1 - Struttura/morfologia e Tassonomia

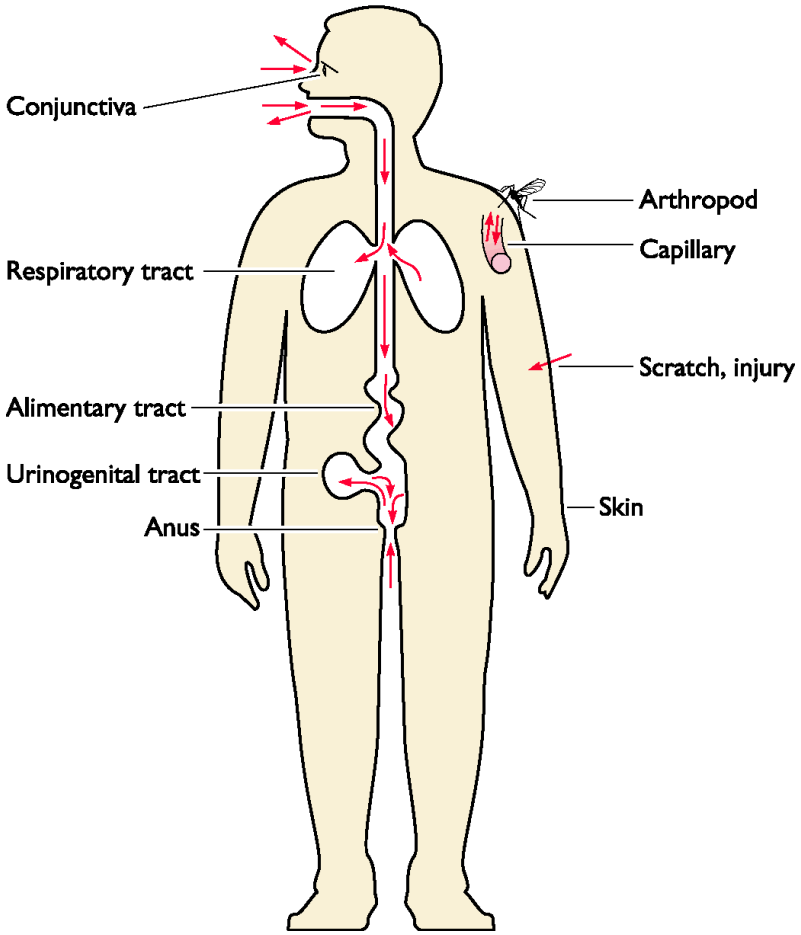
2- Ciclo vitale/replicazione

3- Effetto sulle cellule e variabilità

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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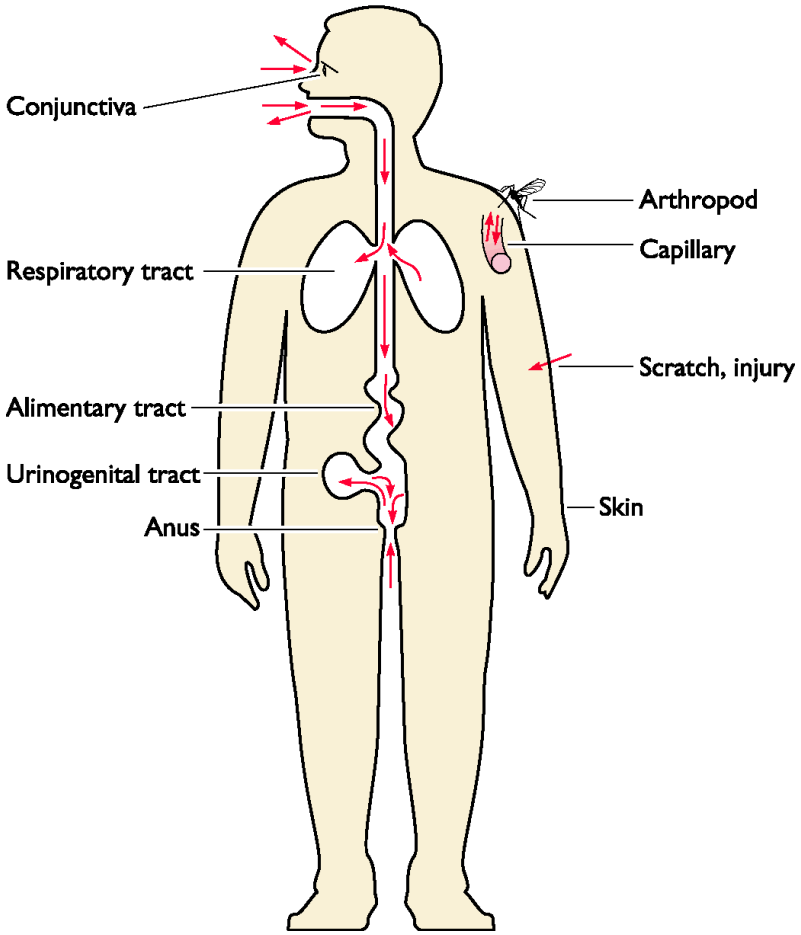
Virus Dissemination - Entry

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.



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

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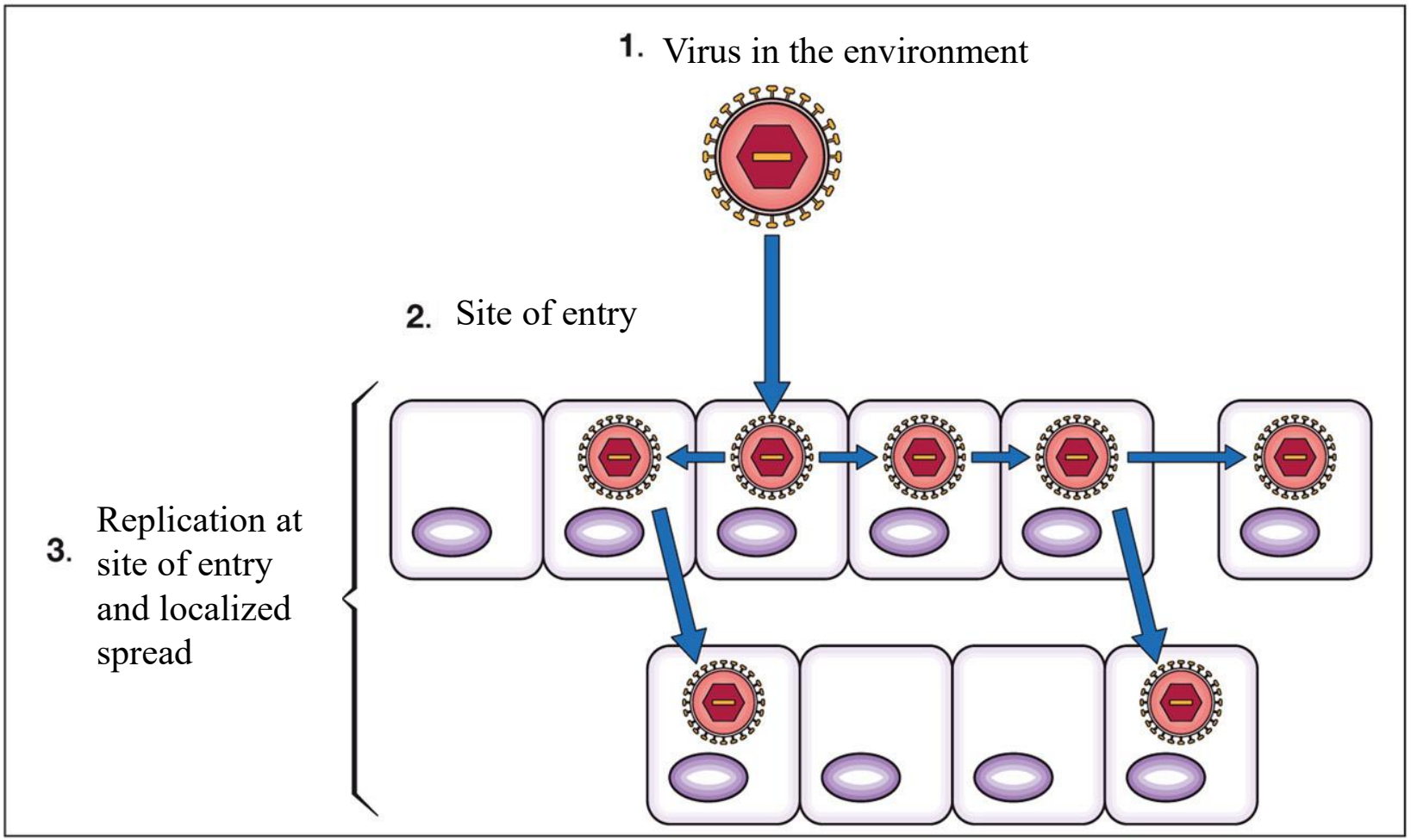
Virus spread during localized infection



