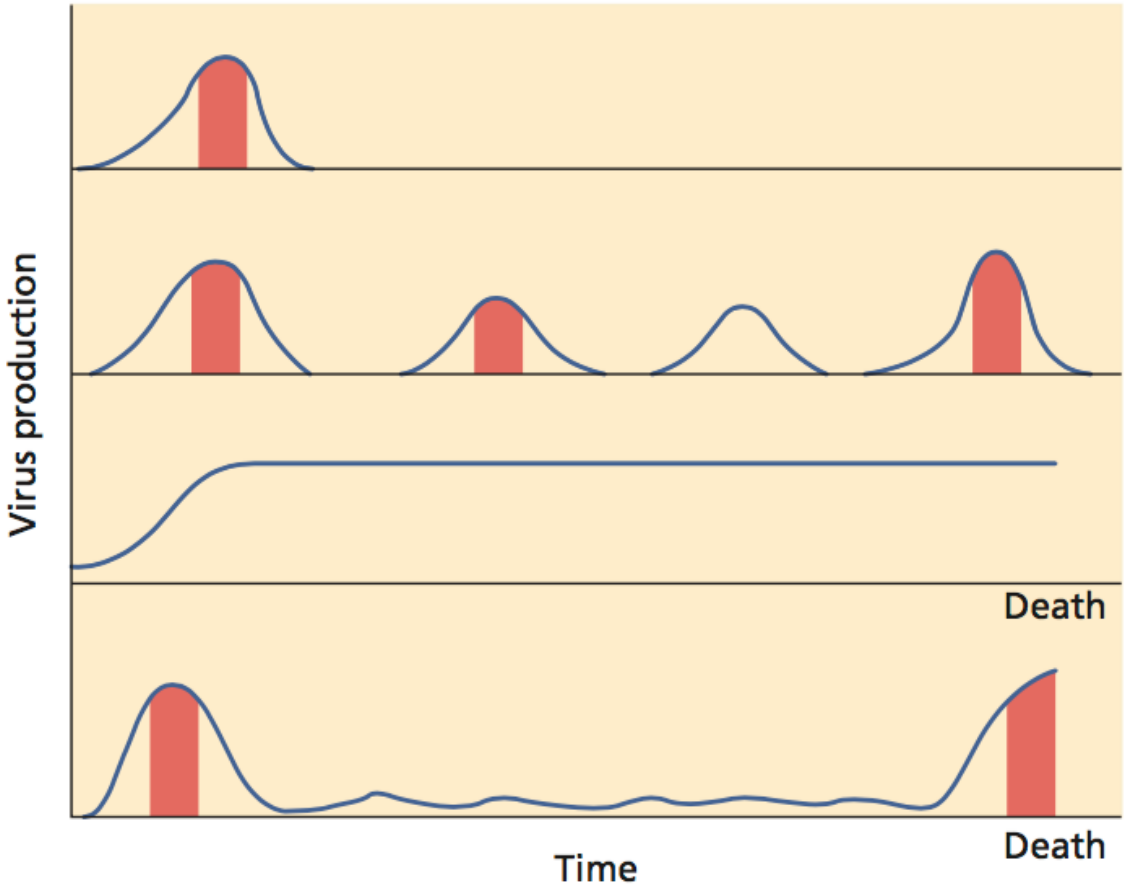
Acute Infections

Lecture 16
Biology 3310/4310
Virology
Spring 2017

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

Persistent: asymptomatic
- Lymphocytic choriomeningitis virus
- JC virus

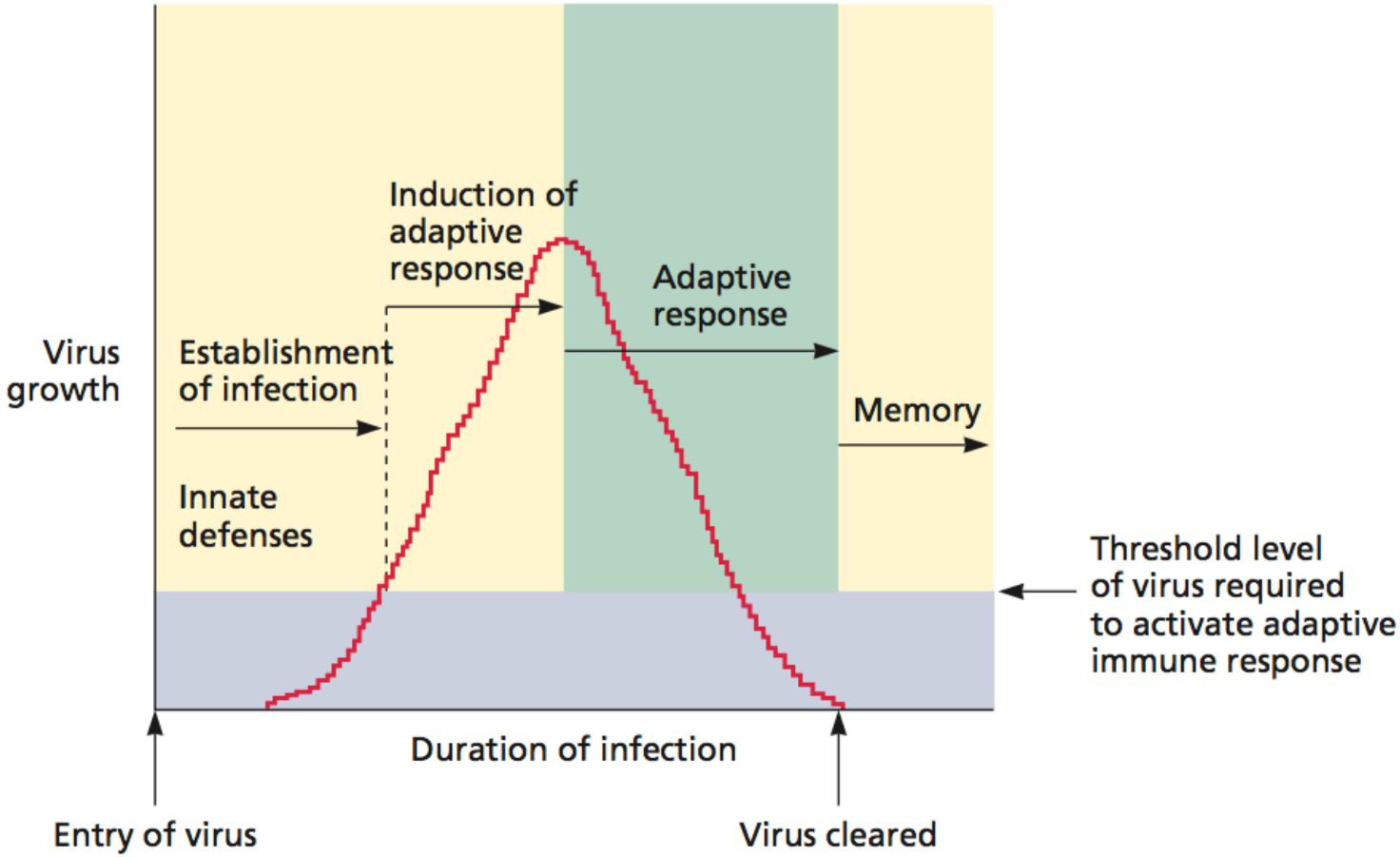
Persistent: pathogenic
- Human immunodeficiency virus
- Human T-lymphotropic virus
- Measles virus SSPE

Acute infections

- Rapid onset of viral reproduction
- Short but possibly severe course of disease
- Production of large numbers of virus particles
- Immune clearance

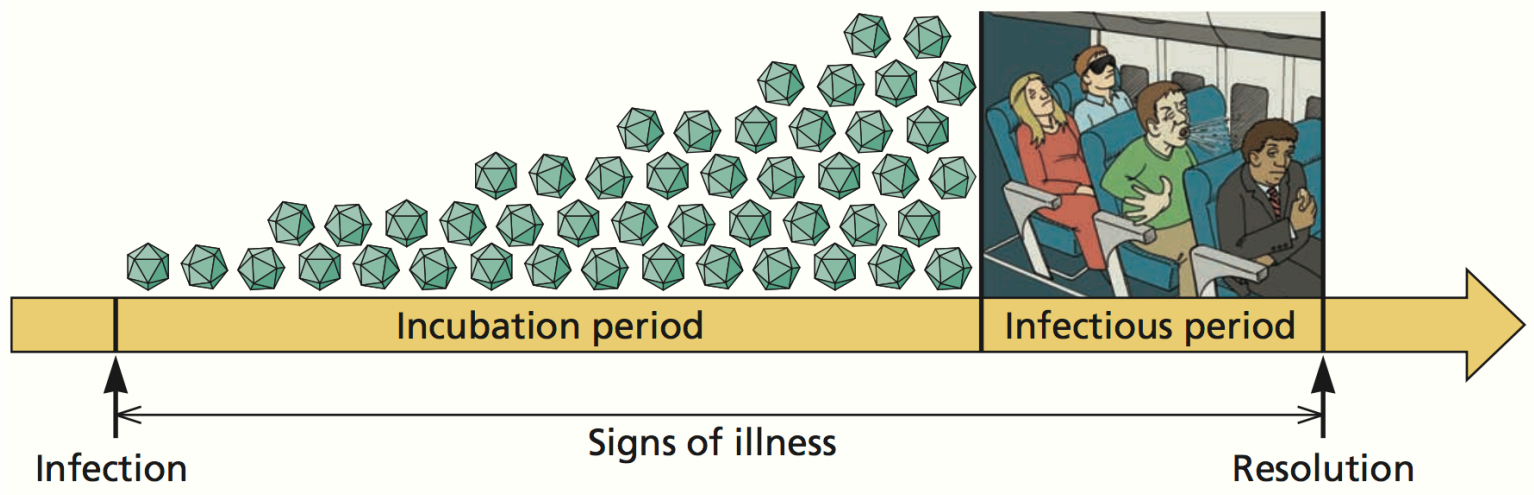
The course of a typical acute infection

Rapid and self-limiting



Principles of Virology, ASM Press

Incubation period



- Initial period before *symptoms* of disease are obvious
- Viral genomes are replicating
- Host is responding
- Virus may or may not be transmitted

Principles of Virology, ASM Press

Incubation periods of some viral infections

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

[a]Until first appearance of prodromal symptoms.

Short - replication at primary site produces symptoms

Prodrome - Period of symptoms before those characteristic of disease
Gr *prodromos* = precursor

Long - Symptoms beyond primary site

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

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

Go to:

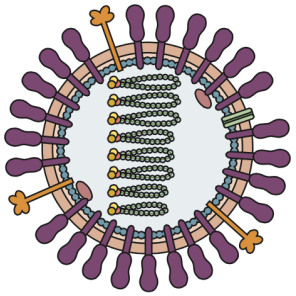
b.socrative.com/login/student
room number: virus

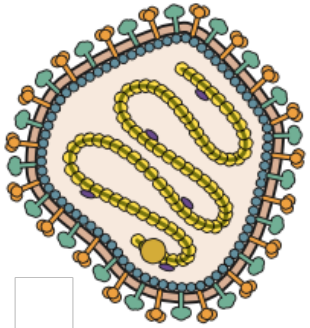
Which of the following do acute infections and incubation periods have in common?

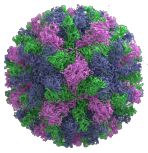
A. The virus is not replicating
B. No symptoms are visible
C. Immune defenses are engaged
D. The immune system does not respond
E. All of the above

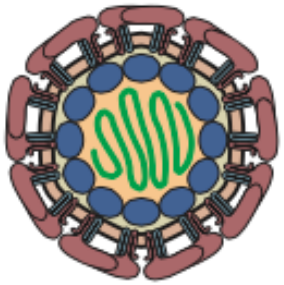
Viruses that cause acute infections

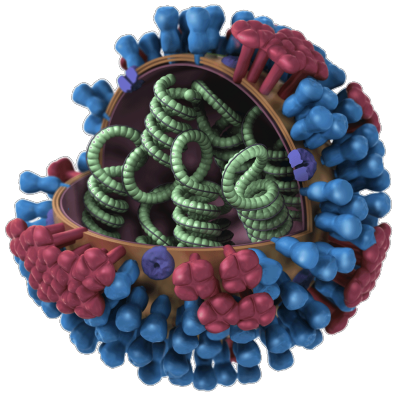
- Influenza virus
- Poliovirus
- Measles virus
- Norovirus
- West Nile virus



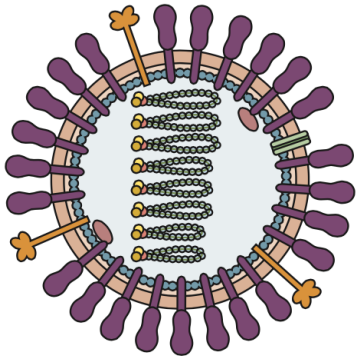








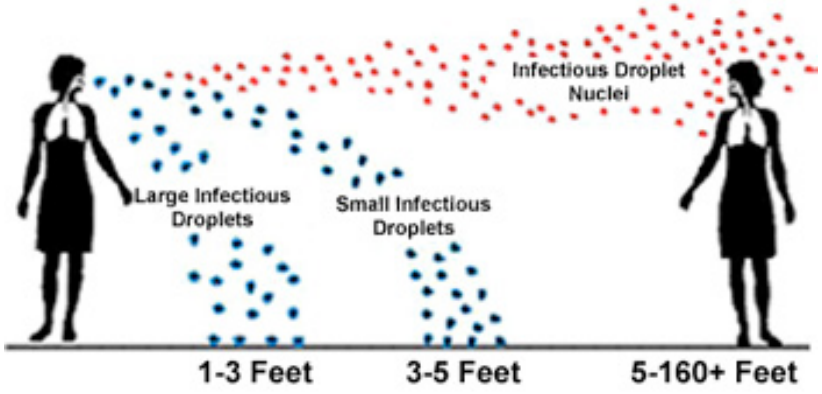
Influenza



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

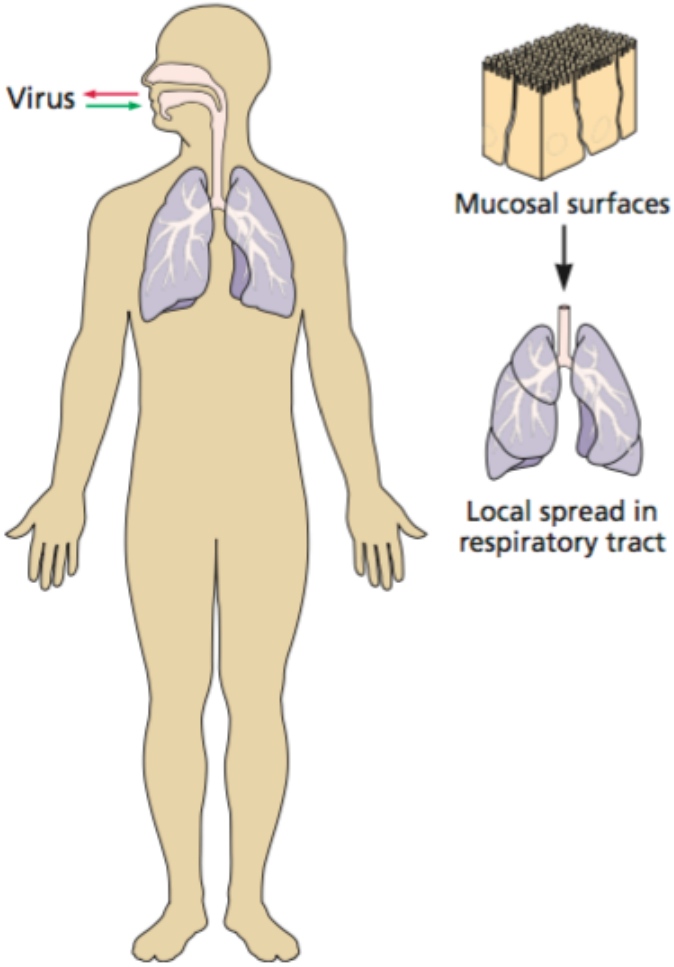
http://www.virology.ws/2009/09/22/the-a-b-and-c-of-influenza-virus/

