Infection Basics

Session 12

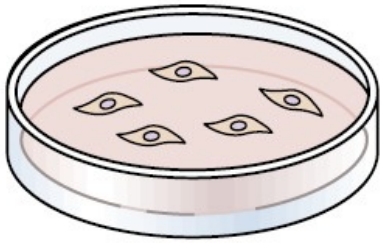
Virology Live

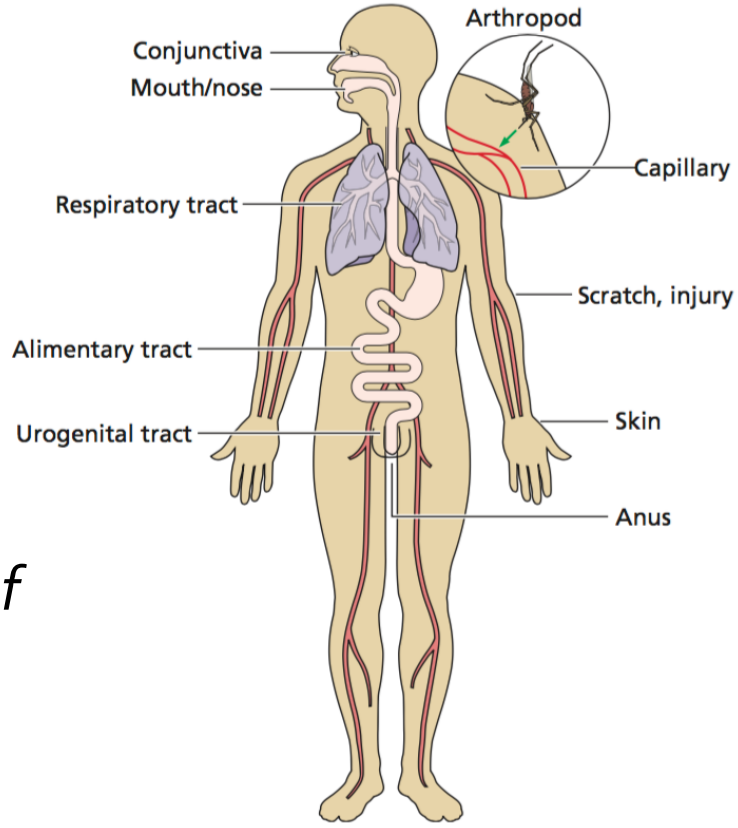
Fall 2021

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

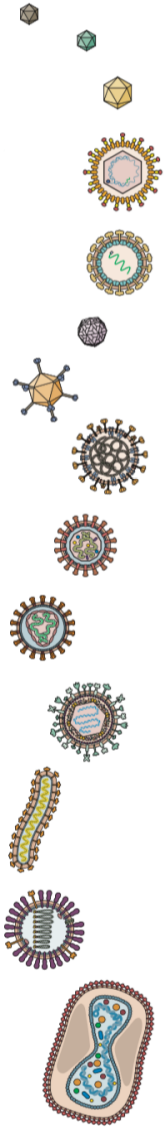
The nature of host-parasite interactions





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

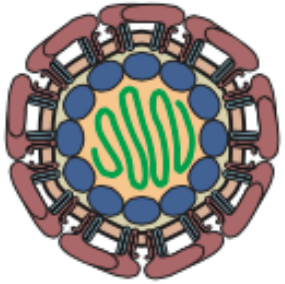
In both the infected cell and the infected host, viruses must get in and they must get out

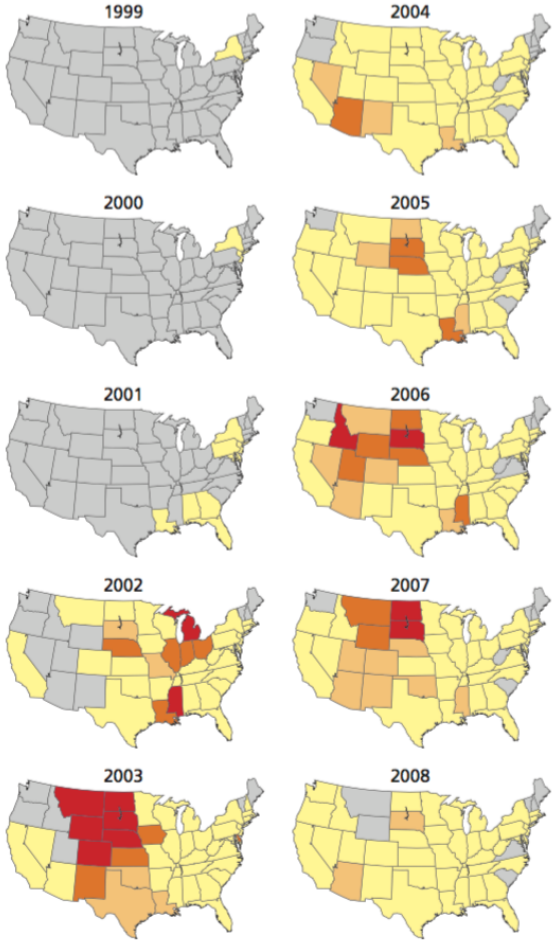


We live and prosper in a cloud of viruses

- 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

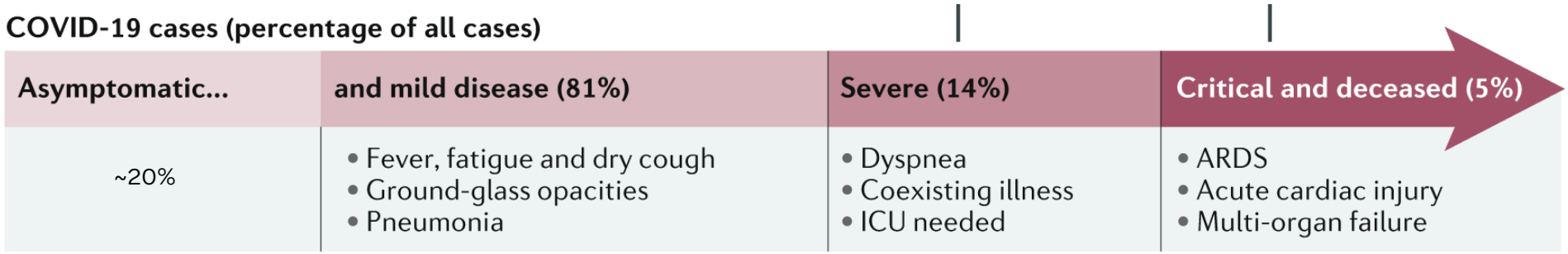
Example: West Nile virus





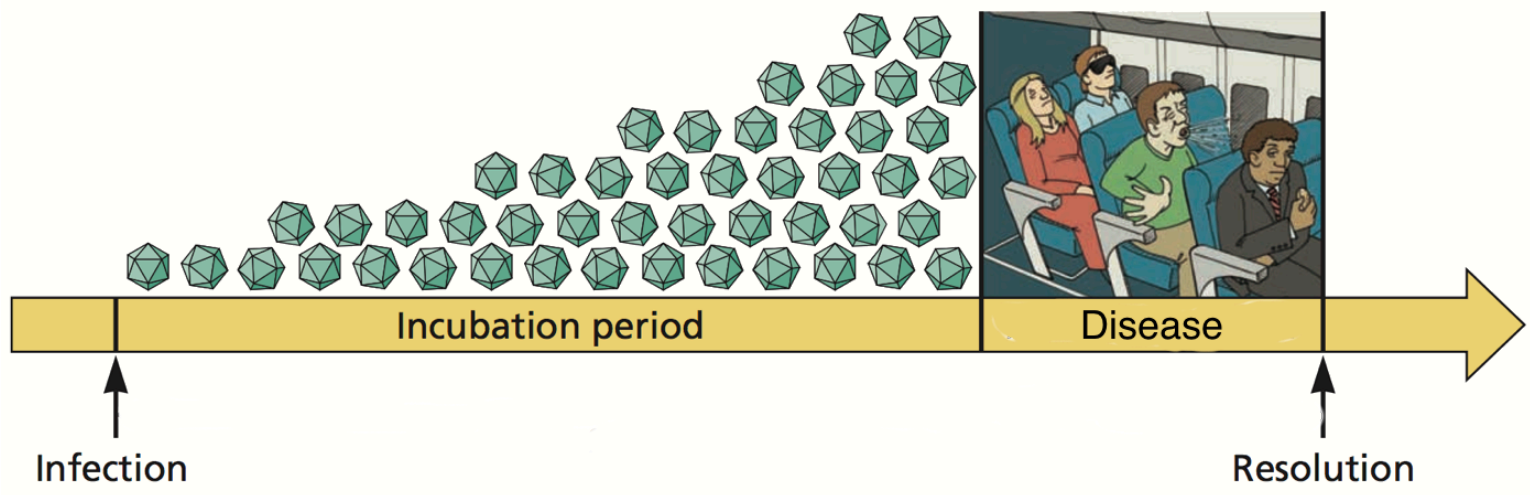
- WNV spread across the US in less than 4 years (’99)
  - By October 2004 about 1 million people were infected (Ab+)
  - Febrile illness developed in 20% of infected people
  - Central nervous system illness developed in 1% of infected people
- Many people were infected with no obvious disease
  - Inability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

Example: SARS-CoV-2



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

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

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.

SARS-CoV-2 1-14 days

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

Short - replication at primary site produces symptoms

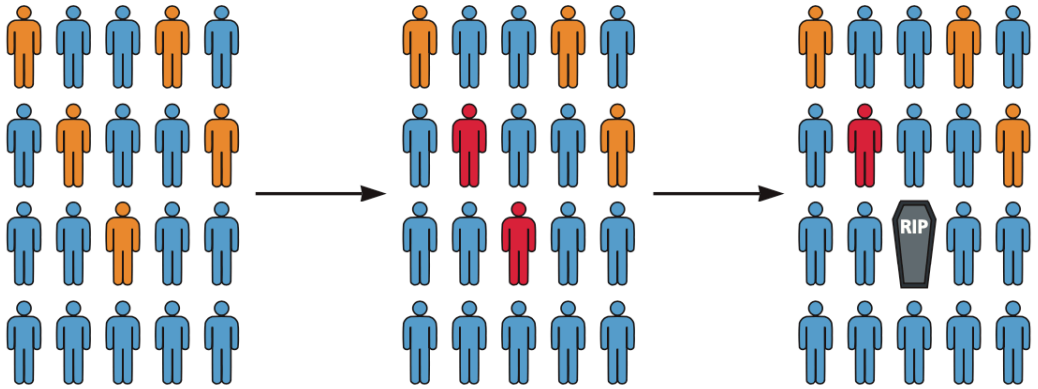
Long - Symptoms beyond primary site

Morbidity, mortality, incidence, fatality

Each icon = 10,000

Infected (PCR+)

Signs/symptoms (PCR+)



Incidence
25%

Morbidity
10%

Mortality
5%

CFR
10,000/50,000
25%

- 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

Basic reproductive number, R_0

$R_0 = tau * c * d$

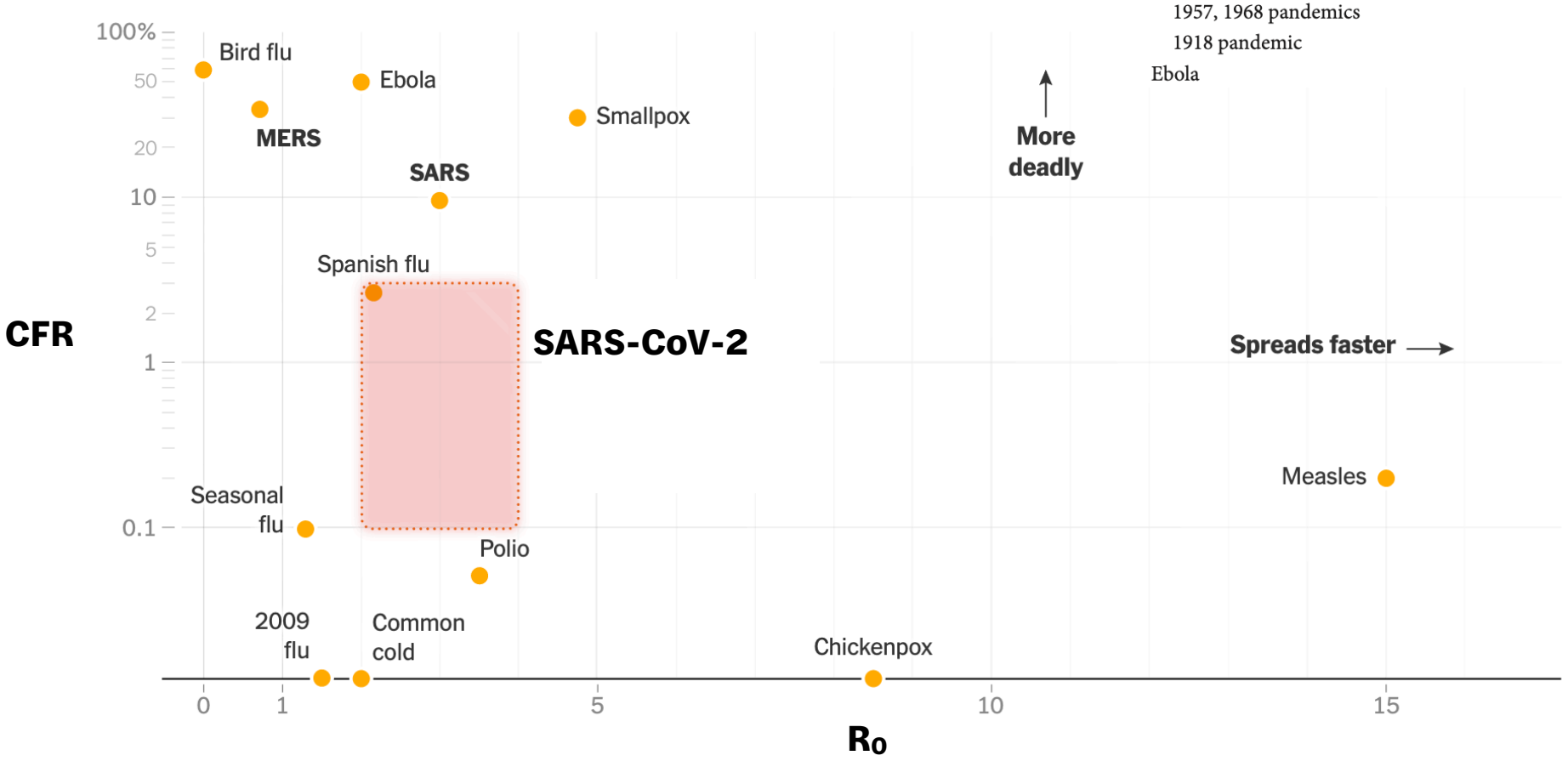
Tau = probability of infection given contact

