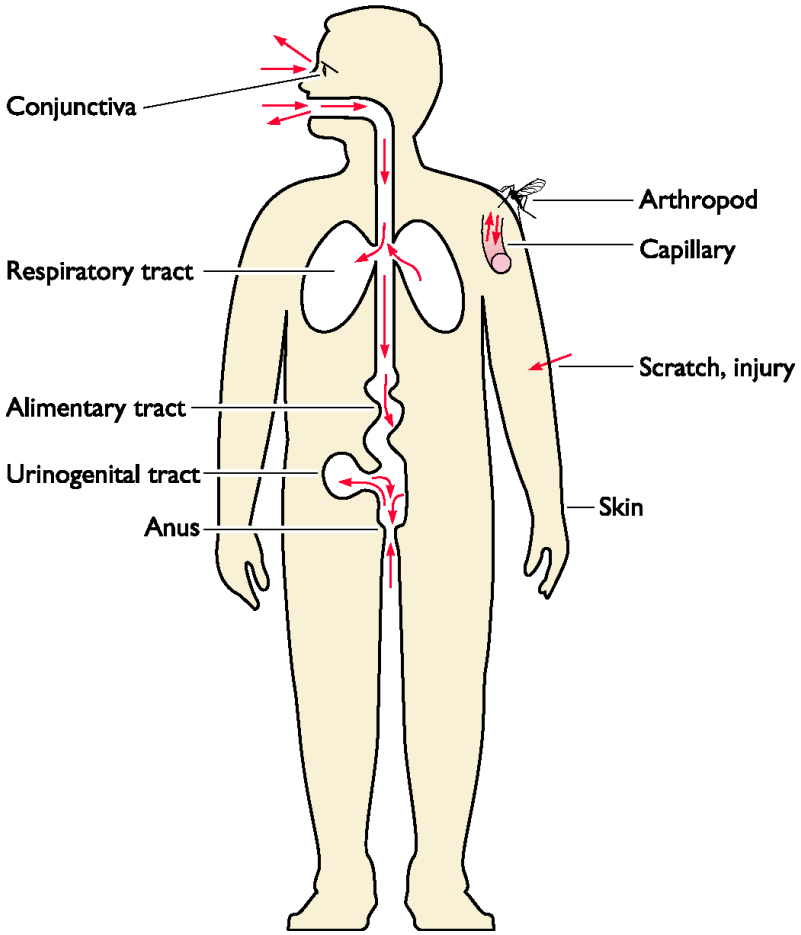
PATHOGENESIS OF VIRAL INFECTIONS

Virus Dissemination - Entry

Figure 17.1 Sites of virus entry into the host. A representation of the human host is shown with sites of virus entry and shedding indicated. The body is covered with skin, which has a relatively impermeable (dead) outer layer, but it cannot cover the entire body. Layers of living cells must be present to absorb food, exchange gases, and release urine and sexual products. These layers offer easier pathways for the entry of viruses than the skin does. Viruses can also be introduced through the skin by a scratch or injury, a vector bite, or inoculation with a needle.



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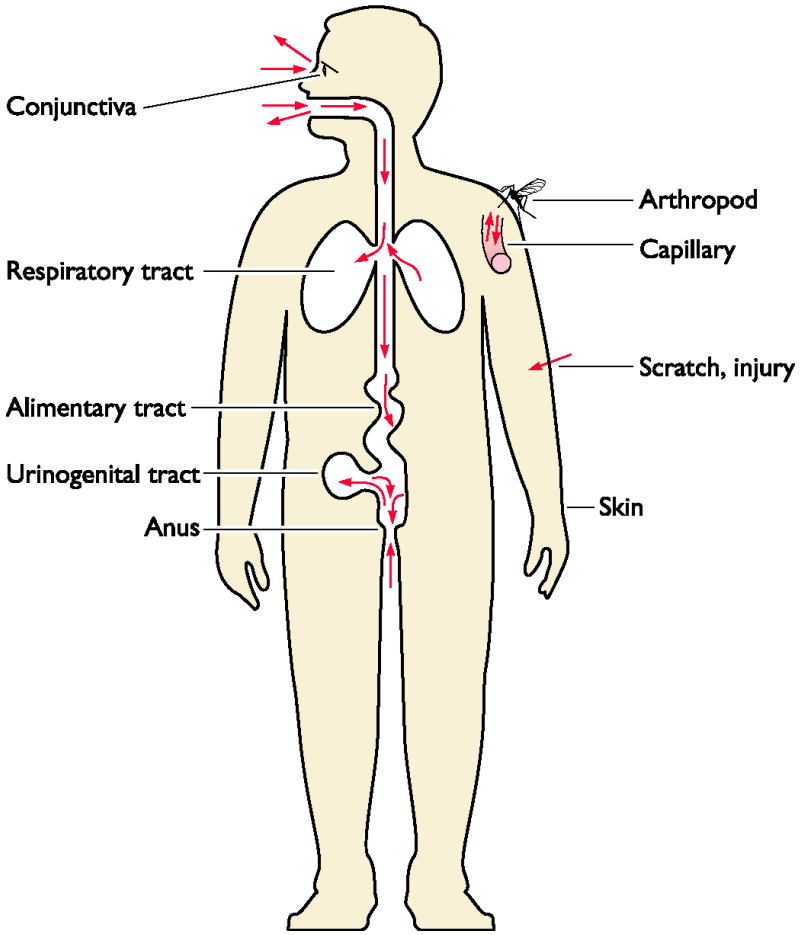

The respiratory route is the most common and more difficult to control

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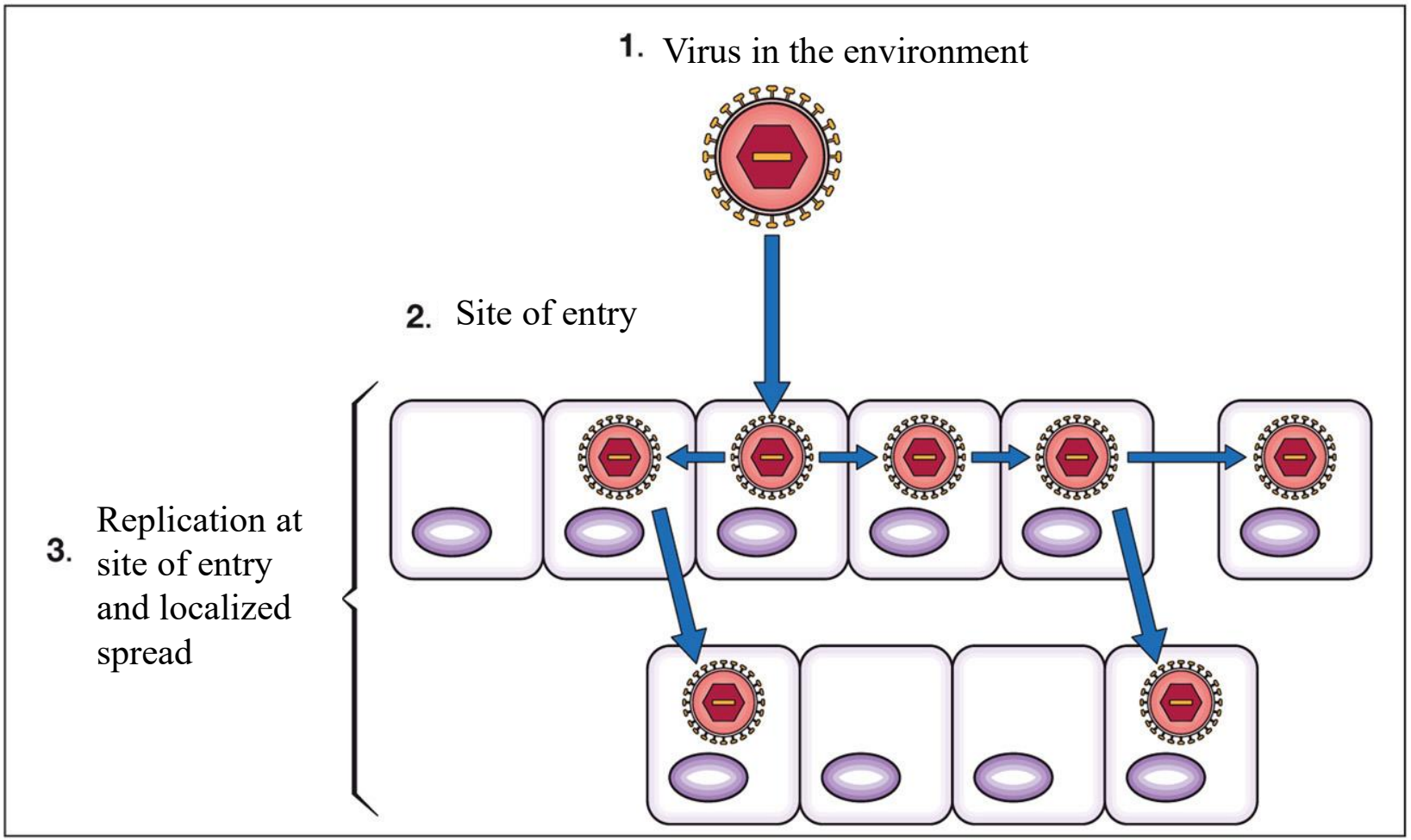
Virus spread during localized infection



Virus spread during localized infection

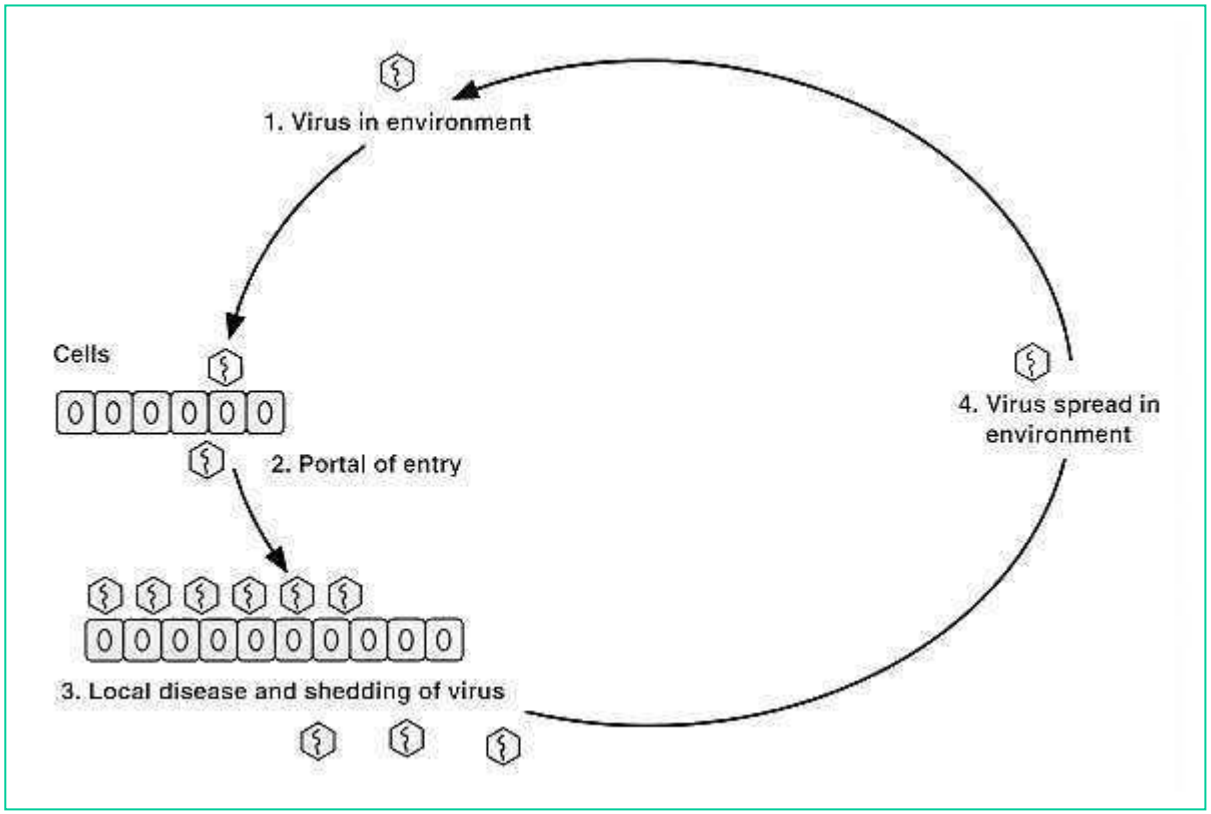
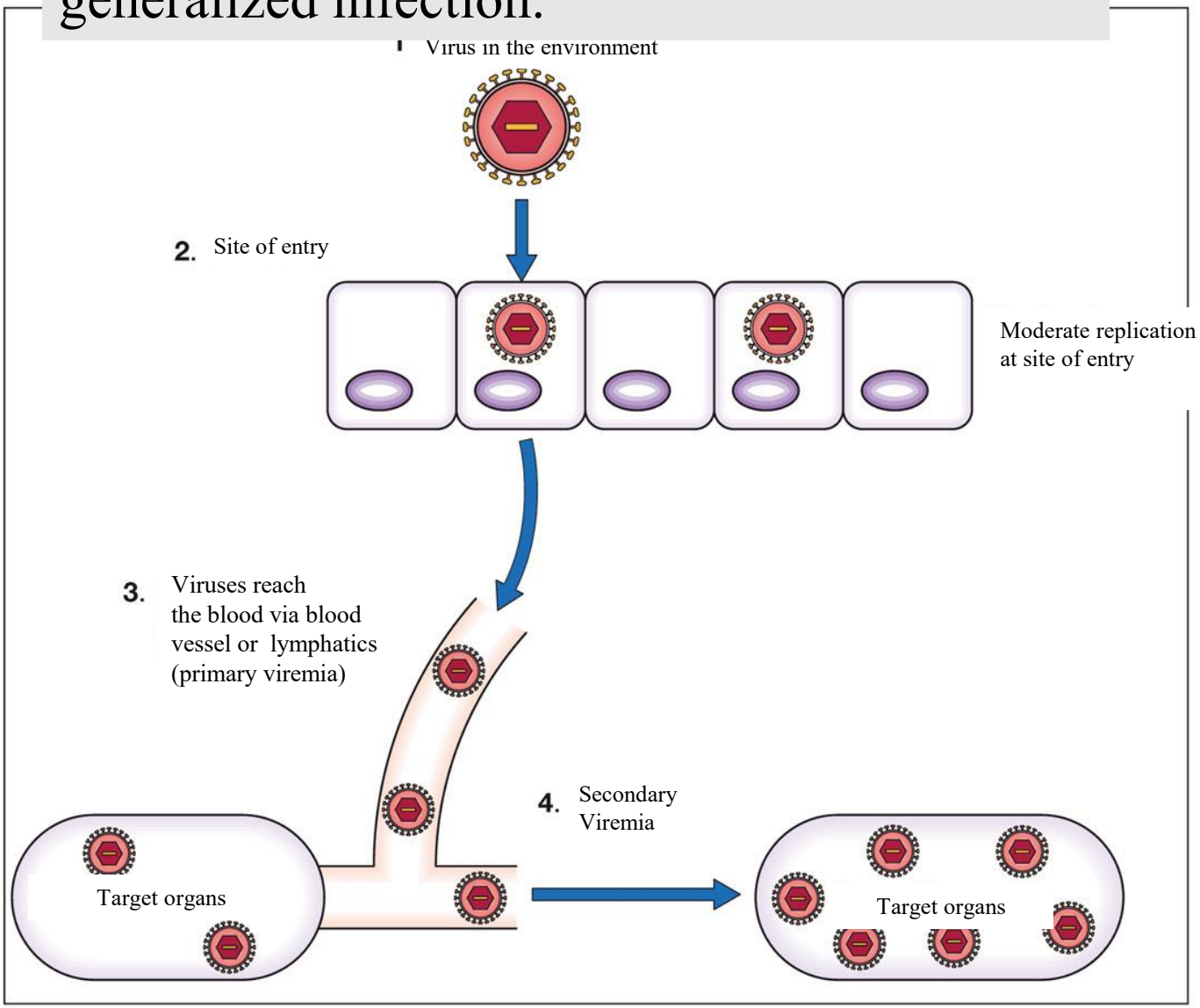