Virus spread during localized infection

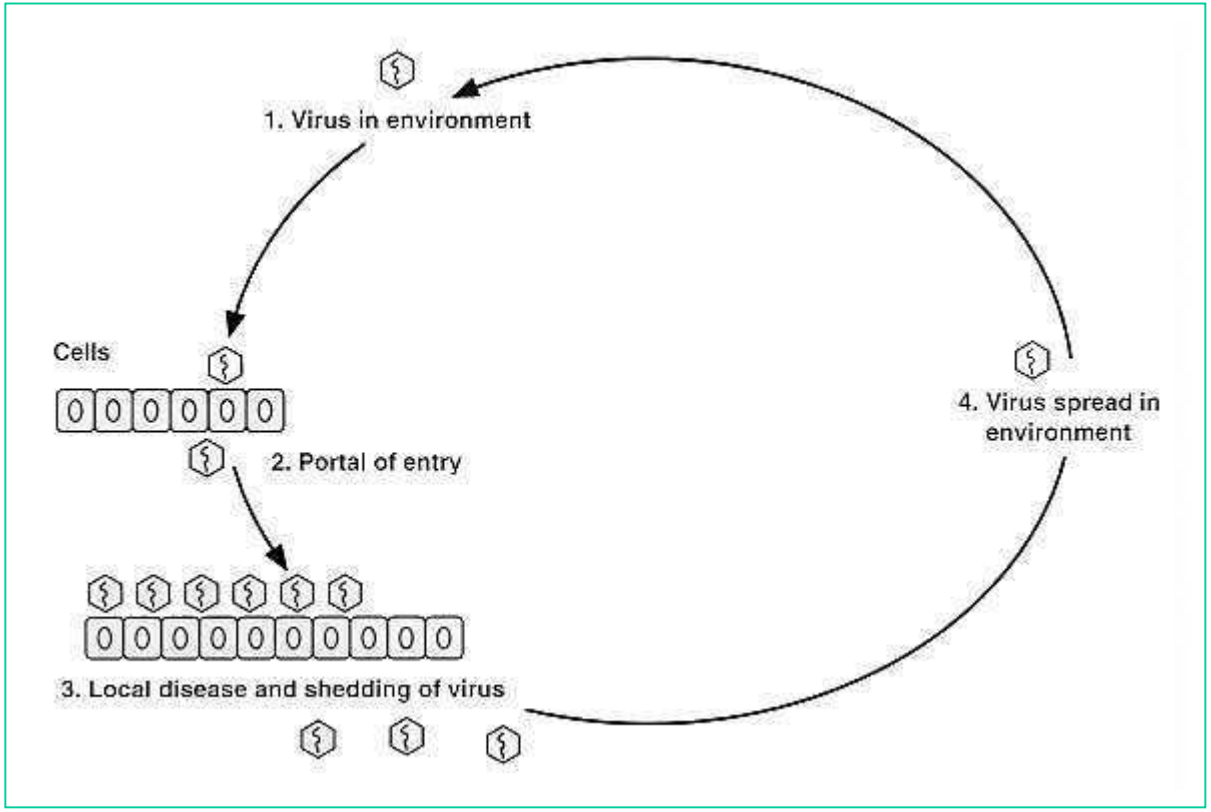
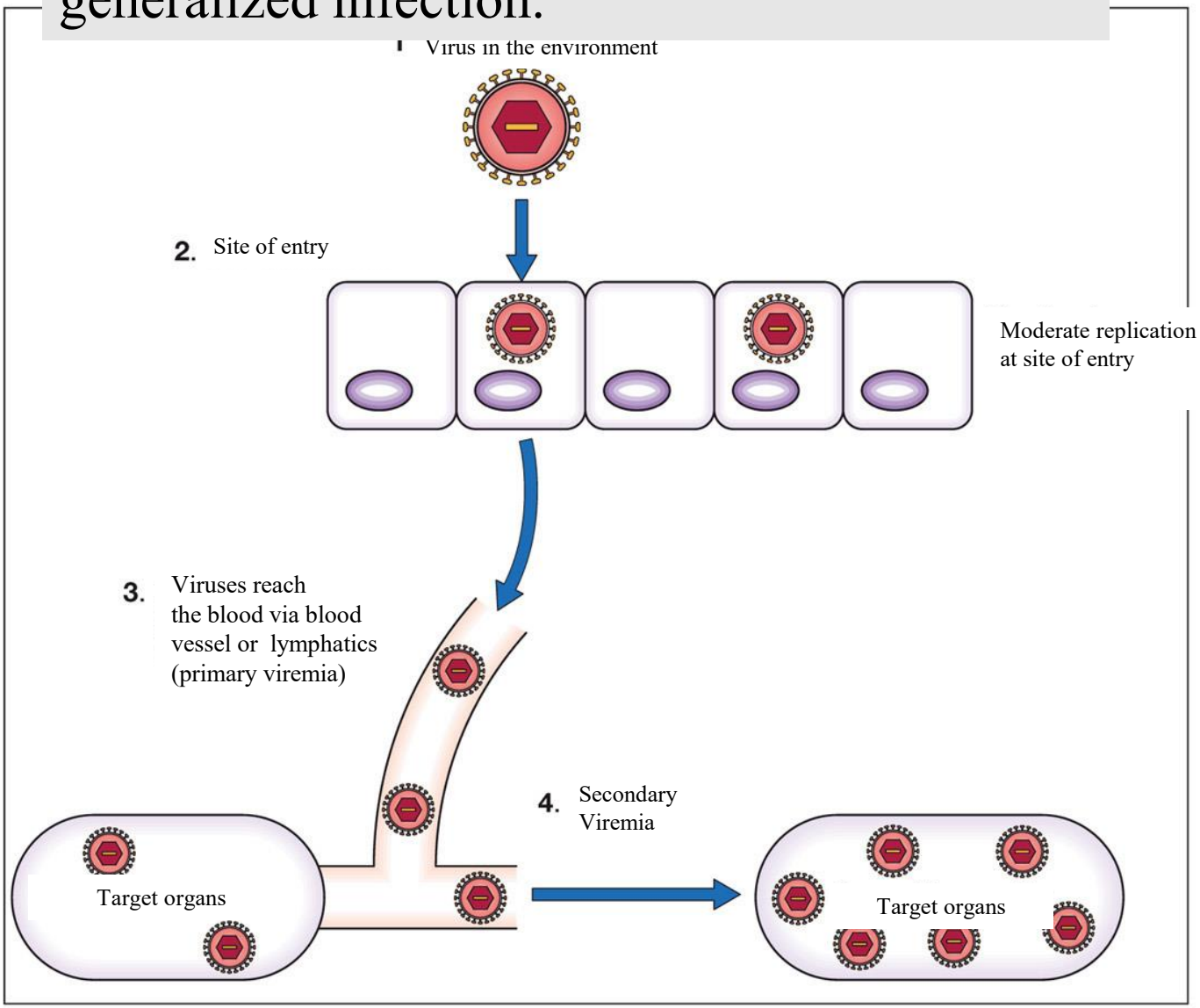


TABLE 45-1 Pathogenesis of Selected Virus Infection: Localized Infections

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.



Virus spread through nerves during a generalized infection

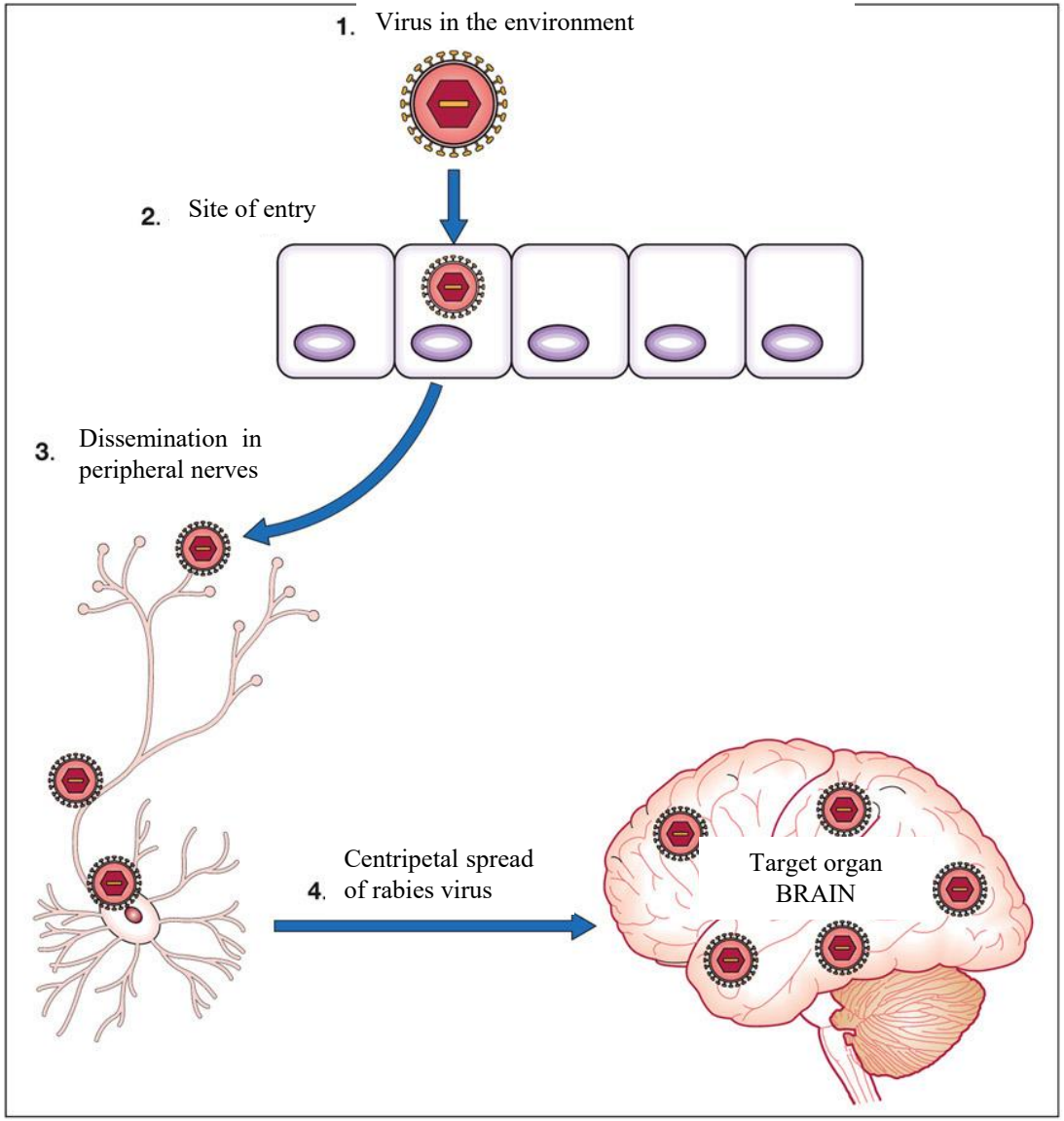


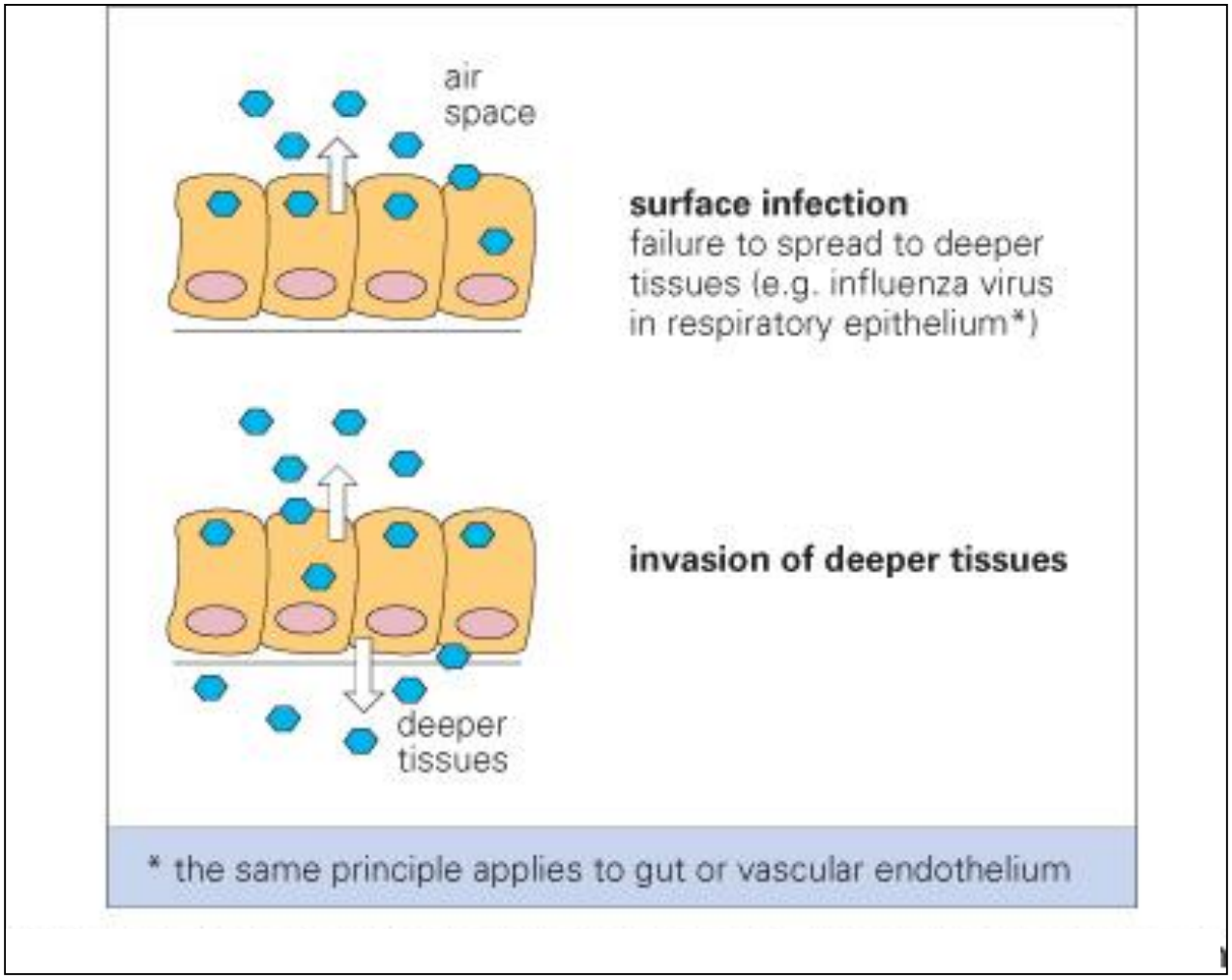
TABLE 45-2 Pathogenesis of Selected Virus Infections: Disseminated Infections