C = average duration of contact between infected and uninfected host

D = duration of infectivity

- Number of secondary infections that can arise in population of susceptible hosts from a single infected individual
- Calculated early in an outbreak before interventions or population immunity; subsequently estimated at $R_{e/t}$
- 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



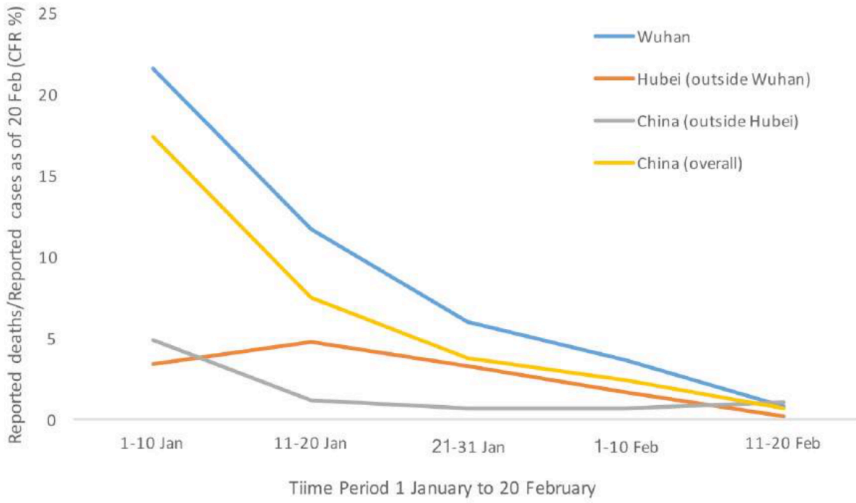
Influenza	
2009 (H1N1)	1.47
1957, 1968 pandemics	1.8
1918 pandemic	2.4-5.4
Ebola	1.3–1.8[b]

https://www.nytimes.com/interactive/2020/world/asia/china-coronavirus-contain.html

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

Baseline Characteristics	Confirmed Cases, N (%)	Deaths, N (%)	Case Fatality Rate, %
Overall	44,672	1,023	2.3
Age, years			
0–9	416 (0.9)	–	–
10–19	549 (1.2)	1 (0.1)	0.2
20–29	3,619 (8.1)	7 (0.7)	0.2
30–39	7,600 (17.0)	18 (1.8)	0.2
40–49	8,571 (19.2)	38 (3.7)	0.4
50–59	10,008 (22.4)	130 (12.7)	1.3
60–69	8,583 (19.2)	309 (30.2)	3.6
70–79	3,918 (8.8)	312 (30.5)	8.0
≥80	1,408 (3.2)	208 (20.3)	14.8
Sex			
Male	22,981 (51.4)	653 (63.8)	2.8
Female	21,691 (48.6)	370 (36.2)	1.7

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 R0=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

Superspreader events

nature medicine

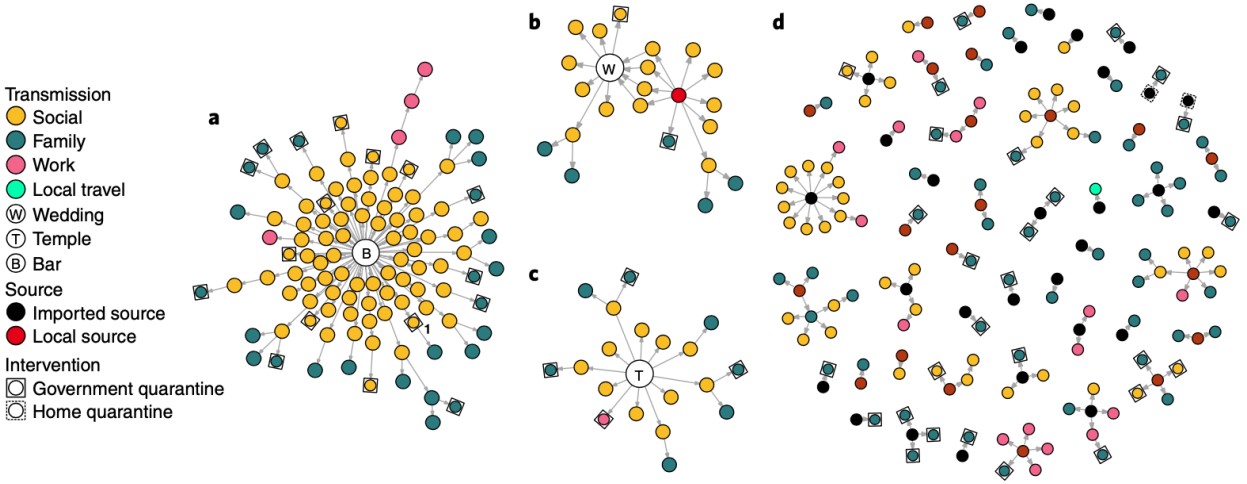
LETTERS

https://doi.org/10.1038/s41591-020-1092-0

Check for updates

Clustering and superspreading potential of SARS-CoV-2 infections in Hong Kong

Dillon C. Adam[1,2], Peng Wu[1]✉, Jessica Y. Wong[1], Eric H. Y. Lau[1], Tim K. Tsang[1], Simon Cauchemez[3], Gabriel M. Leung[1,4] and Benjamin J. Cowling[1,4]



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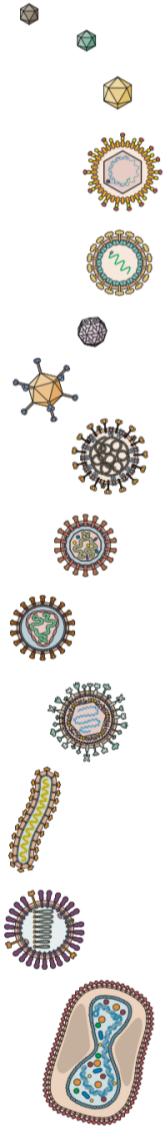
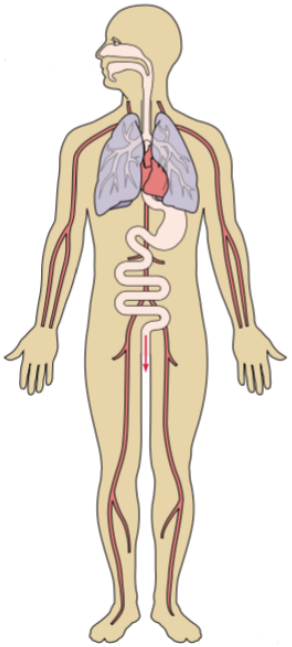
Which of the following parameters is not influenced by human interventions?

A. Mortality rate
B. Case fatality ratio
C. Reproductive index
D. Incidence
E. Incubation period



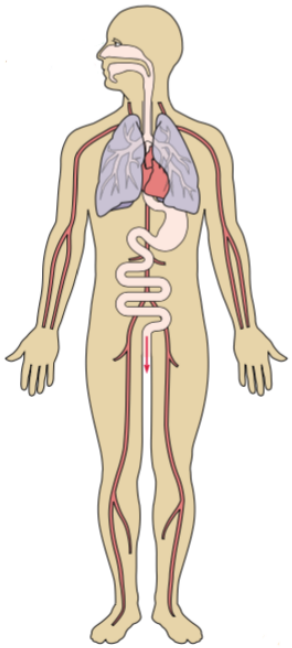
Viral pathogenesis

- *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



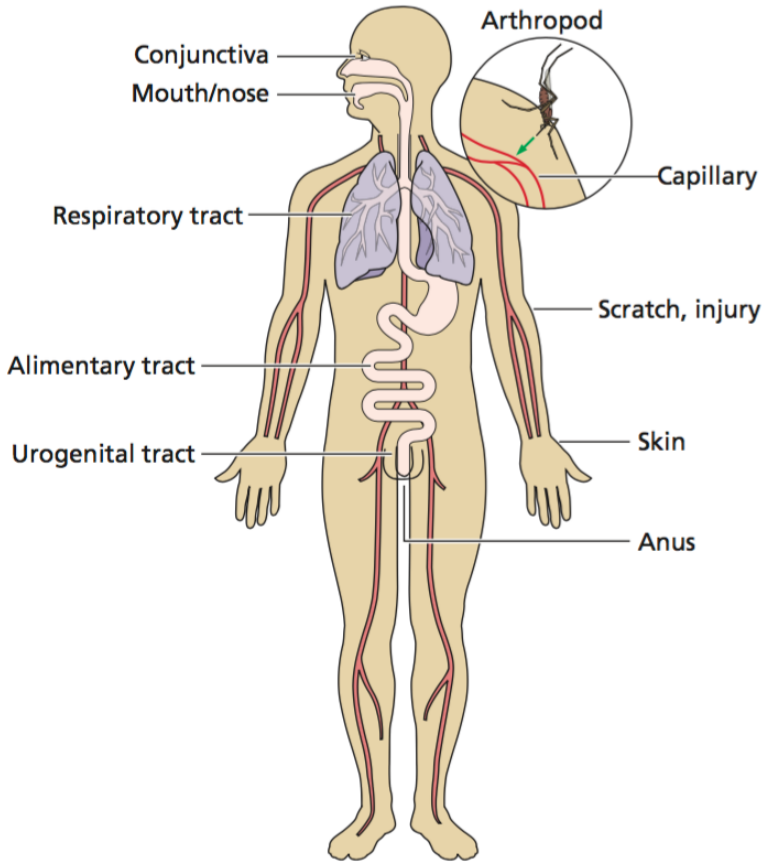
Fundamental questions of viral pathogenesis

- 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?



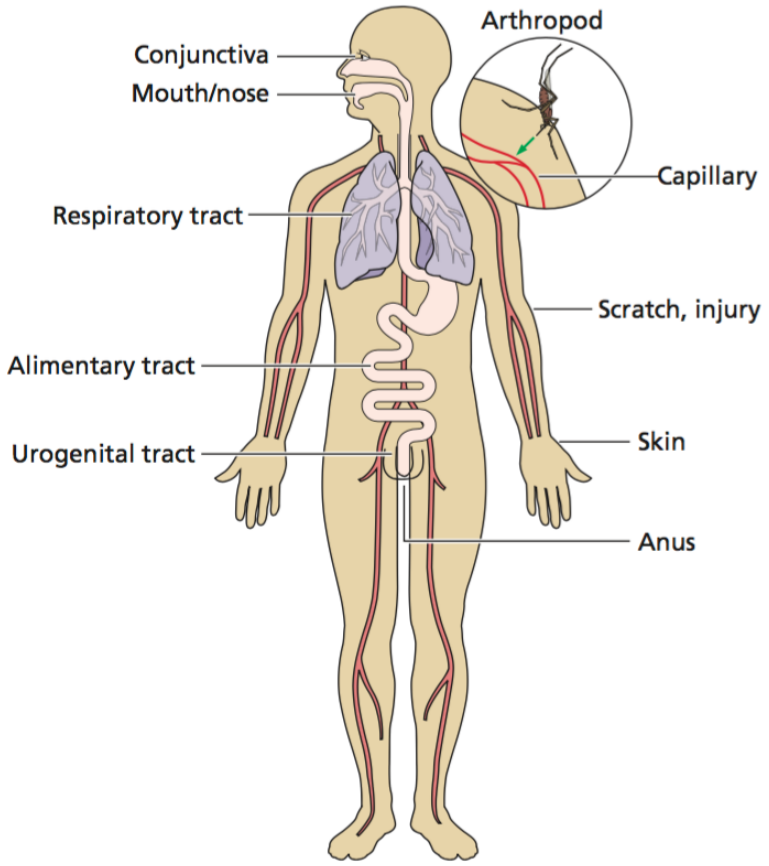
Three requirements for a successful infection

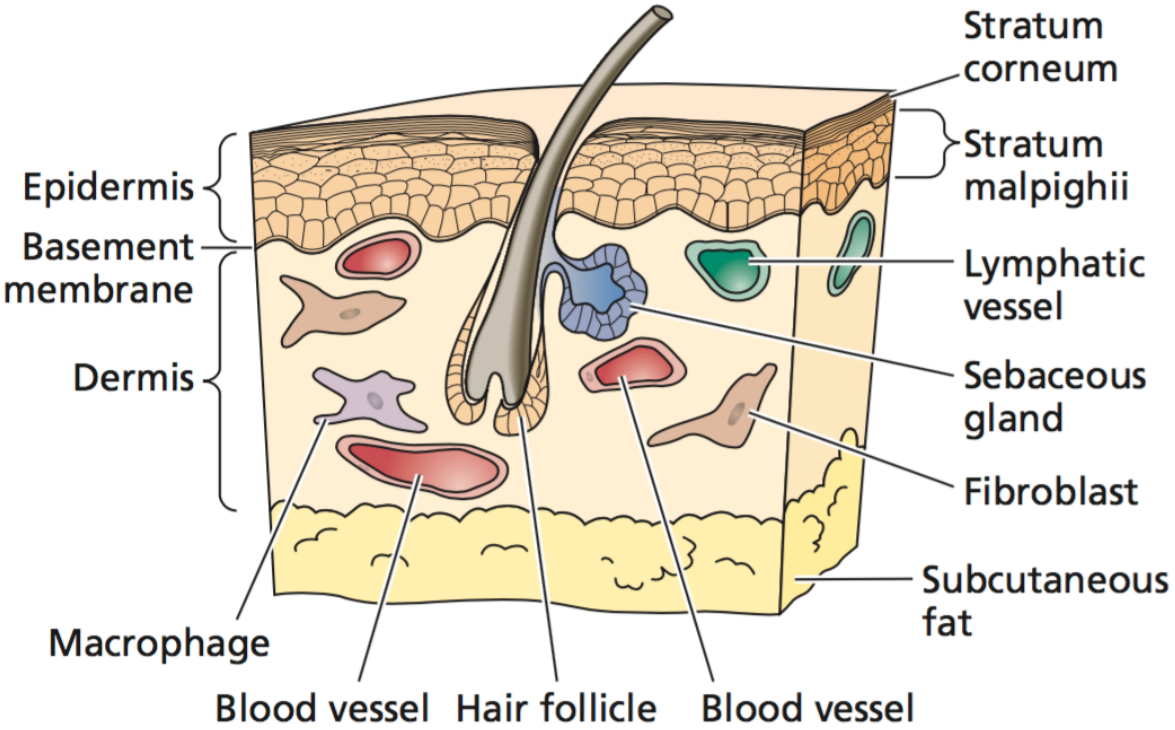
- Enough virus
- Cells accessible, susceptible, permissive
- Local antiviral defense absent or overcome