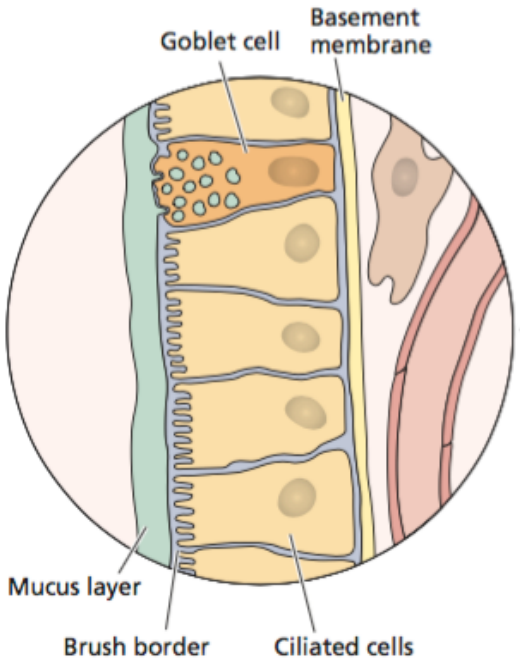
Influenza transmission

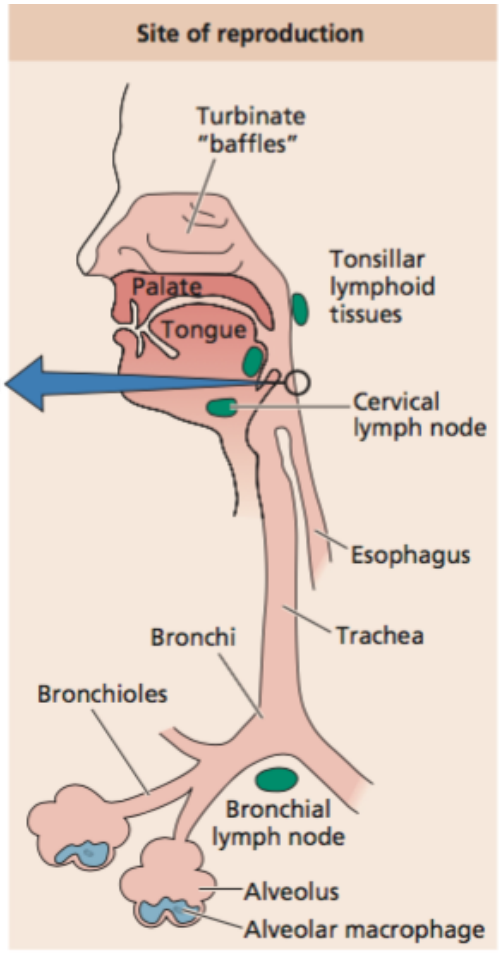


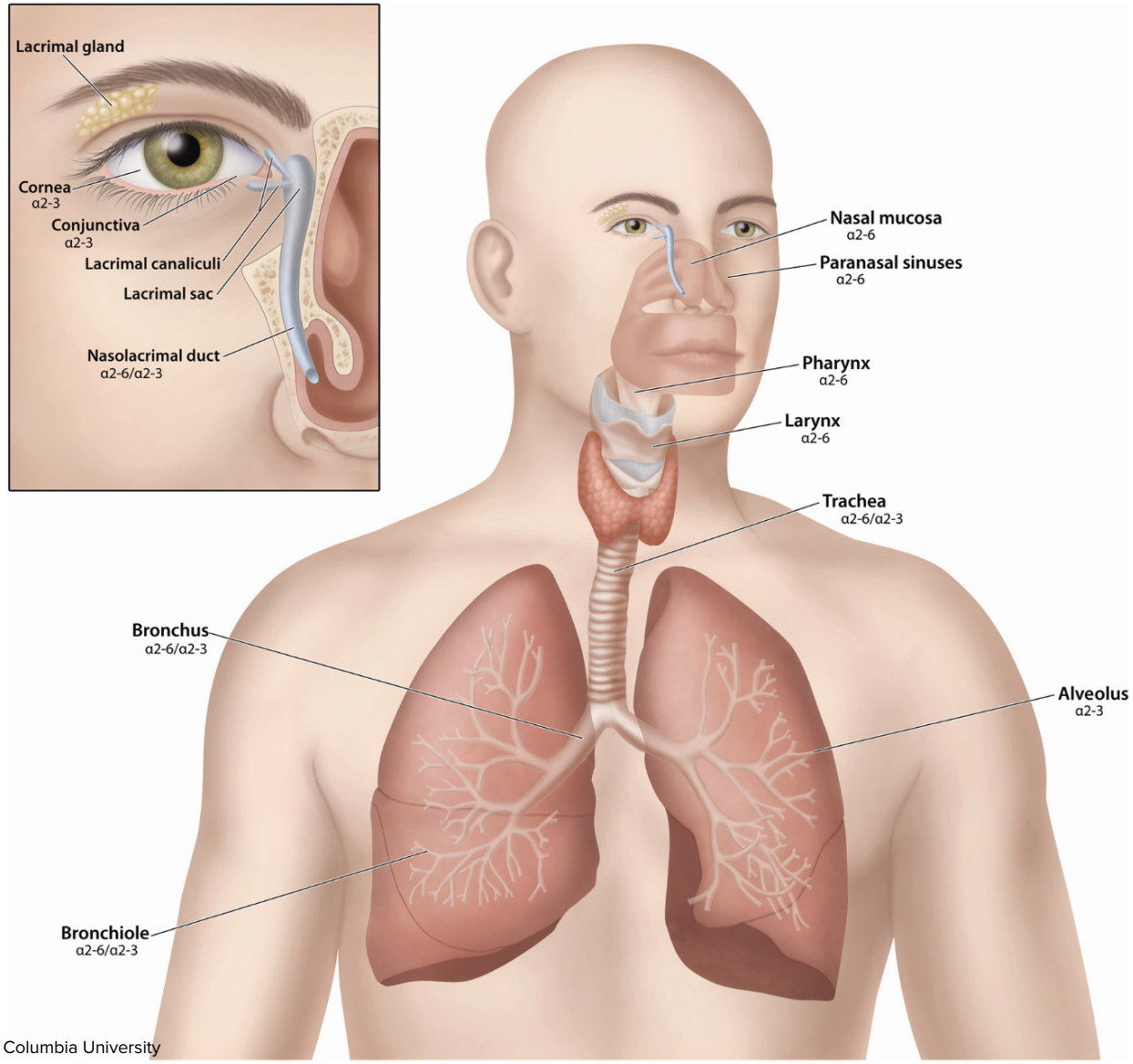
- Droplets produced by coughing, sneezing, talking
- Direct contact with infected individuals
- Contact with contaminated surface, touch mouth, eyes, nose

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

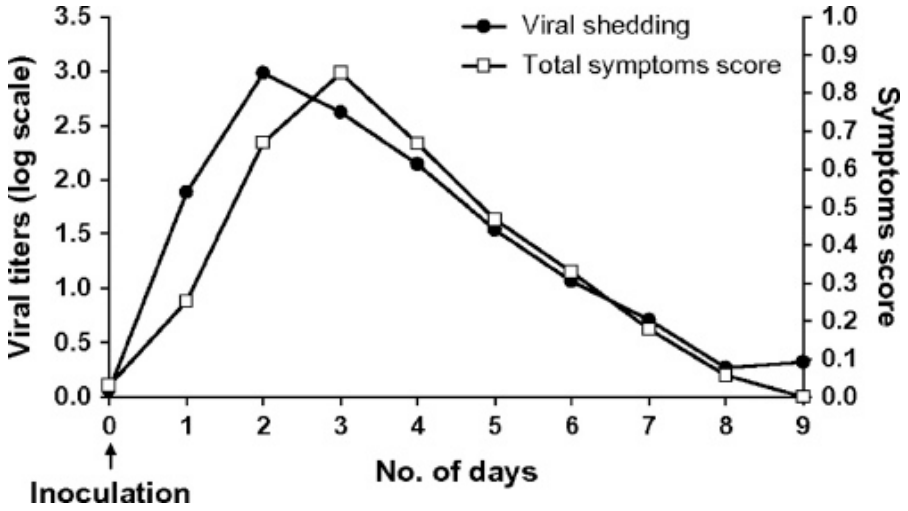
- Incubation period 1-5 days, depending on dose, immune status of host
- Abrupt onset: headache, chills, dry cough
- High fever, myalgias, malaise, anorexia
- Fever peaks within 24 hr, 38° - 40°C
- Fever declines day 2-3, gone by day 6
- Symptoms may differ in children, elderly

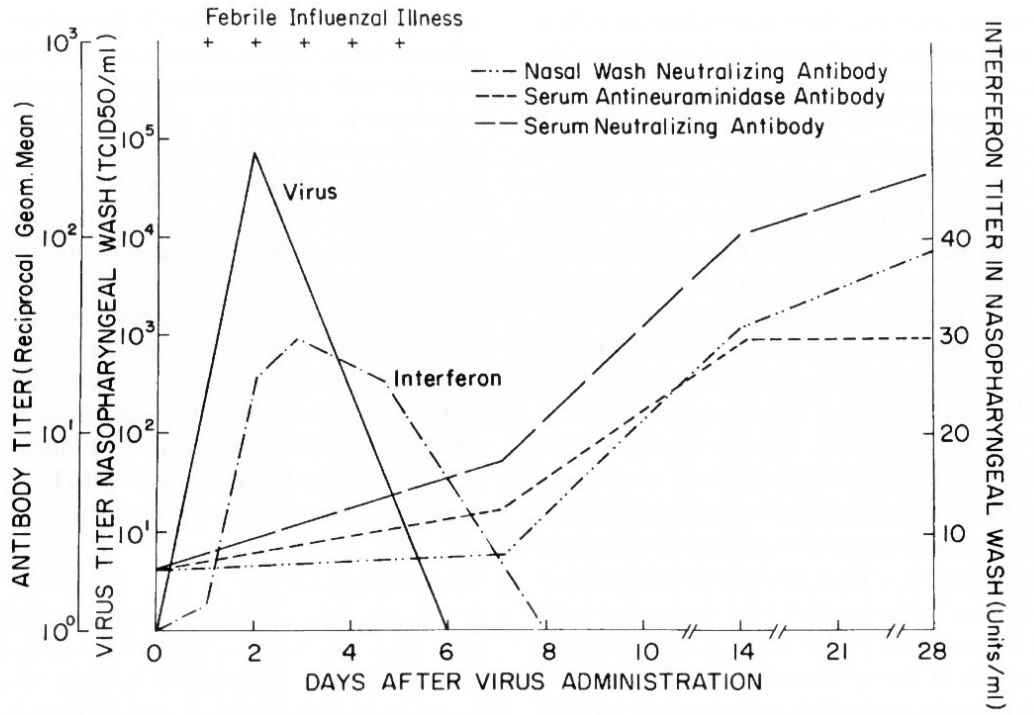
Uncomplicated influenza

- As fever declines, respiratory signs intensify
- Cough changes from dry to productive
- Cough, weakness can persist 1-2 weeks
- Virus replicates throughout the tract, depending on sialic acid receptors for strain

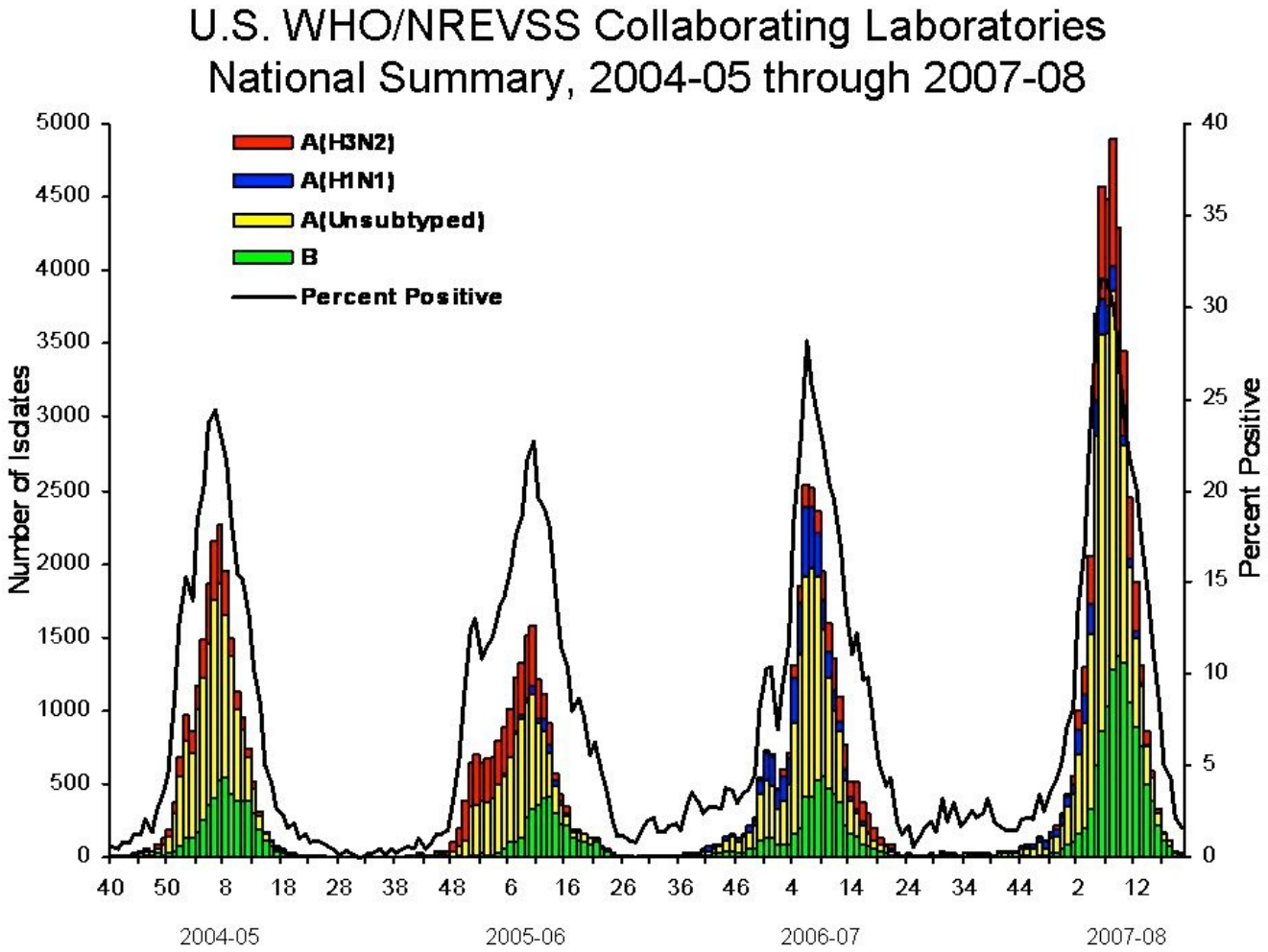
How is influenza diagnosed?