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

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

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



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

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

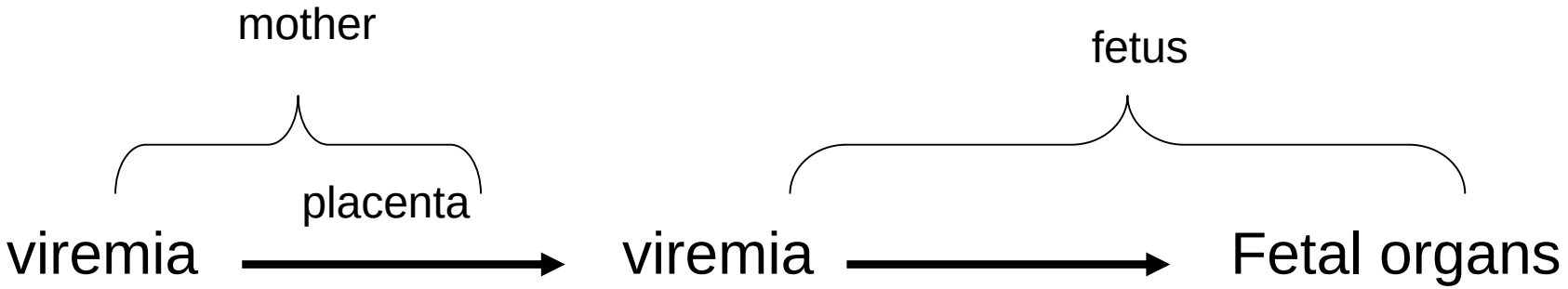
However in many cases the placenta is an efficient barrier

Tabella 37.1 **Vie di trasmissione dei virus.**

Verticale (dalla madre al figlio)	Orizzontale
Attraverso le cellule gametiche contenenti il virus	Diretta (passaggio diretto da un soggetto infetto a uno non infetto: ad es. trasmissione sessuale)
Per via trans-placentare	Indiretta (strumenti infetti, cibi infetti, vettori)
Nella vita perinatale	

Pathogenesis /congenital infection

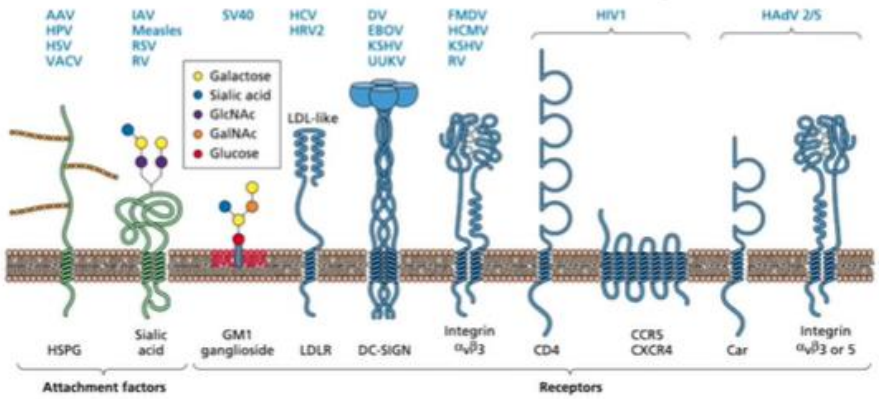
- **Immature immune system**
- **The cells are in an active proliferation state and then highly permissive to the replication of viruses**
- **The cells are not differentiated and then more sensitive to the viral infections**



PATHOGENESIS OF VIRAL INFECTIONS

Tissue tropism

- The spectrum of tissues infected by a virus
  - *Enterotropic, neurotropic, hepatotropic*
- Ranges from limited to pantropic
- Some determinants: Susceptibility, permissivity, accessibility, defense



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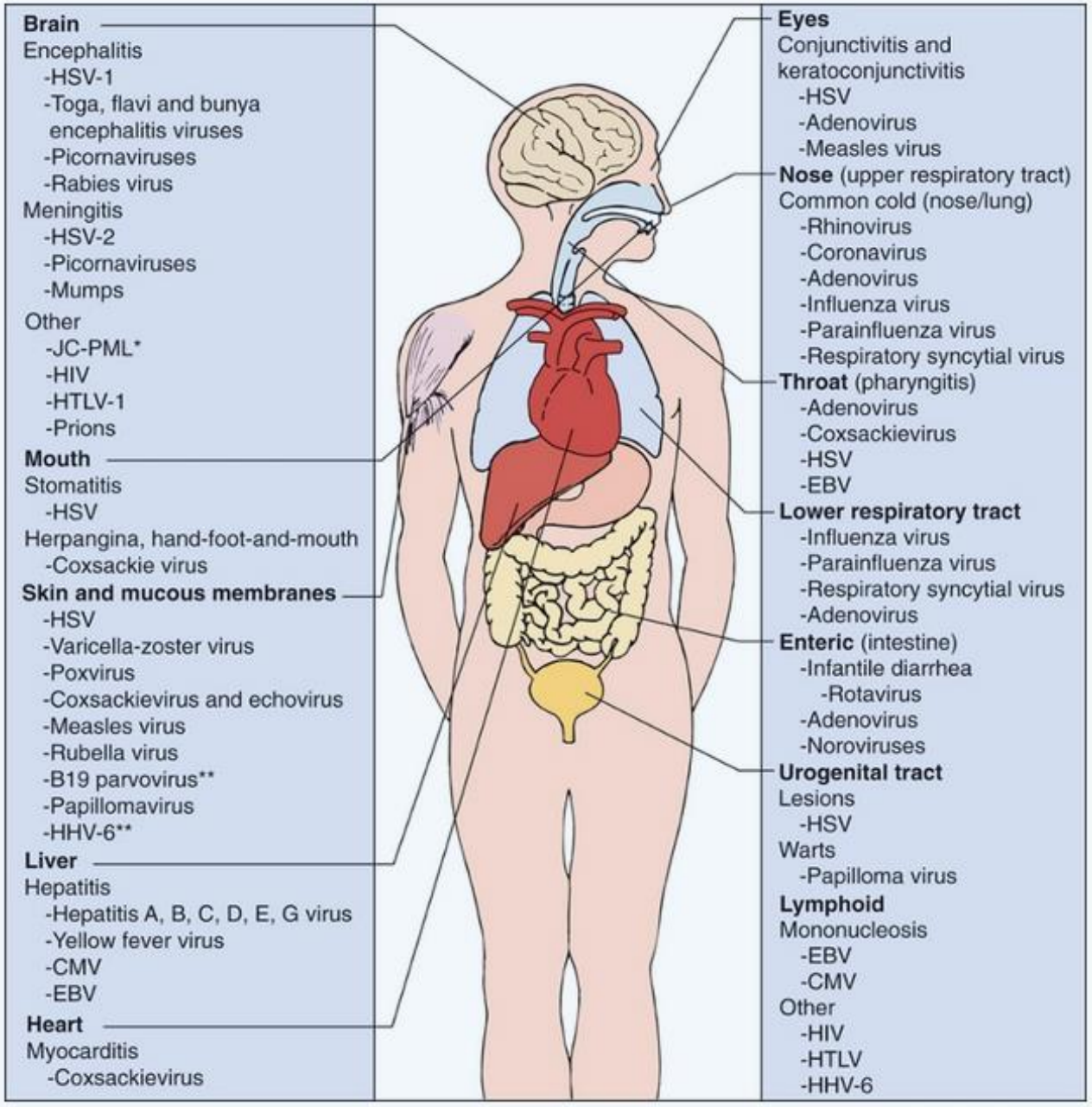
Brain
Encephalitis
-HSV-1
-Toga, flavi and bunya encephalitis viruses
-Picornaviruses
-Rabies virus
Meningitis
-HSV-2
-Picornaviruses
-Mumps
Other
-JC-PML*
-HIV
-HTLV-1
-Prions
Mouth
Stomatitis
-HSV
Herpangina, hand-foot-and-mouth
-Coxsackie virus
Skin and mucous membranes
-HSV
-Varicella-zoster virus
-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

Direct damage

- **Lysis**
- **Transformation**

Indirect damage
(Immuno-pathology)

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

Il danno cellulare irreversibile a cui segue la morte cellulare dovuta a processi patologici viene chiamato **necrosi**. È una morte cellulare incontrollata che provoca rigonfiamento degli organuli cellulari, rottura della membrana plasmatica ed eventuale lisi della cellula e fuoriuscita di contenuto intracellulare nel tessuto circostante con conseguente danno tissutale.

L'autofagia (dal greco, "mangiare se stesso") è un processo catabolico lisosomiale che la cellula mette in atto in risposta a condizioni di stress particolarmente elevate (carenza nutrizionale, stress ossidativi) degradando alcuni dei propri elementi al fine di rifornirsi di energia e garantirsi la sopravvivenza.

L'apoptosi (dal termine greco che indica la caduta dei petali dei fiori e delle foglie degli alberi) è invece una forma di suicidio della cellula che avviene in modo programmato e ordinato, di norma quindi non in risposta a situazioni di stress, e che contribuisce al mantenimento del normale numero di cellule di un sistema (organo e/o tessuto).