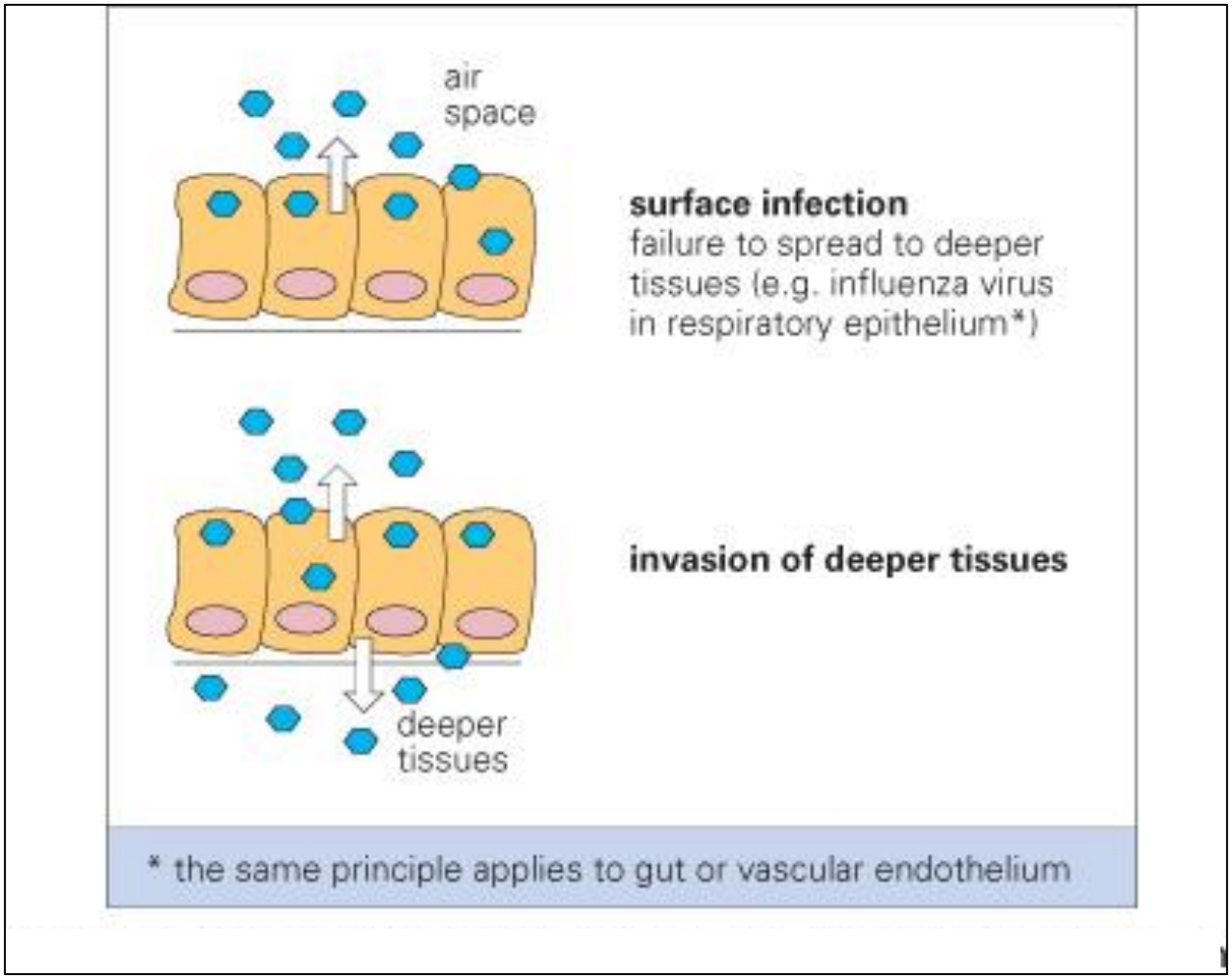
TABLE 45-1 Pathogenesis of Selected Virus Infection: Localized Infections

Disease	Site of Implantation	Route of Spread	Target Organ	Site of Shedding
Influenza	Respiratory tract	Local	Respiratory tract	Respiratory tract
Coryza	Respiratory tract	Local	Respiratory tract	Respiratory tract
Gastroenteritis	Alimentary tract	Local	Alimentary tract	Alimentary tract
Warts	Skin and mucosa	Local	Skin and mucosa	Skin and mucosa

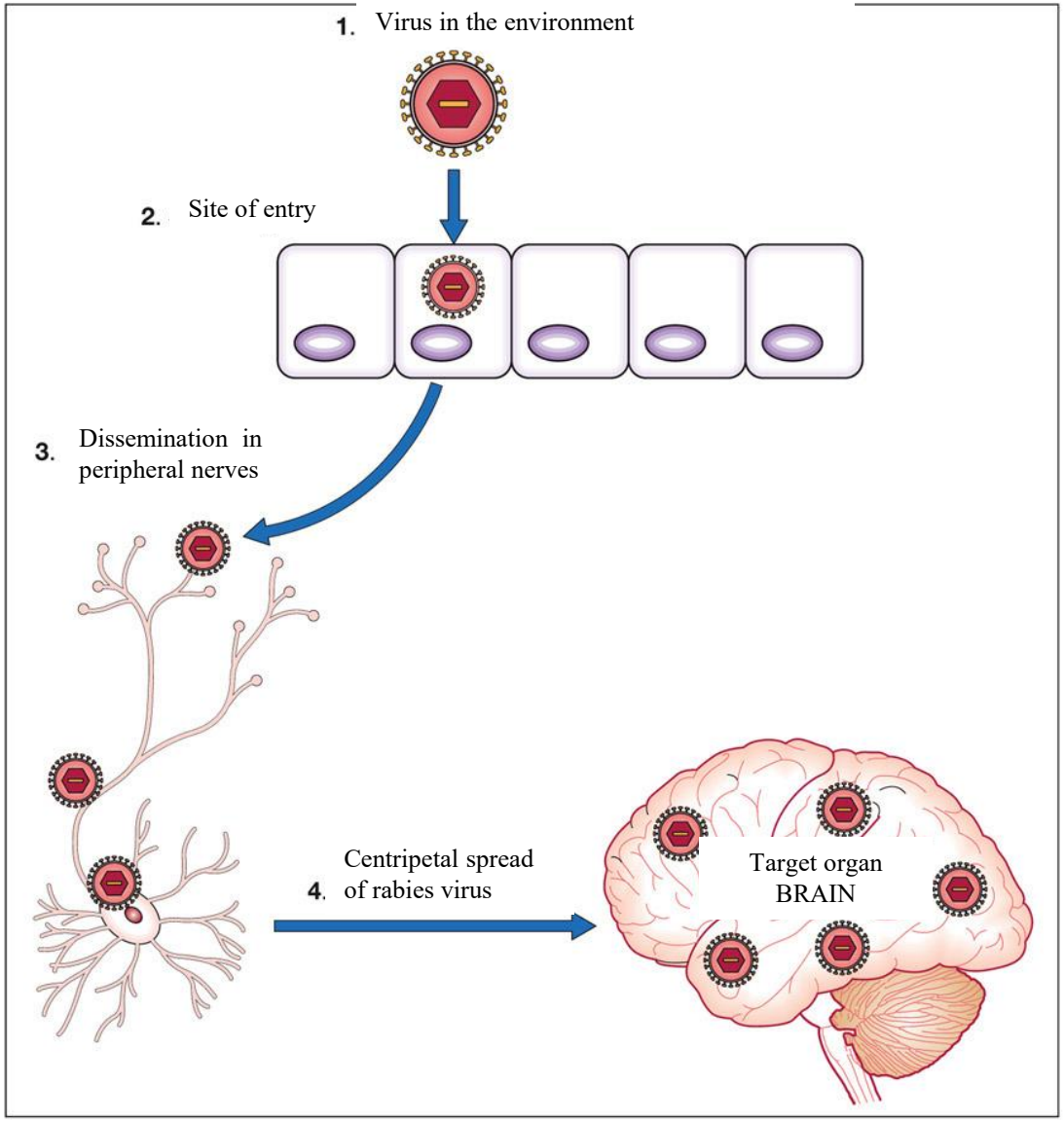
Virus spread through bloodstream during a generalized infection.



Topography of virus release from epithelial surfaces can determine the pattern of infection.