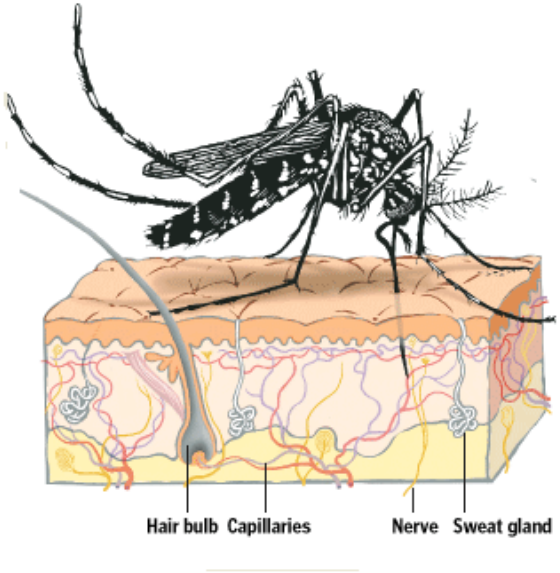


Gaining access: site of entry is critical

The human body presents only a
limited spectrum
of entry sites for viral infection

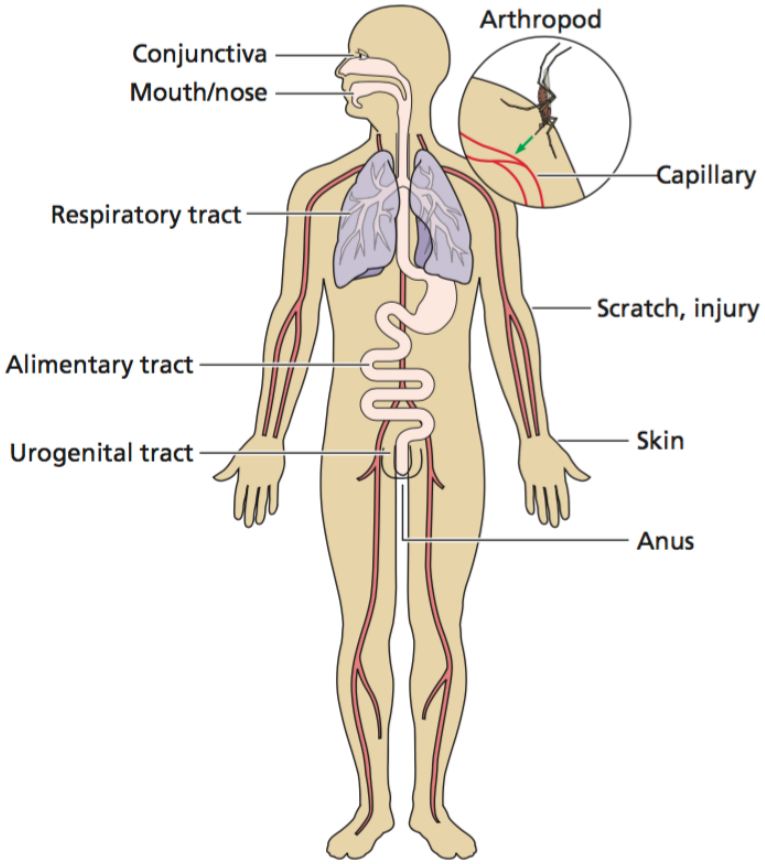




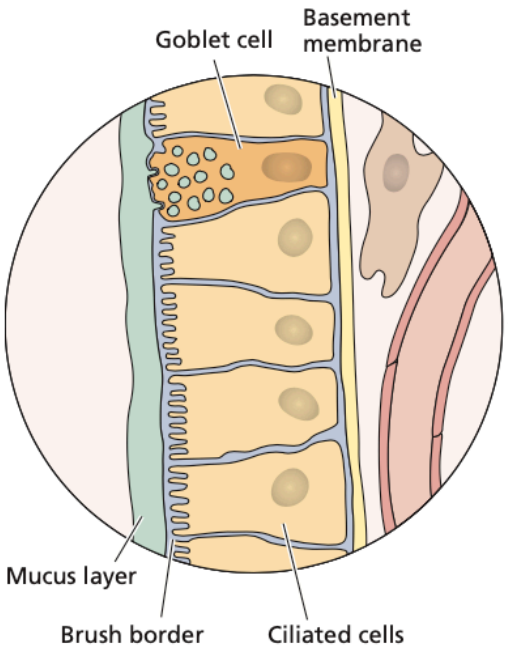


How Mosquitoes Spread Viruses
https://youtu.be/7wsk8a3ze80

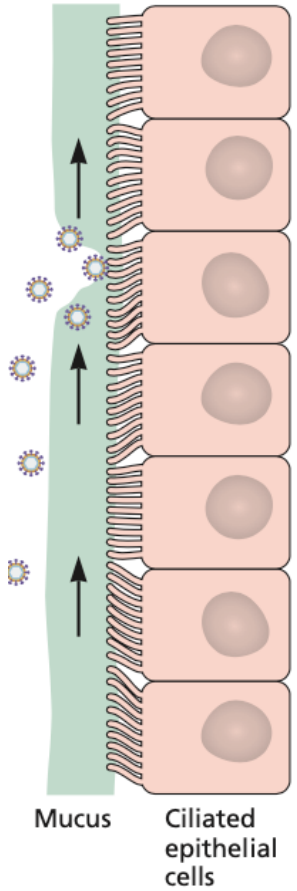
Mucosal surfaces are ripe for viral infection



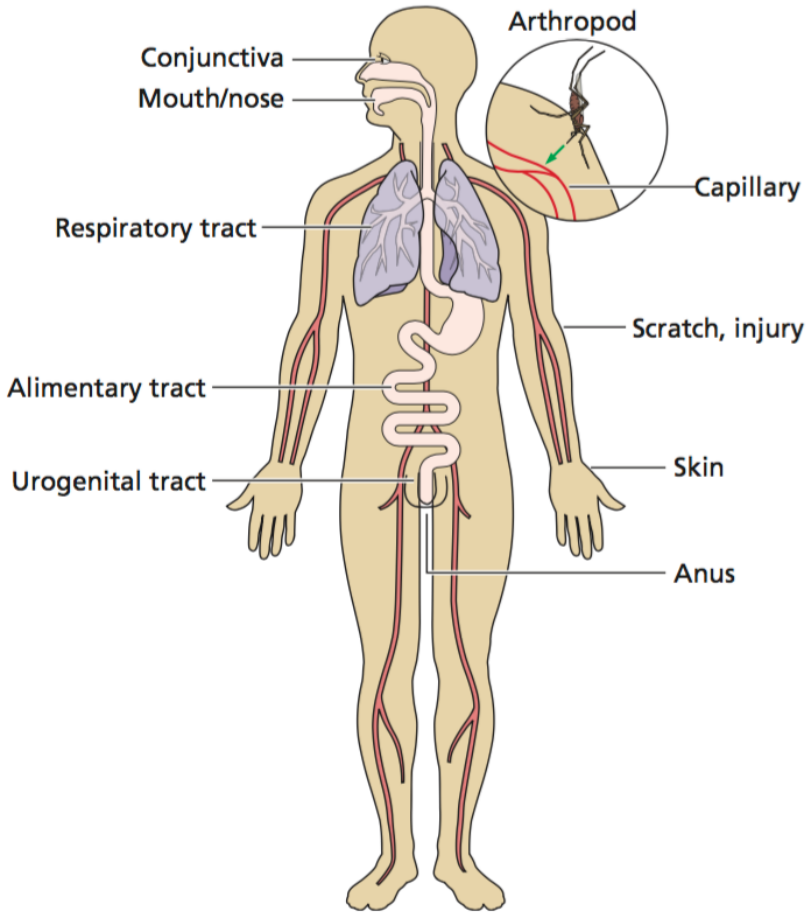
Lined by living cells

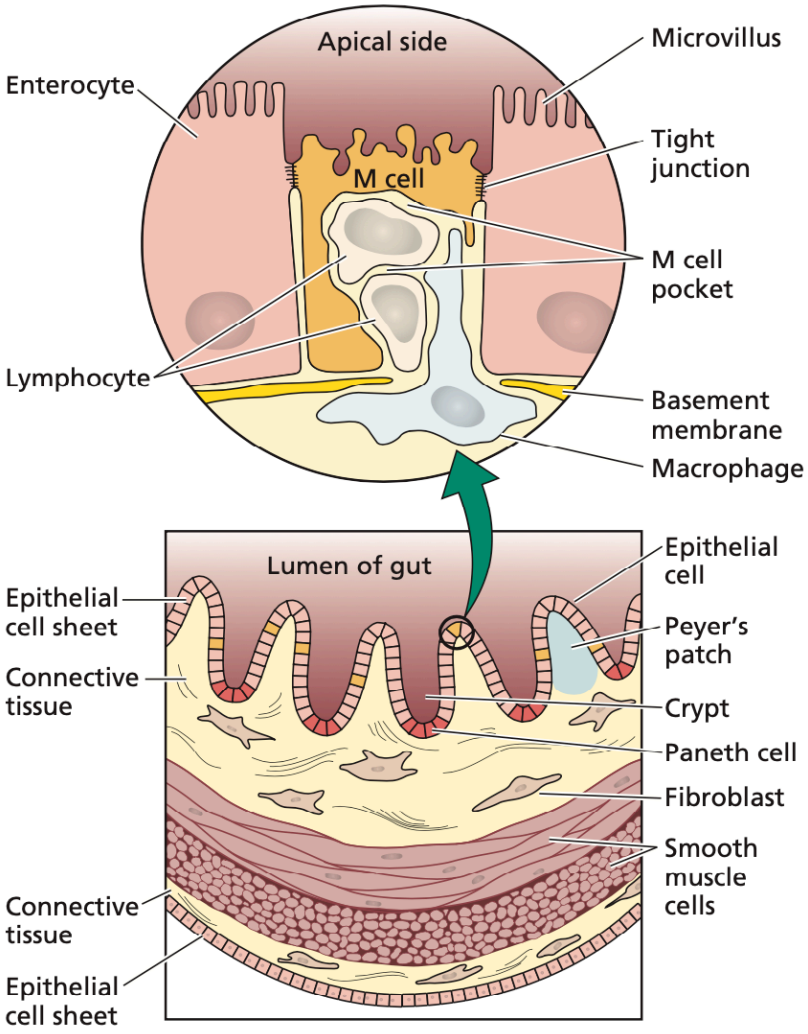


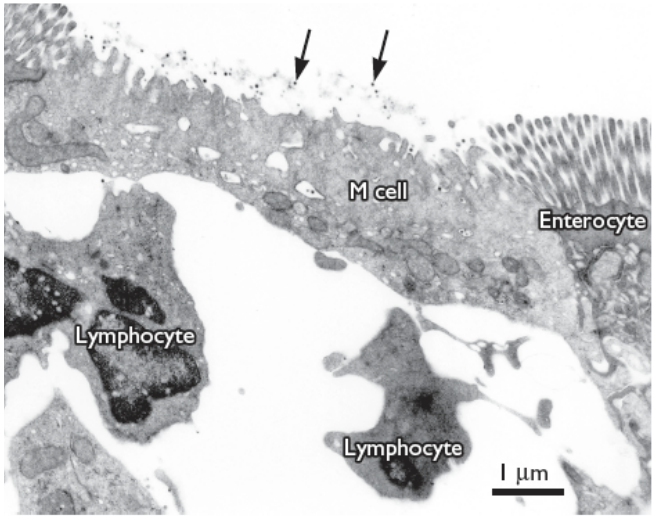
Site of reproduction	Virus	Clinical manifestation
Turbinate "baffles" Palate Tonsillar lymphoid tissues Tongue Cervical lymph node Esophagus Trachea	**Upper respiratory** Rhinovirus Coronavirus Parainfluenza virus Respiratory syncytial virus Influenza virus Adenovirus Herpes simplex virus Epstein-Barr virus	Rhinitis (common cold) Pharyngitis Laryngitis
Bronchi Bronchioles Bronchial lymph node Alveolus Alveolar macrophage	**Lower respiratory** Parainfluenza virus Respiratory syncytial virus Influenza virus Adenovirus Measles SARS MERS	Tracheitis Bronchitis Bronchiolitis Bronchopneumonia