Autofagia e apoptosi sono anche importanti meccanismi che la cellula, quando è infettata, usa per contrastare la diffusione dei virus (sia a RNA che a DNA).

La necroptosi e piroptosi condividono diversi processi chiave sia con l'apoptosi che con l'autofagia

Interrelazioni fra apoptosi, autofagia e necrosi

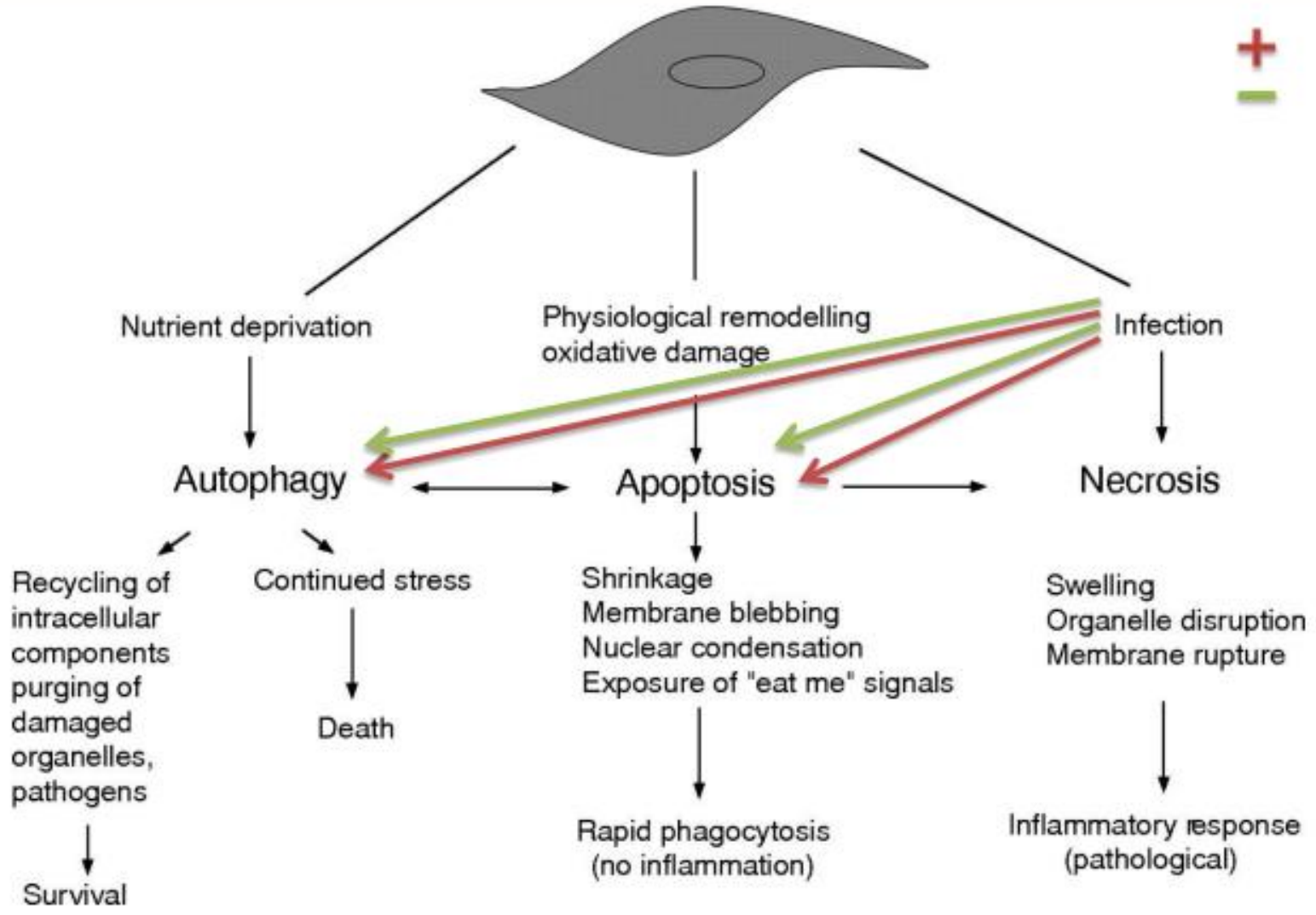

Tabella 37.3 Alcuni meccanismi usati dai virus per contrastare l'apoptosi.

Virus	Meccanismo di inibizione dell'apoptosi
Adenovirus	La proteina E1B-19K forma eterodimeri con varie proteine pro-apoptotiche della famiglia Bcl-2 (Bax, Bak, BNIP3, Bnip3L) stabilizzando la membrana mitocondriale, prevenendone la permeabilizzazione e di conseguenza bloccando il rilascio di una varietà di fattori attivanti le caspasi (citocromo c, AIF, apoptosoma) Le proteine E1B-55k e E4 ORF6 promuovono la degradazione di p53 e di conseguenza diminuiscono l'espressione di membri pro-apoptotici della famiglia Bcl-2
EBV	La proteina LMP-1 interagisce con proteine della famiglia Bcl-2 e up-regola proteine anti-apoptotiche cellulari come A20 e bfl-1. Il virus codifica anche 2 proteine omologhe a Bcl-2: una, detta BHRF-1, funziona in senso anti-apoptotico, l'altra interagisce con Bax e Bak e inibisce l'apoptosi
HHV-8	Codifica una proteina omologa a Bcl-2 che blocca l'apoptosi anche, ma non solo, formando eterodimeri con Bcl-2 L'antigene nucleare LNA-1 lega pRB/E2F e interagisce con p53
HPV	La proteina E6 promuove la degradazione di p53 attraverso il complesso E6-proteina ligasi AP

Tabella 37.2 Alcuni meccanismi usati dai virus per contrastare l'autofagia cellulare.

Virus	Meccanismo di inibizione dell'autofagia	Effetto sull'interazione ospite-patogeno
Virus a DNA		
HSV-1	La proteina virale ICP34.5 inibisce il signaling PKR e lega direttamente la beclina 1 nei neuroni	Determina neurovirulenza
HHV-8	Le proteine virali Bcl-2-like legano direttamente la beclina 1 in molte linee cellulari	Sconosciuto
CMV	Sconosciuto, in fibroblasti primari	Sconosciuto
Virus a RNA		
HIV-1	Sono ridotti i livelli di beclina 1 in linfociti $CD4^+$ primari e in macrofagi della linea cellulare U937	Sconosciuto
SIV-1	L'infezione della microglia induce la produzione di molecole non note inibenti l'autofagia nei neuroni	Accumulo di aggregati proteici nei neuroni con potenziale contributo alla neurodegenerazione

Pathogenetic Mechanisms

Direct damage

- **Lysis**
- **Transformation**

Indirect damage
(Immuno-pathology)

- **Damage on inflammatory base**
- **- T-Cell dependent Immunopathology Via Generation of CD8 T Cells**
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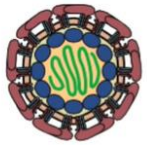
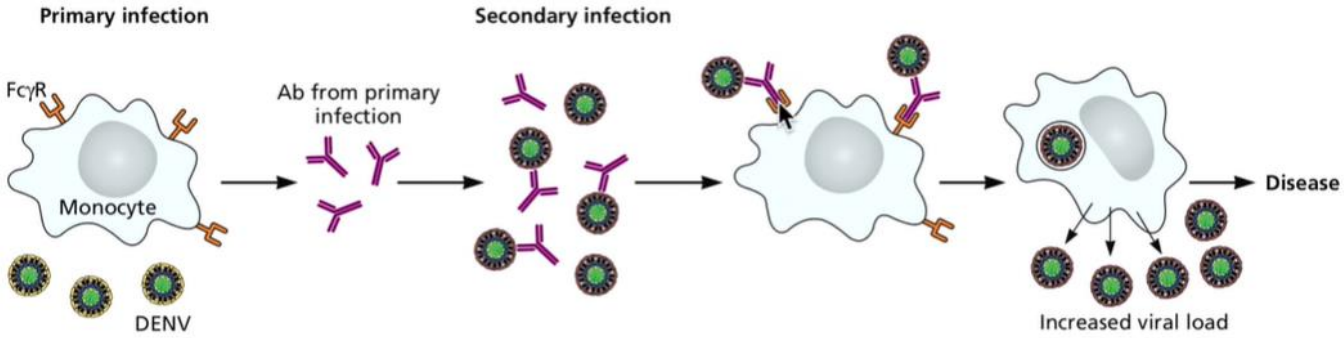


Dengue fever

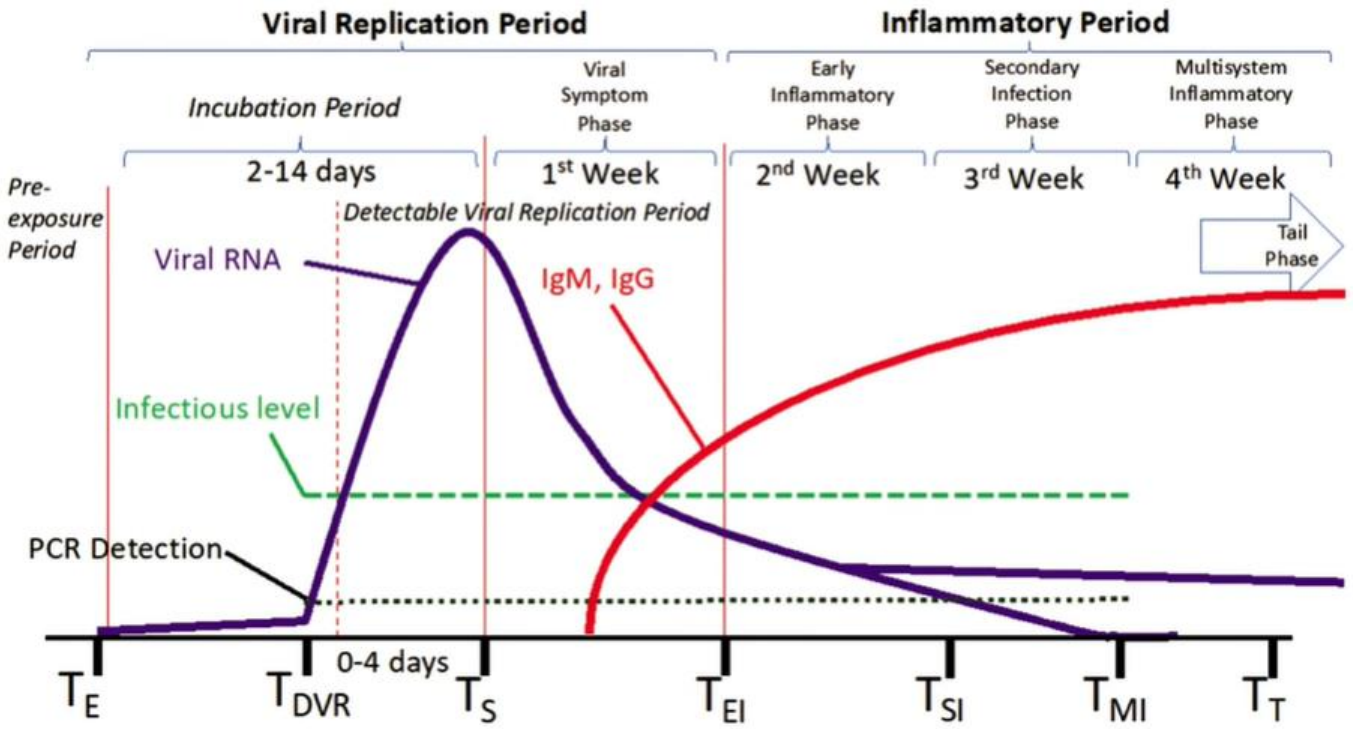
- Primary infection asymptomatic or *acute febrile illness with severe headache, back and limb pain and rash. Severe aches and pains in the bones.*
  - Normally self-limiting, patients recover in 7-10 days
  - In 1/14,000 primary infections: dengue hemorrhagic fever, life threatening disease
  - Internal bleeding leads to fatal dengue shock syndrome
- Antibodies to virus made; four serotypes, no cross-protection