Virus spread through nerves during a generalized infection



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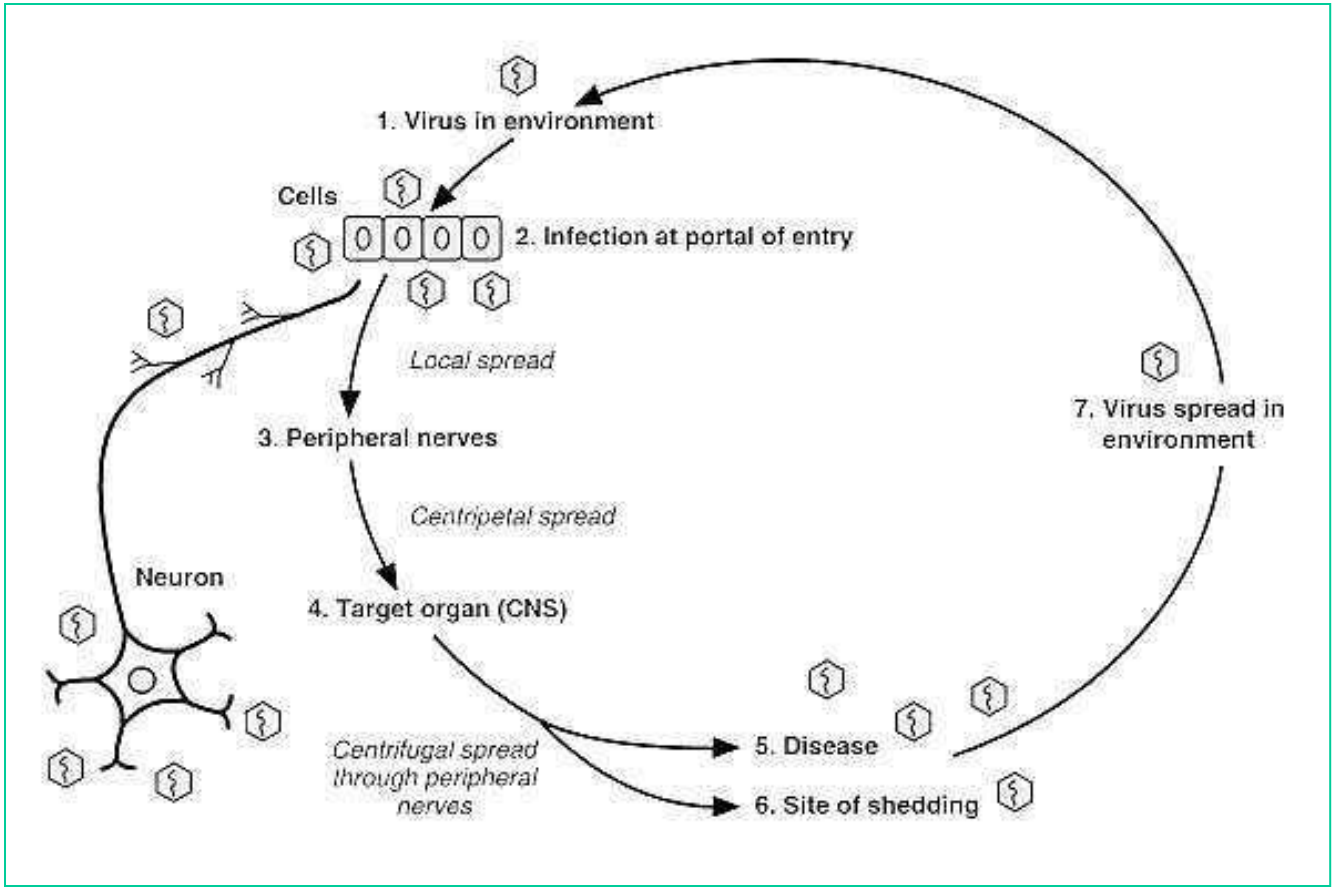
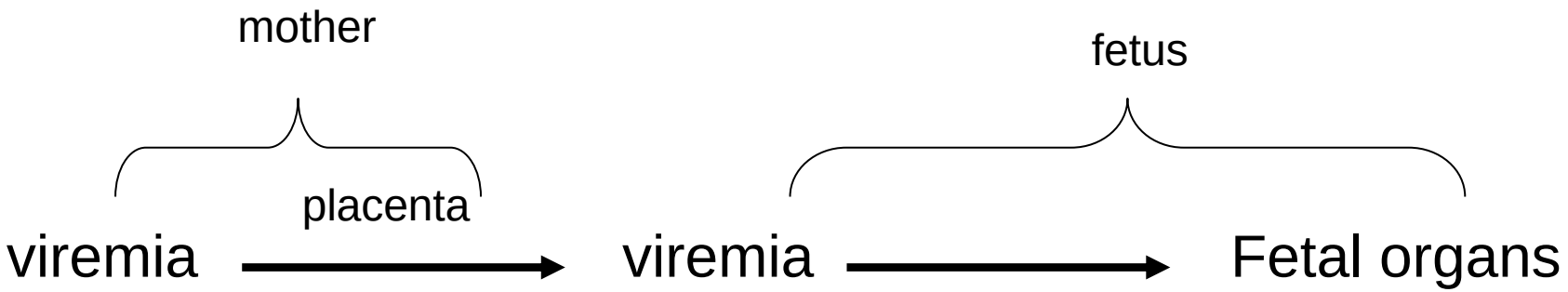


TABLE 45-2 Pathogenesis of Selected Virus Infections: Disseminated Infections

Disease	Common Site of Implantation	Route of Spread	Target Organ(s)	Site of Shedding
Poliomyelitis	Alimentary tract	Blood (nerves)	Central nervous system	Alimentary tract
Hepatitis A	Alimentary tract	Blood	Liver	Alimentary tract
AIDS	Injection, trauma, intestine	Blood	Immune system, brain	Blood, semen
Kuru	Alimentary tract	Blood	Brain	Brain (transmitted by ingestion)
Rubella	Respiratory tract	Blood	Skin, lymph nodes, fetus	Respiratory tract, excreta in newborn
Measles	Respiratory tract	Blood	Skin, lungs, brain	Respiratory tract
Chickenpox	Respiratory tract	Blood, nerves (to site of latency)	Skin, lungs	Respiratory tract, skin
Herpes simplex type 1				
Acute	Respiratory tract	Nerves, leukocytes	Many (e.g., brain, liver, skin)	Respiratory tract, epithelial surfaces
Recurrent	Ganglion	Nerves (to site of latency)	Skin, eye	Skin, eyes
Rabies	Subcutaneously (bite)	Nerves	Brain	Salivary glands
Arbovirus infection	Subcutaneously (bite)	Blood	Brain and others	Lymph and blood (via insect bite)
Hepatitis B	Penetration of skin	Blood	Liver	Blood
Herpes simplex type 2	Genital tract	Nerves (to site of latency)	Genital tract	Genital tract

Pathogenesis /congenital infection

- **Immature immune system**
- **The cells are in an active proliferation state and then highly permissive to the replication of viruses**
- **The cells are not differentiated and then more sensitive to the viral infections**



Virus spread

- Infections can be localized, or can spread beyond the initial site of replication *(a disseminated infection)*.
- With many organs involved the infection becomes *systemic*

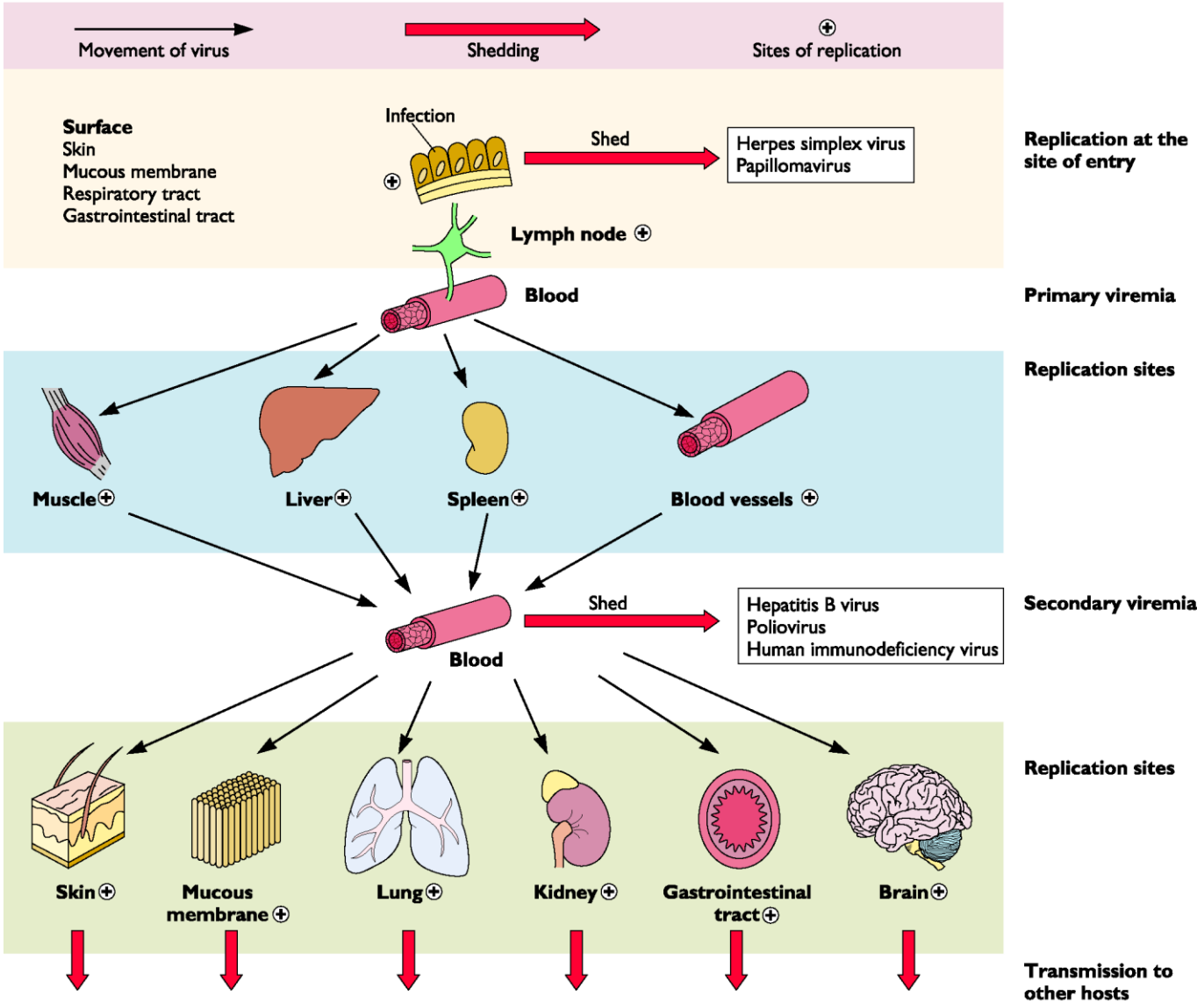


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Table 45-4 Incubation Periods of Common Viral Infections

Disease	Incubation Period (Days)*
Influenza	1-2
Common cold	1-3
Herpes simplex	2-8
Bronchiolitis, croup	3-5
Acute respiratory disease (adenoviruses)	5-7
Dengue	5-8
Enteroviruses	6-12
Poliomyelitis	5-20
Measles	9-12
Smallpox	12-14
Chickenpox	13-17
Mumps	16-20
Rubella	17-20
Mononucleosis	30-50
Hepatitis A	15-40
Hepatitis B	50-150
Rabies	30-100+
Papilloma (warts)	50-150
Human immunodeficiency virus	1-15 years

Table 45-2 Pathogenesis of Selected Virus Infections: Disseminated Infections

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Acute	Respiratory tract	Nerves, leukocytes	Many (e.g., brain, liver, skin)	Respiratory tract, epithelial surfaces
Recurrent	Ganglion	Nerves (to site of	Skin, eye	Skin, eyes

- Because of the diversity of viruses, virtually every possible site of shedding is utilized; however, the most frequent sites are the respiratory and alimentary tracts. Blood and lymph are sites of shedding for the arboviruses, since biting insects become infected by this route. HIV is shed in blood and semen. Milk is a site of shedding for viruses such as some RNA tumor viruses (retroviruses) and cytomegalovirus (a herpesvirus). Several viruses (e.g., cytomegaloviruses) are shed simultaneously from the urinary tract and other sites more commonly associated with shedding. The genital tract is a common site of shedding for herpesvirus type 2 and may be the route through which the virus is transmitted to sexual partners or the fetus. Saliva is the primary source of shedding for rabies virus. Cytomegalovirus is also shed from these last two sites. Finally, viruses such as tumor viruses that are integrated into the DNA of host cells can be shed through germ cells.

Shedding of Virus

(ensures the permanence of the virus in a particular ecological niche)

- The most frequent sites are the respiratory and alimentary tracts
- Other: urinary tract, genital tract, milk, blood and lymph
- Several viruses are shed simultaneously from several sites

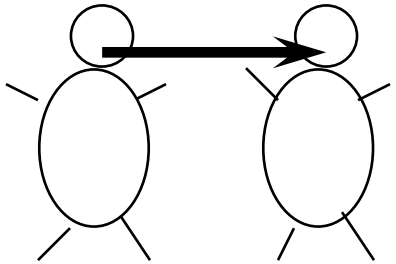
Figure 13.15 Droplet dispersal following a violent sneeze. Most of the 20 000 particles seen are coming from the mouth. (Reprinted with permission from FR Moulton (ed.), Aerobiology, 1942. American Association for the Advancement of Science.)

Microorganisms (and viruses) and respiratory system

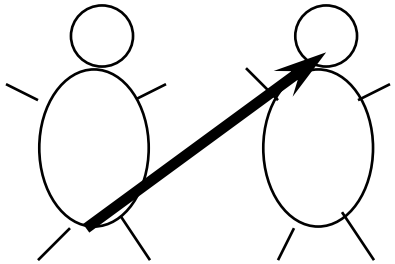
- In a closed environment, there are on average 500-1000 organisms/cubic meter.
- The ventilation rate (at rest) is 6 liters / minute.
- It is estimated that our lungs inhale about 12,000 liters of air per day.