Alimentary tract





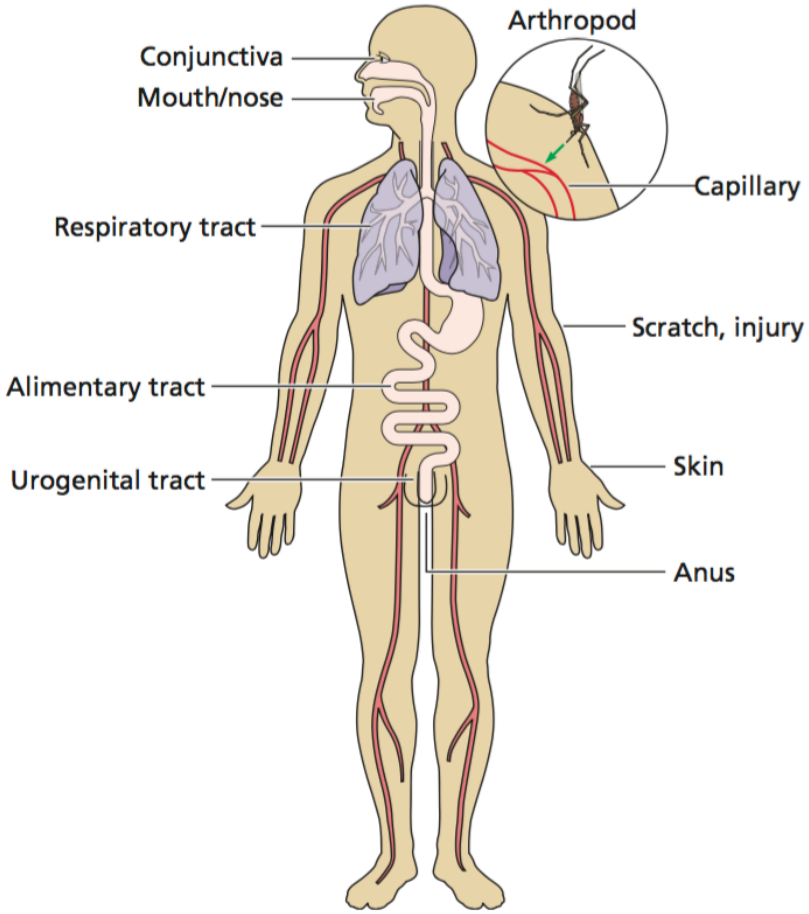


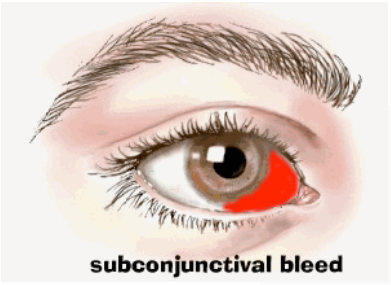
The small intestine

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

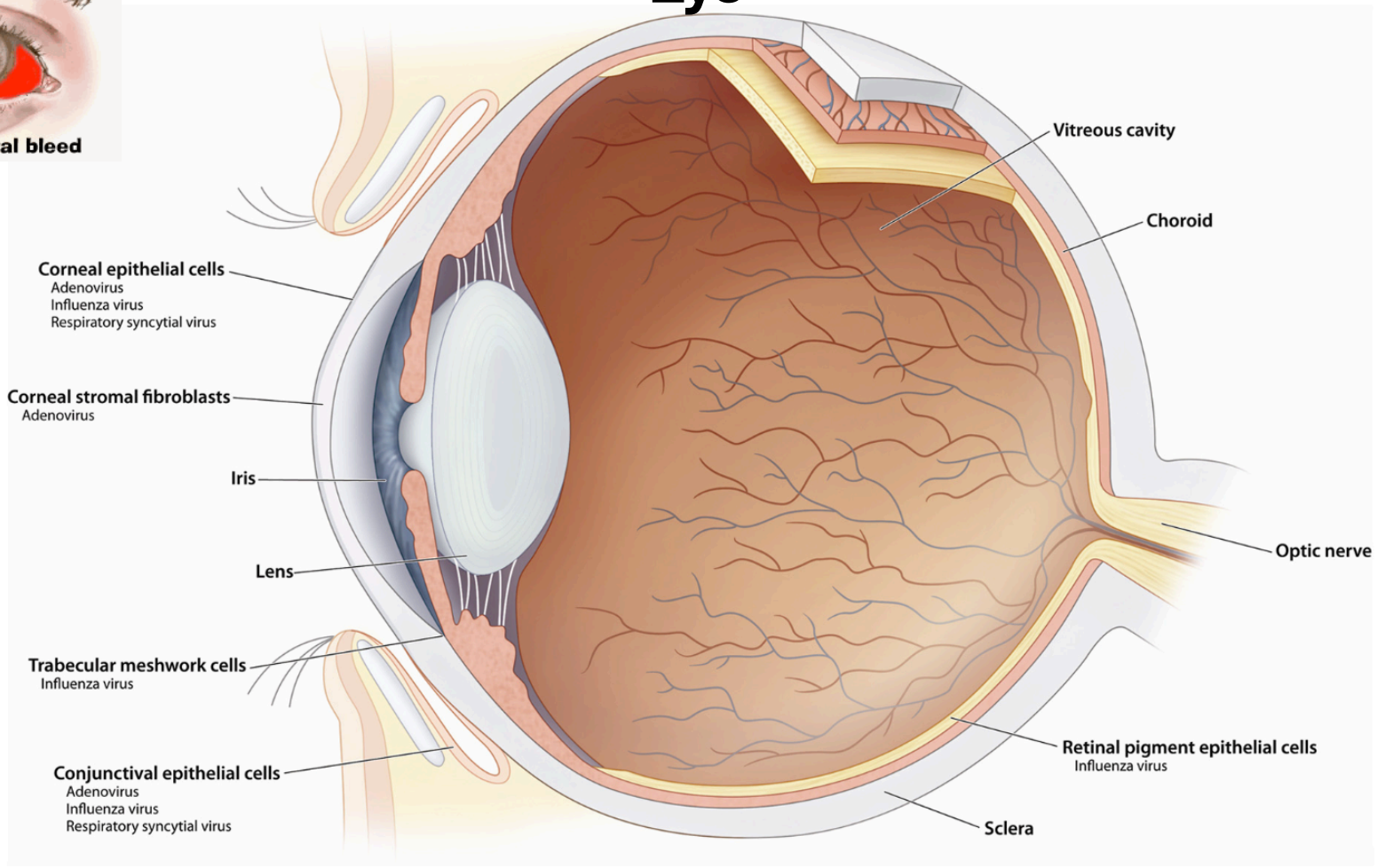
Urogenital tract

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



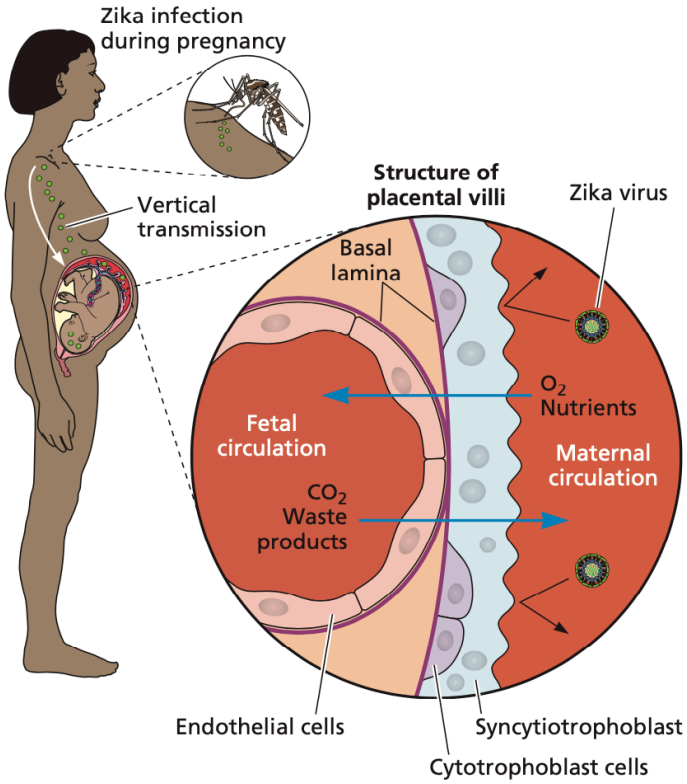


Eye



doi: 10.1128/MMBR .00058-12

The fetus



- Transplacental vs perinatal infection
- TORCH pathogens: Toxoplasma, rubella, cytomegalovirus, HIV, other
- Zika virus

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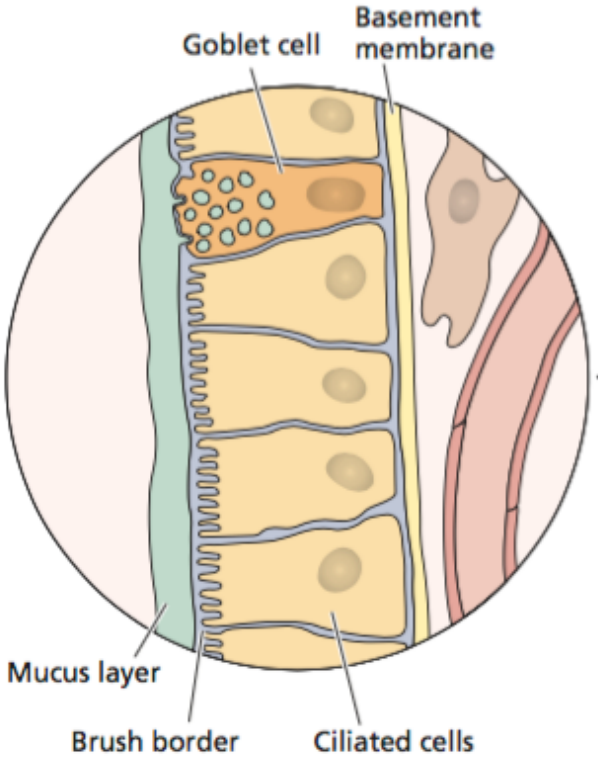
The outer layer of which of the following is dead but can still serve as a portal of virus entry?

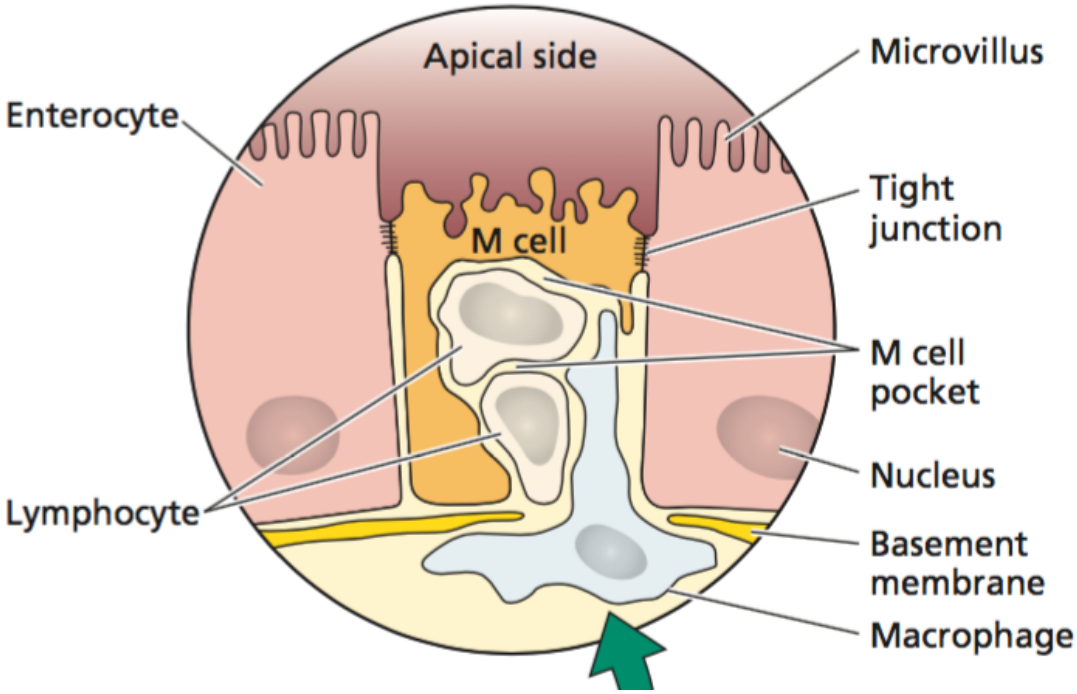
A. Respiratory tract
B. Alimentary tract
C. Eye
D. Skin
E. Urogenital tract