Dengue fever



After secondary dengue infections, incidence of hemorrhagic fever and shock (severe dengue) 1/90 and 1/50

Stages of COVID-19



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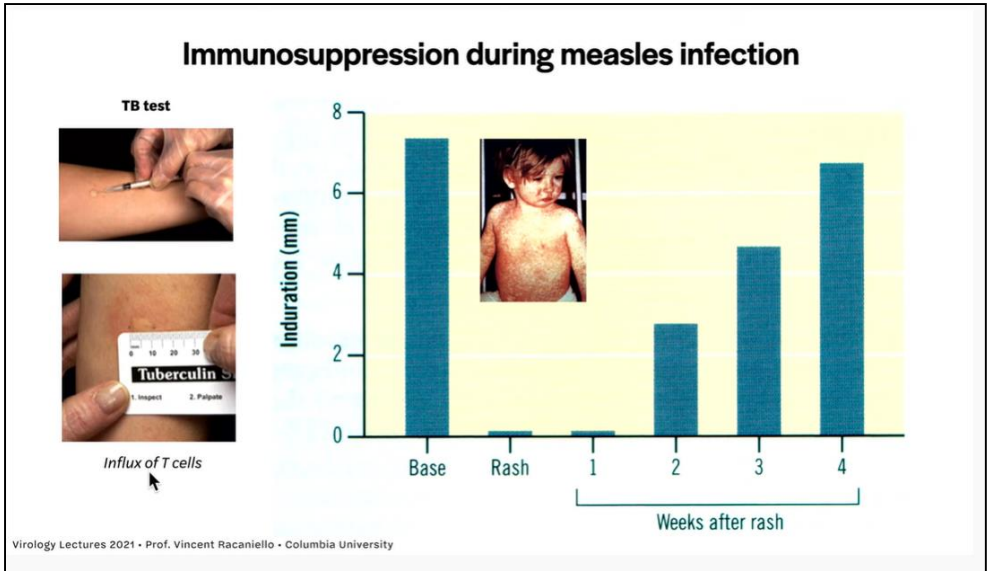
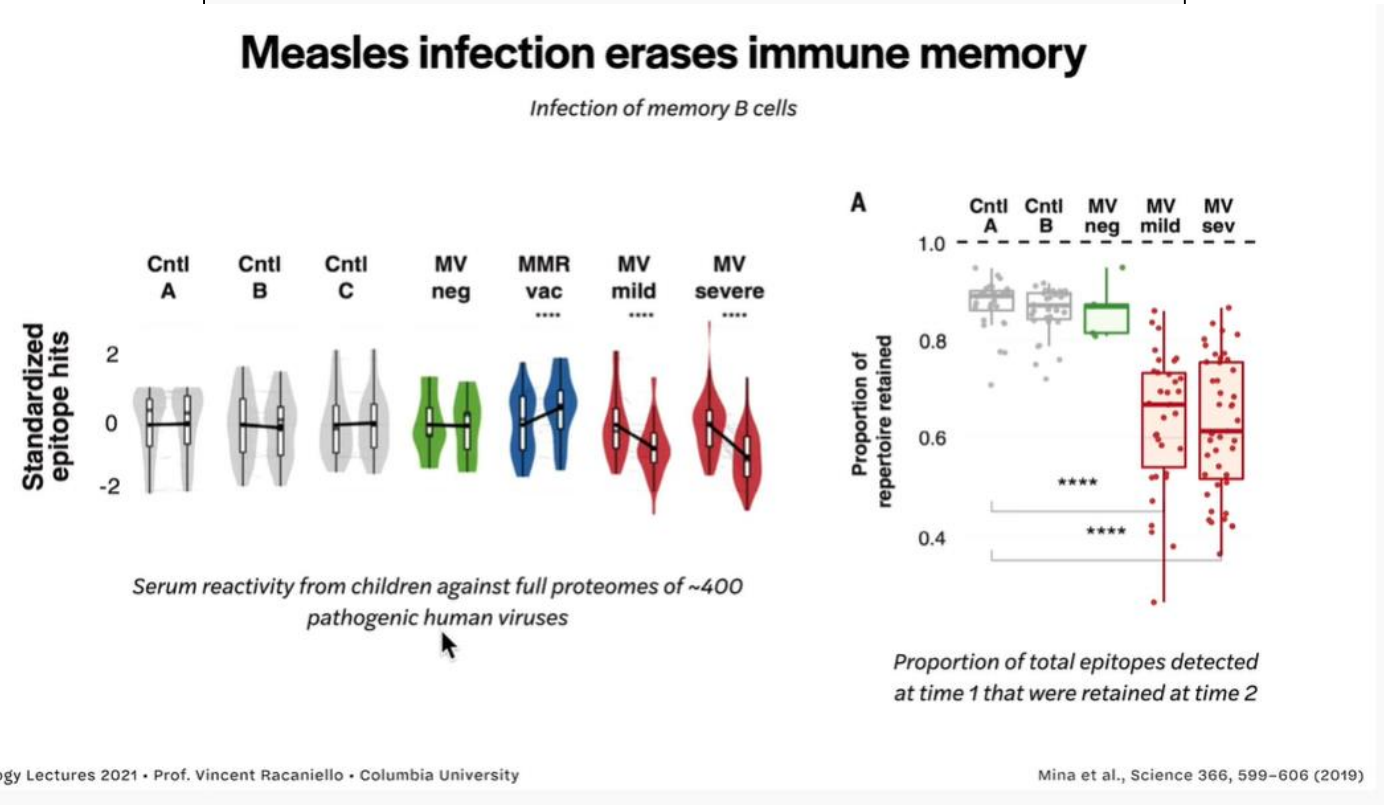
https://pubmed.ncbi.nlm.nih.gov/33556957/

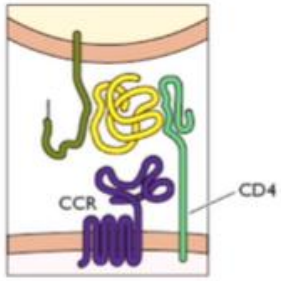
The skin test is read by palpating the site of injection to find an area of induration. The diameter of the indurated area should be measured across the forearm (perpendicular to the long axis). Erythema (redness) should not be measured.





I fattori cellulari e/o relativi all’ospite che possono influenzare un’infezione virale con riflessi sulla patogenesi sono molteplici, hanno diversa natura e possono intervenire in diverse fasi del ciclo replicativo del virus.

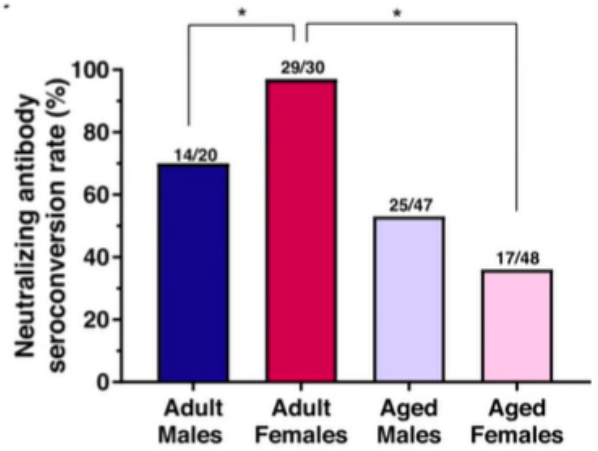
Host genes that determine *susceptibility*



- Ccr5-delta32 mutation protects vs HIV-1 infection
- Present in 4-16% of European descent
- Stem cell therapy cured German AIDS patient
- And the London patient: http://www.virology.ws/2019/03/13/the-london-patient/

Host determinants of virulence

- In general, males/men are slightly more susceptible to viral infections than females/women (but not always)
- Elevated humoral immunity in females compared with males is phylogenetically conserved - reproductive success?
- Female antibody responses correlate with elevated estradiol
- Pregnancy: hepatitis A, B, E, influenza, COVID-19 more lethal



npj Vaccines (2019)4:29 ; https://doi.org/10.1038/s41541-019-0124-6

Other determinants of virulence: Age

- Very young and very old humans most susceptible to disease
- Young - immaturity of immune response
- Old - less elastic alveoli, weaker respiratory muscles, diminished cough reflex; reduced rate of production of new immune cells (bone marrow diminishes with age)