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

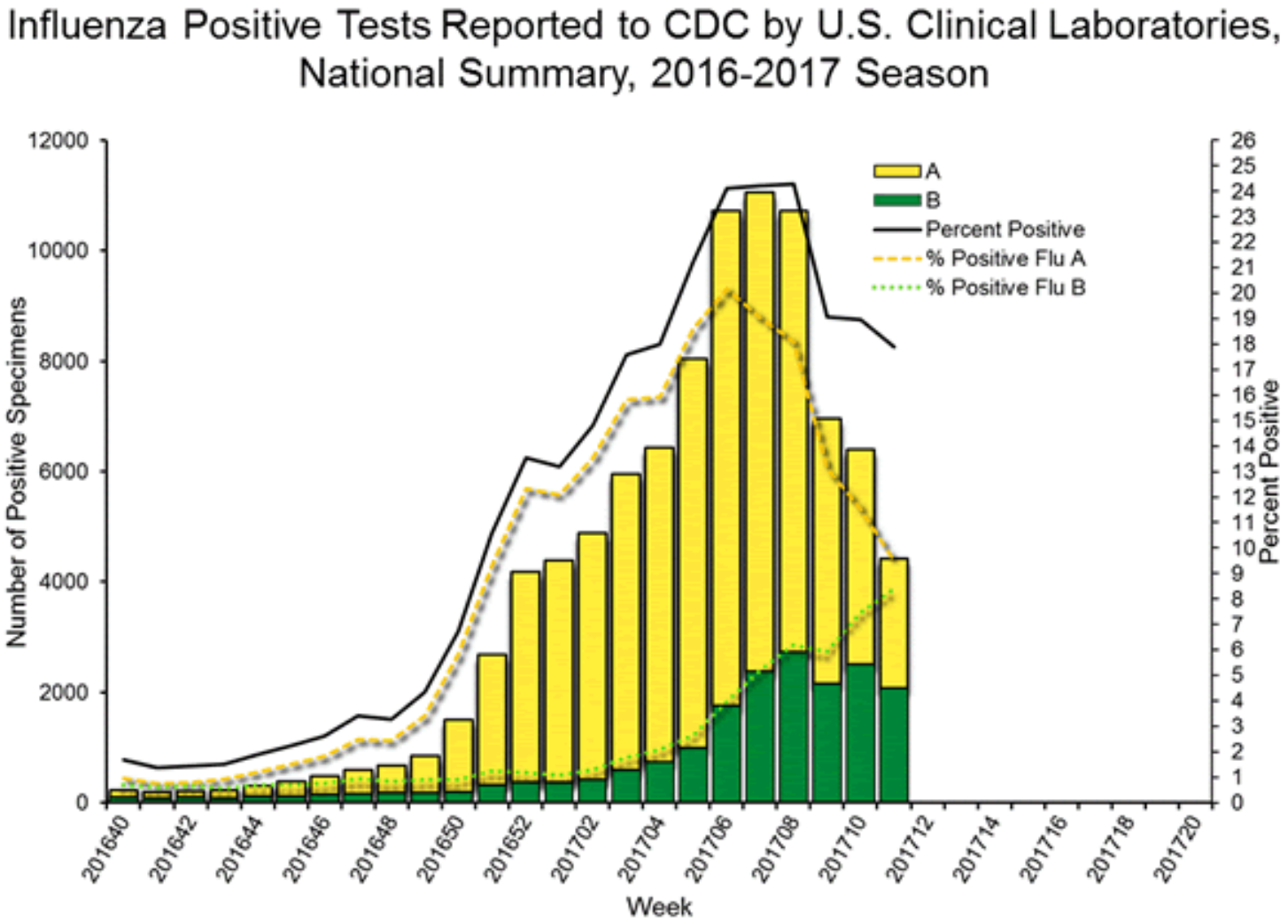

Viral shedding
Total symptoms score
Viral titers (log scale)
Symptoms score
No. of days
Inoculation


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

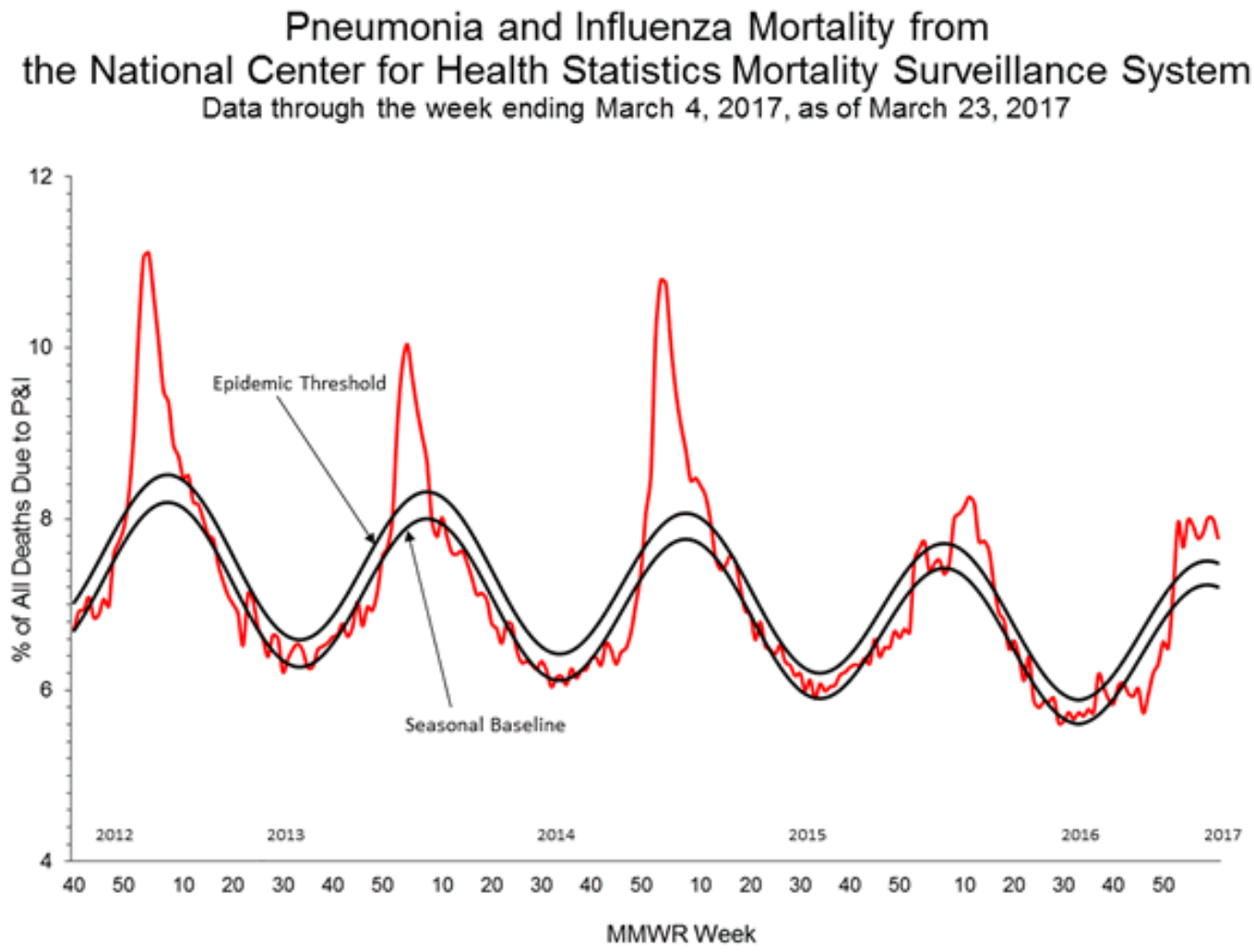
Seasonal influenza



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



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



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

Influenza statistics, US

- 35-50 million cases (CDC estimate)
- 3,000 - 49,000 deaths (range past 31 yr)

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)
- Vaccine

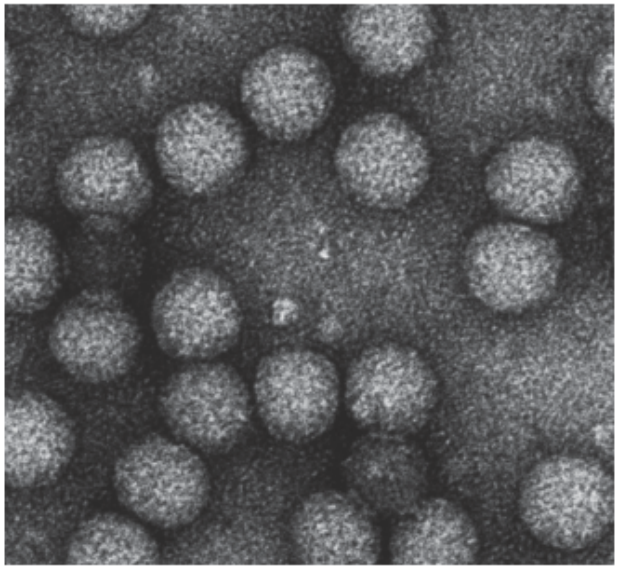
Go to:

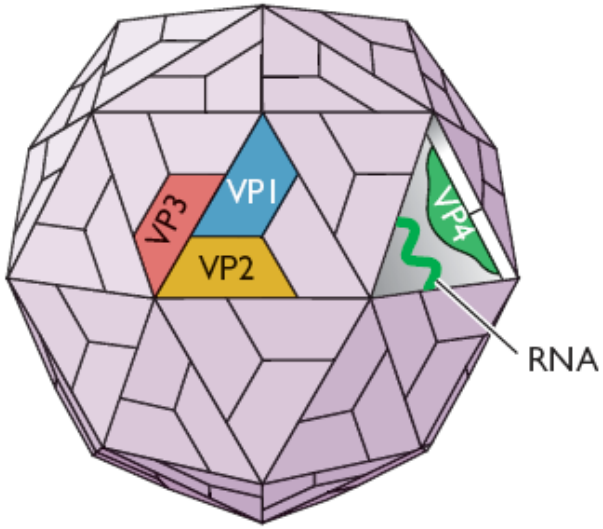
b.socrative.com/login/student
room number: virus

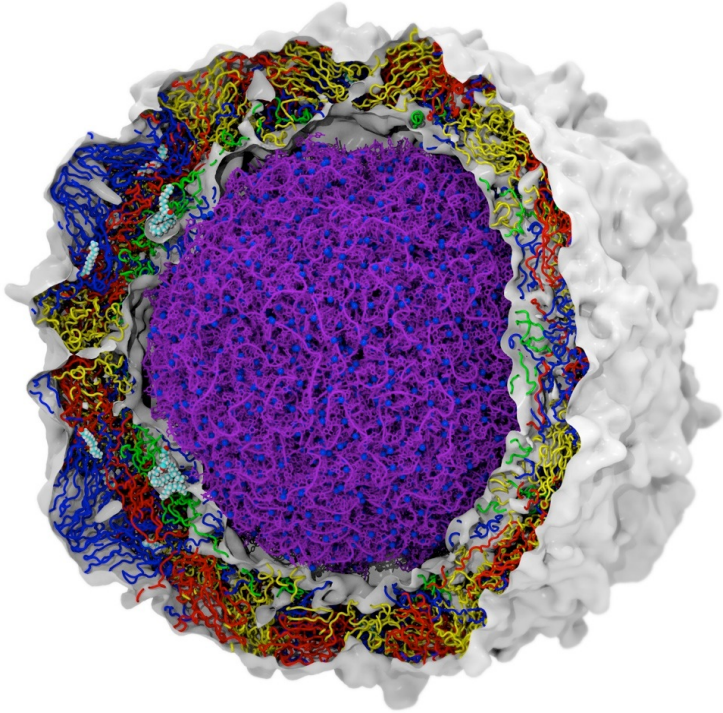
Which of the following is characteristic of uncomplicated influenza?