Viral spread

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

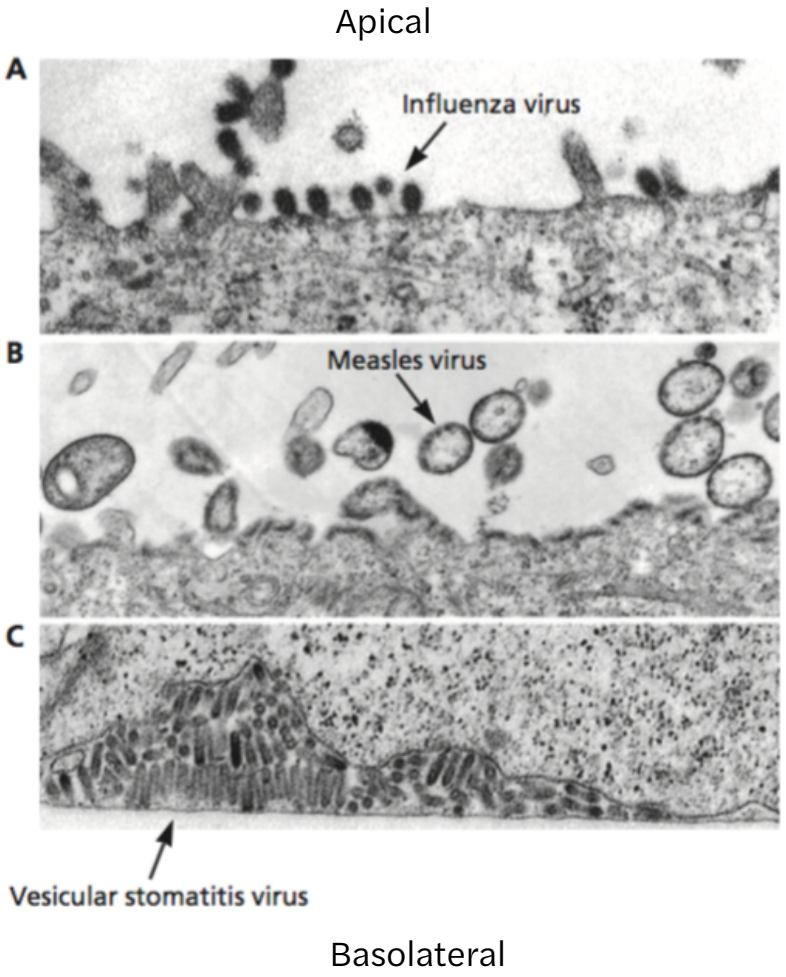


Viral spread

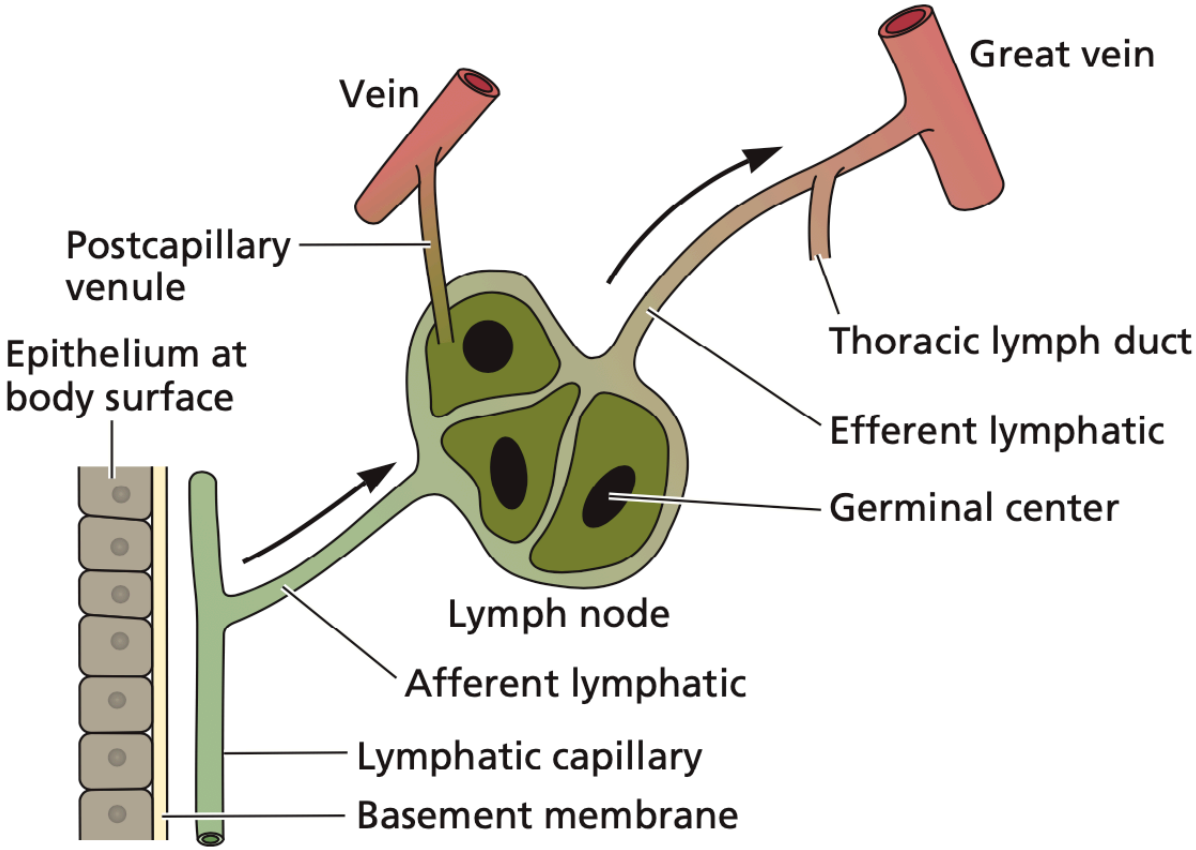


Viral spread

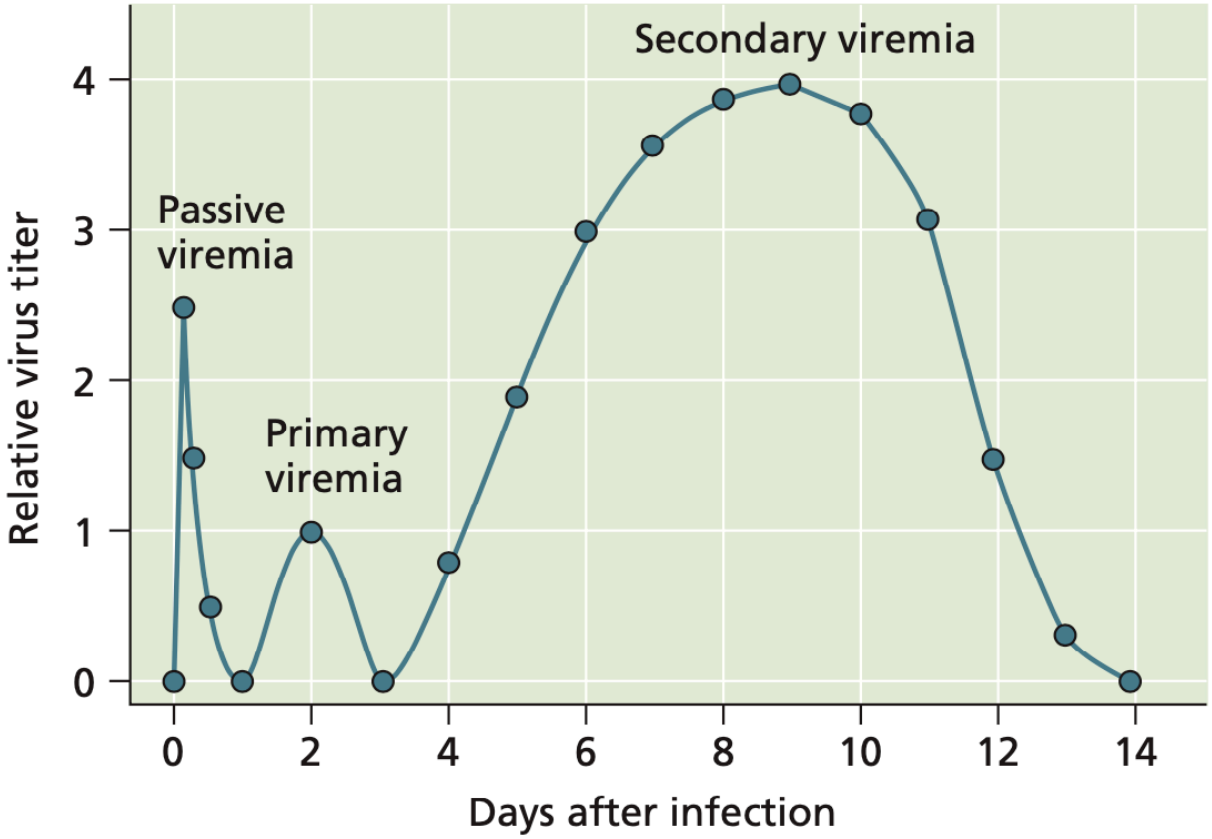
- Apical release facilitates virus dispersal (poliovirus)
- Basolateral release provides access to underlying tissues, may facilitate systemic spread
- Sendai virus



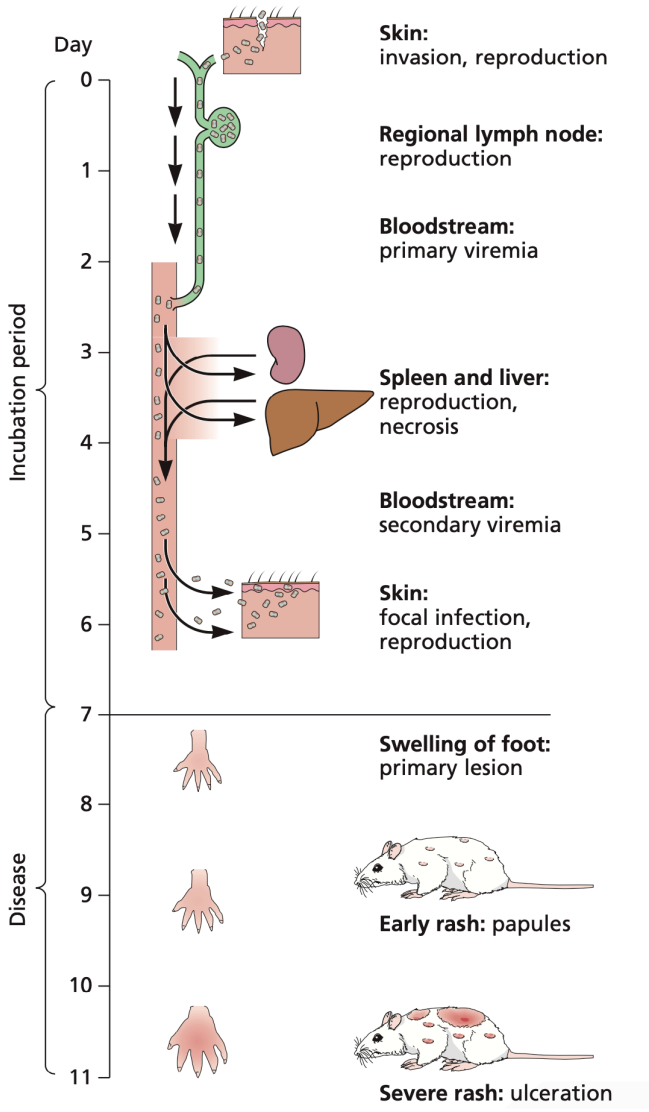
Hematogenous spread



Viremia

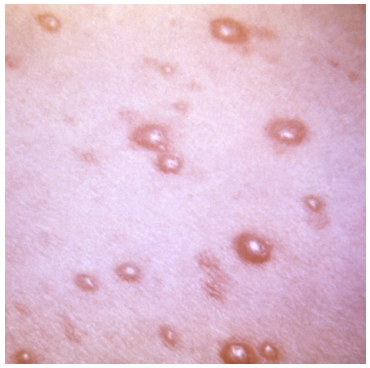


Pathogenesis of mousepox

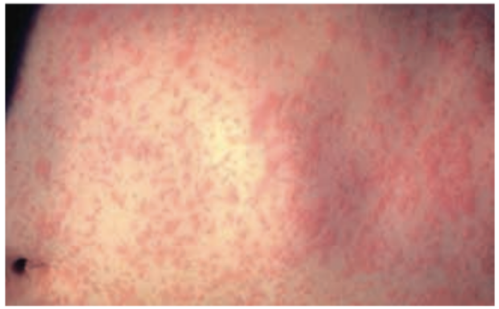


Viruses that cause skin rashes in humans

Virus	Disease	Features
Coxsackievirus A16	Hand-foot-and-mouth disease	Maculopapular rash
Measles virus	Measles	Maculopapular rash
Parvovirus	Erythema infectiosum	Maculopapular rash
Rubella virus	German measles	Maculopapular rash
Varicella-zoster virus	Chickenpox, shingles	Vesicular rash
Zika virus	ZIKV illness	Maculopapular rash

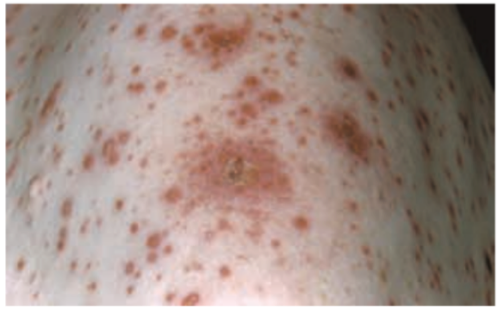


Measles



Smallpox

Chickenpox



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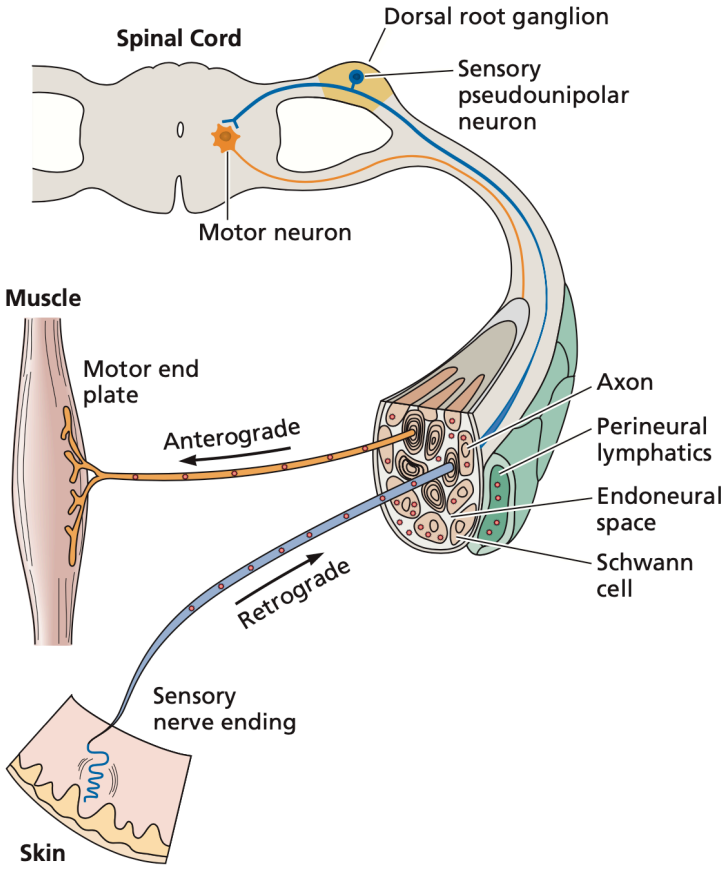
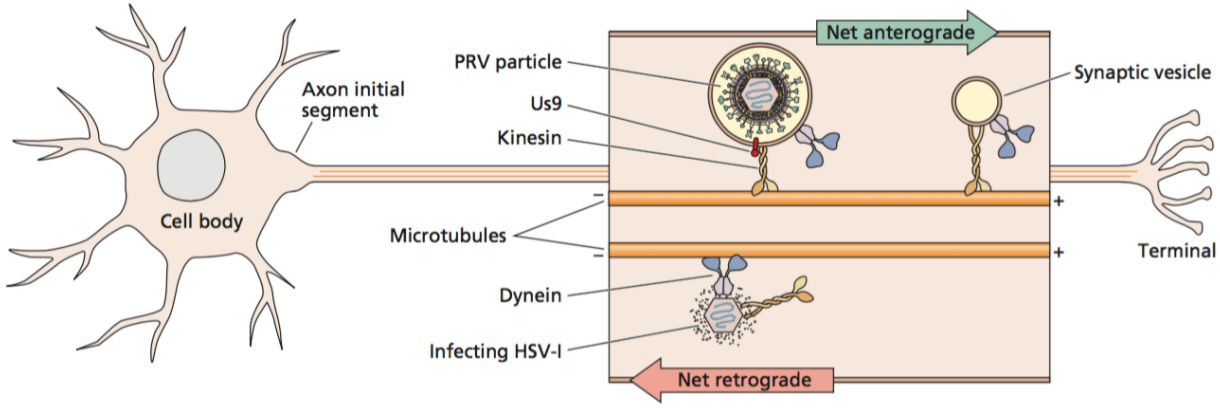
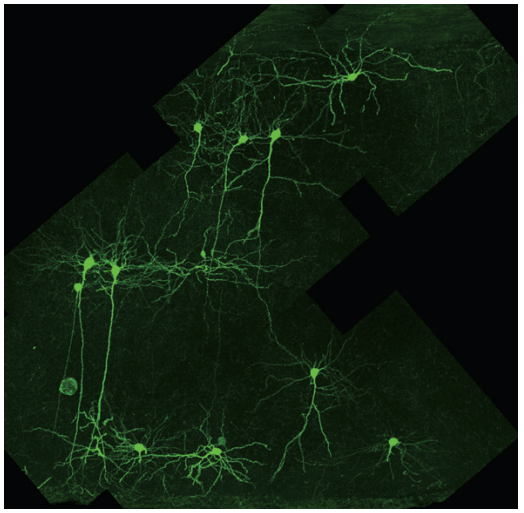
Which of the following assist in viral dissemination in the infected animal?