Influenza, US, 1911-1915

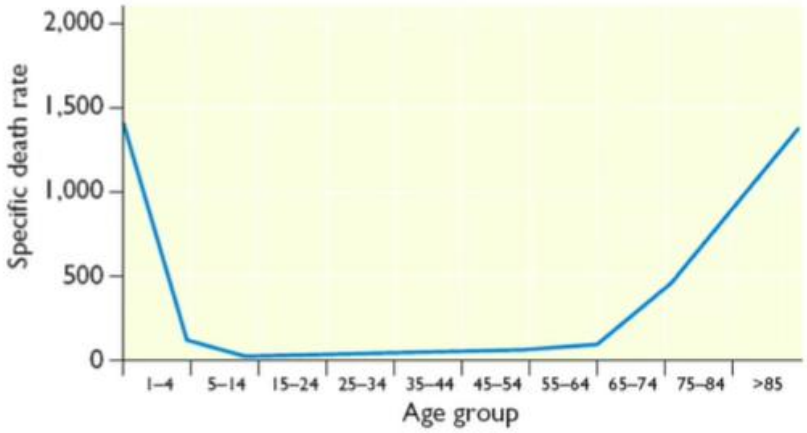


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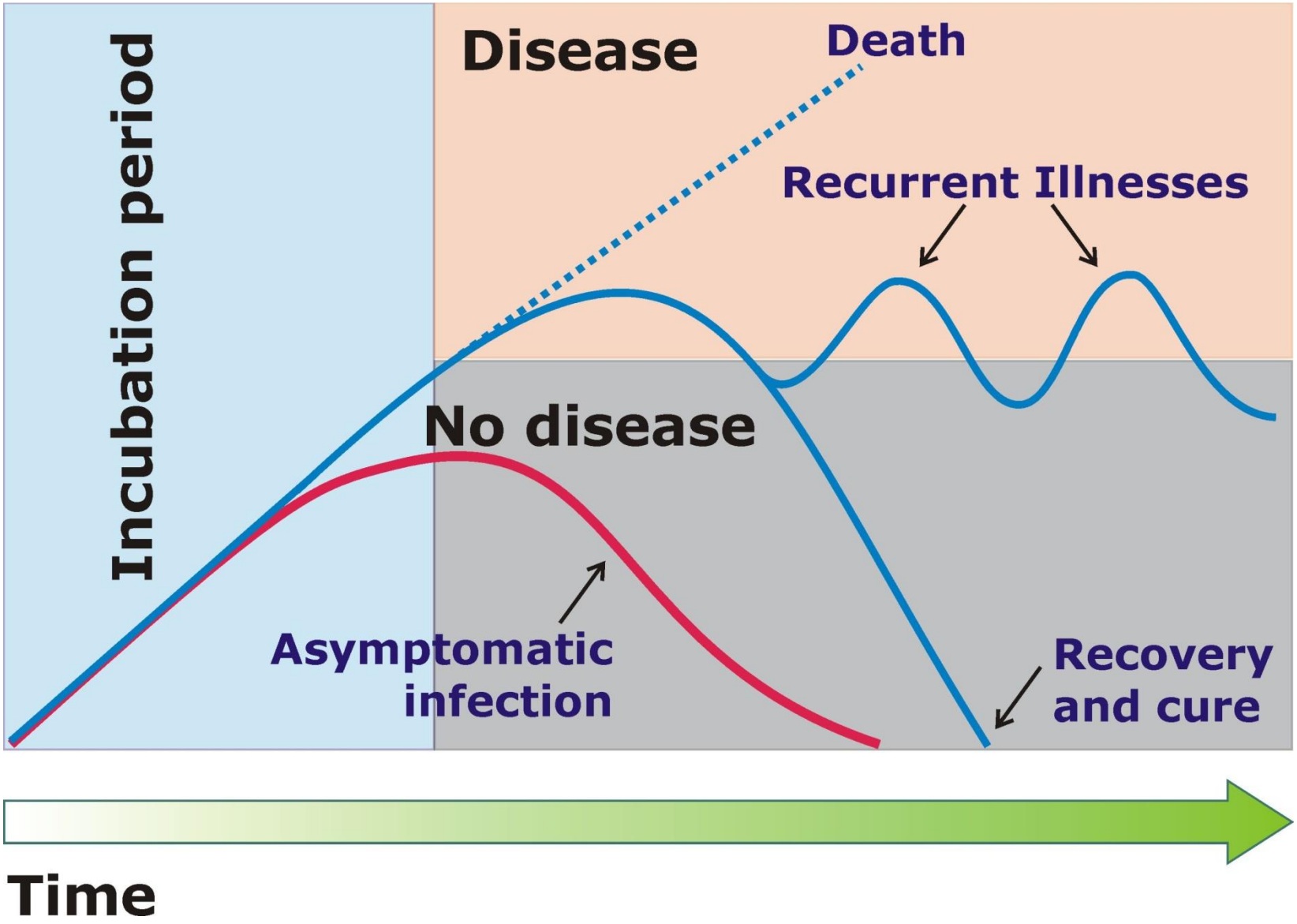
Tabella 37.4 **Progressione clinica delle infezioni virali.**

Infezioni virali clinicamente manifeste	Infezioni virali asintomatiche
1. Il virus è direttamente citopatico e distrugge nella sua replicazione le cellule infettate	**1**. Nessun danno al tessuto infettato da parte della replicazione virale
2. Il virus, ancorché non direttamente citopatico, induce nella sua replicazione una risposta citotossica verso le cellule infettate	**2**. Il tessuto infettato non ha un ruolo funzionale di rilievo
3. Il virus non è citopatico, ma nel corso dell'infezione fa acquisire alla cellula infettata, attraverso diversi meccanismi, le caratteristiche di "cellula trasformata"	**3**. Il danno prodotto dall'infezione è al di sotto della soglia di funzionalità del tessuto infettato
	4. Il tessuto è rapidamente riparato successivamente al danno prodotto dalla replica virale

Outcome of Viral Infections



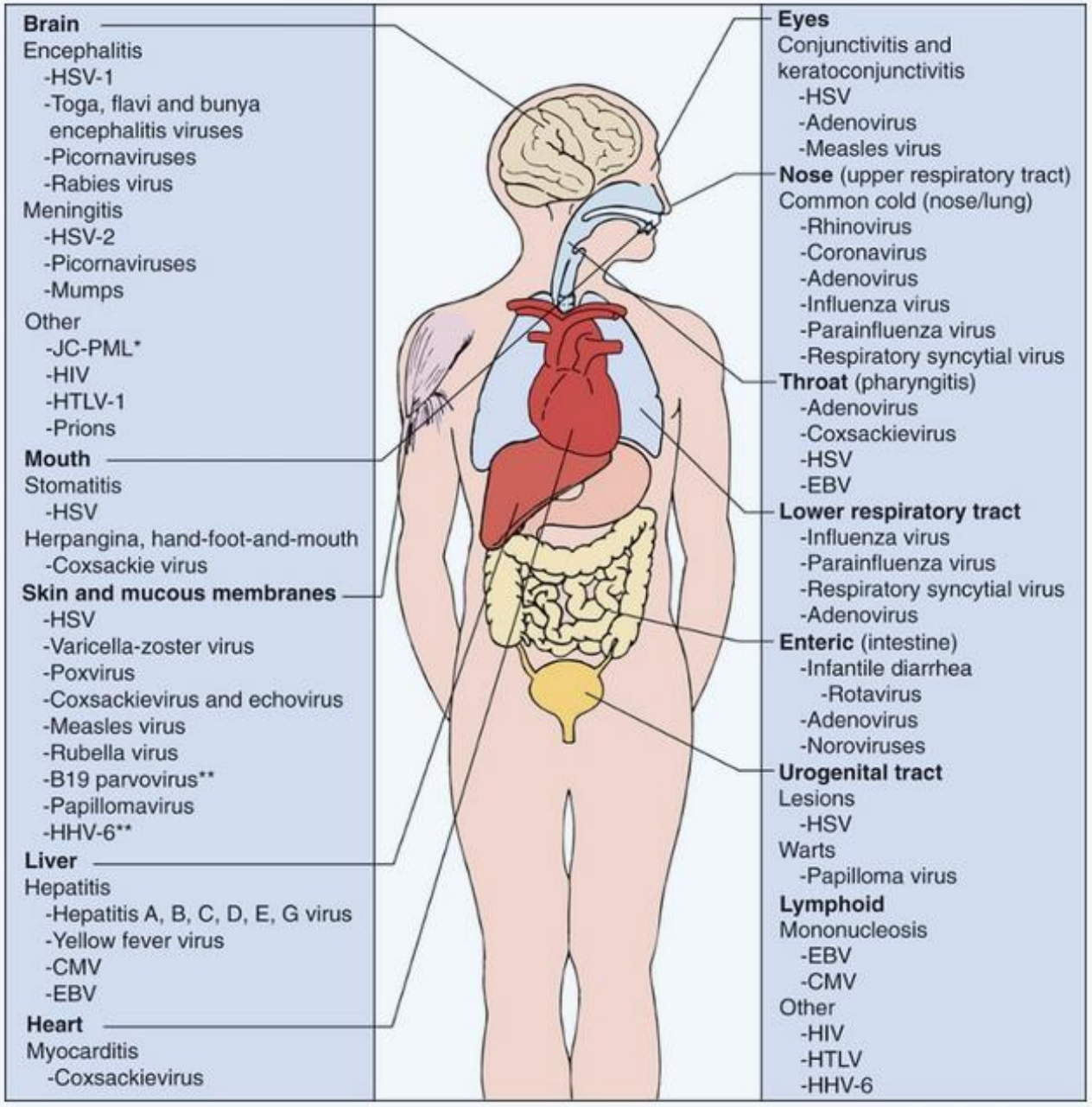
La **patogenicità** è la capacità di un virus di determinare in vivo lesioni o una malattia valutabile clinicamente. La patogenicità di virus diversi può, conseguentemente, essere valutata su una base clinica (ad es. infezione respiratoria clinicamente modesta o infezione respiratoria grave con insufficienza respiratoria) o con esami di laboratorio.

Con il termine **virulenza** si descrive invece una caratteristica del singolo isolato virale, abitualmente riferita alla quantità di virus necessaria a determinare un peculiare evento, sia in vivo sia in vitro, o alla capacità e velocità replicativa.

Patogenicità e virulenza hanno specifiche basi molecolari.

Per questo motivo sono stati moltiplicati gli studi finalizzati a evidenziare i determinanti genetici di specifiche caratteristiche fenotipiche dei virus patogeni, confrontandoli con quelli a patogenicità attenuata. La maggioranza di questi studi ha utilizzato strategie di mutagenesi sito-specifica per valutare il ruolo di singoli prodotti virali.