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

Poliomyelitis - poliovirus

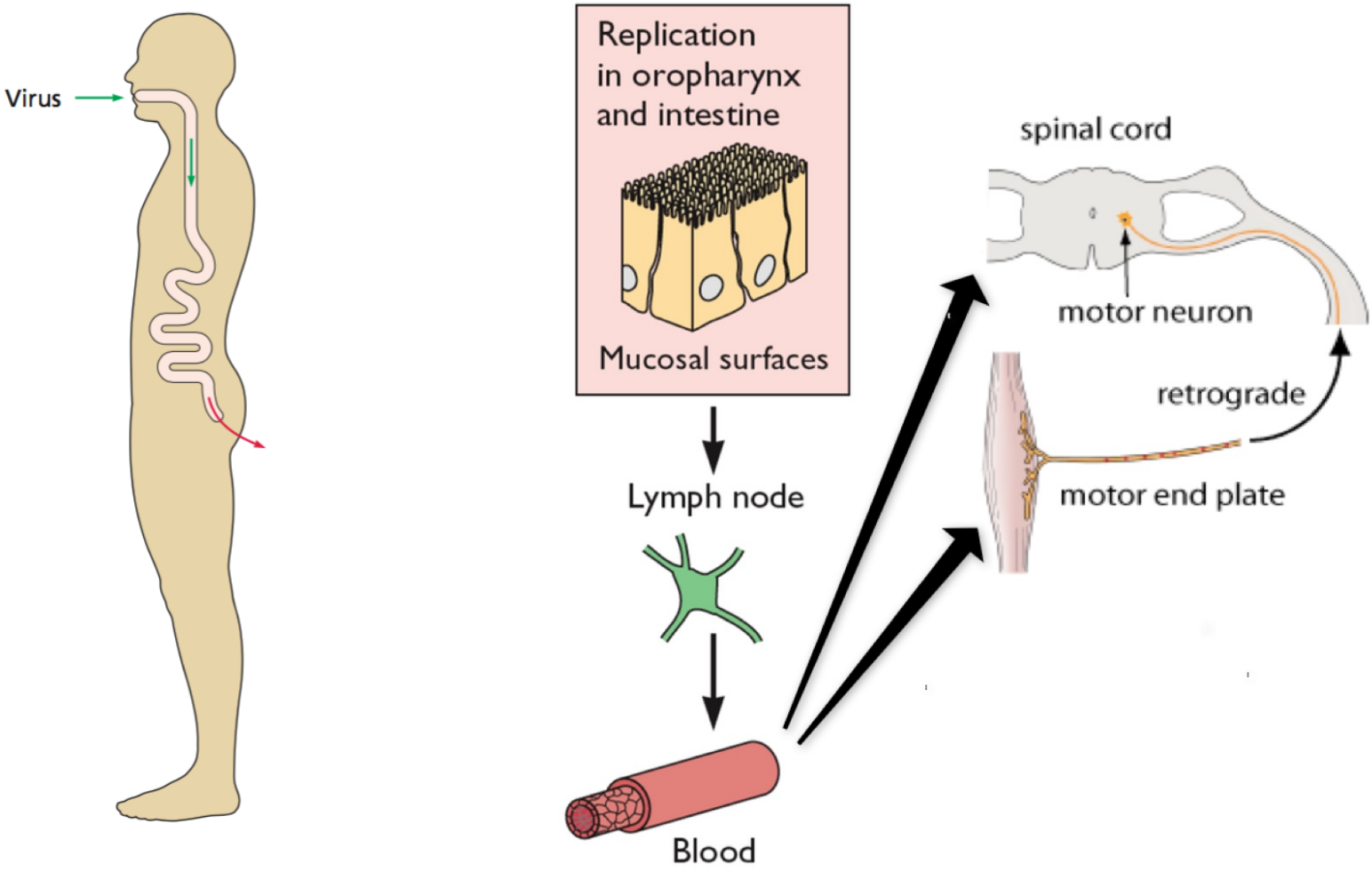




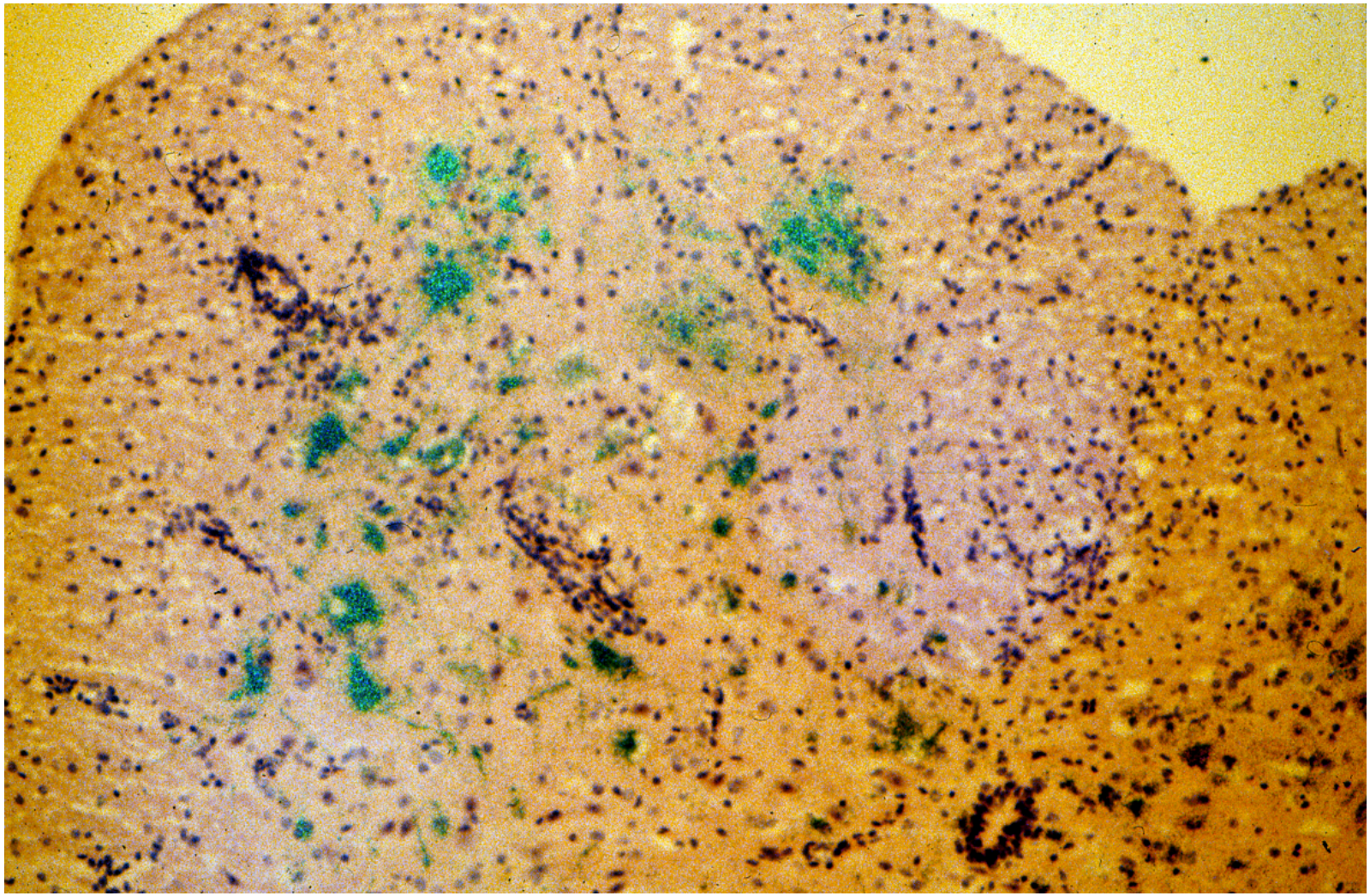


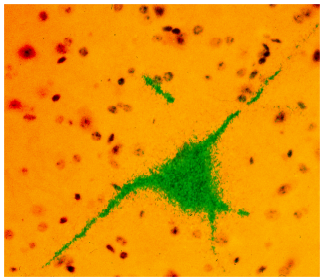
Principles of Virology, ASM Press

Poliovirus pathogenesis

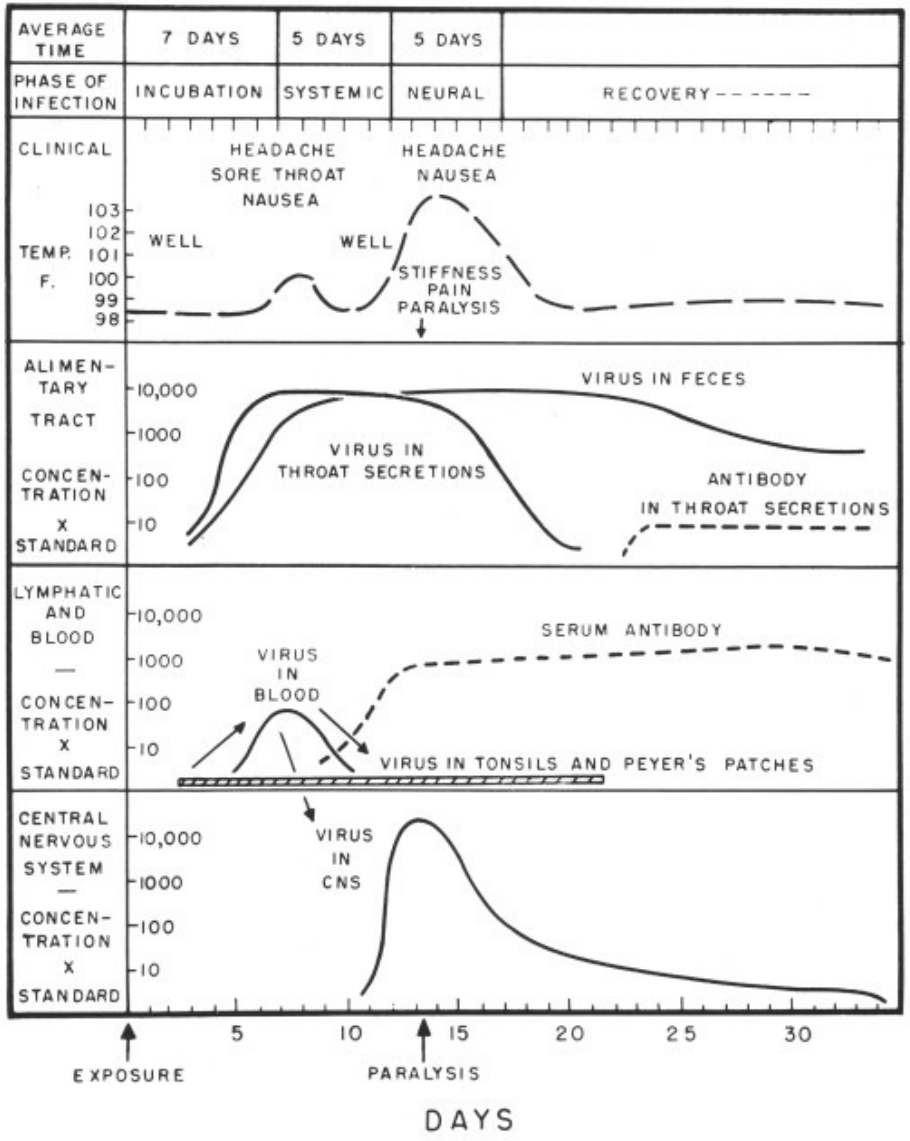


Principles of Virology, ASM Press





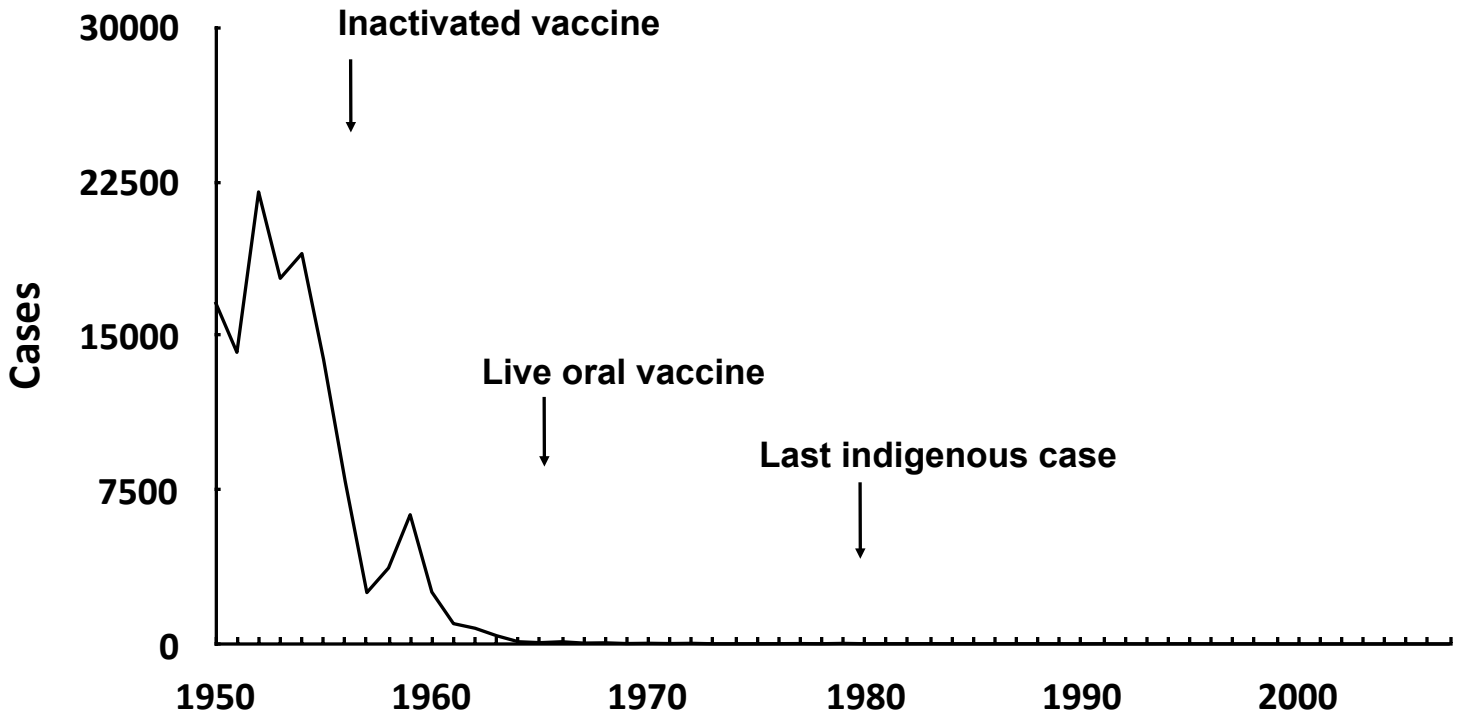
http://www.virology.ws/2009/03/11/chronology-of-an-acute-infection/



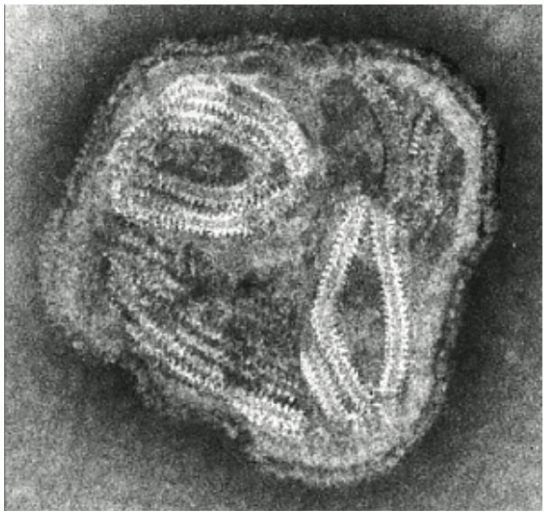
Pathogenesis of poliomyelitis

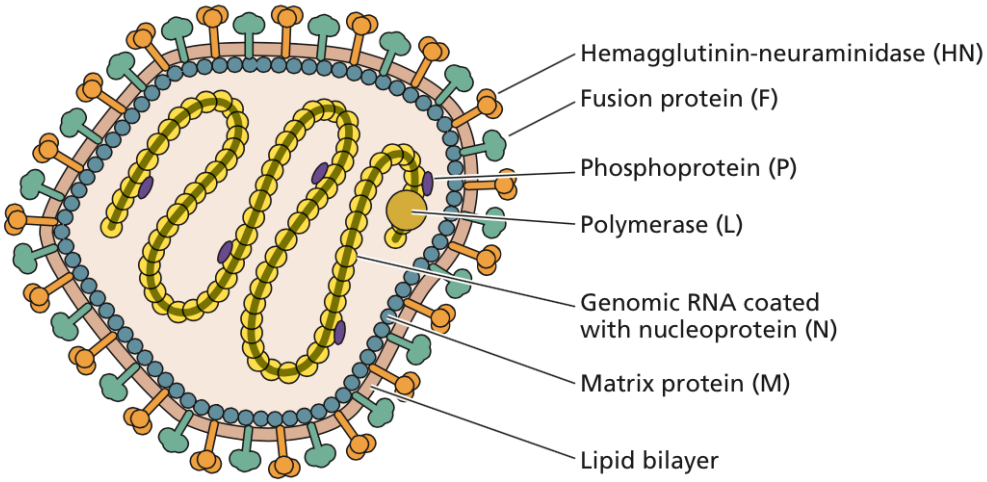
- Humans are only known reservoir
- Spread by fecal-oral transmission
- Peaks during warm months in temperate climates
- Complication: post-polio syndrome
  - 30-40 year interval
  - 25-40%
  - Not an infectious process

Poliomyelitis—United States, 1950-2007

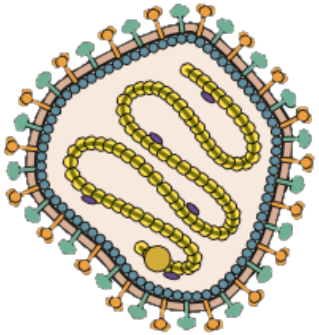


Measles



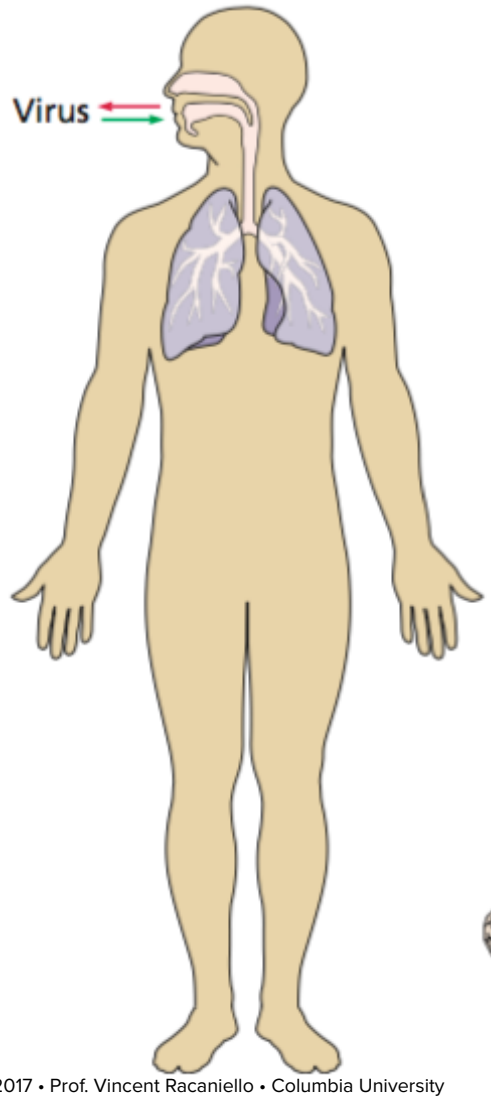


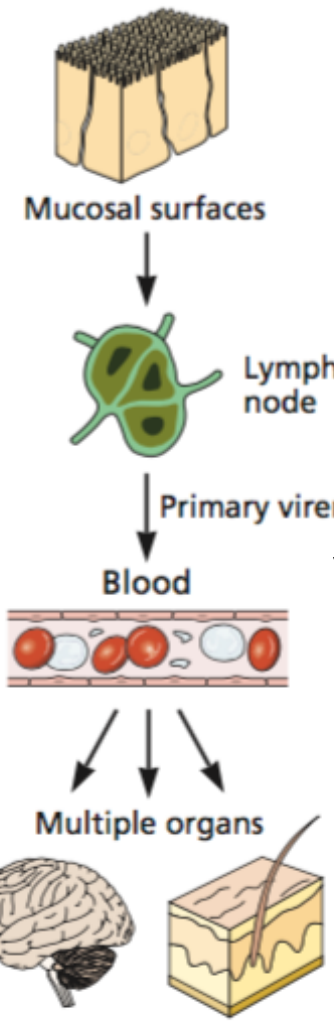
- Measles virus, *Paramyxoviridae*
- One of the most contagious human viruses (R_0 = 15)

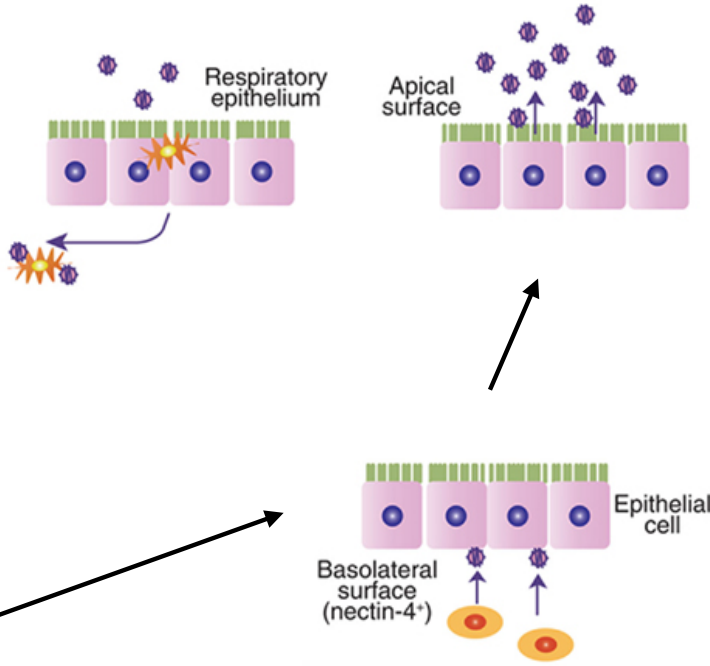


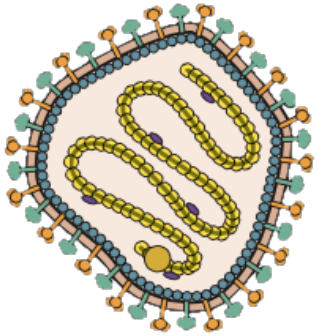
Measles pathogenesis

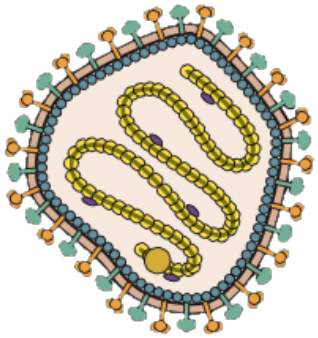
- One viral serotype, infection confers life-long protection
- Transmitted by inhalation of respiratory secretions
- Period of maximum contagiousness 2-3 days before rash
- Nearly all infected individuals show signs of disease