About 10,000 organisms/day are introduced into the respiratory system

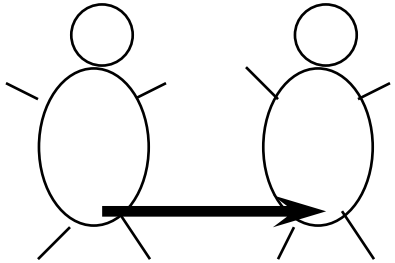
Direct interhuman transmission



Respiratory route
eg. Influenza A

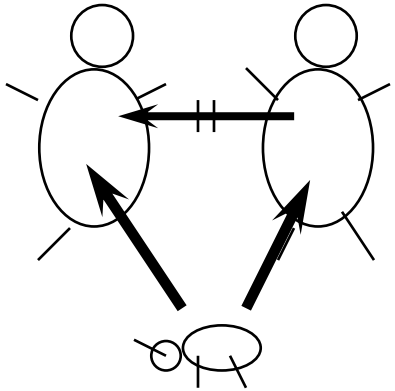


Fecal-oral route
eg. Hepatitis A

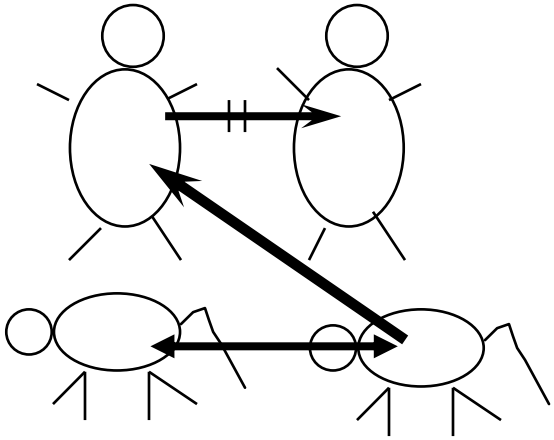


Sexually transmitted route, eg. papillomaviruses

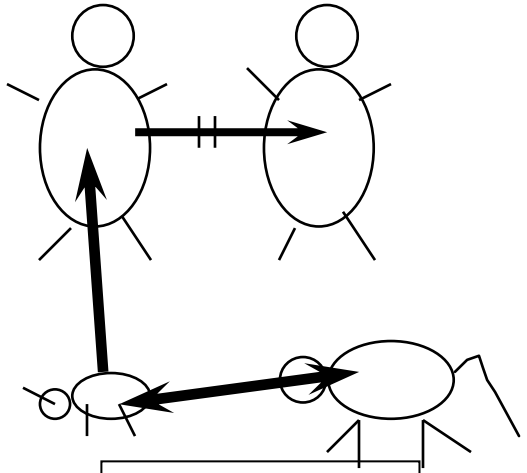
Zoonosis



Yellow Fever Virus



Rabies Virus



Flaviviruses

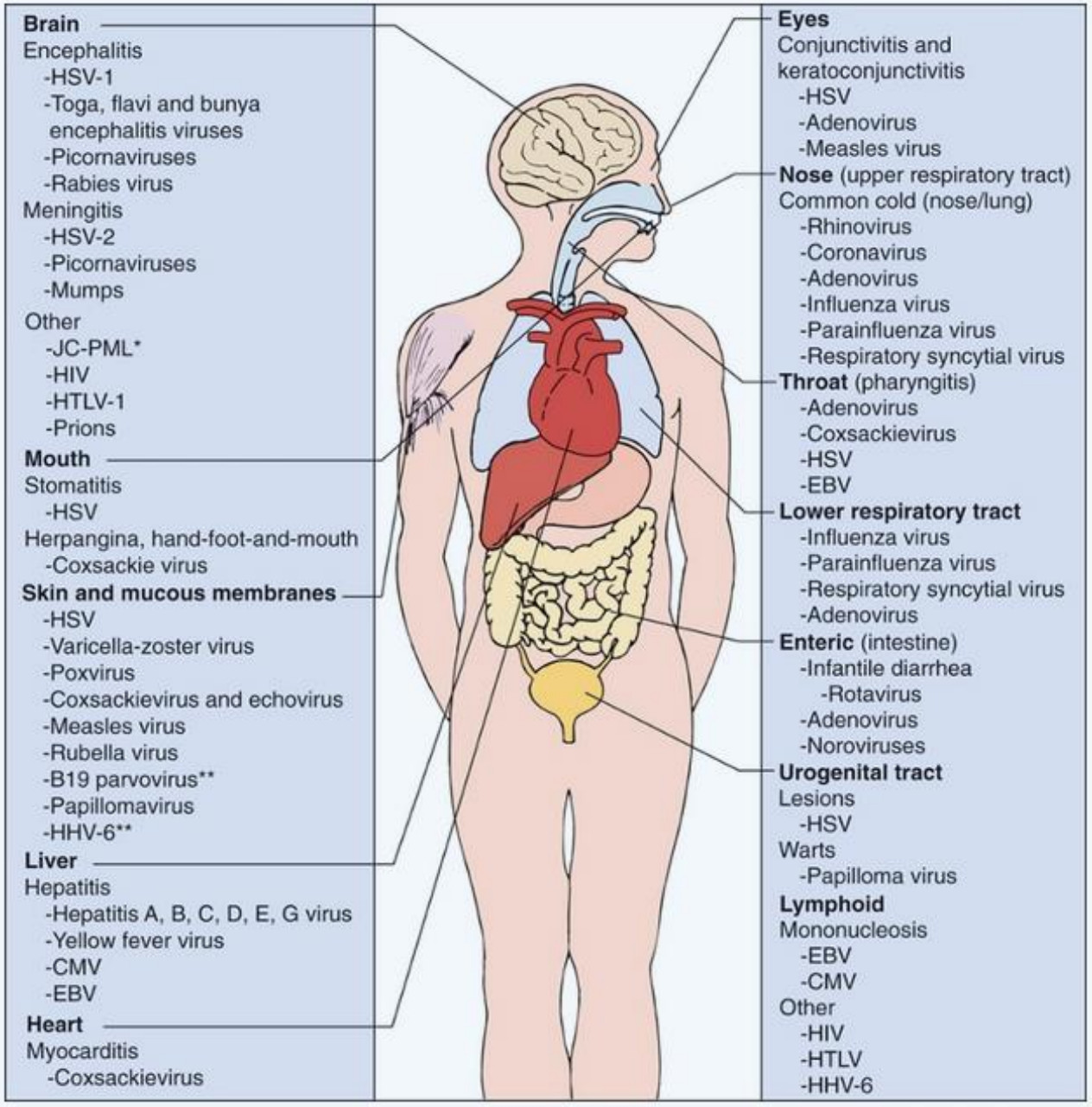
Viral infections: vertical transmission

Virtually all viruses that spread via the blood can be transmitted to the fetus

Viral infections: vertical transmission

Virtually all viruses that spread via the blood can be transmitted to the fetus

However in many cases the placenta is an efficient barrier


Brain
Encephalitis
-HSV-1
-Toga, flavi and bunya encephalitis viruses
-Picornaviruses
-Rabies virus
Meningitis
-HSV-2
-Picornaviruses
-Mumps
Other
-JC-PML*
-HIV
-HTLV-1
-Prions
Mouth
Stomatitis
-HSV
Herpangina, hand-foot-and-mouth
-Coxsackie virus
Skin and mucous membranes
-HSV
-Varicella-zoster virus
-Poxvirus
-Coxsackievirus and echovirus
-Measles virus
-Rubella virus
-B19 parvovirus**
-Papillomavirus
-HHV-6**
Liver
Hepatitis
-Hepatitis A, B, C, D, E, G virus
-Yellow fever virus
-CMV
-EBV
Heart
Myocarditis
-Coxsackievirus
Eyes
Conjunctivitis and keratoconjunctivitis
-HSV
-Adenovirus
-Measles virus
Nose (upper respiratory tract)
Common cold (nose/lung)
-Rhinovirus
-Coronavirus
-Adenovirus
-Influenza virus
-Parainfluenza virus
-Respiratory syncytial virus
Throat (pharyngitis)
-Adenovirus
-Coxsackievirus
-HSV
-EBV
Lower respiratory tract
-Influenza virus
-Parainfluenza virus
-Respiratory syncytial virus
-Adenovirus
Enteric (intestine)
-Infantile diarrhea
-Rotavirus
-Adenovirus
-Noroviruses
Urogenital tract
Lesions
-HSV
Warts
-Papilloma virus
Lymphoid
Mononucleosis
-EBV
-CMV
Other
-HIV
-HTLV
-HHV-6

Pathogenetic Mechanisms

Pathogenetic Mechanisms

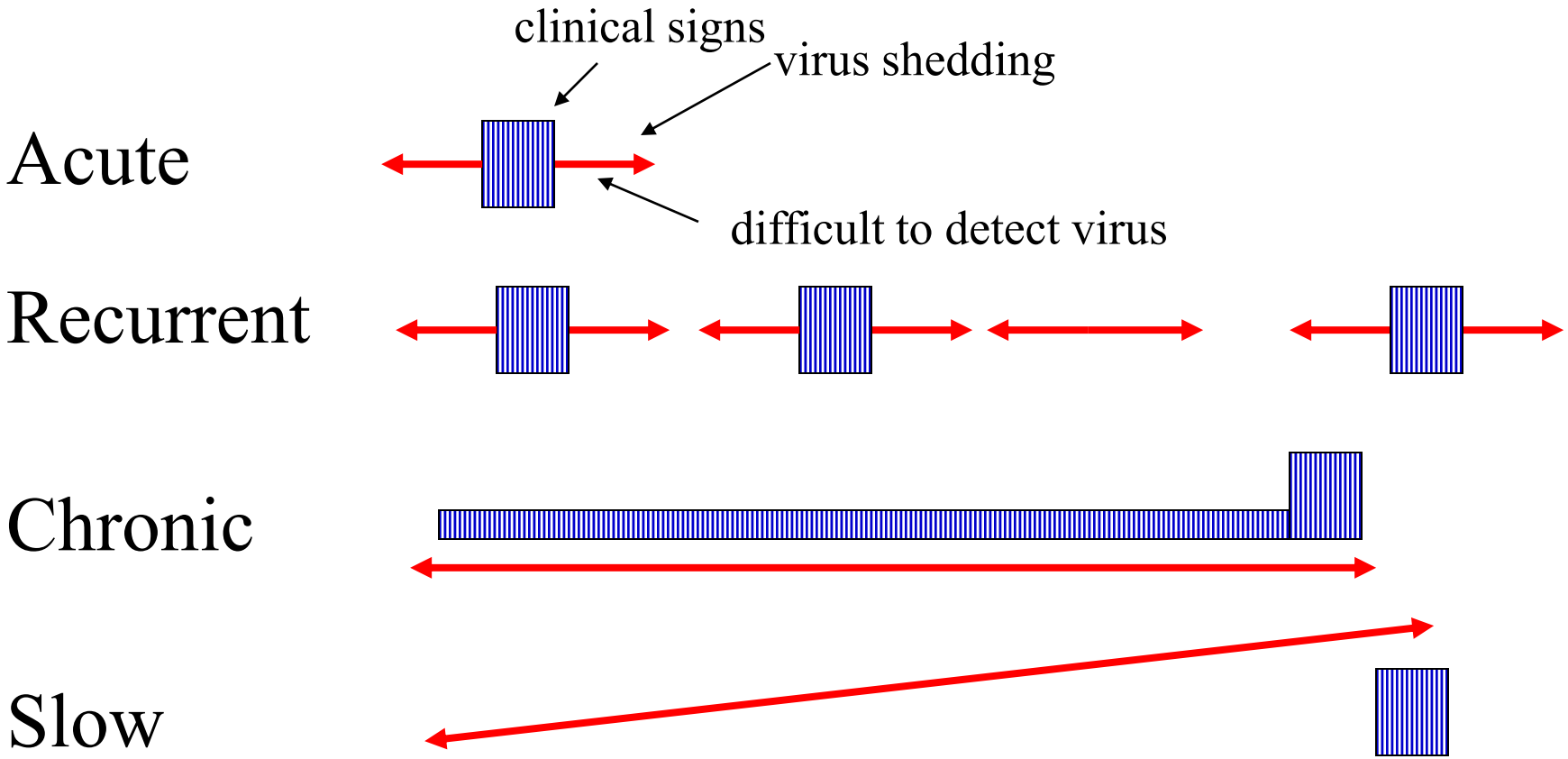
Direct damage

- **Lysis**
- **Tranformation**

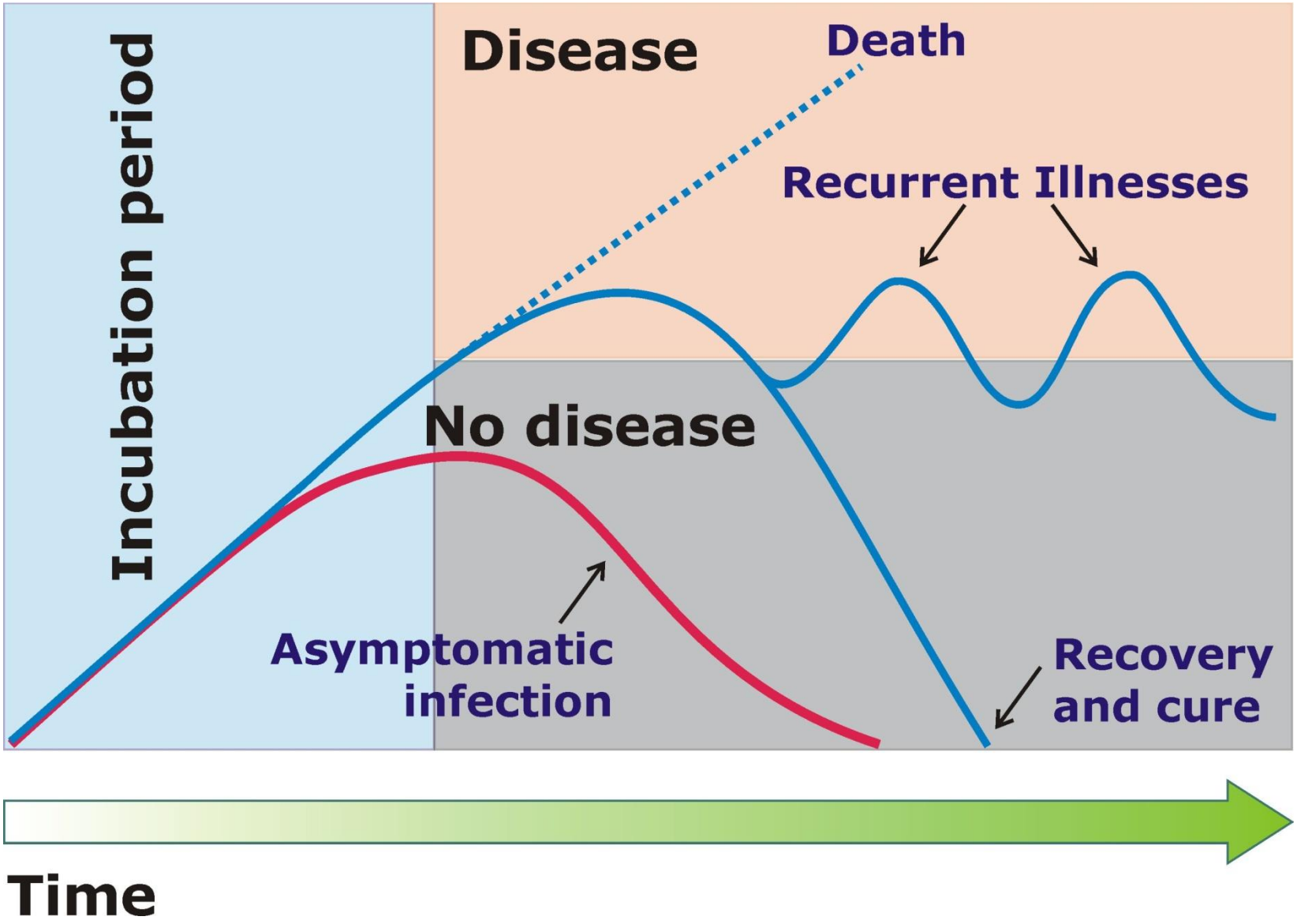
Indirect damage
(Immuno-pathology)