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

Neural spread



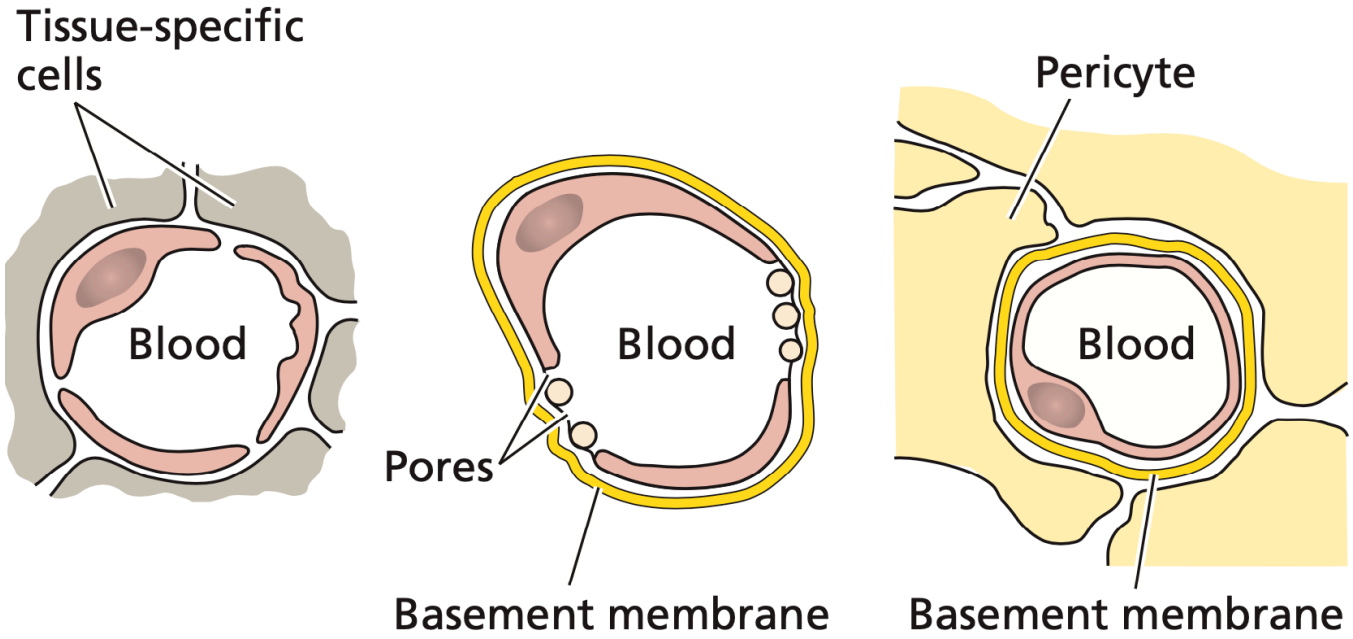




Infections of the CNS

- **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

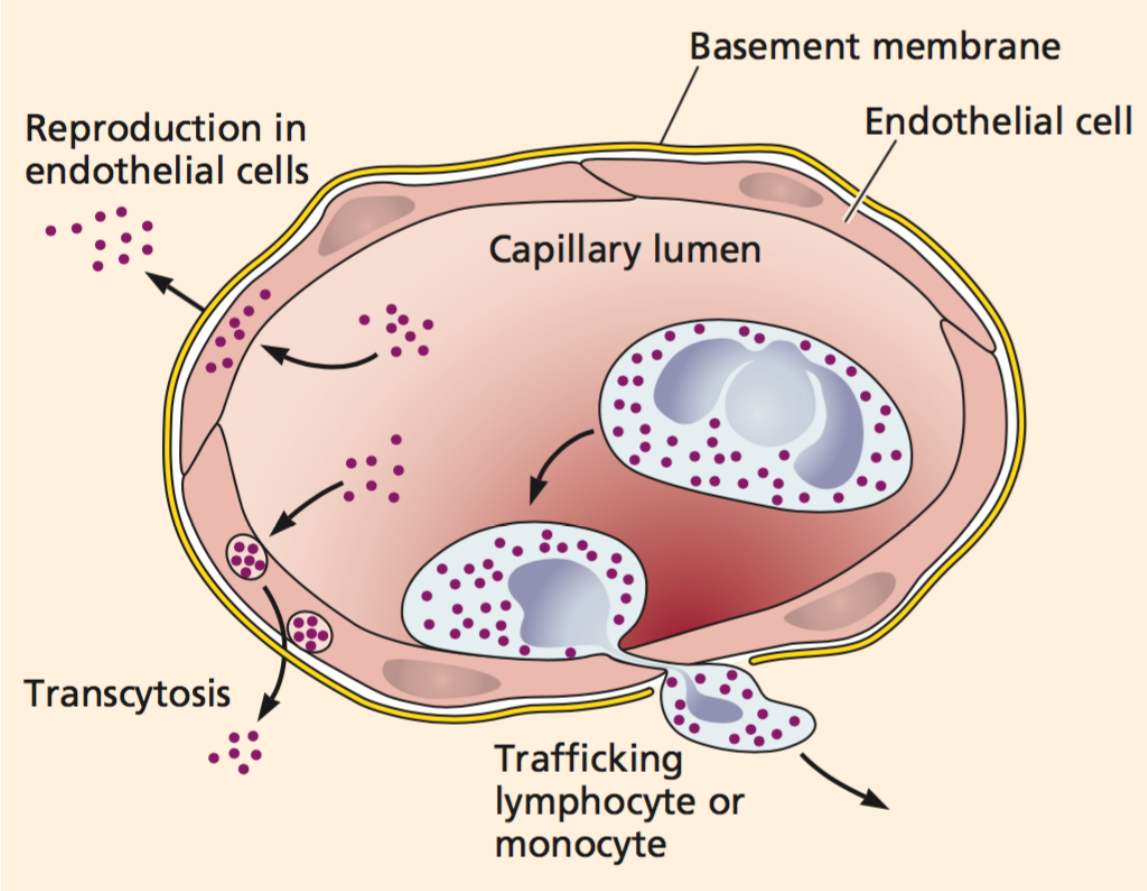
Venule
Intestine
Pancreas
Endocrine gland

Renal glomerulus, pancreas, ileum, colon

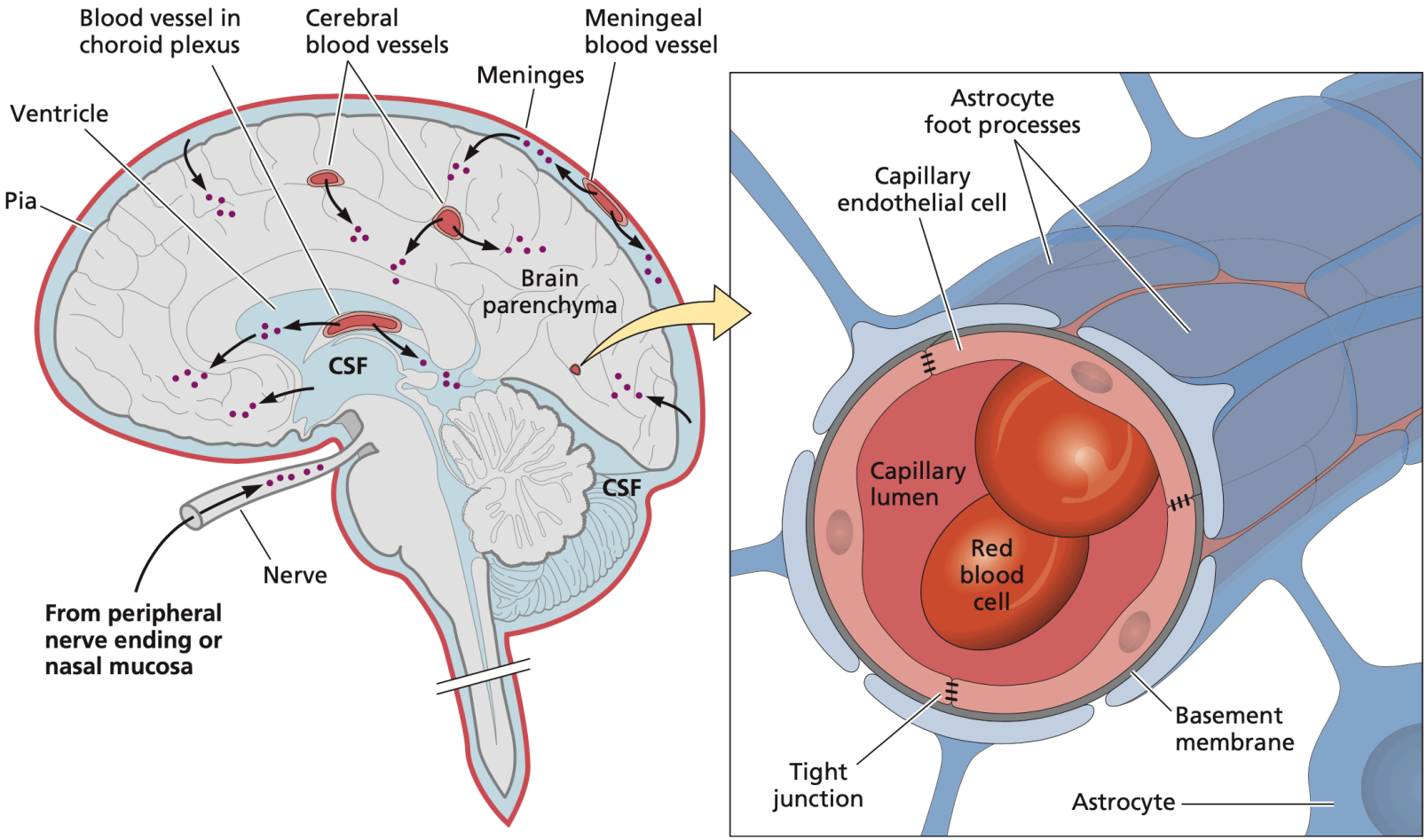
Capillary
CNS
Skeletal muscle
Lungs

Liver, spleen, bone marrow, adrenal glands

Tissue invasion: Traversing the basement membrane

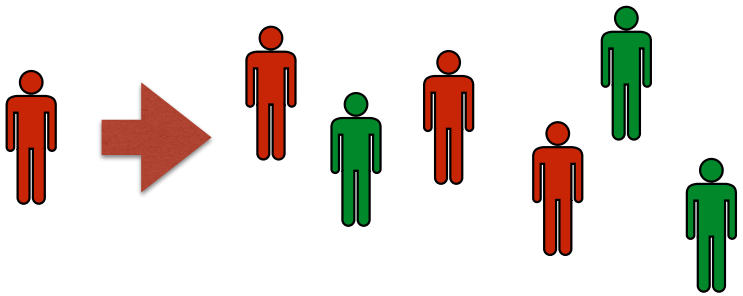


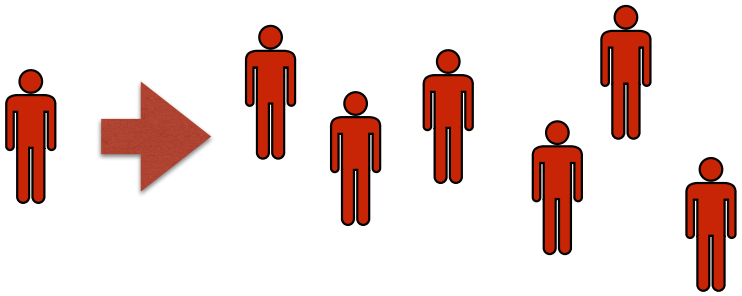
Virus entry into the central nervous system



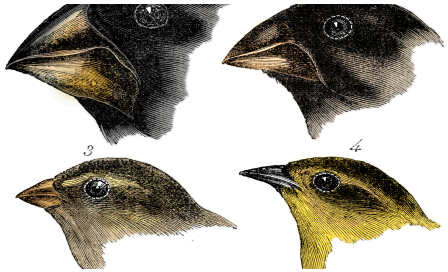
Transmission of infection

- Spread of infection from one susceptible host to another; required to maintain chain of infection
- Influenced by both *viral* properties and *host* behavior (R_0)
- Are SARS-CoV-2 variants of concern intrinsically more *transmissible*?
- Not proven: the human factor has not been considered
- Variants of concern are more FIT



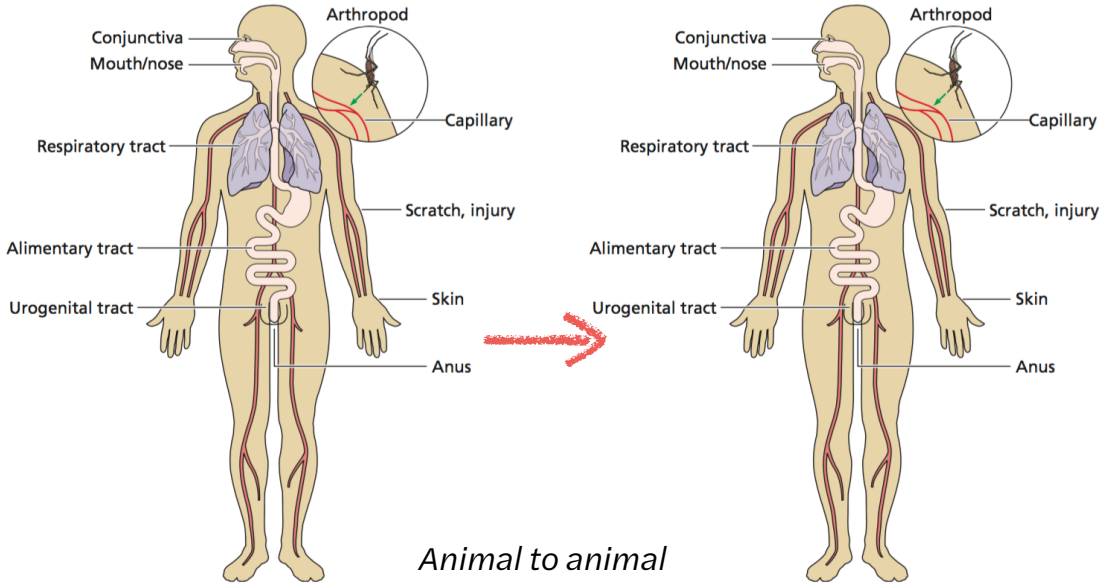


Often confused with transmission: Viral fitness

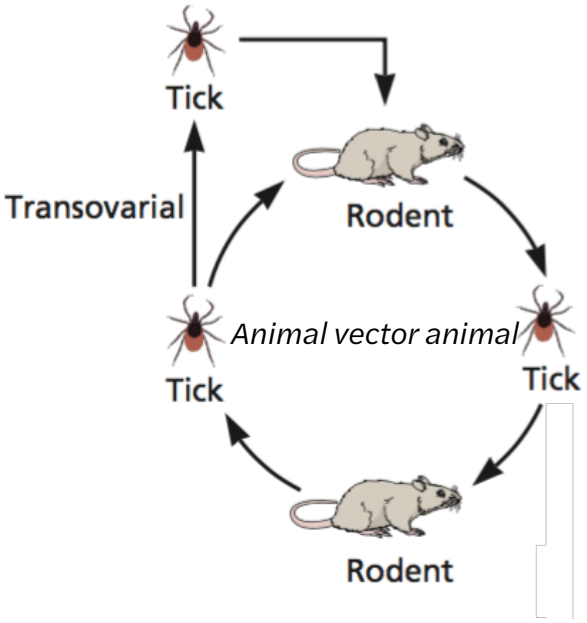


- Think Darwin's survival of the fittest
- Fitness also applies to viruses
- Viral fitness can be influenced by many factors, including transmission, levels of reproduction, particle stability, immune evasion
- Variants of concern are more fit: they displace previous variants
- Influenza virus antigenic variants arise each year that are more fit, not more transmissible