Virus


Mucosal surfaces
Lymph node
Primary viremia
Blood
Multiple organs

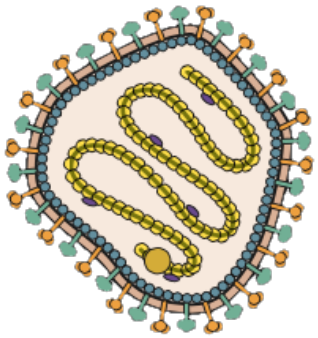

Respiratory epithelium
Apical surface
Epithelial cell
Basolateral surface (nectin-4+)





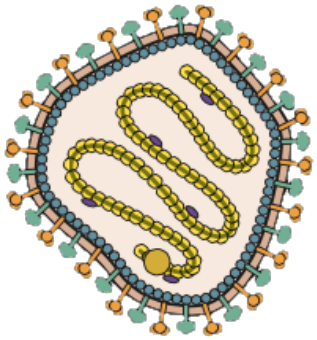
Uncomplicated measles

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



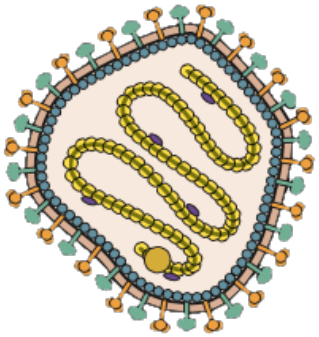
Measles complications

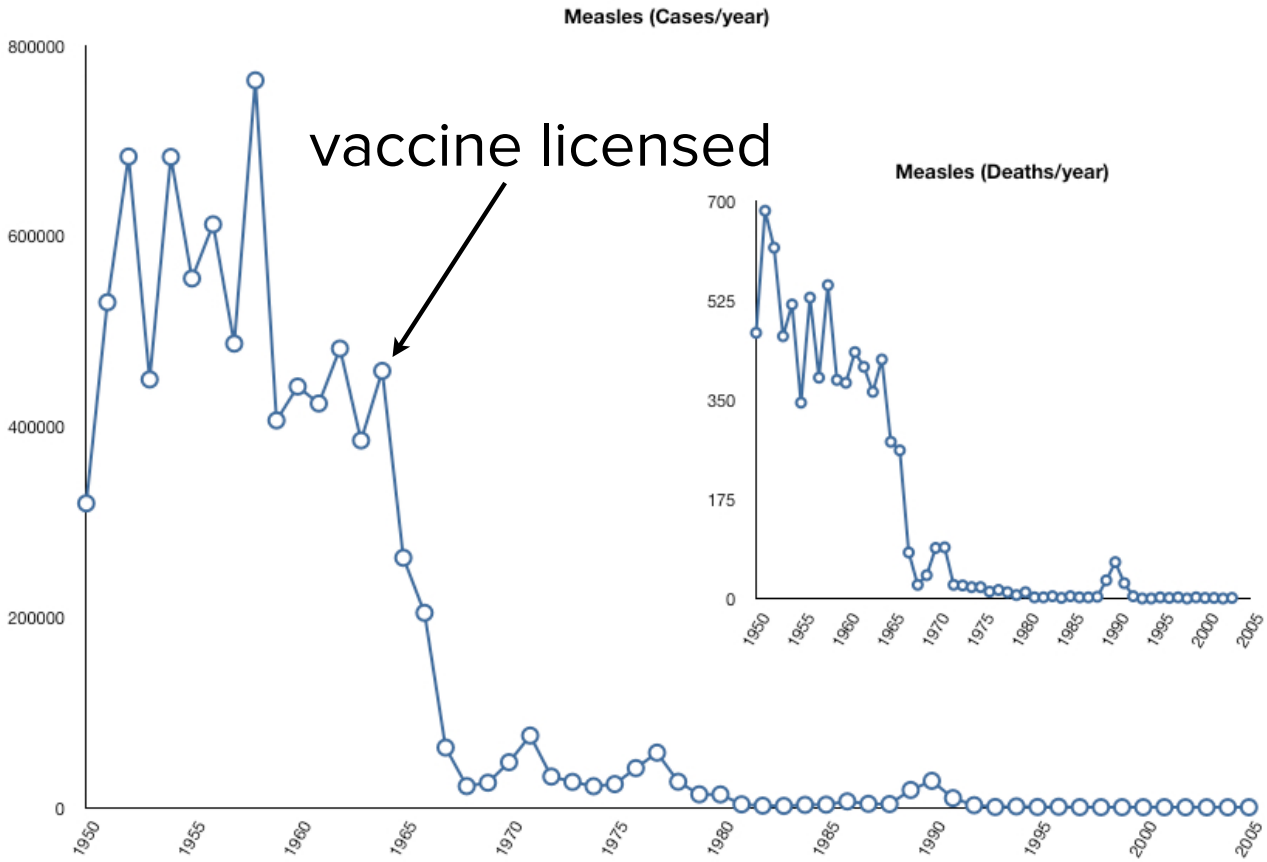
- Acute postinfectious encephalitis (1/1,000)
- Bronchitis, pneumonia, ear infection
- Fatality 1-2/1000 (28% poor nutrition)
- Subacute sclerosing panencephalitis (SSPE)
- Immunosuppression leading to secondary infections (main cause of death in Third World children)

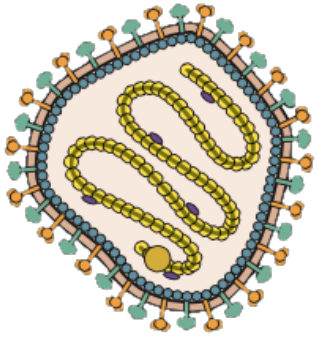


Measles prevention

- 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




Measles (Cases/year)
800000
600000
400000
200000
0
vaccine licensed
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
Measles (Deaths/year)
700
525
350
175
0
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005



Measles Cases and Outbreaks

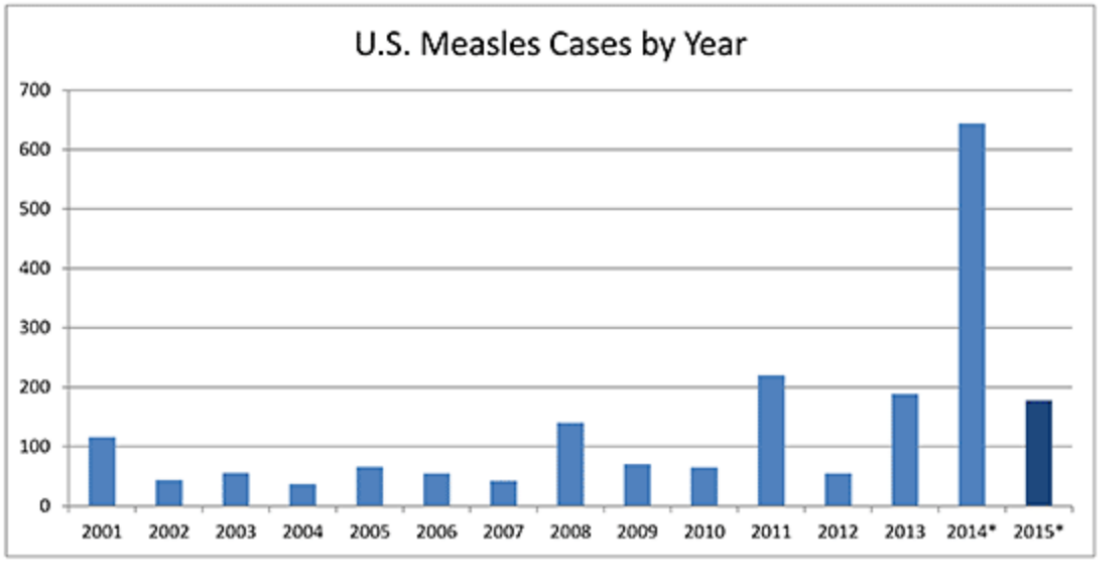
January 1 to March 20, 2015*

178
Cases

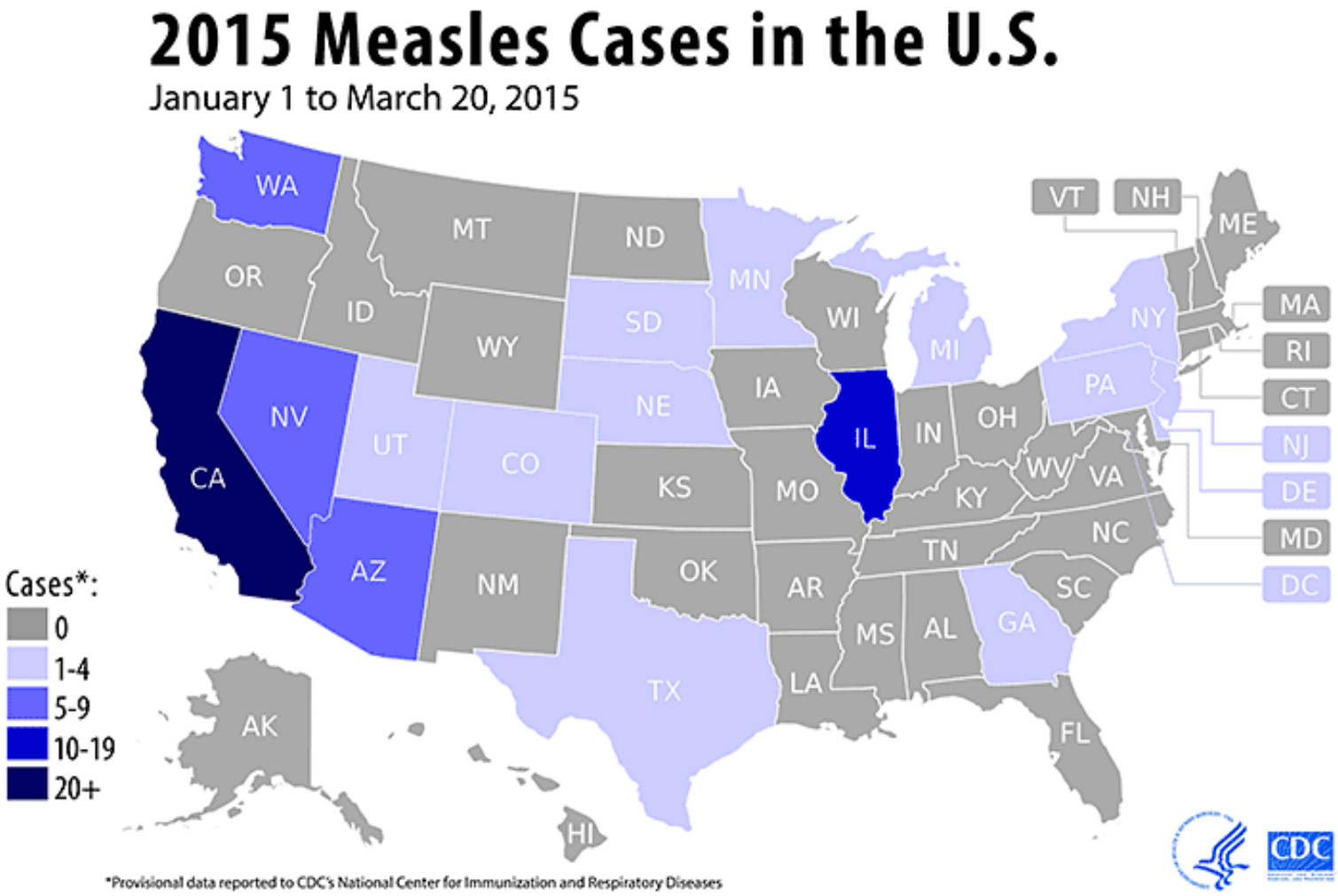
reported in 17 states and the District of Columbia: Arizona, California, Colorado, Delaware, Georgia, Illinois, Michigan, Minnesota, Nebraska, New Jersey, New York, Nevada, Pennsylvania, South Dakota, Texas, Utah, Washington

4
Outbreaks

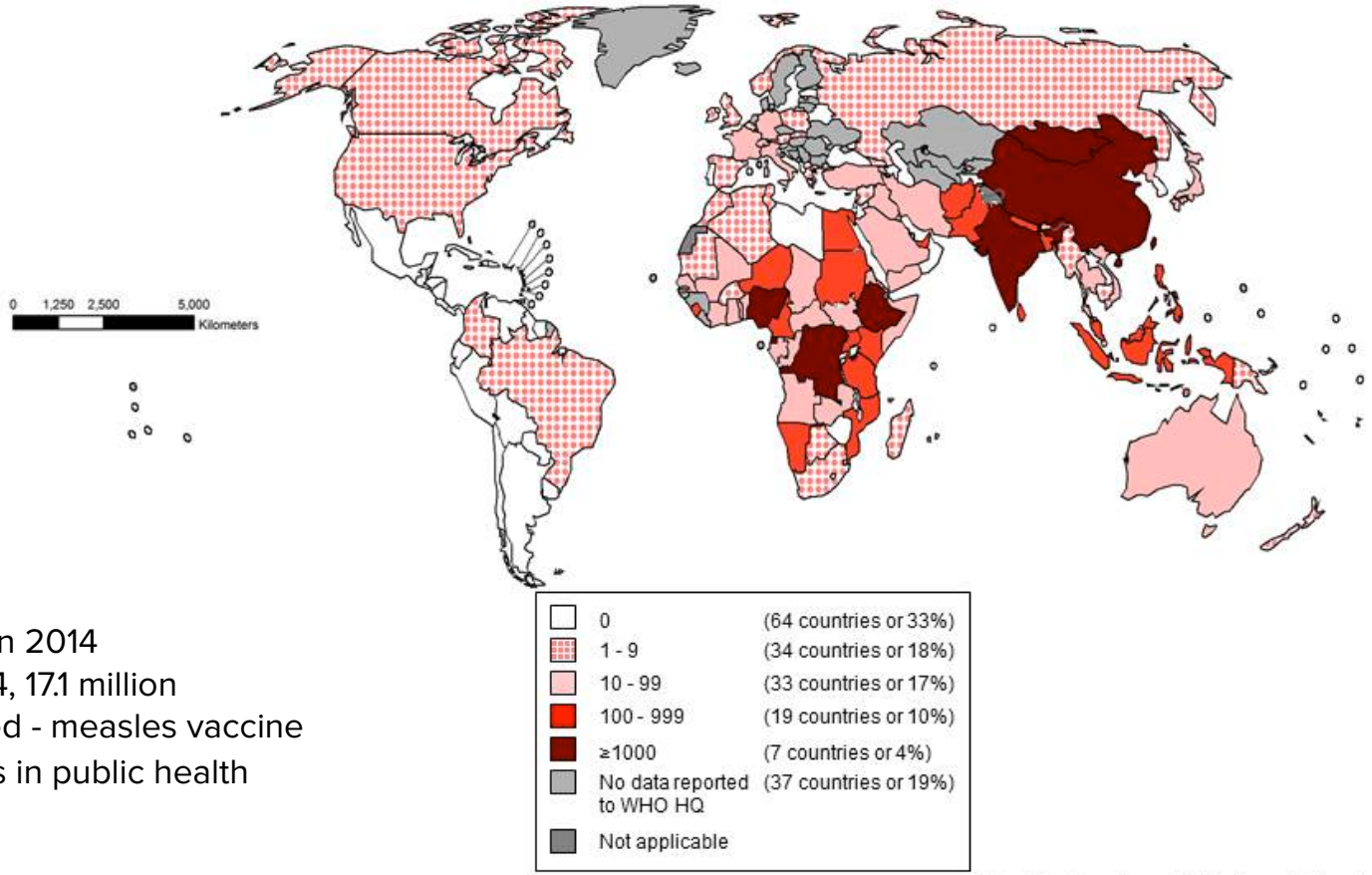
representing 89% of reported cases this year



*Provisional data reported to CDC's National Center for Immunization and Respiratory Diseases


2015 Measles Cases in the U.S.
January 1 to March 20, 2015
WA
OR
CA
ID
NV
MT
WY
UT
AZ
CO
NM
ND
SD
NE
KS
OK
TX
MN
IA
MO
AR
LA
WI
IL
MS
MI
IN
KY
TN
AL
OH
WV
GA
FL
SC
NC
VA
PA
NY
VT
NH
ME
MA
RI
CT
NJ
DE
MD
DC
AK
HI
Cases*:
0
1-4
5-9
10-19
20+
*Provisional data reported to CDC's National Center for Immunization and Respiratory Diseases
CDC

Number of Reported Measles Cases with onset date from Aug 2015 to Jan 2016 (6M period)



114,900 deaths in 2014
From 2000-2014, 17.1 million deaths prevented - measles vaccine one of best buys in public health

Data source: surveillance DEF file
Data in HQ as of 7 March 2016

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. ©WHO 2016. All rights reserved.