- **Damage on inflammatory base**
- **- T-Cell dependent Immunopathology Via Generation of CD8 T Cells**
- **- Damage by circulatory mmunocomplexes**
- **- Priming of autoimmunity processes**

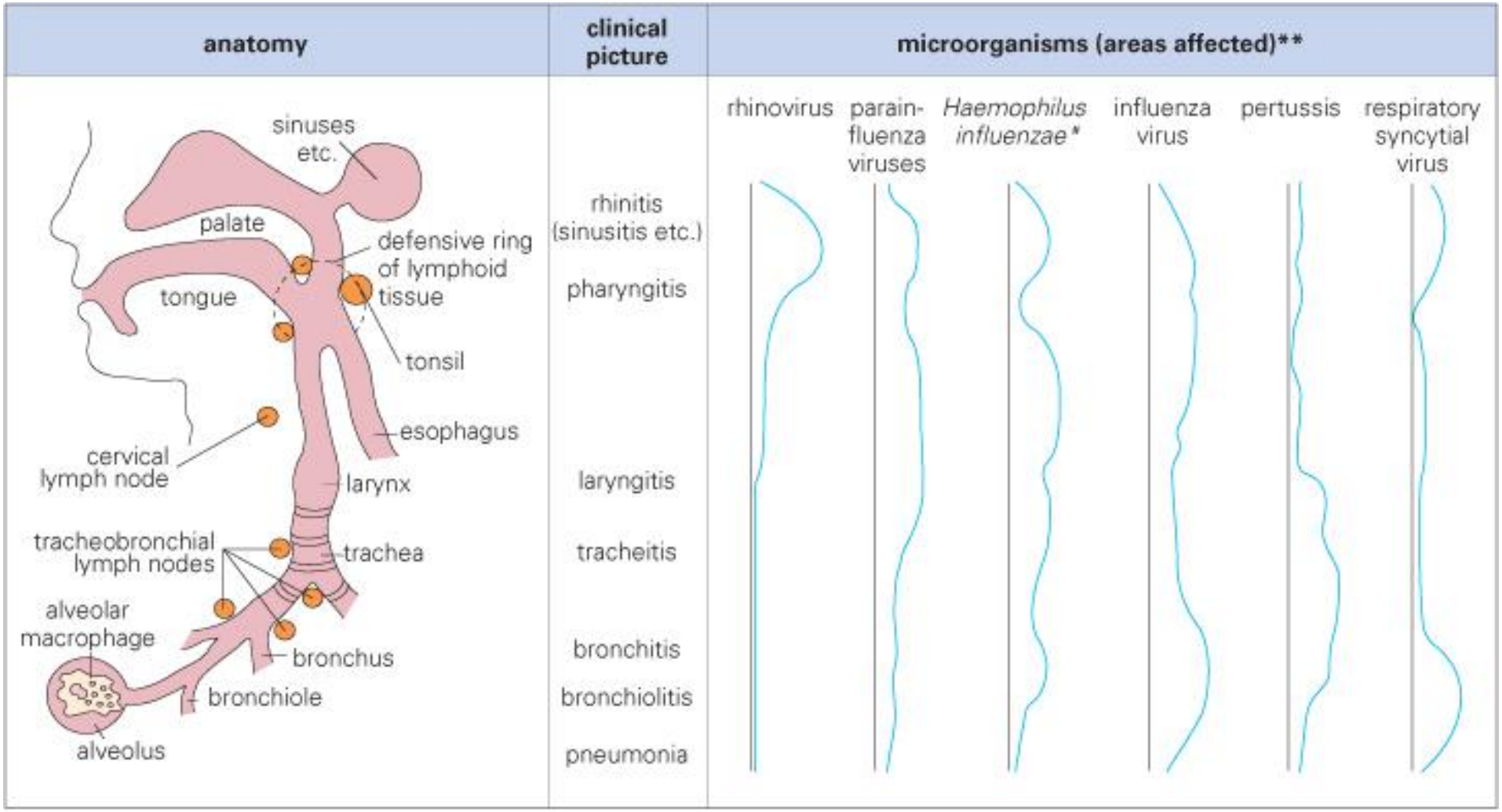
Patterns of disease



Outcome of Viral Infections



The respiratory tract is a continous apparatus



VIRUSES CAUSING COMMON COLDS			
virus	**types involved**	**attachment mechanism**	**disease**
rhinoviruses (>100 types)*	several at any given time in the community	capsid protein binds to ICAM-1 type molecule on cell**	common cold
coxsackie virus A (24 types)†	especially A21	capsid protein binds to ICAM-1 type molecule on cell**	common cold; also oropharyngeal vesicles (herpangina) and hand, foot and mouth disease (A16)
influenza viruses	several	hemagglutinin binds to neuraminic acid-containing glycoprotein on cell	may also invade lower respiratory tract
parainfluenza virus (4 types)	1, 2, 3, 4	viral envelope protein binds to glycoside on cell	may also invade larynx
respiratory syncytial virus	(2 types)	G protein on virus attaches to receptor on cell	may also invade lower respiratory tract
coronaviruses (several types)	all	viral envelope protein binds to glycoprotein receptors on cell	common cold; severe acute respiratory syndrome
adenovirus (41 types)	5–10 types	penton fiber binds to cell receptor	mainly pharyngitis; also conjunctivitis, bronchitis
echovirus (34 types)	4, 9, 11, 20, 25	—	common cold

*a given type shows little or no neutralization by antibody against other types

**ICAM-1: intercellular adhesion molecule expressed on a wide variety of normal cells; member of immunoglobulin superfamily, coded on chromosome 19

† Coxsackie virus A9 binds to vitronectin, an integrin protein; types 1 and 8 bind to very-late-activating antigen-2 (an integrin) and 6, 7, 12, 21 to decay-accelerating factor (CD55) on cell.

Fig. 18.5 Common cold viruses and their mechanisms of attachment.

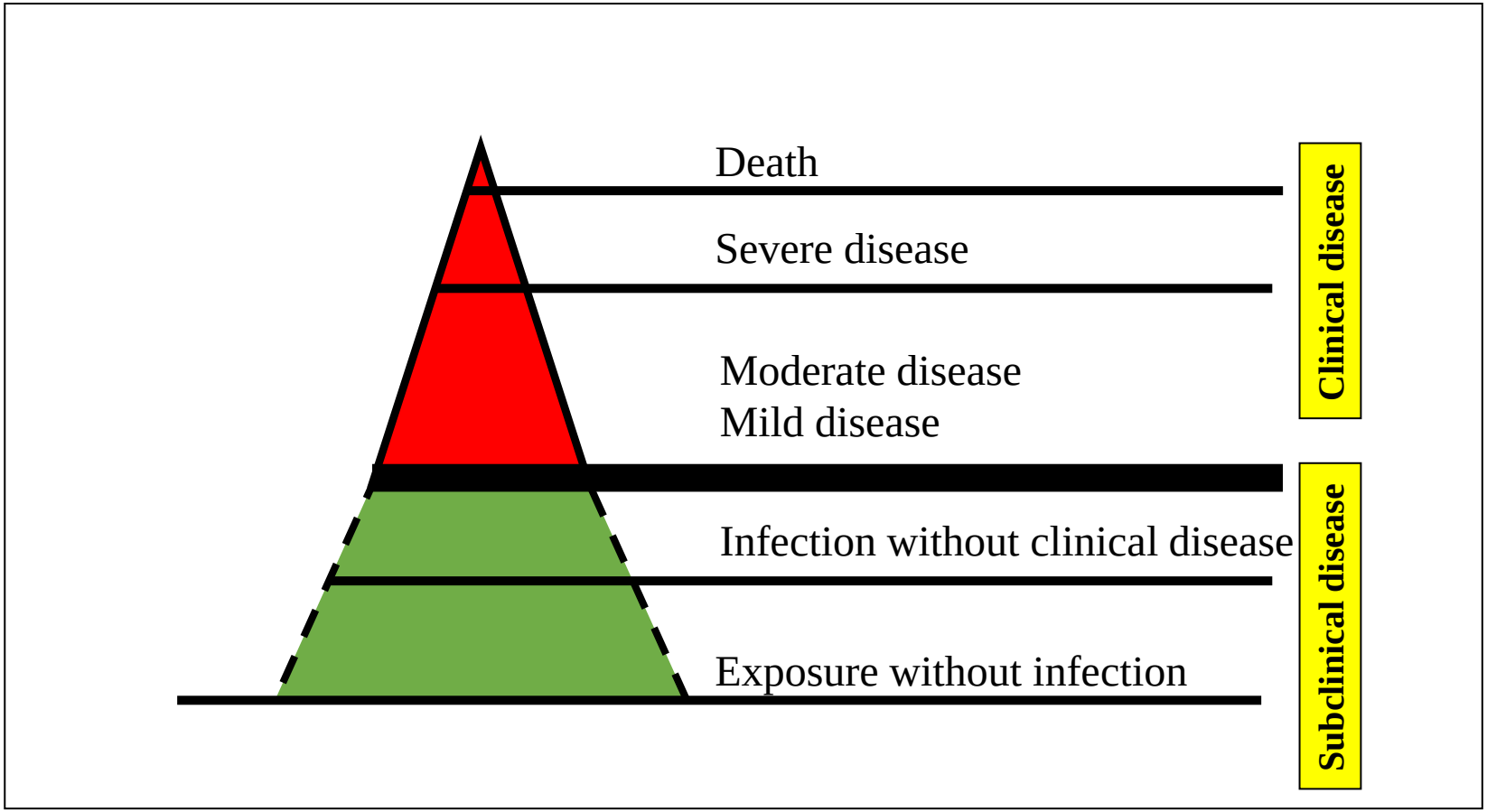
VIRAL PNEUMONIA		
virus	**clinical condition**	**comments**
influenza A or B	primary viral pneumonia or pneumonia associated with secondary bacterial infection	pandemics (type A) and epidemics (type A or B); increased susceptibility in elderly or in certain chronic diseases; antivirals and vaccine available
parainfluenza (types 1–4)	croup, pneumonia in children less than 5 years of age; upper respiratory illness (often subclinical) in older children and adults	antiviral (ribavirin) available; vaccines not available
measles	secondary bacterial pneumonia common; primary viral (giant cell) pneumonia in those with immunodeficiency	adult infection rare but severe; King and Queen of Hawaii both died of measles when they visited London in 1824; antivirals and vaccine available
respiratory syncytial virus	bronchiolitis (infants); common cold syndrome (adults)	peak mortality in 3–4-month-old infants; secondary bacterial infection rare; antivirals available
adenovirus	pharyngoconjunctival fever, pharyngitis, atypical pneumonia (military recruits)	vaccines not available, antivirals under study
cytomegalovirus	interstitial pneumonia	in immunodeficient patients (e.g. bone marrow transplant recipients); antivirals and immunoglobulin available
varicella-zoster virus	pneumonia in young adults suffering primary infection	uncommon; recognized 1–6 days after rash; lung lesions may eventually calcify; antivirals and vaccine available

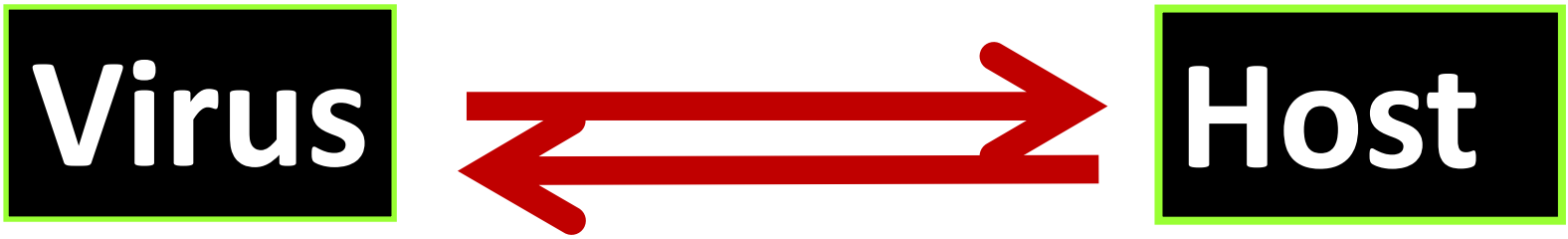
Fig. 19.13 Several different groups of viruses cause infection of the lower respiratory tract, particularly in children. Some, such as influenza and measles, leave the patient particularly prone to secondary bacterial infection.