Two general patterns of transmission

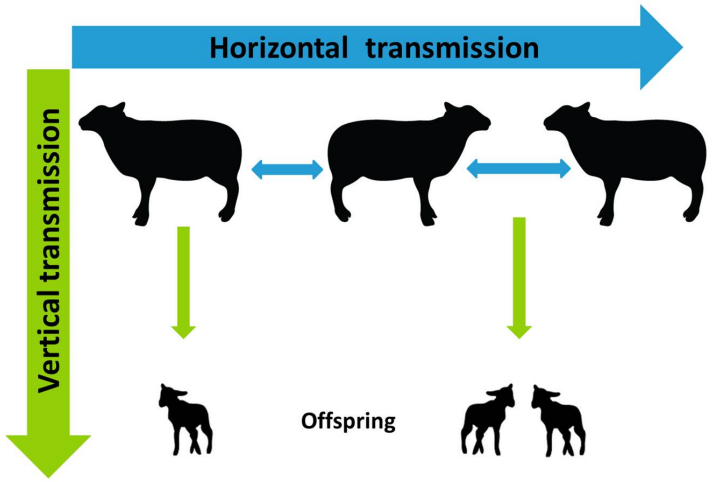


Animal to animal



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

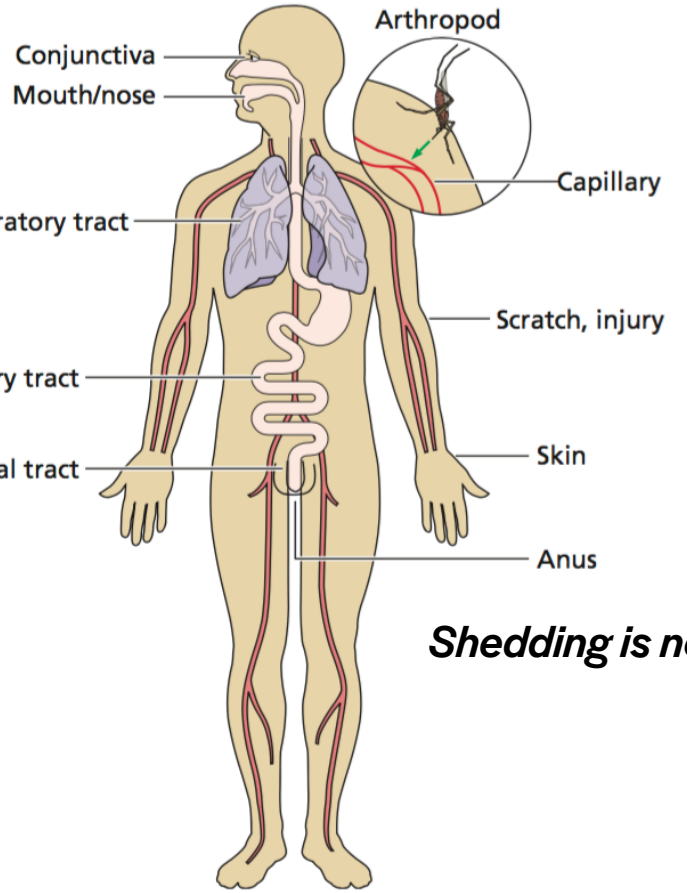
Respiratory secretions

Mucosal shedding

Urine

Semen

Feces



Skin lesions

Blood

Shedding is not always needed for transmission!

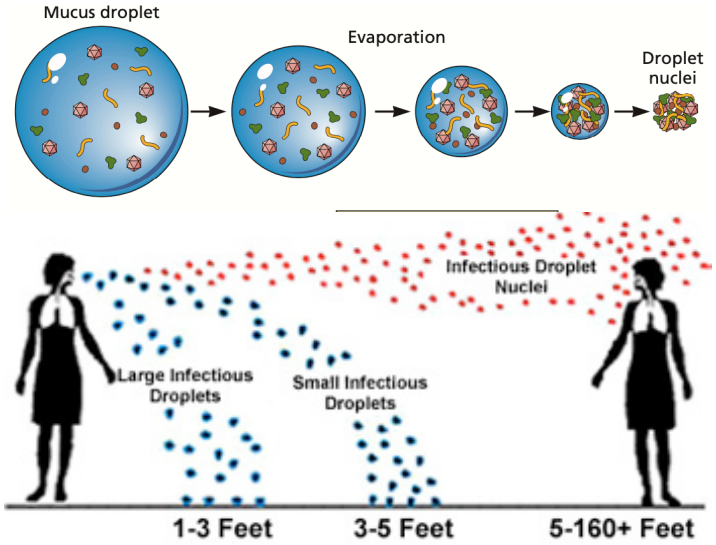
Blood supply

Insect vectors

Germline

Vertical* (Mother to baby)

Virus shedding



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

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

Gesundheit-II

TWiV 480: The PFU in your achoo

http://www.microbe.tv/twiv/twiv-480/

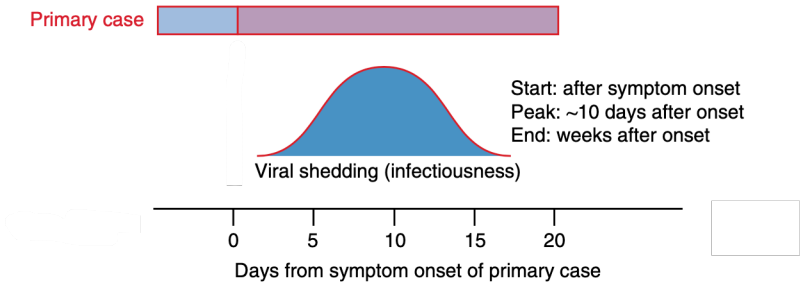
- 156 individuals in college community with confirmed influenza
- Infectious virus shedding in fine aerosols produced by breathing, speaking
- Sneezing does not make important contribution to virus shedding in aerosols
- Coughing not necessary for infectious aerosol generation

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

Viral shedding and transmissibility

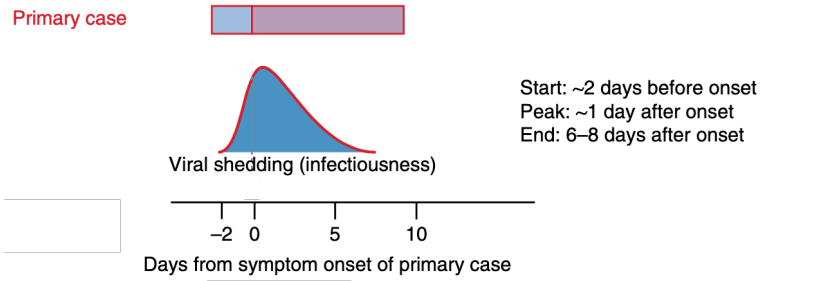
SARS 2003

Estimated incubation period: 4–5 days

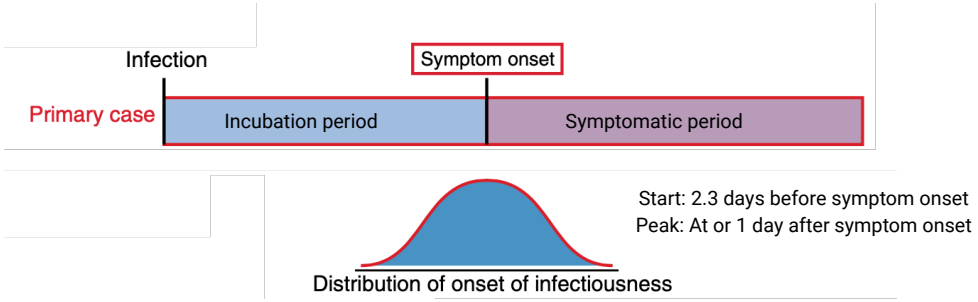


Seasonal influenza

Estimated incubation period: 2 days



Estimated incubation period: 14 days (5.2 avg)



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

https://doi.org/10.1038/s41591-020-0869-5

Go to:

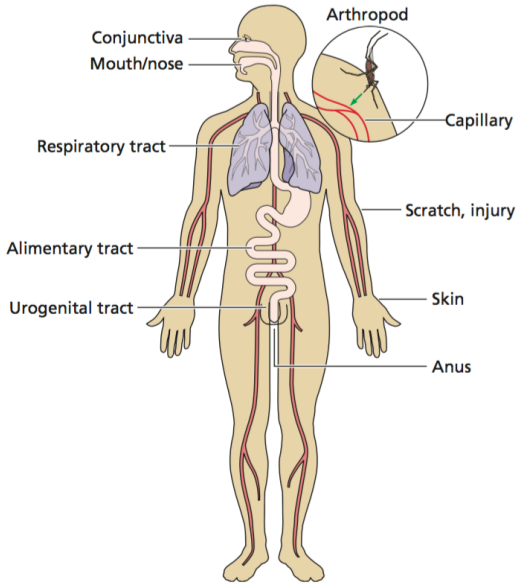
b.socrative.com/login/student
room number: virus

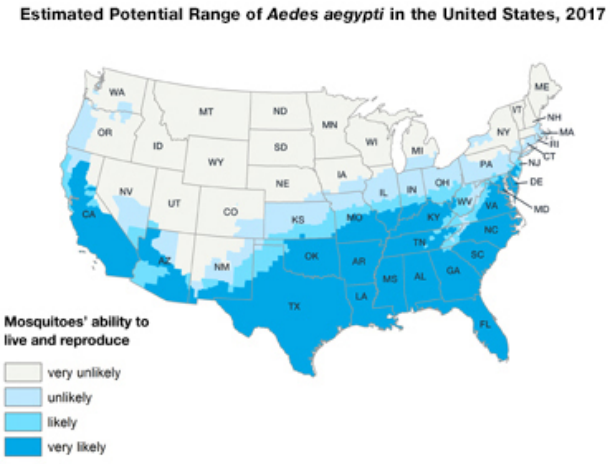
Which statement about viral transmission is not correct?

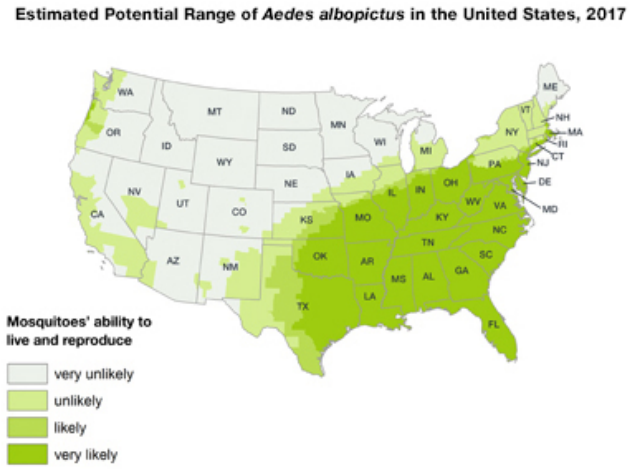
A. All virus infections are transmitted by shedding
B. The route is determined by the site of virus shedding
C. Transmission is required to maintain a chain of infection
D. Speaking can produce an aerosol that can transmit infection
E. Horizontal transmission is among members of one species

Influence of geography

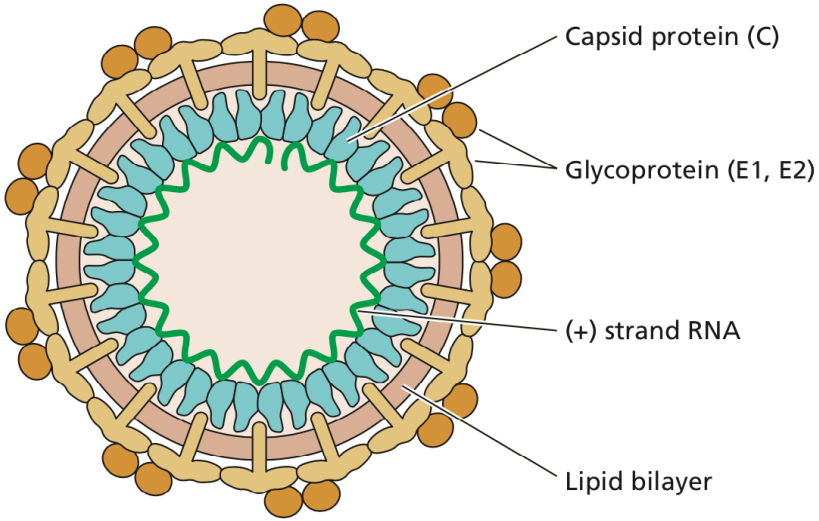
- Geography may restrict presence of virus - requirement for specific vector or animal reservoir
- Chikungunya virus - how vector can affect localization of viral infection