WHO

Go to:

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

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

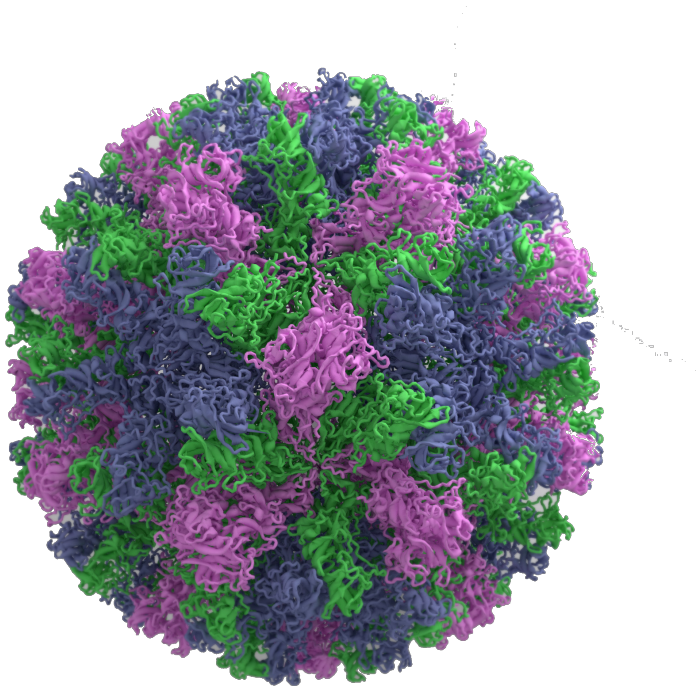
A. There is a 1/1000 chance of acute post-infection encephalitis
B. There is a 1-2/1000 chance of death from measles
C. Each infected person spreads measles virus to 15 others
D. Immunosuppression can lead to secondary infections
E. All of the above

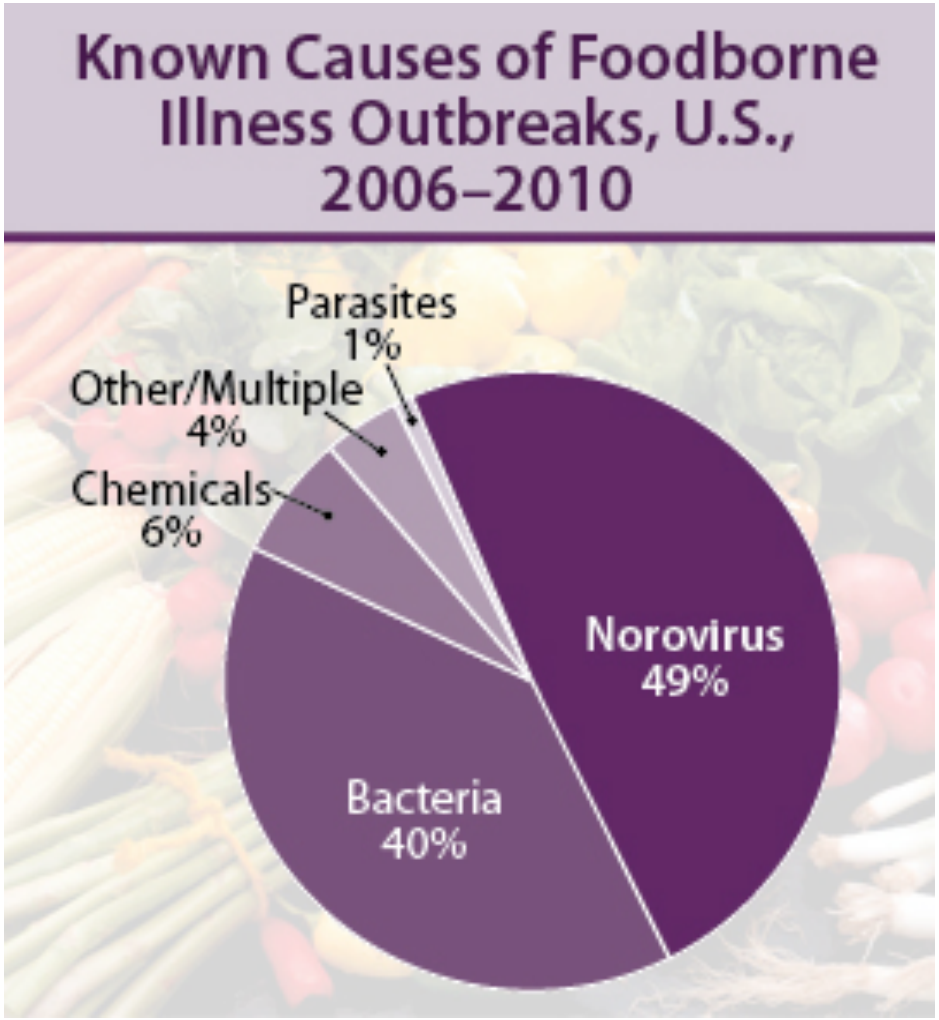
In a 24 hour period...

- 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

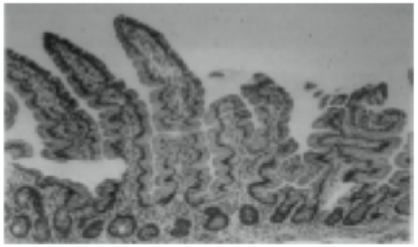
- *Caliciviridae*
- (+) strand RNA virus
- Cause 50% of all food-borne outbreaks of gastroenteritis (23 million/yr US)

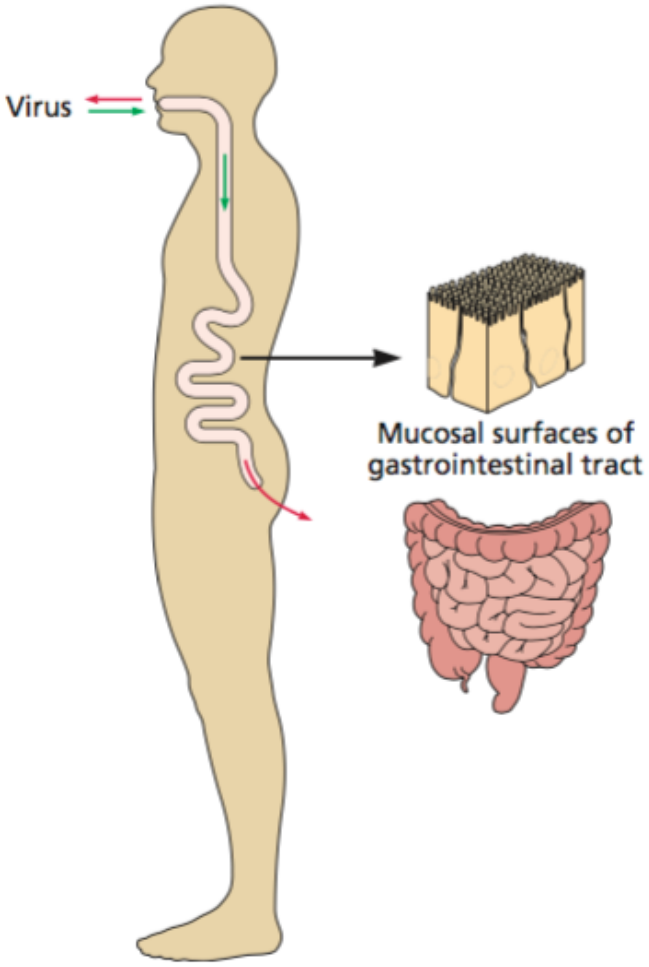




Pathogen	Estimated number of illnesses
Norovirus	5,461,731
Salmonella, nontyphoidal	1,027,561
Clostridium perfringens	965,958
Campylobacter spp.	845,024
Staphylococcus aureus	241,148
Subtotal	

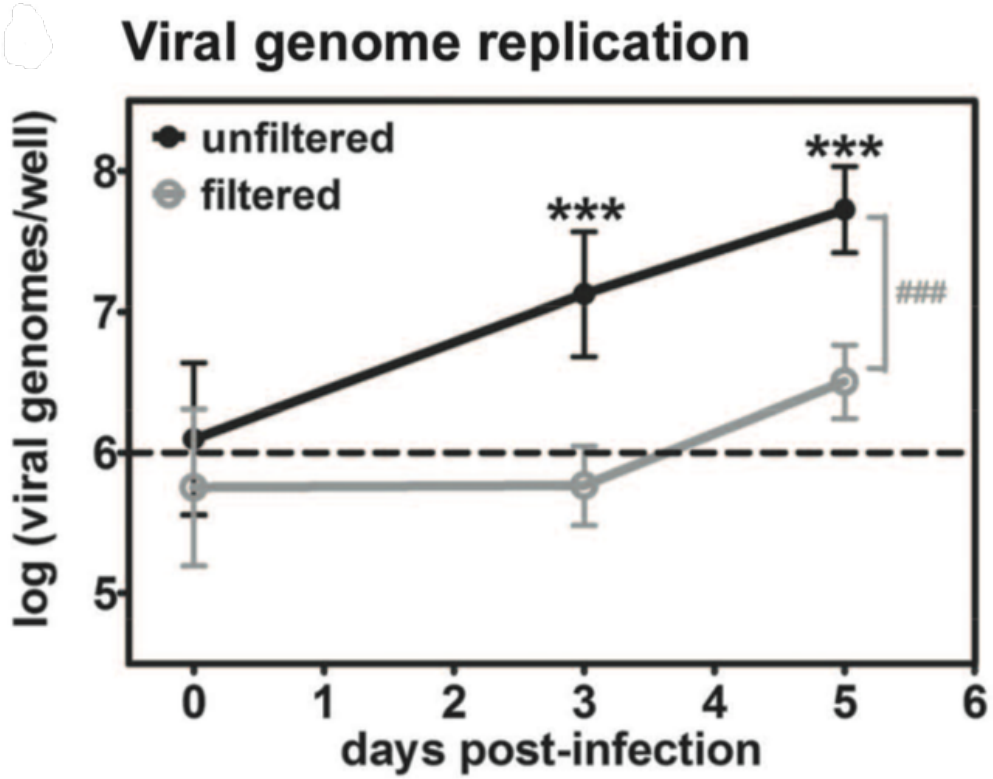
- Fecal-oral spread
- Retain infectivity passing through stomach
- Blunting of villi in proximal jejunum
- Basis for vomiting, diarrhea not known



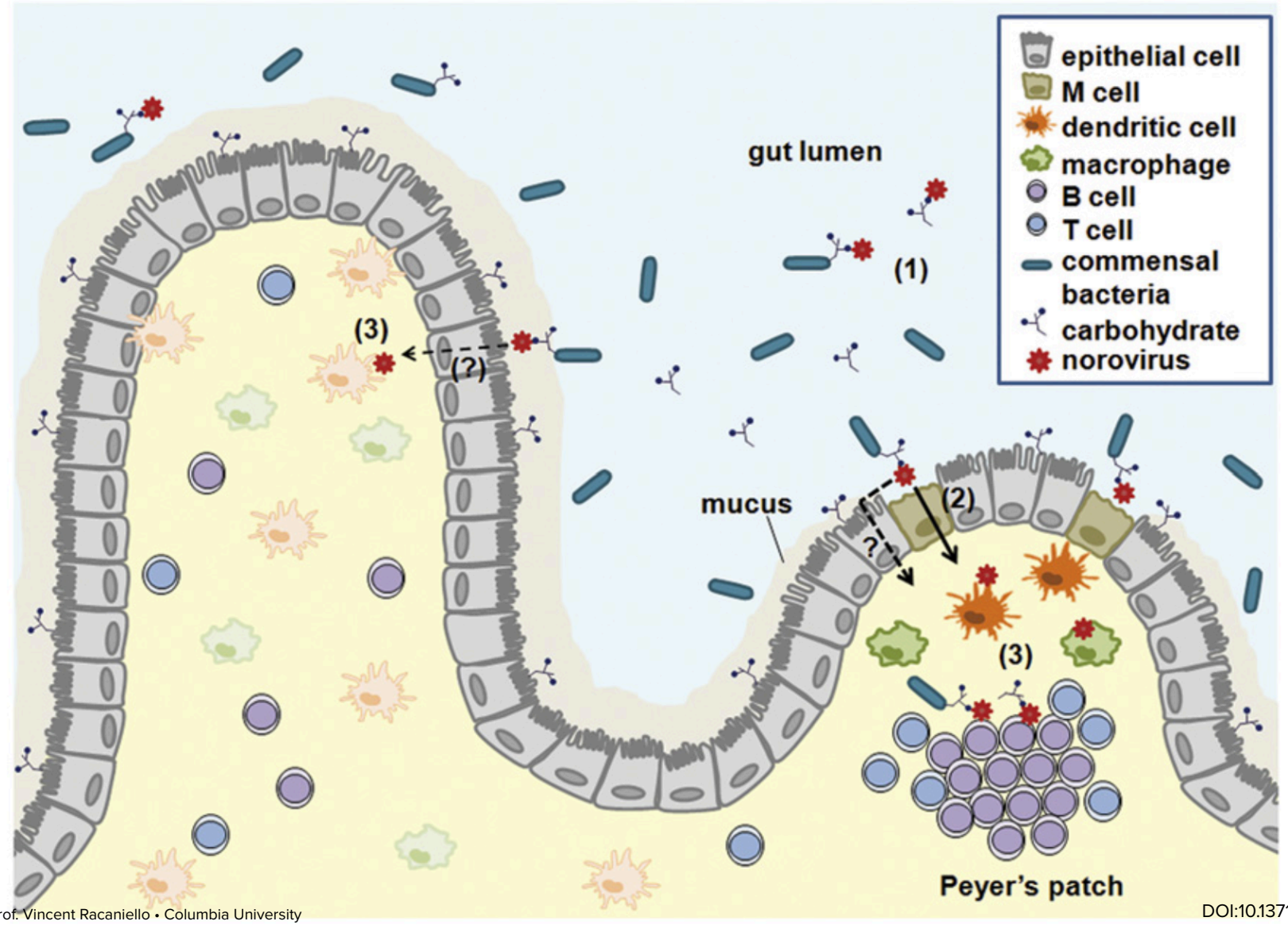


Principles of Virology, ASM Press

Enteric bacteria promote human and mouse norovirus infection of B cells

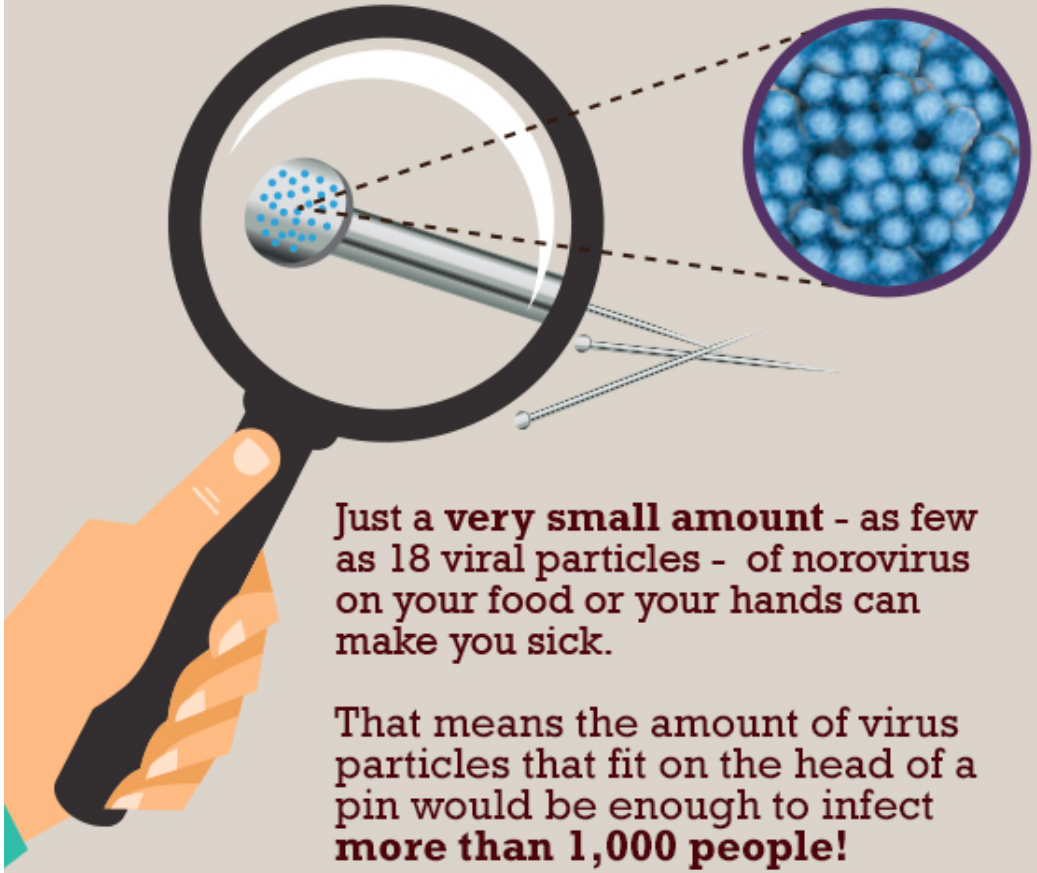


Science 346:6210 (2014)



DOI:10.1371/journal.ppat.1004626

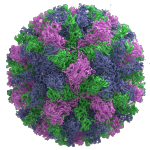
How contagious is norovirus?