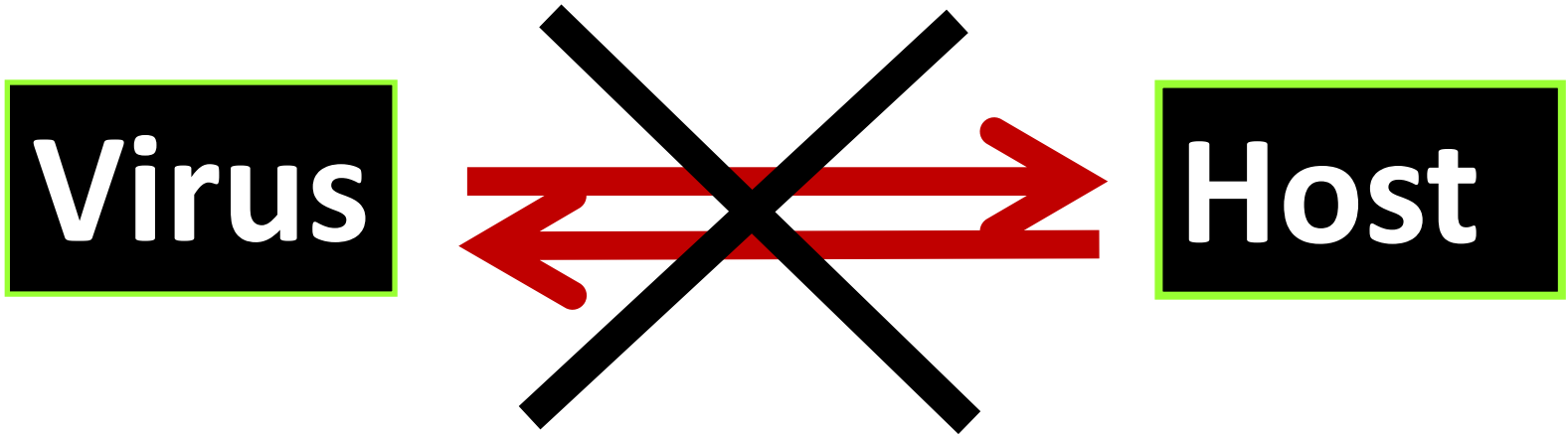
HOST FACTORS INFLUENCING SUSCEPTIBILITY TO INFECTIOUS DISEASE			
factor	**example**	**alteration in susceptibility**	**mechanism**
pregnancy	hepatitis viruses	more lethal outcome	?increased metabolic burden for liver in pregnancy
	urinary infections	pyelonephritis more common	reduced peristalsis in ureter
malnutrition	measles	more severe; more lethal	vitamin A deficiency; depressed CMI
age	respiratory syncytial virus	more severe; more lethal in infant	small diameter of airways
	mumps, chickenpox, Epstein–Barr virus infection	more severe in adult	?increased immunopathology

Fig. 15.12 Host factors influencing susceptibility to infectious disease. (CMI, cell-mediated immunity.)