Varianti virali attenuati e tropismo selettivo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-Picornaviruses
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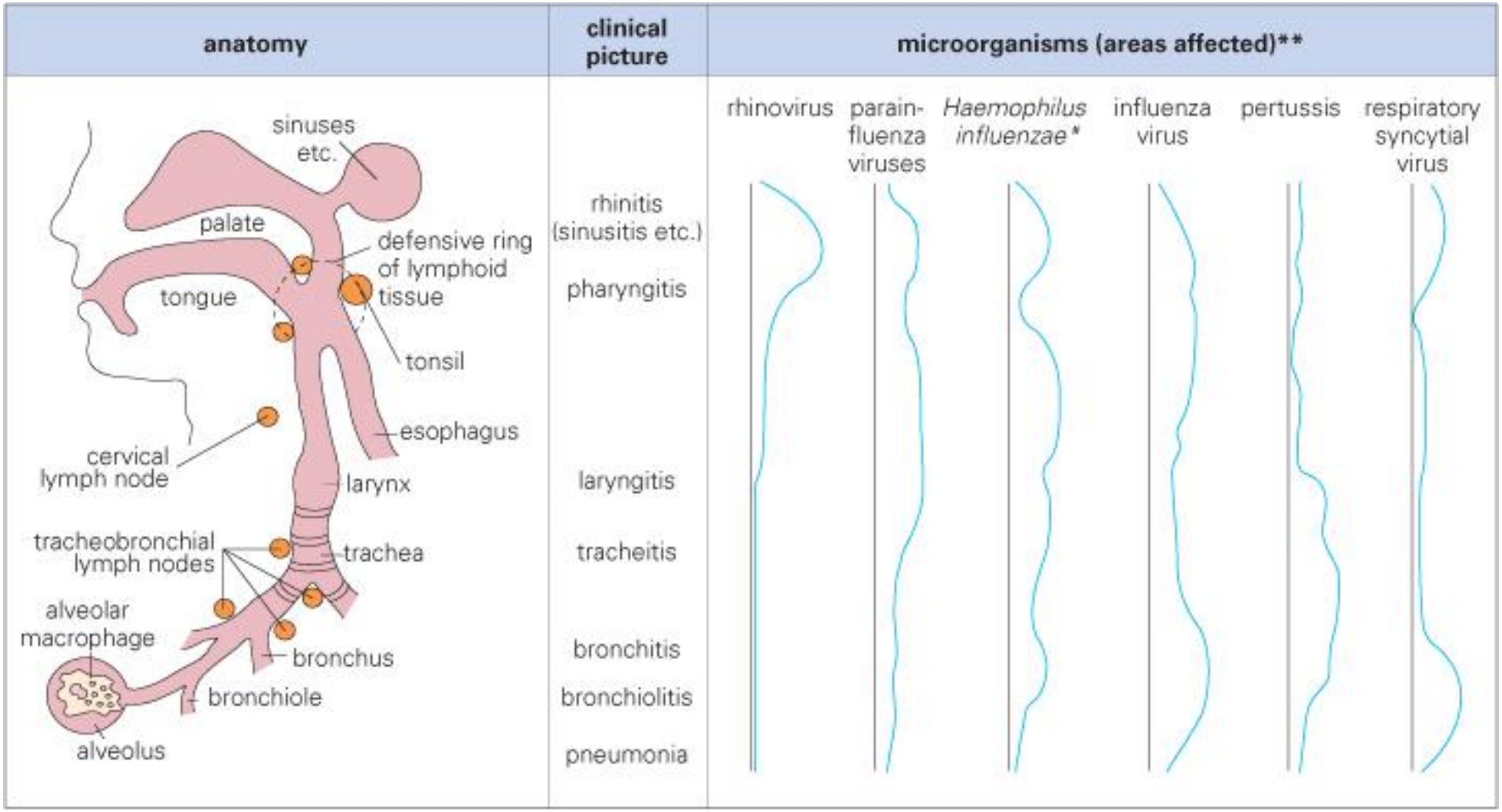
-Picornaviruses
-Mumps
Other
-JC-PML*
-HIV
-HTLV-1
-Prions
Mouth
Stomatitis
-HSV
Herpangina, hand-foot-and-mouth
-Coxsackie virus
Skin and mucous membranes
-HSV
-Varicella-zoster virus
-Poxvirus
-Coxsackievirus and echovirus
-Measles virus
-Rubella virus
-B19 parvovirus**
-Papillomavirus
-HHV-6**
Liver
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

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.

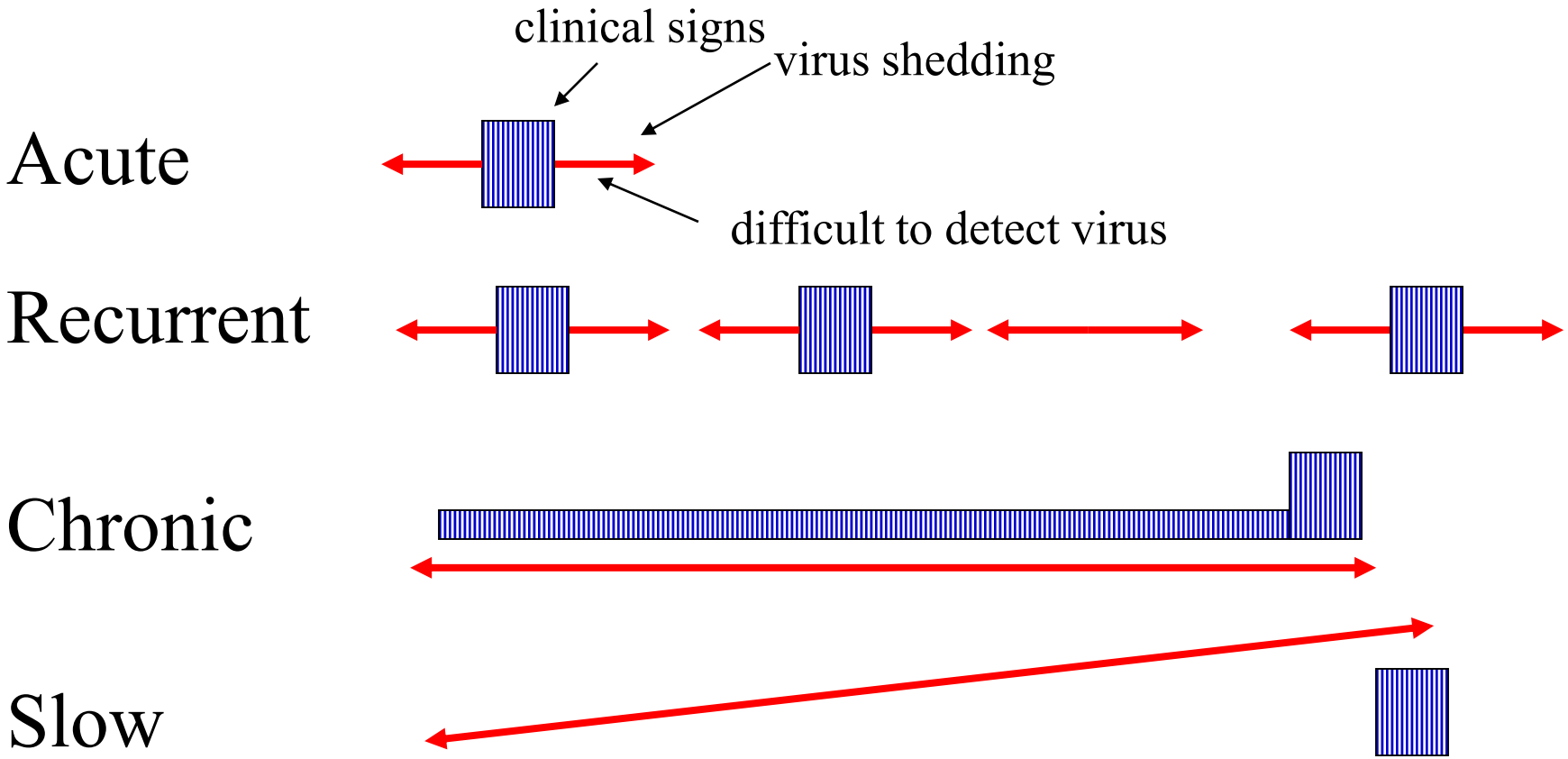
VIRAL PNEUMONIA		
virus	**clinical condition**	**comments**
influenza A or B	primary viral pneumonia or pneumonia associated with secondary bacterial infection	pandemics (type A) and epidemics (type A or B); increased susceptibility in elderly or in certain chronic diseases; antivirals and vaccine available
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.)

Patterns of disease

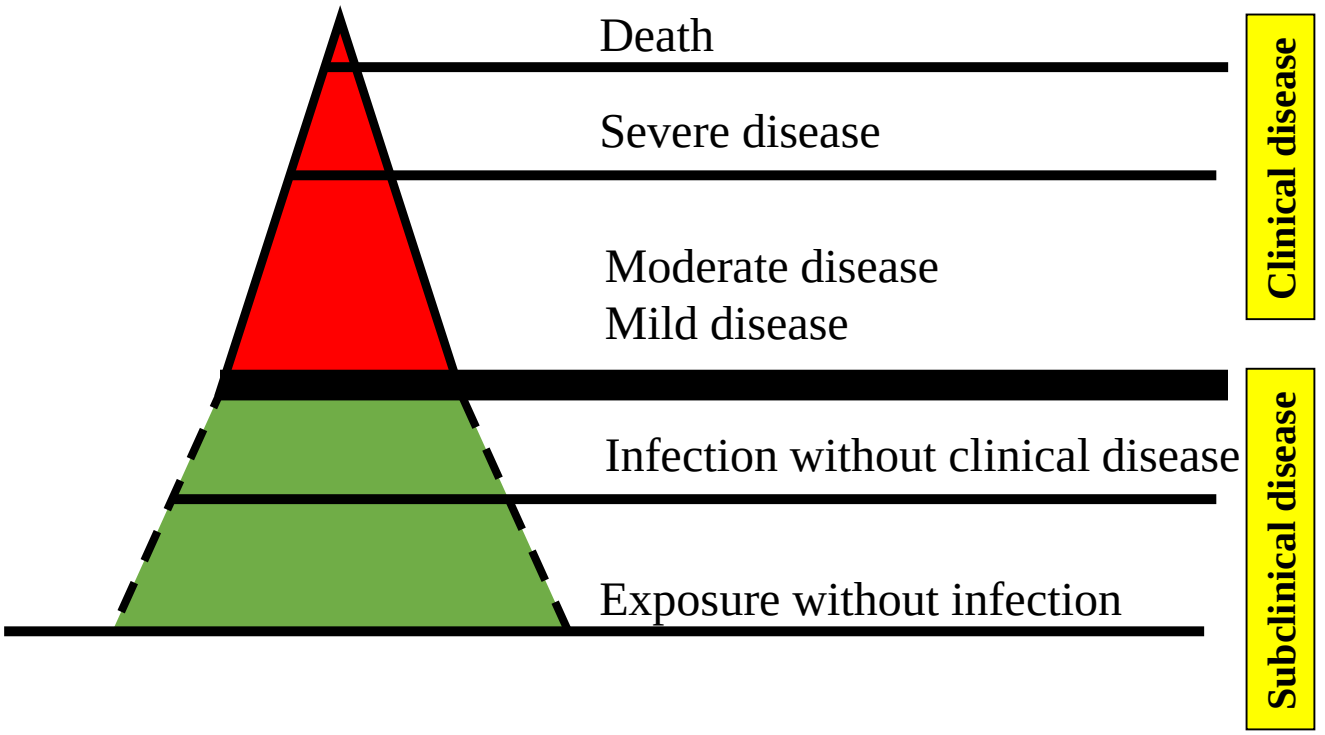


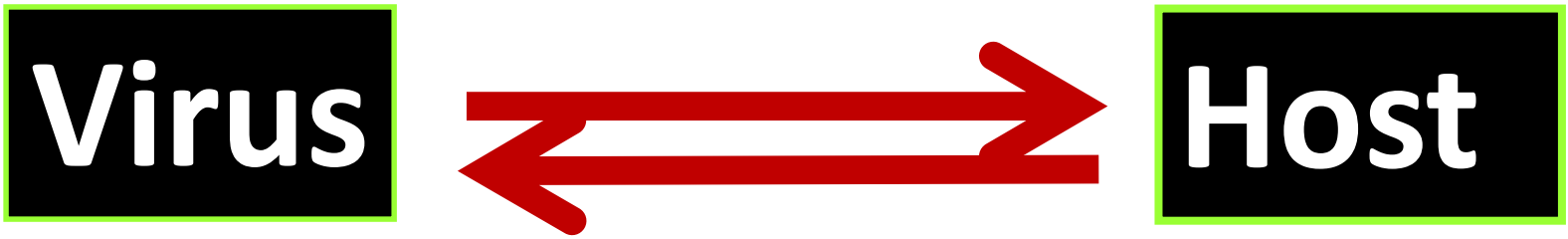
Microorganisms (including viruses) and respiratory system