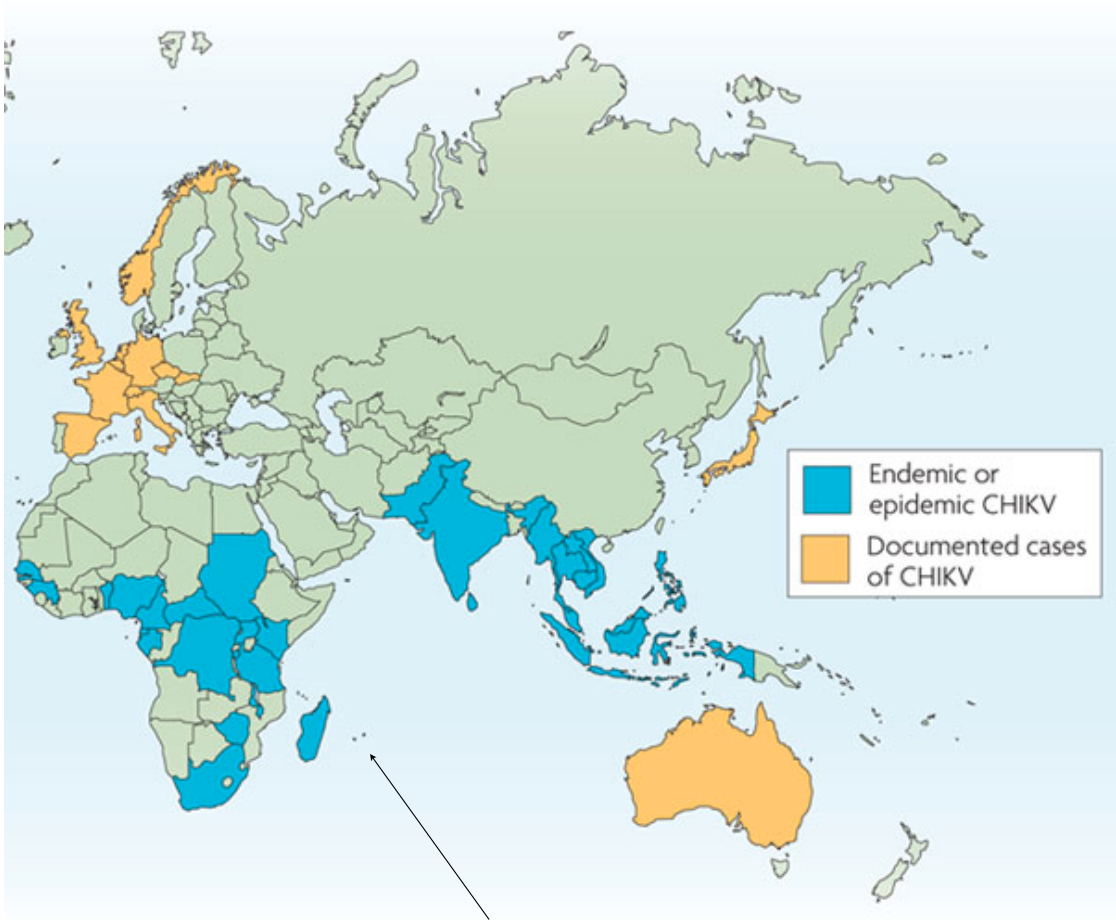
Chikungunya virus



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

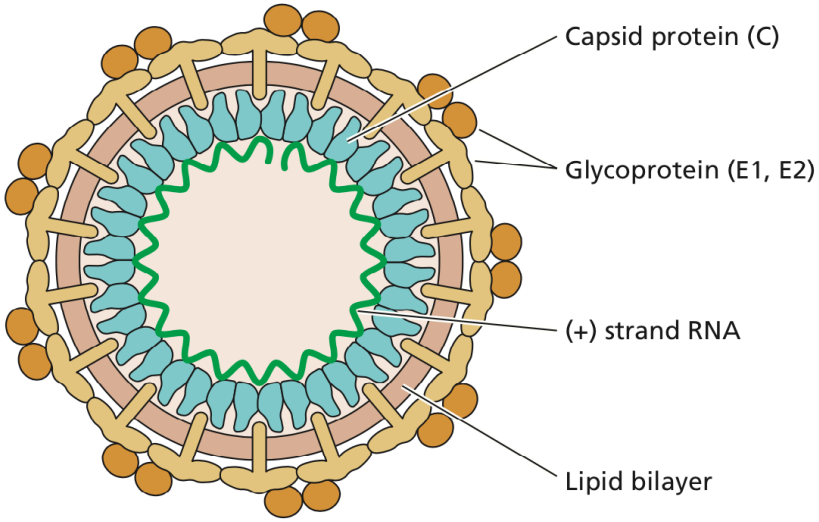
Chikungunya virus

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



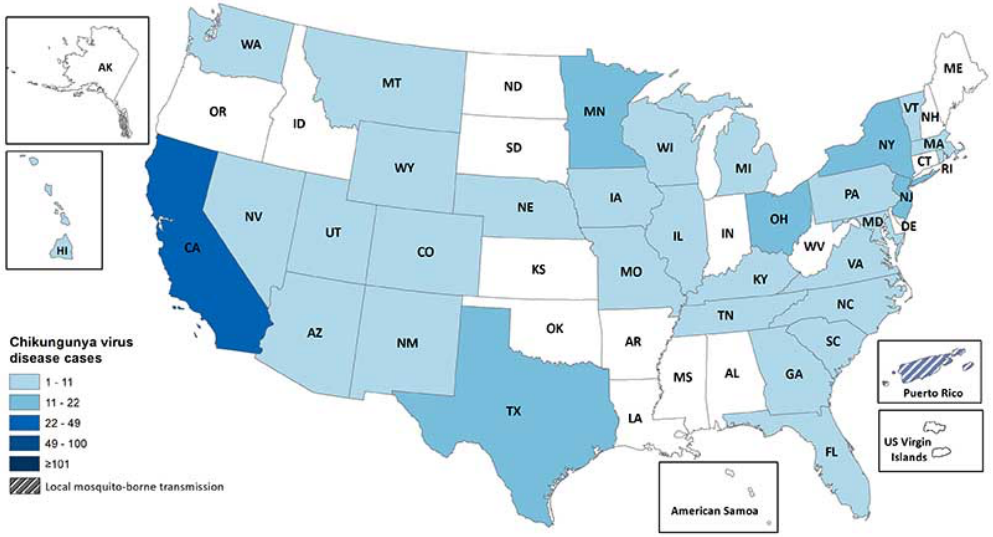
Réunion

Chikungunya virus



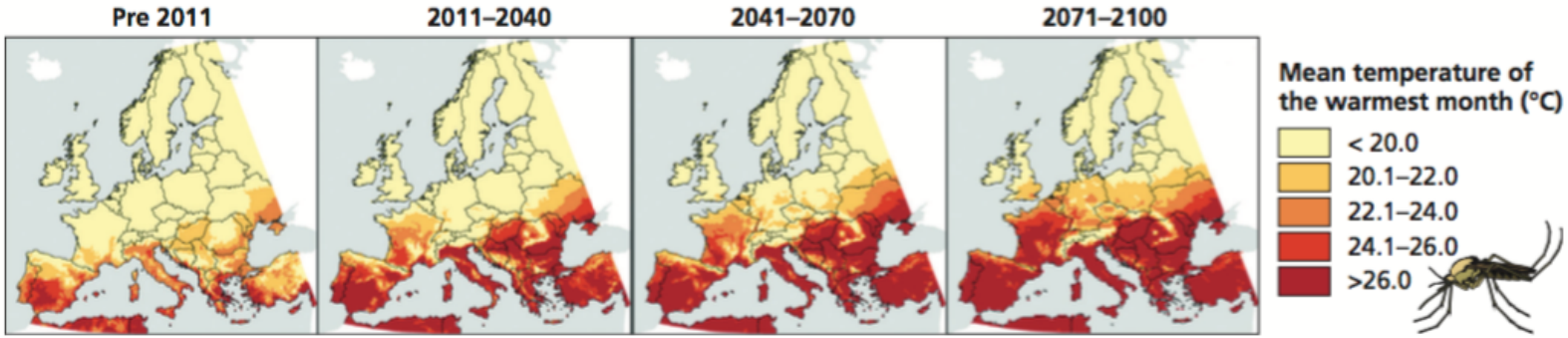
- Recent outbreaks associated with *Aedes albopictus*
- One amino acid change in viral E1 glycoprotein

Chikungunya virus infections, US 2017

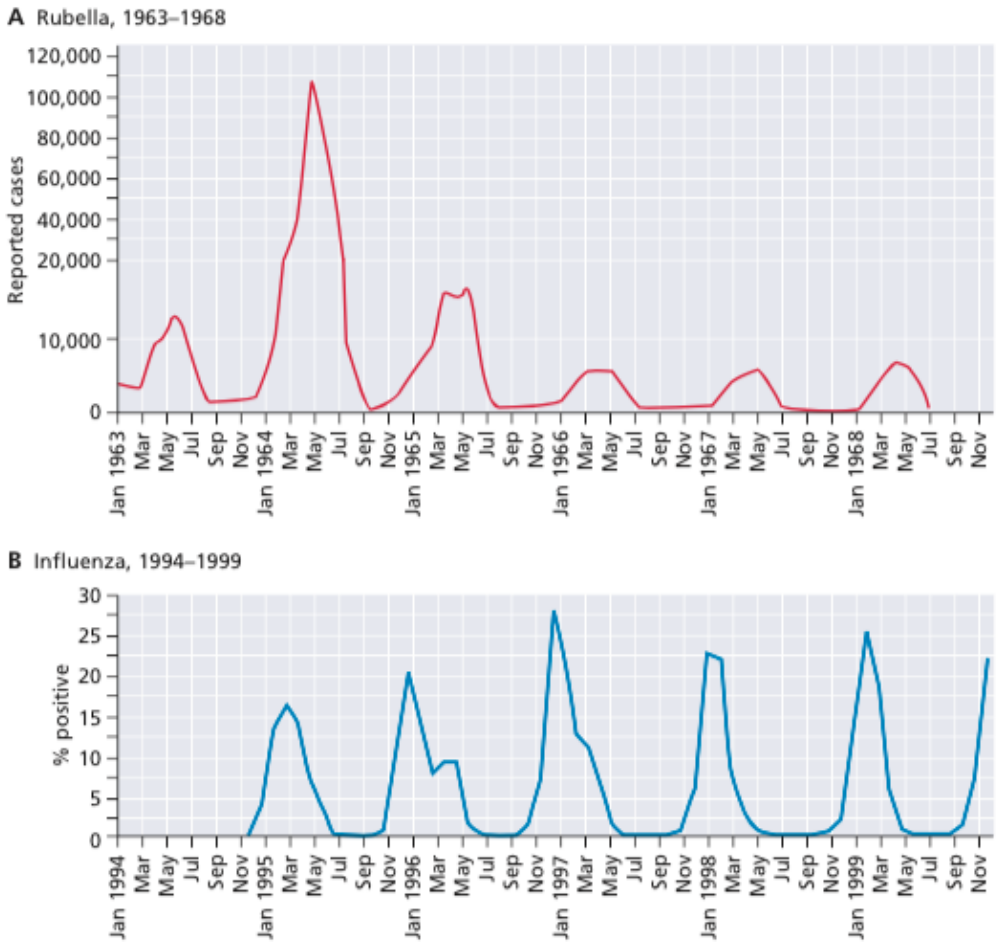


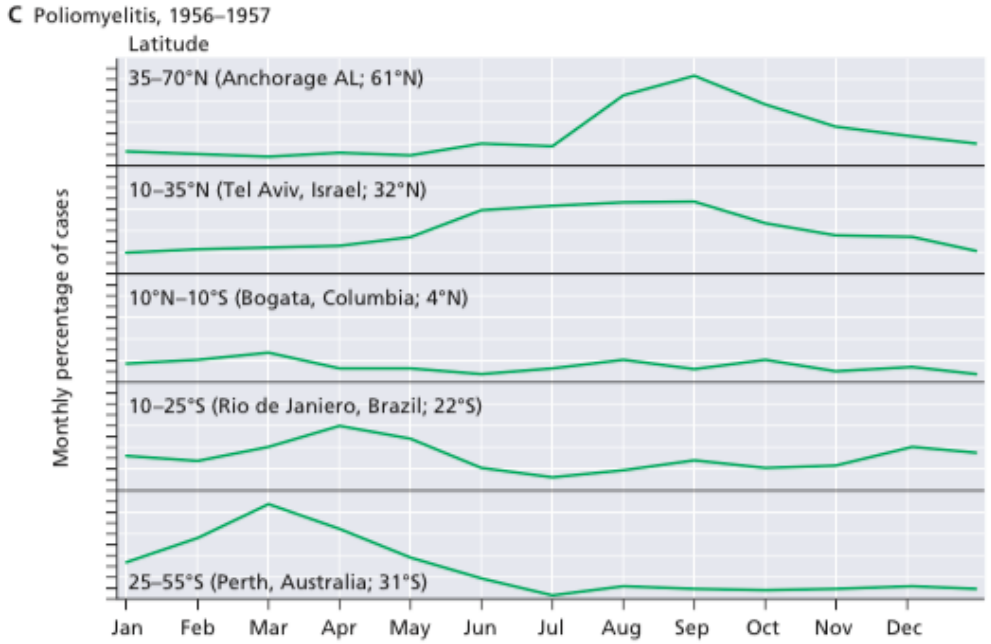
192 imported cases
2 local transmission PR
(rare before 2006)

A. albopictus range

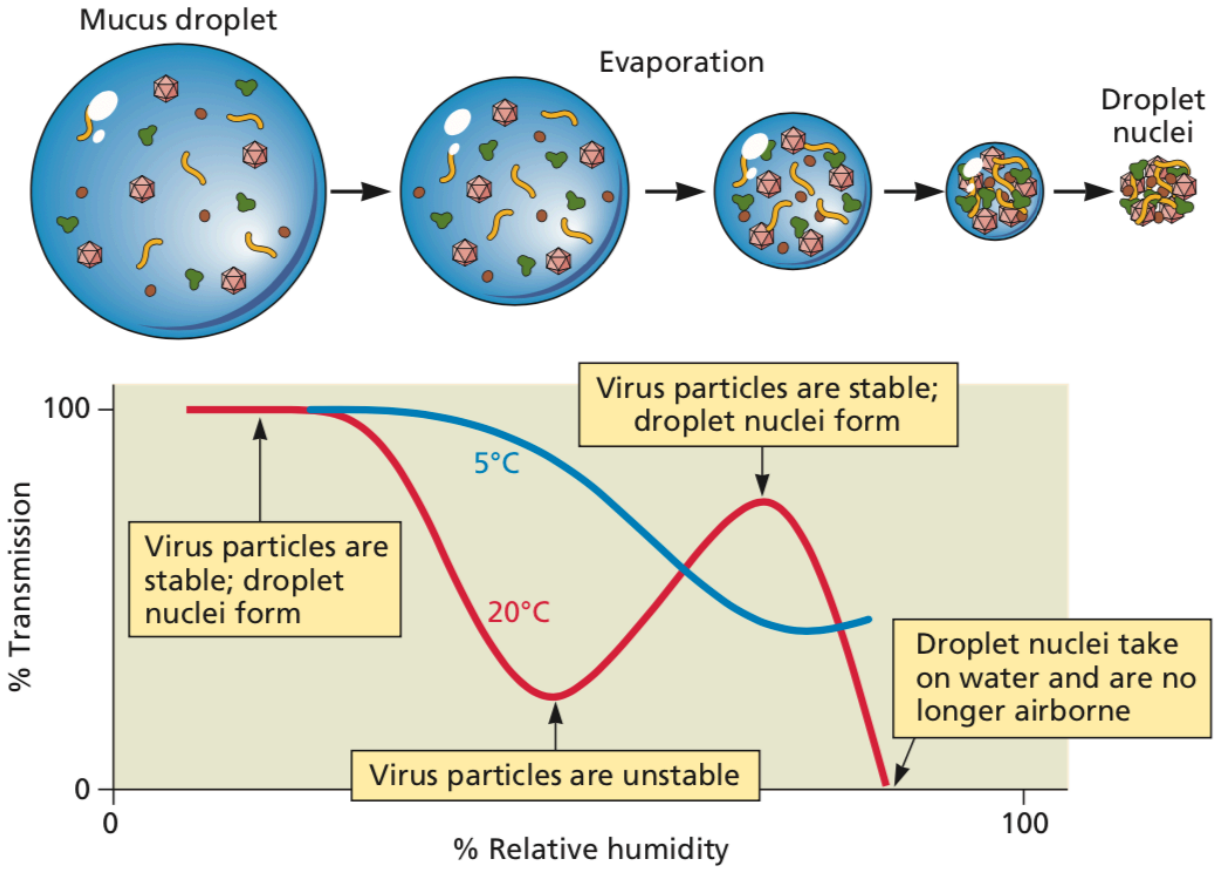


Seasonality of virus infections





Temperature and humidity influence influenza virus transmission



Next time: Host defenses