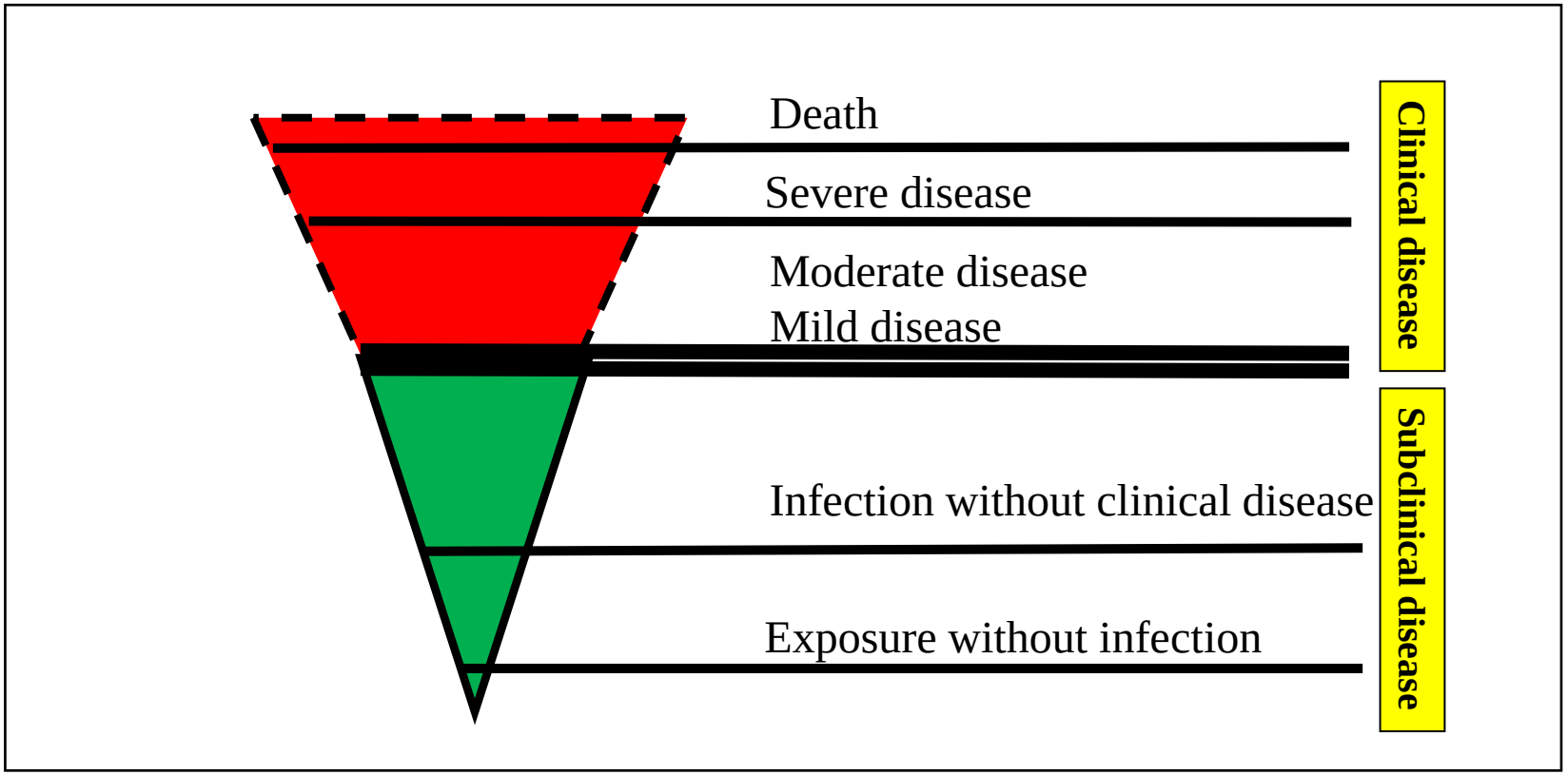
ICEBERG CONCEPT OF INFECTIOUS DISEASES

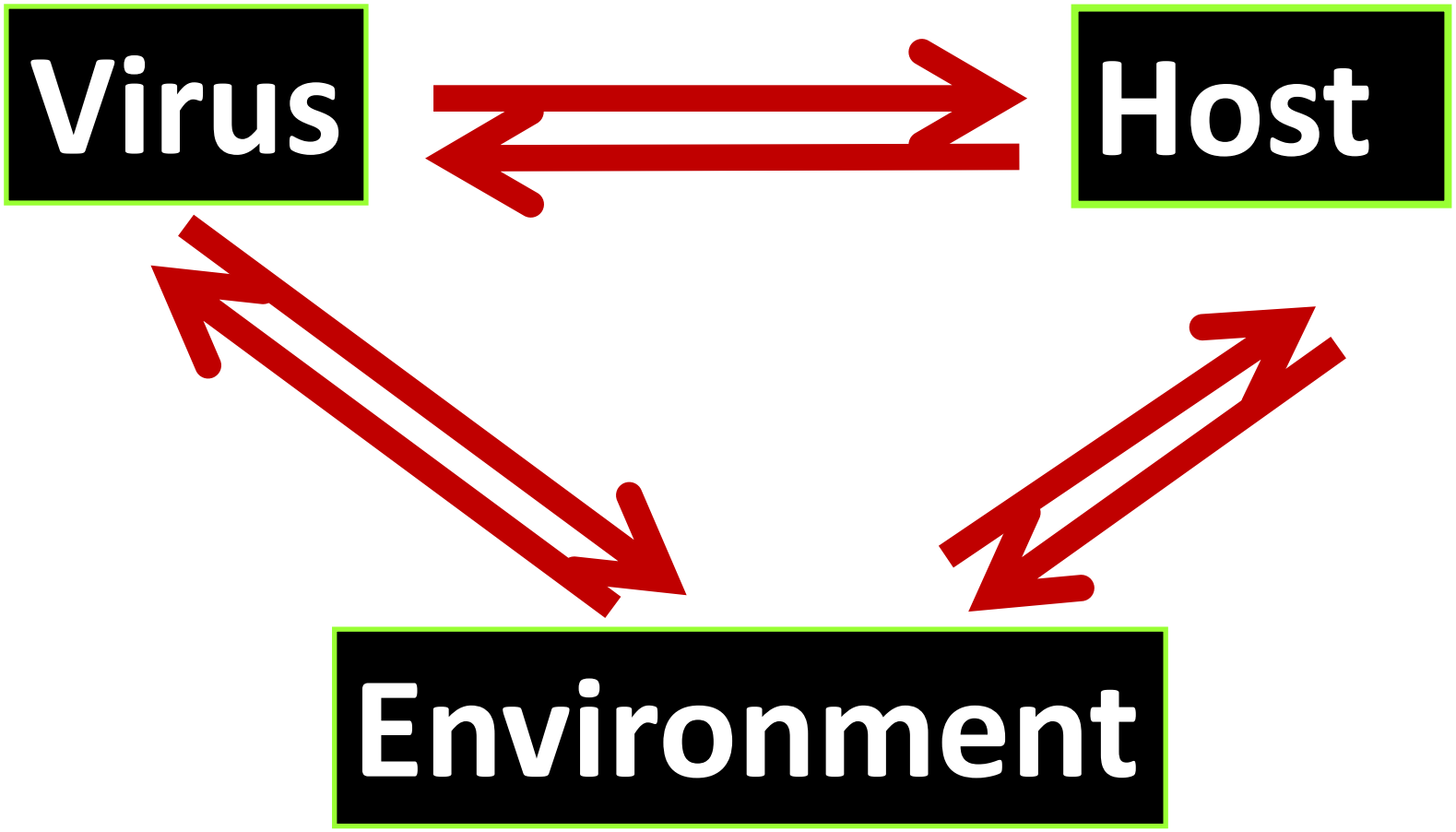



Virus
Host

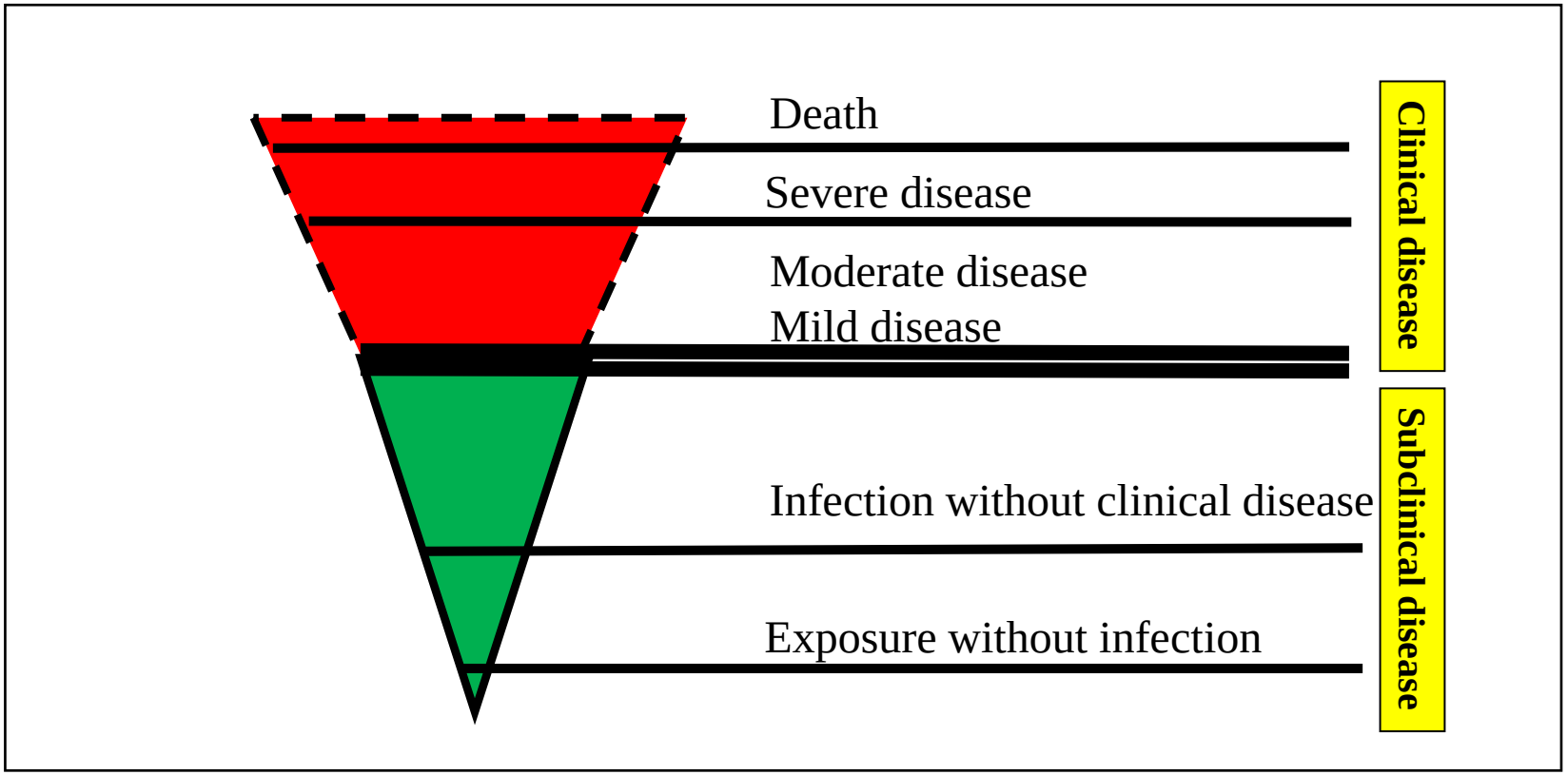

Virus
Host

ICEBERG CONCEPT OF INFECTIOUS DISEASES



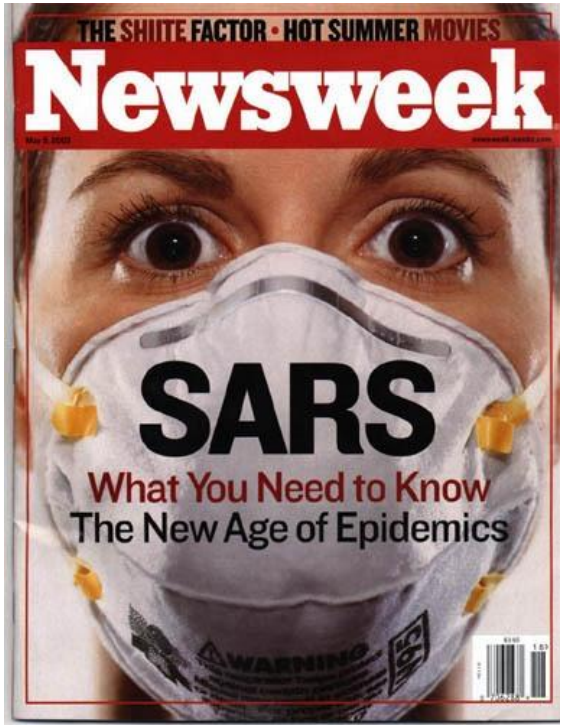

Virus
Host
Environment

ICEBERG CONCEPT OF INFECTIOUS DISEASES



When the iceberg concept of infection is broken

- *Newborns and elderly*
- *Immunosuppressed subjects*
- *Transplants recipients*
- *Oncologic patients*


THE SHIITE FACTOR • HOT SUMMER MOVIES
Newsweek
SARS
What You Need to Know
The New Age of Epidemics
WARNING


TIME
IRAQ: IS IT TOO LATE TO WIN THIS WAR?
AVIAN FLU
DEATH THREAT
SPECIAL REPORT: Inside the global race to avert a pandemic


TIME
CHASING EBOLA
IN AMERICA
IN WEST AFRICA

Emergence of viral infections may be due to:

- the spread of a new agent
- reappearance (or re-emergence) of a known infection after a decline in incidence
- the recognition of an infection that has been present in the population but was previously unknown

Possible sources of “new viruses”

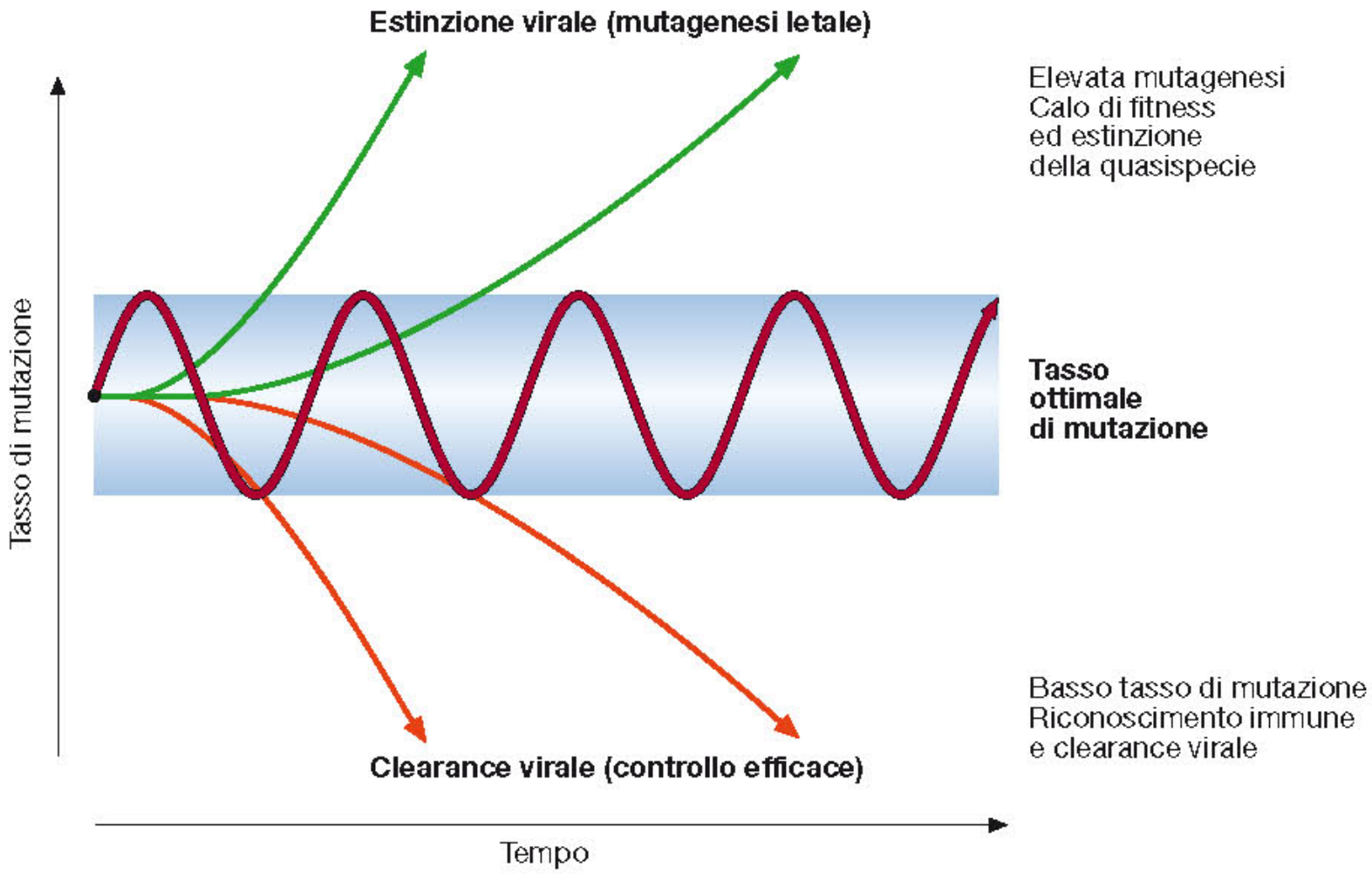
- *De novo* evolution
- “Viral Traffic”

- New virus or new variant
- Interspecies transfer from the “zoonotic pool”
- Dissemination of disease from a geographically localized subpopulation

Possible sources of “new viruses”

- De novo evolution
- “Viral Traffic”

- New virus or new variant
  - Mutation
  - Recombination
  - Reassortment
- Interspecies transfer from the “zoonotic pool”
- Dissemination of disease from a geographically localized subpopulation



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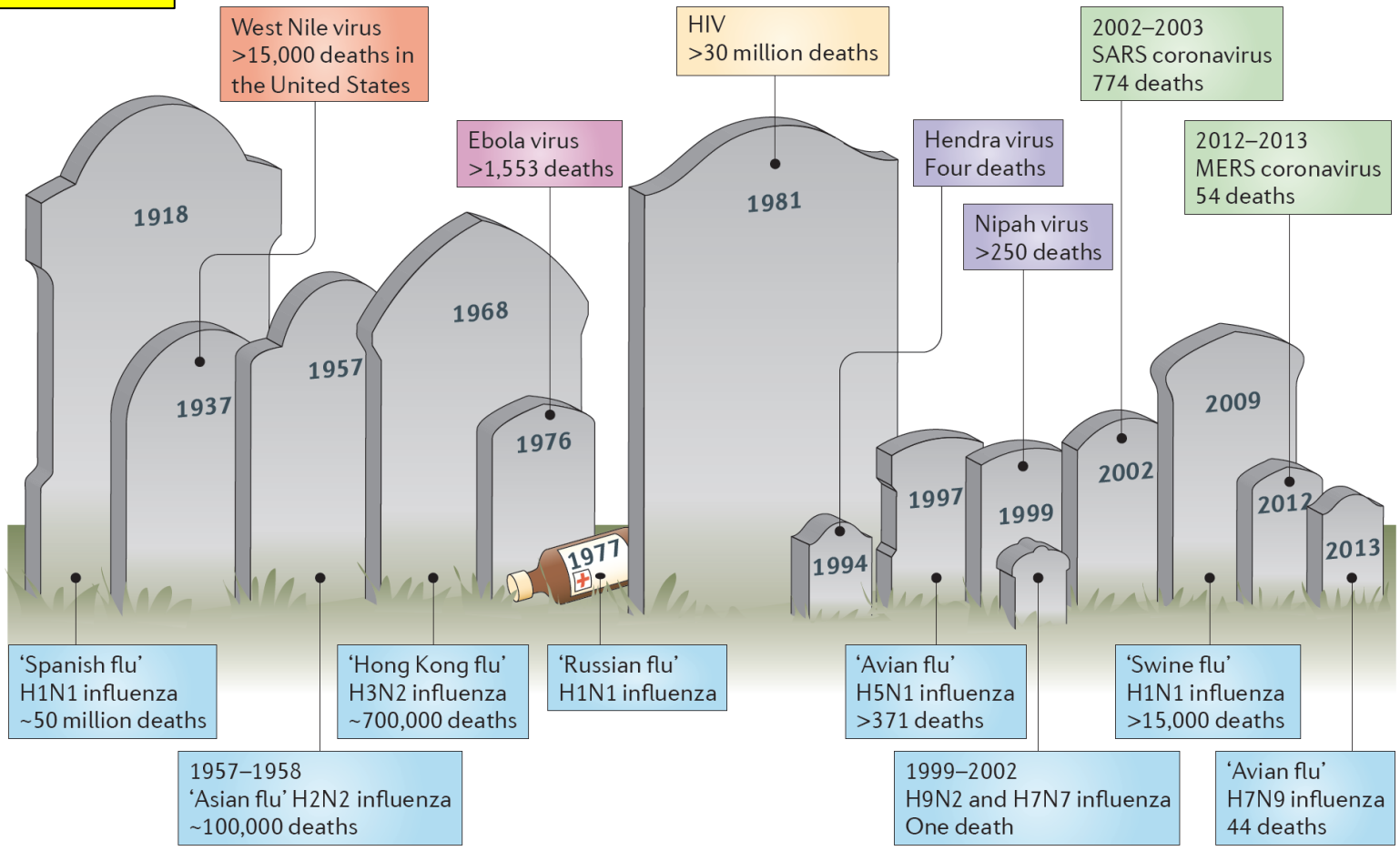
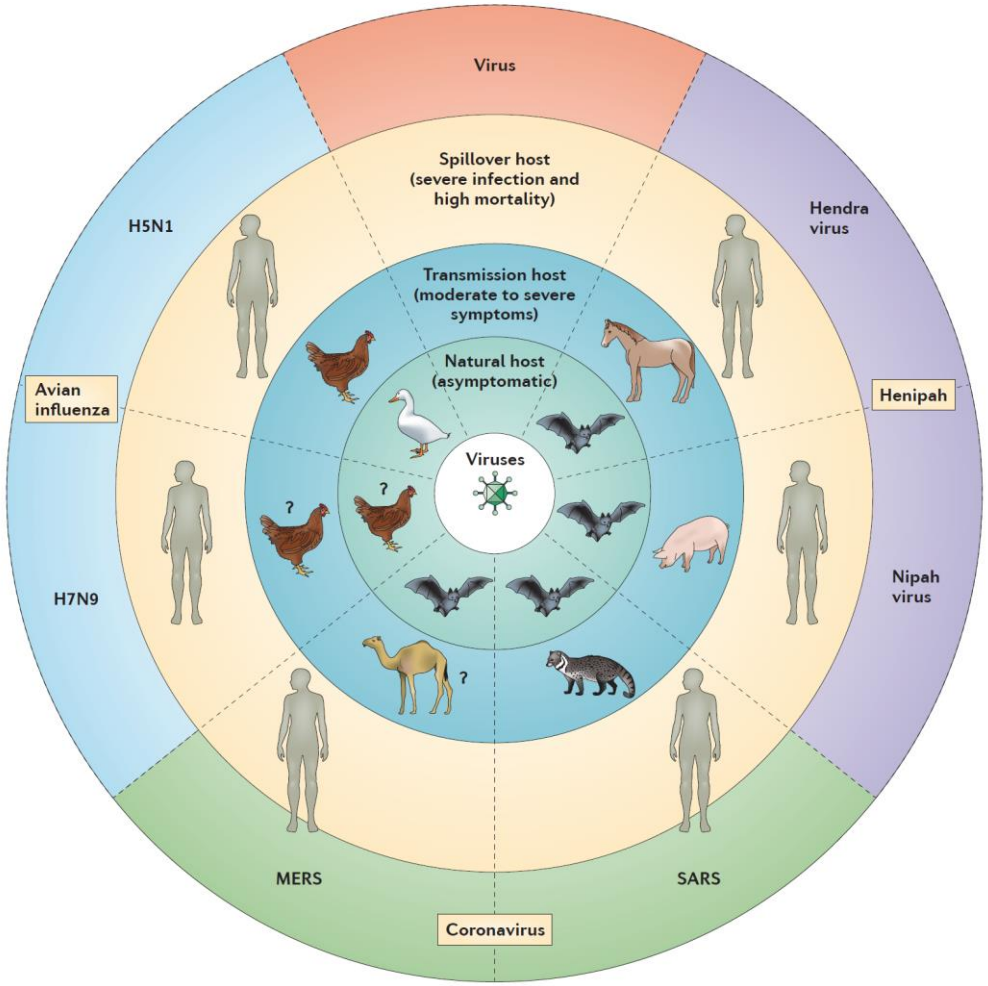
Emergence of zoonoses