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

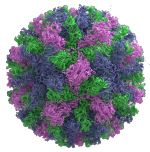
That means the amount of virus particles that fit on the head of a pin would be enough to infect **more than 1,000 people!**

SOURCE: Journal of Medical Virology, August, 2008



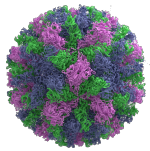
Clinical and epidemiological features

- 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



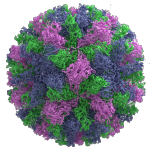
Clinical and epidemiological features

- 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



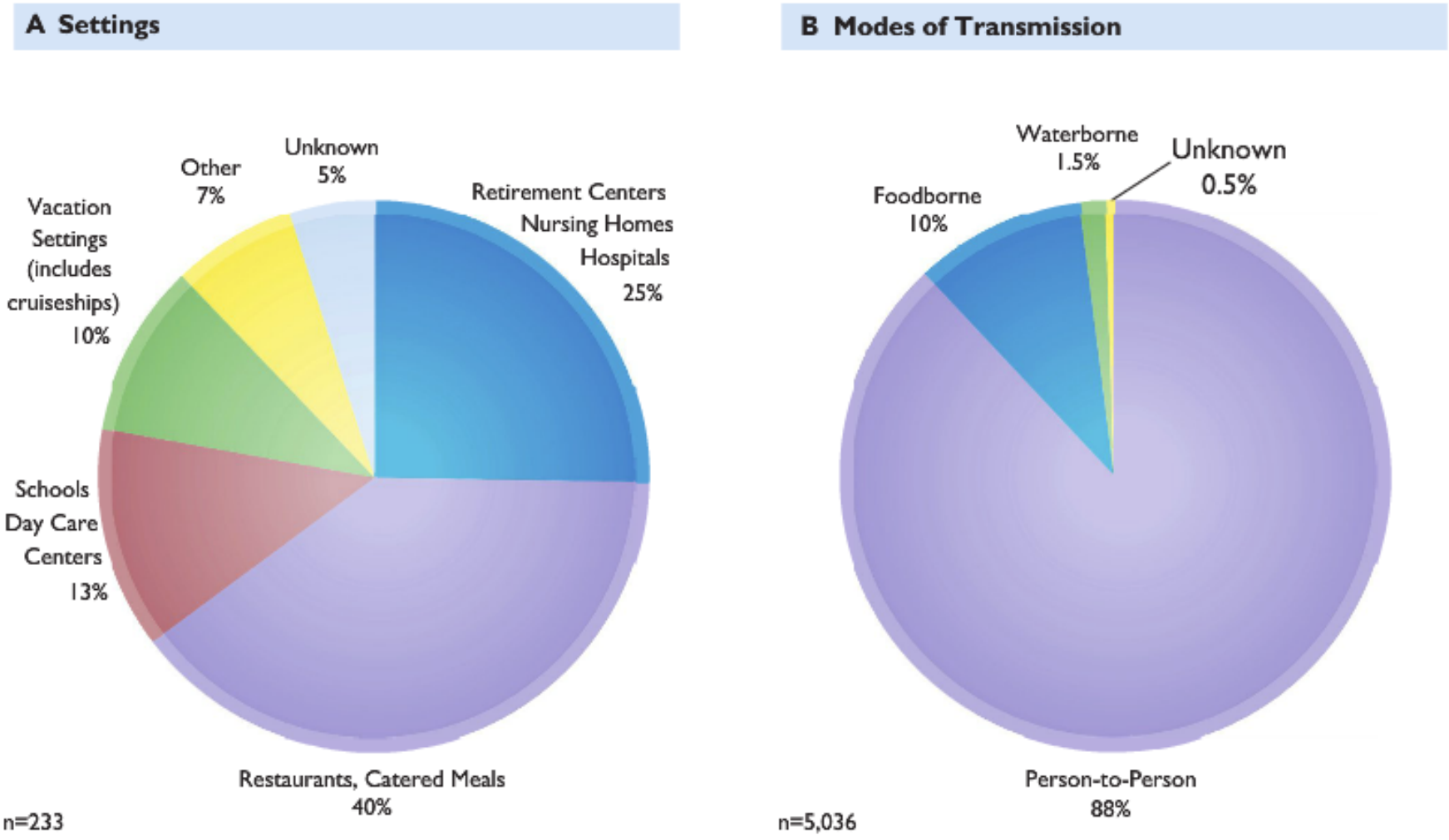
Clinical and epidemiological features

- 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

- Treatment: Supportive to prevent dehydration
- Reservoir: Humans, but evidence for animal reservoir
- Vaccine in early development
- Not usually serious, but can be in persons with underlying illness


A Settings
Unknown
5%
Other
7%
Vacation
Settings
(includes
cruiseships)
10%
Retirement Centers
Nursing Homes
Hospitals
25%
Schools
Day Care
Centers
13%
Restaurants, Catered Meals
40%
n=233
B Modes of Transmission
Waterborne
1.5%
Unknown
0.5%
Foodborne
10%
Person-to-Person
88%
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.

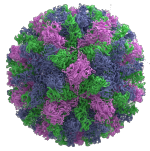
On a recent Air New Zealand flight, a sick passenger passed norovirus along to the crew. "Not only did the crew that cleaned up the mess get sick, but on every successive flight at least one or more crew members got sick with typical symptoms of norovirus," said David Freedman, of the University of Alabama 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^{tm}?

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?

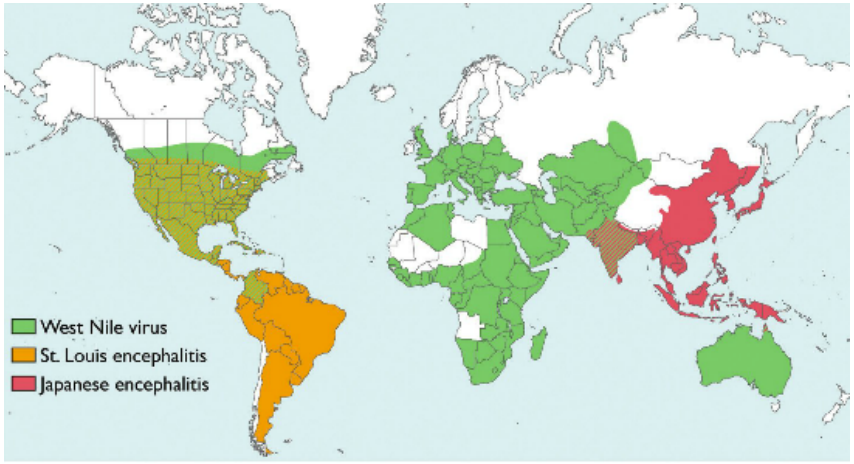
- Health officials track illness on cruise ships, so outbreaks are found and reported more quickly on a cruise ship than on land
- Close living quarters may increase the amount of group contact
- New passenger arrivals may bring the virus to other passengers and crew


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

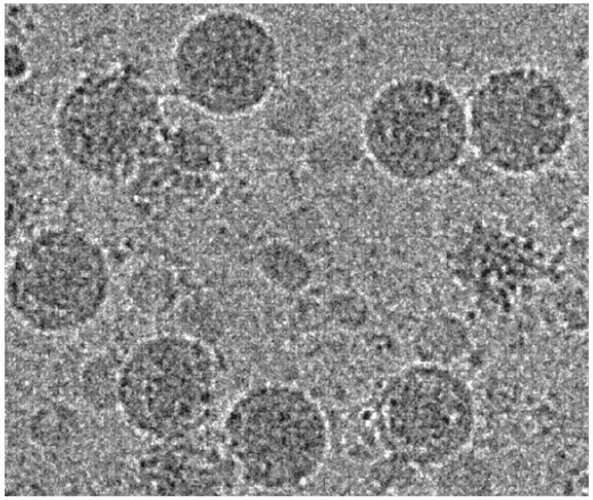
"We're pretty sure it's the West Nile Virus."

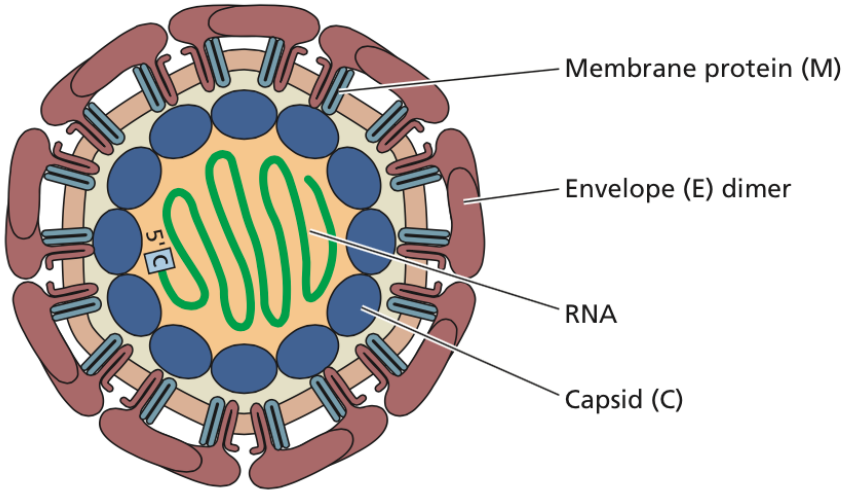
West Nile virus

- *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

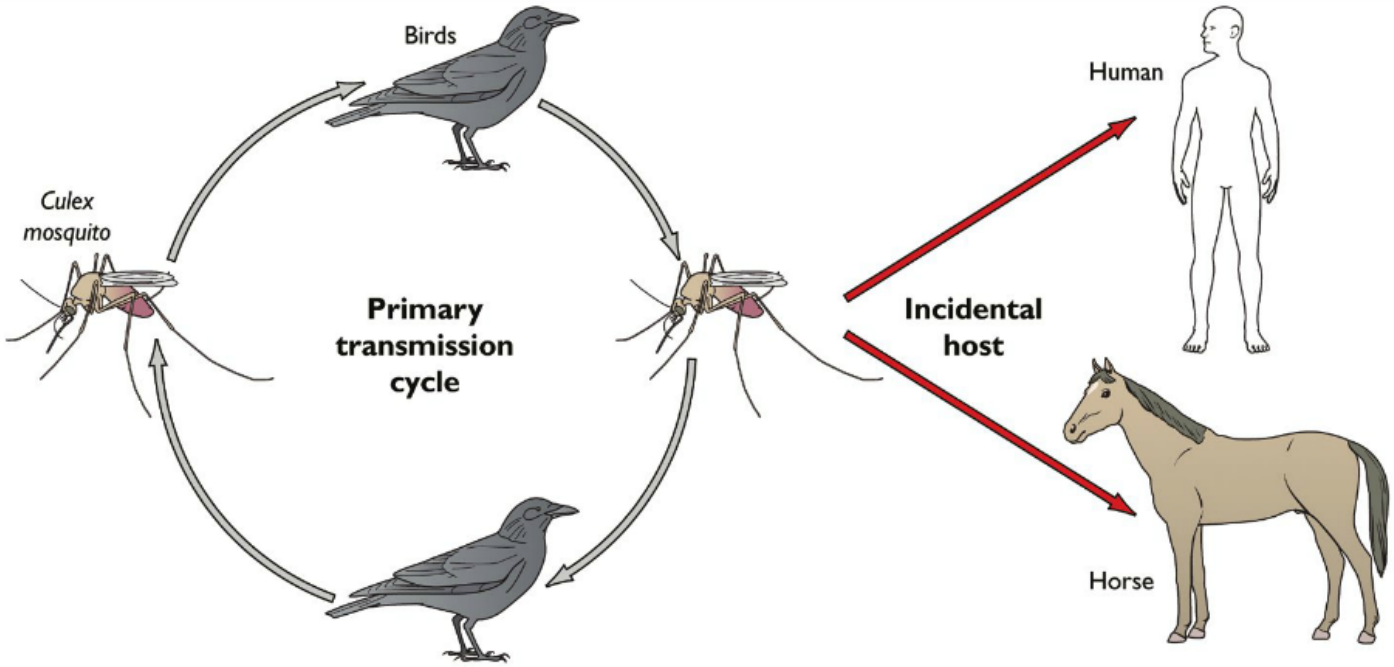


West Nile virus





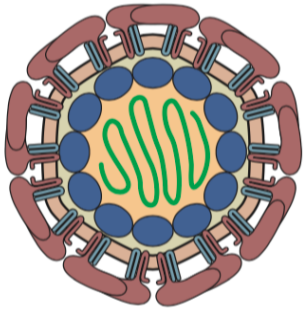
WNV transmission cycle



WNV pathogenesis

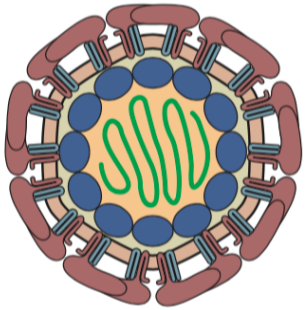
- Transmitted to humans by *Culex* bite
- Incubation period 3-14 days
- 20-30% develop flu-like illness called WNV fever
- 80%: no symptoms

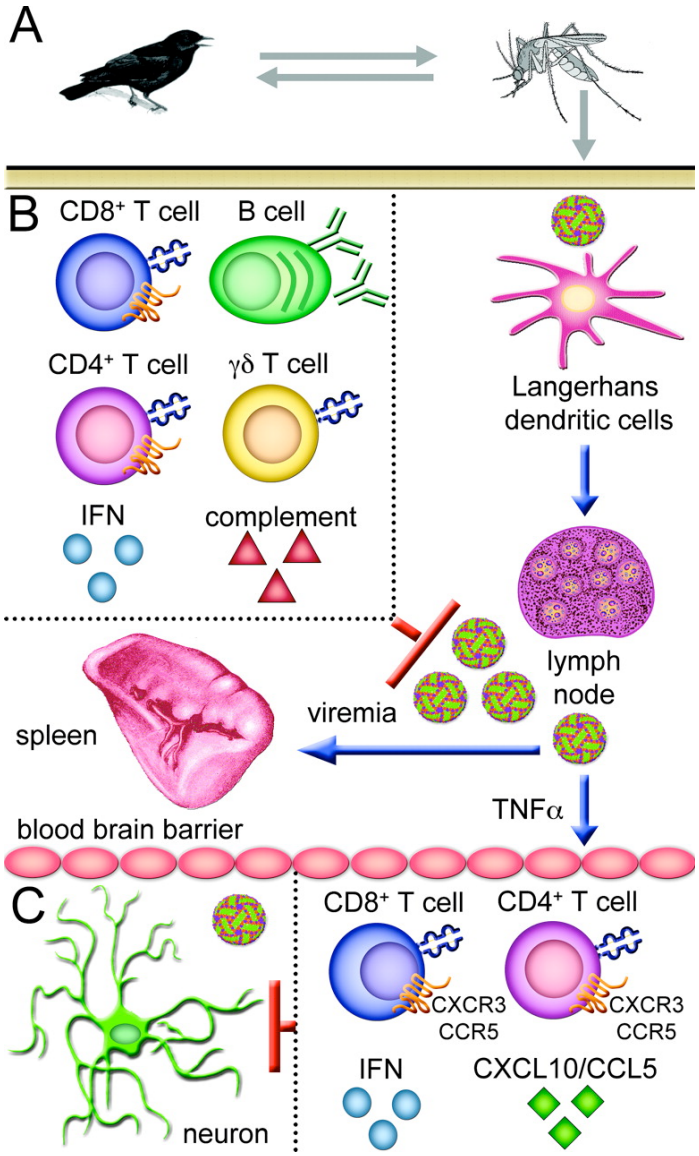
https://en.wikipedia.org/wiki/User:Muhammad_Mahdi_Karim#/media/File:Culex_sp..jpg