Studying immunity to zoonotic diseases in the natural host — keeping it real

Andrew G. D. Bean[1], Michelle L. Baker[1], Cameron R. Stewart[1], Christopher Cowled[1], Celine Deffrasnes[1], Lin-Fa Wang[1,2] and John W. [illegible]



Ecology of zoonoses: natural and unnatural histories

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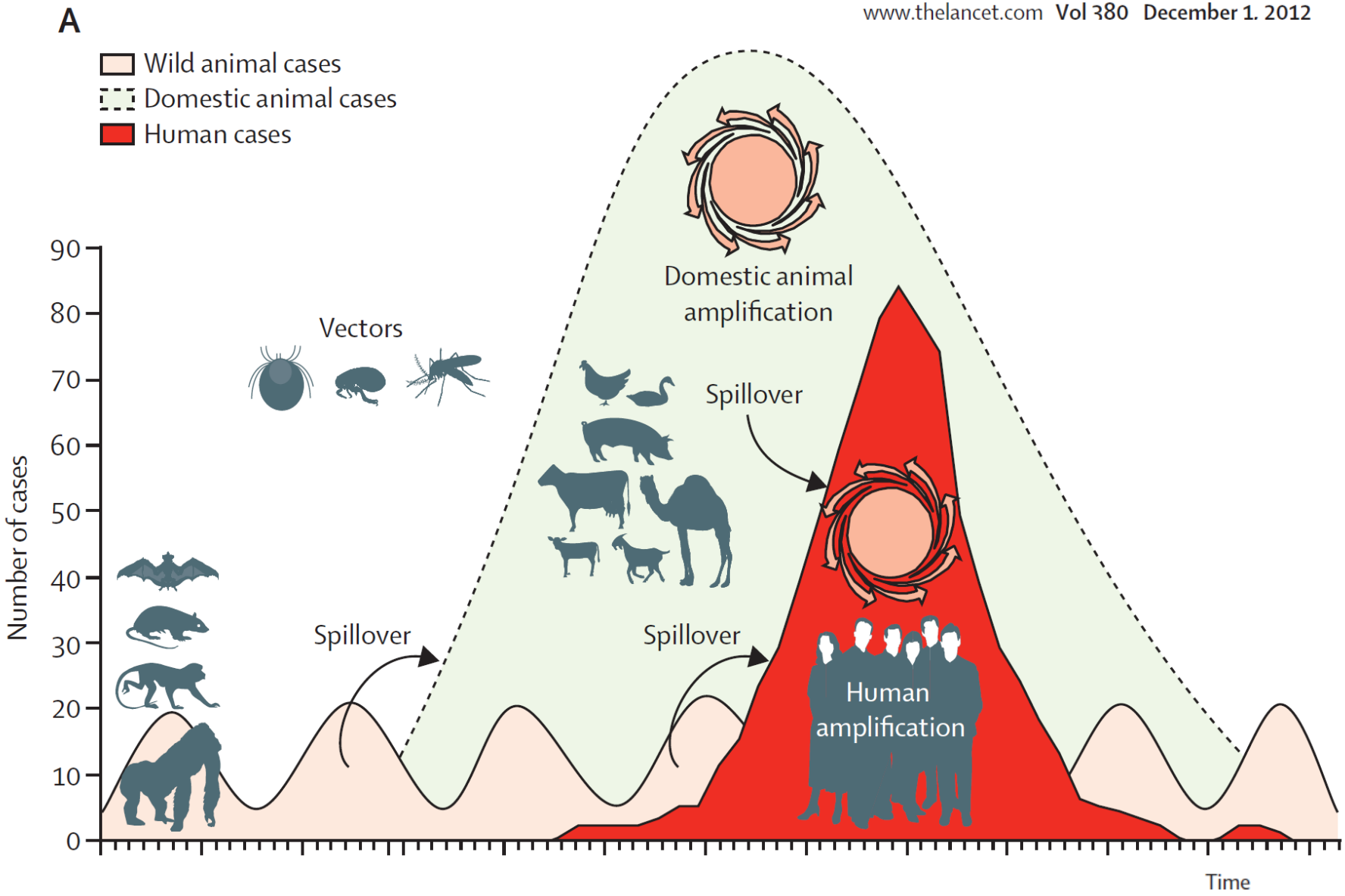
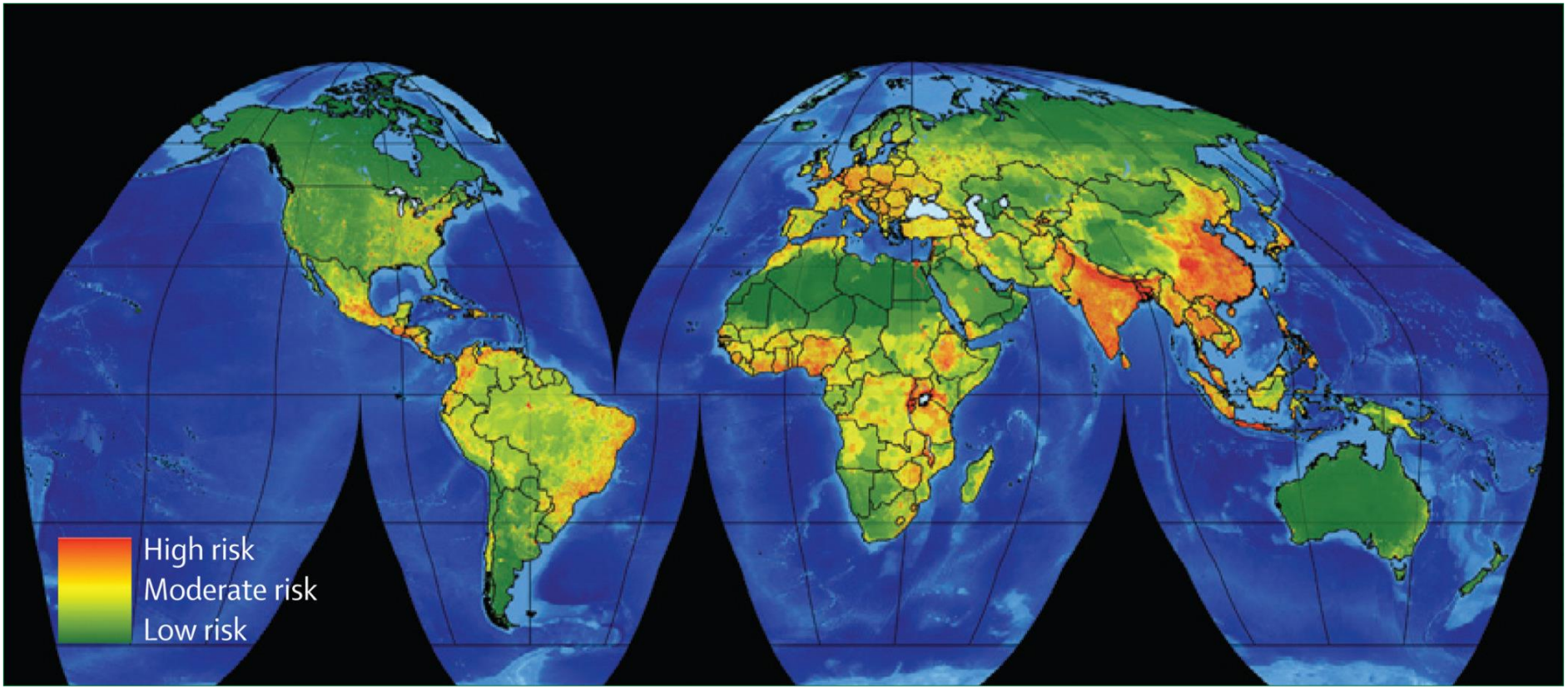


Factors (different from those related to microorganism) in Emerging/Re-emerging Infectious Diseases

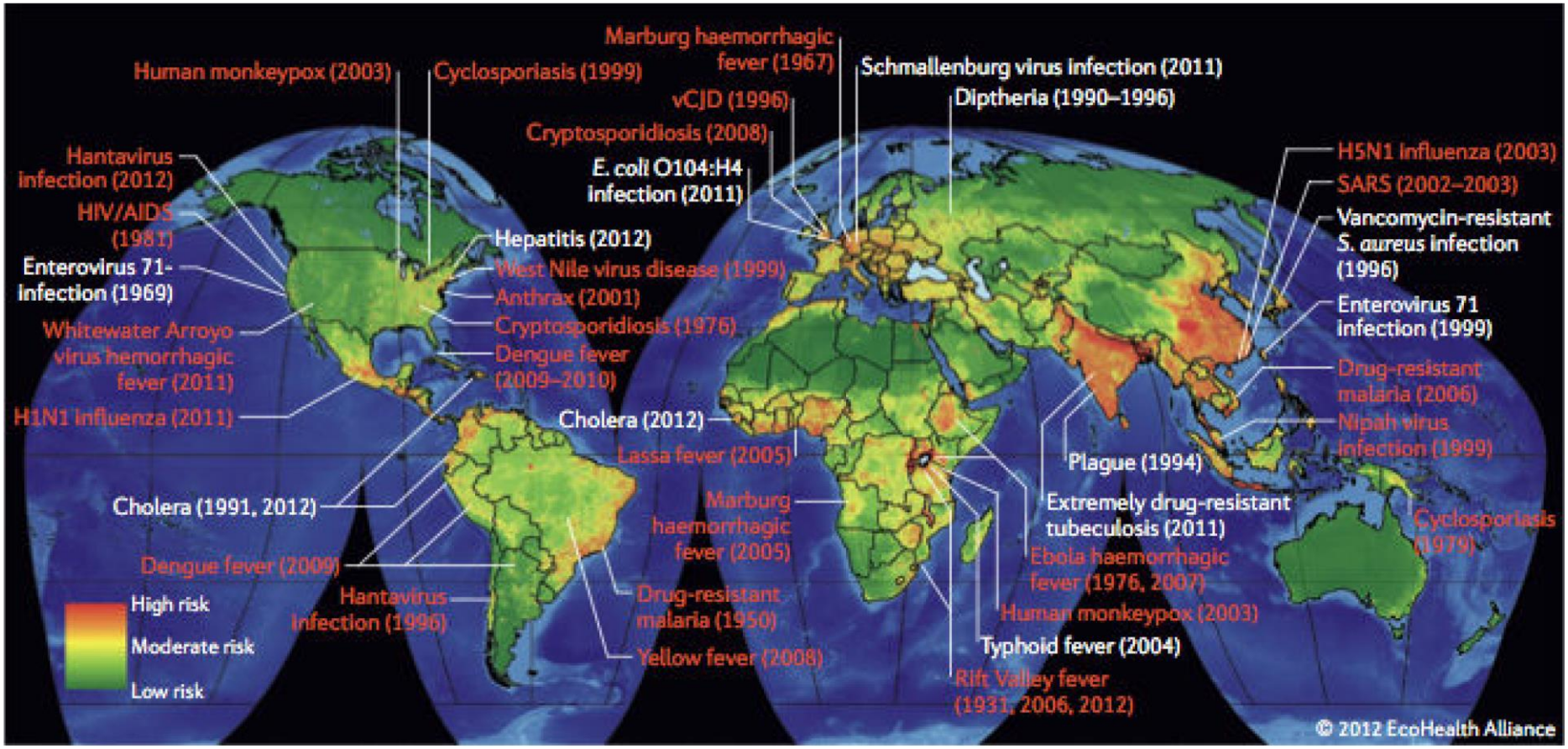
- **Globalization of travel and trade**
- **Population growth and density**
- **Urbanization, social and sexual relations**
- **Live animal markets**
- **Intensified livestock production**
- **Human susceptibility to infection** (ageing, HIV, IV drugs, transplantation, transfusion)
- **Misuse of antibiotics (humans & domestic animals)**
- **Changes to ecosystems (deforestation, biodiversity loss)**
- **Global climate change**

Figure 1: Global hotspots for emerging infectious diseases that originate in wildlife



A database of all known emerging infectious diseases since 1940 was used to identify the most likey origins of each separate emergence event

Figure 1: Global hotspots for emerging infectious diseases that originate in wildlife



W. Ian Lipkin *Nat Rev Microbiol*. 2013 February ; 11(2)