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

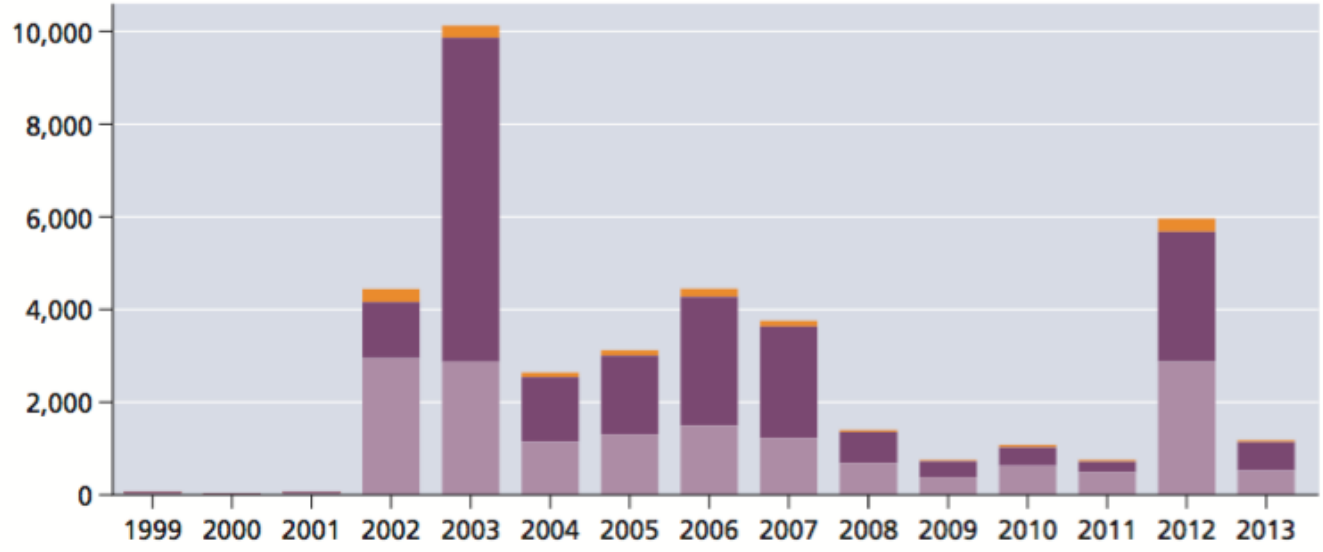




TLR3

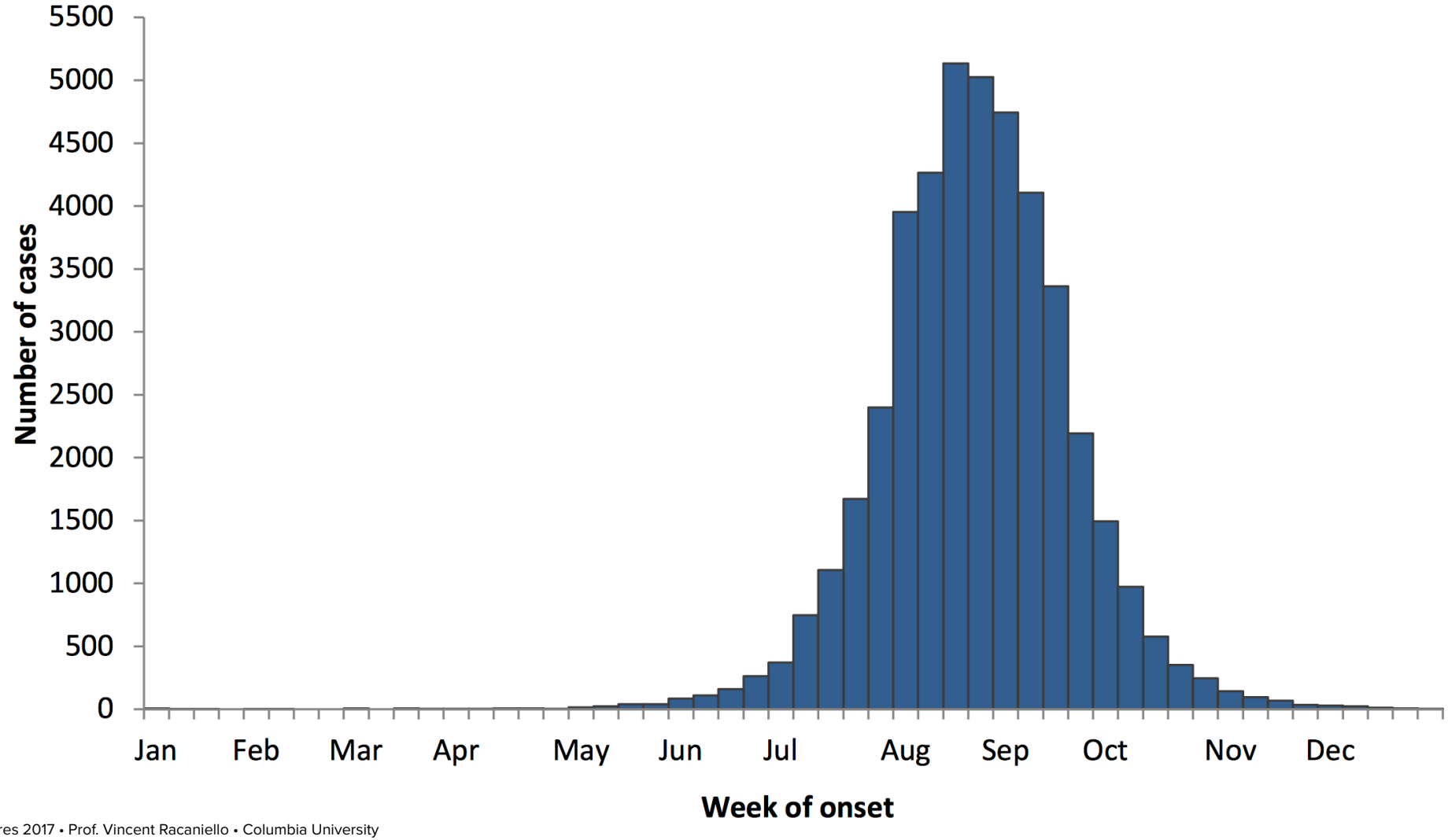
doi:10.1128/JVI.01122-06

West Nile Virus USA

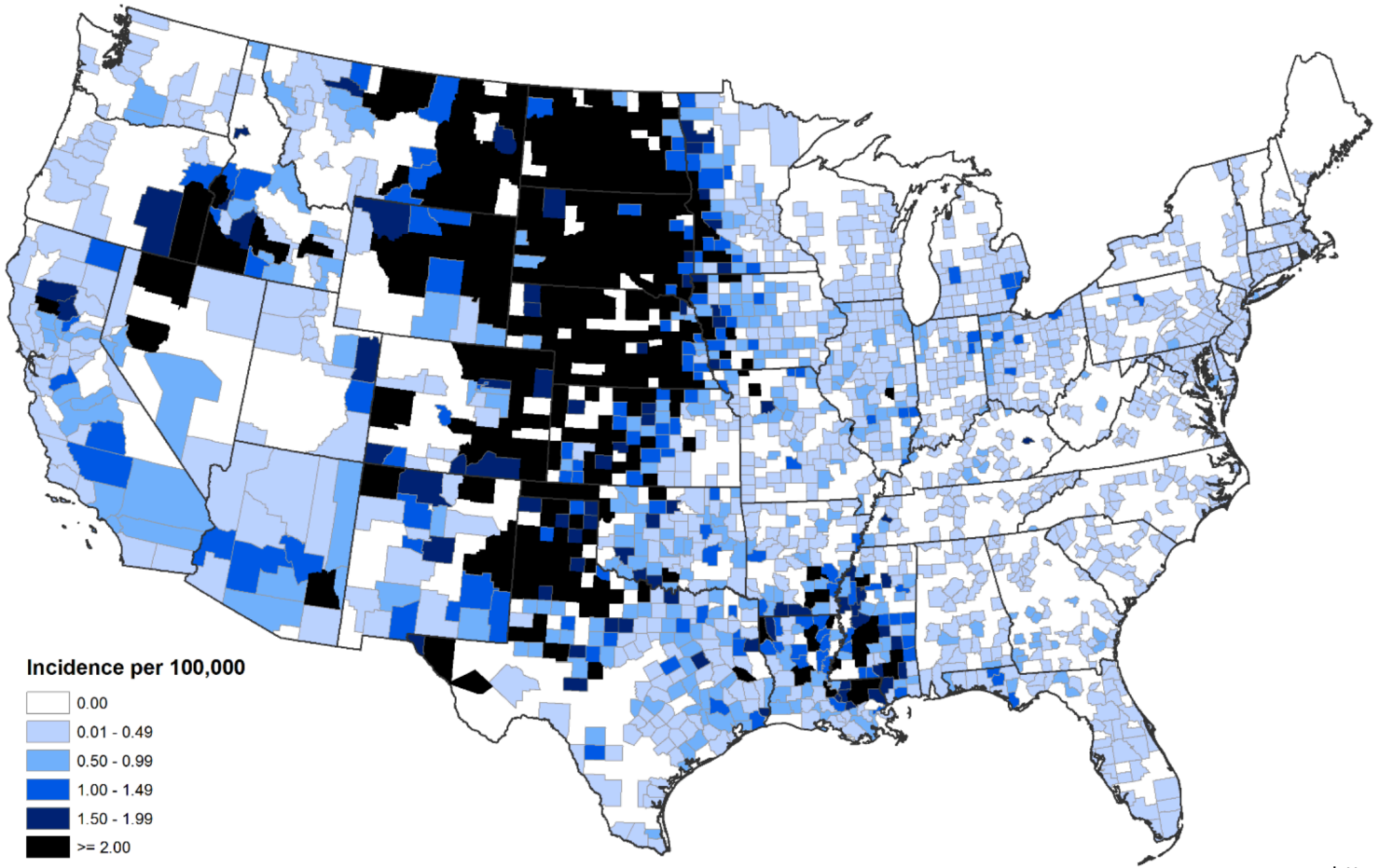


	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Neuroinvasive disease cases	59	19	64	2,946	2,866	1,148	1,309	1,495	1,227	689	386	629	486	2,873	529
Non-neuroinvasive disease cases	3	2	2	1,210	6,996	1,391	1,691	2,774	2,403	667	334	392	226	2,801	606
Total cases	62	21	66	4,156	9,862	2,539	3,000	4,269	3,630	1,356	720	1,021	712	5,674	1,135
Deaths	7	2	10	284	261	100	119	177	124	44	32	57	43	286	44

West Nile virus disease cases reported to CDC 1999-2015

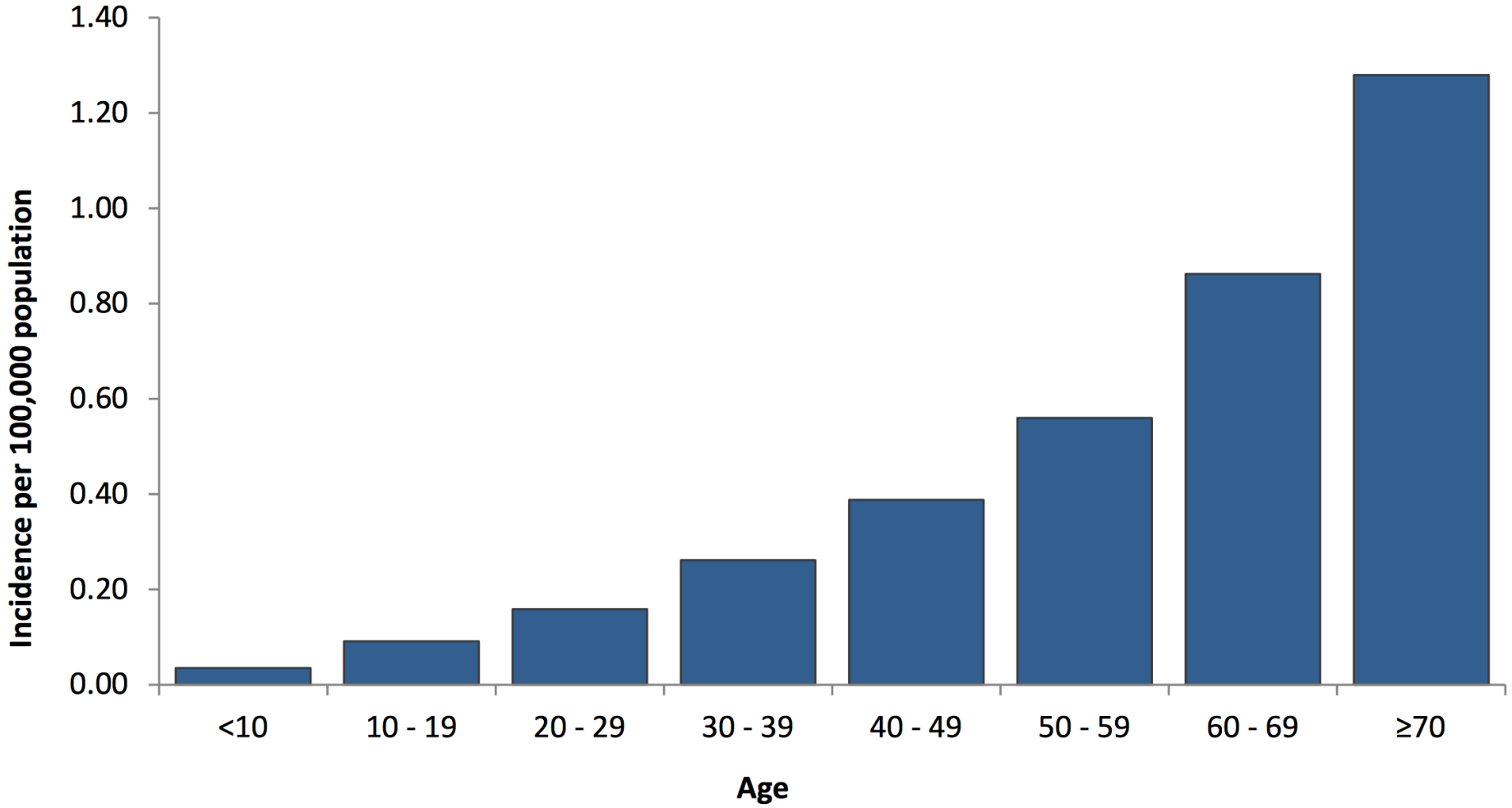


Average annual incidence of WNV neuroinvasive disease by county 1999-2015



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

WNV neuroinvasive disease 1999-2014



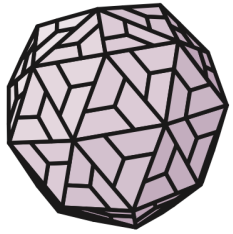
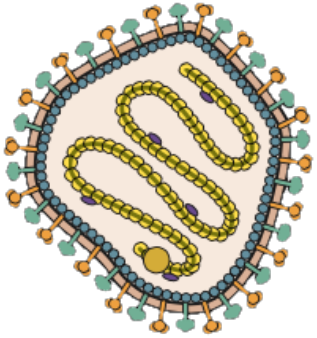
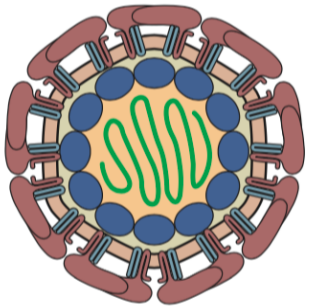
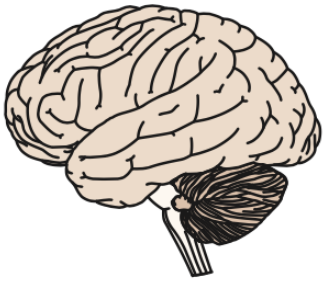
http://www.cdc.gov/westnile/

WNV prevention

- *Culex* species bite evening to morning
- Repellants, screens, clothing
- Vaccines in development

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