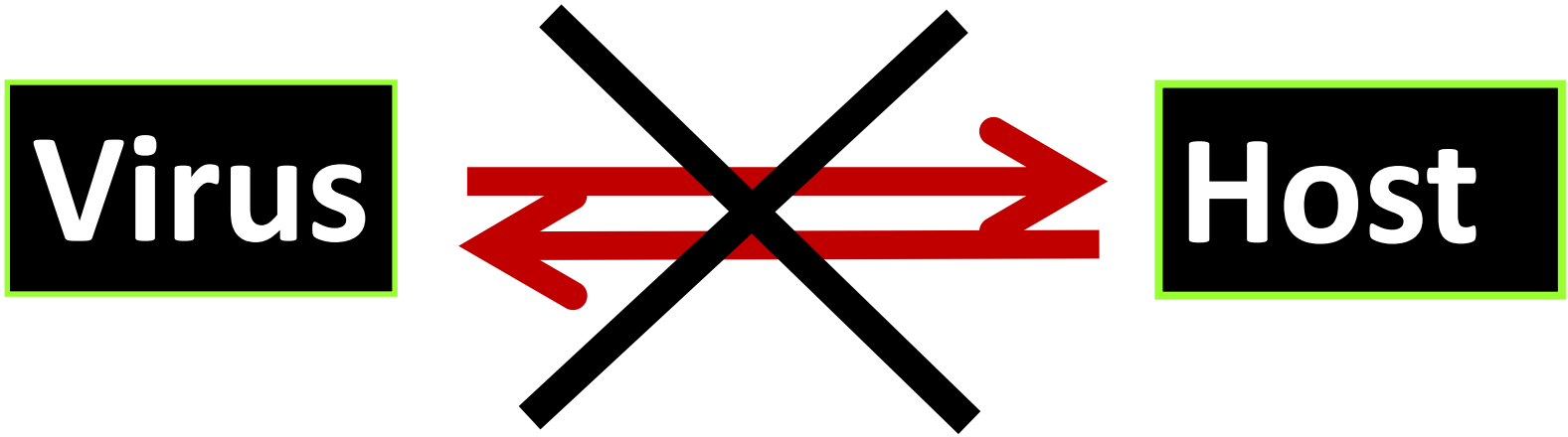
- In a closed environment, there are on average 500-1000 organisms/cubic meter.
- The ventilation rate (at rest) is 6 liters / minute.
- It is estimated that our lungs inhale about 12,000 liters of air per day.

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

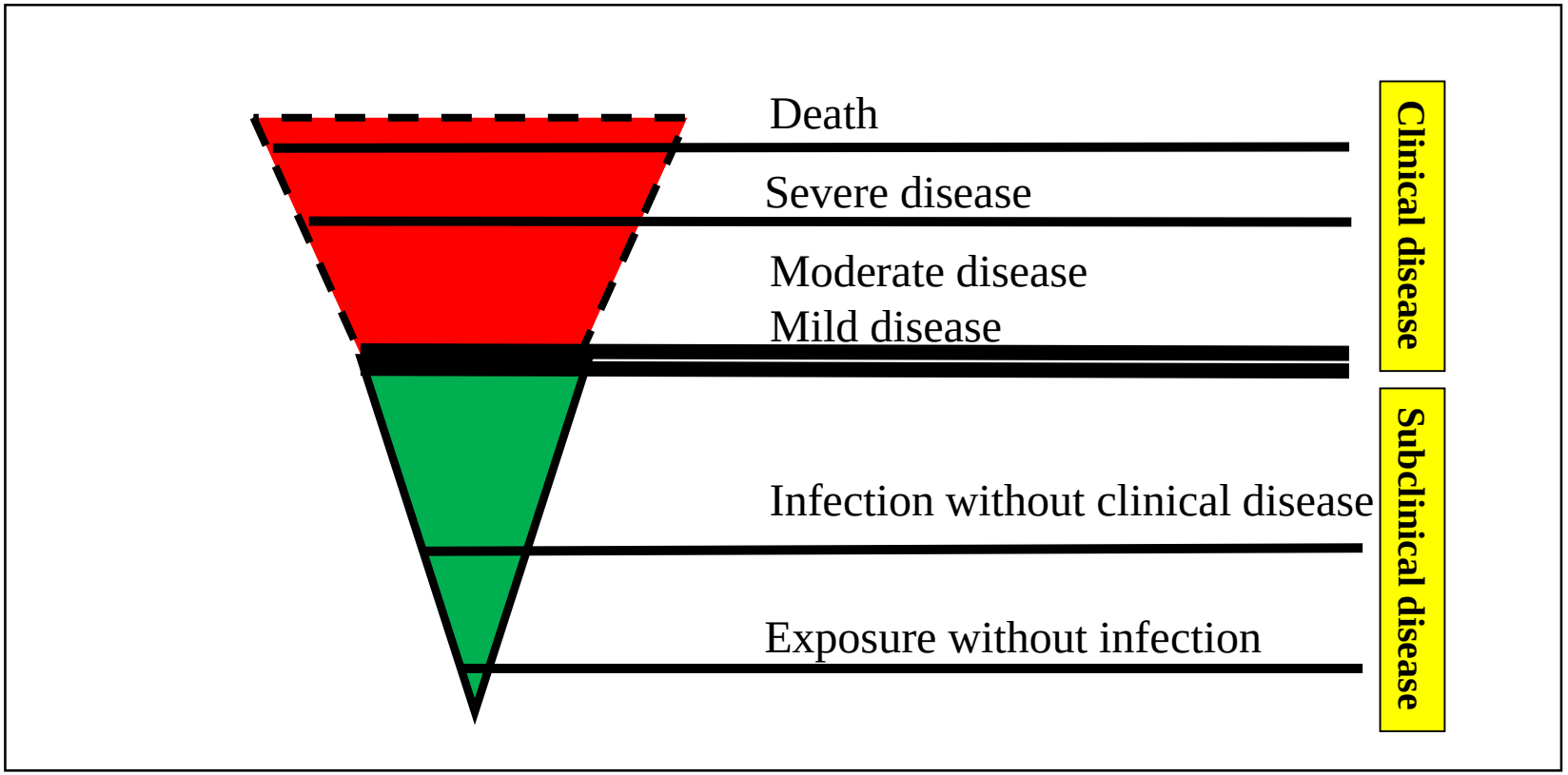
ICEBERG CONCEPT OF INFECTIOUS DISEASES

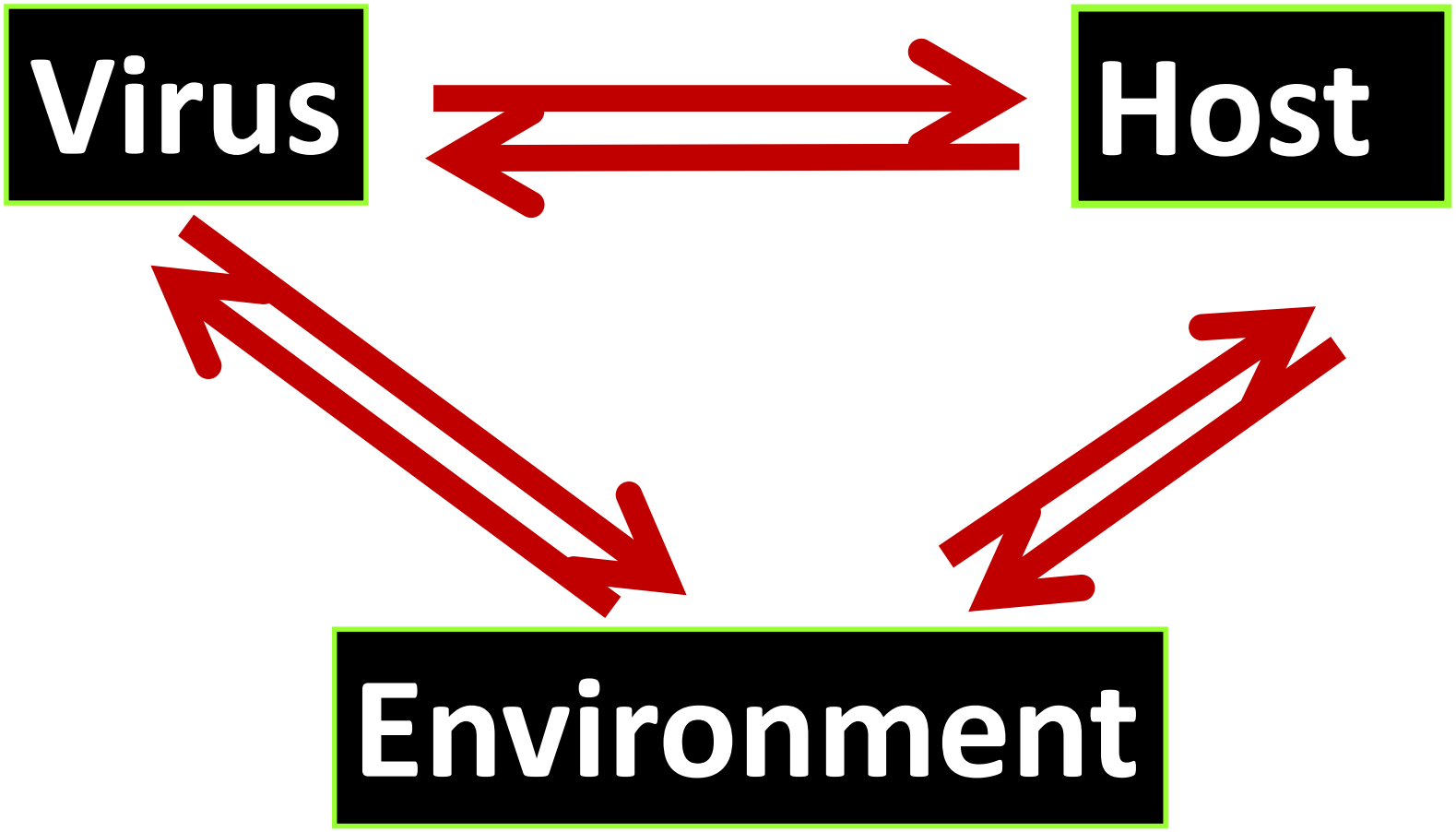



Virus
Host

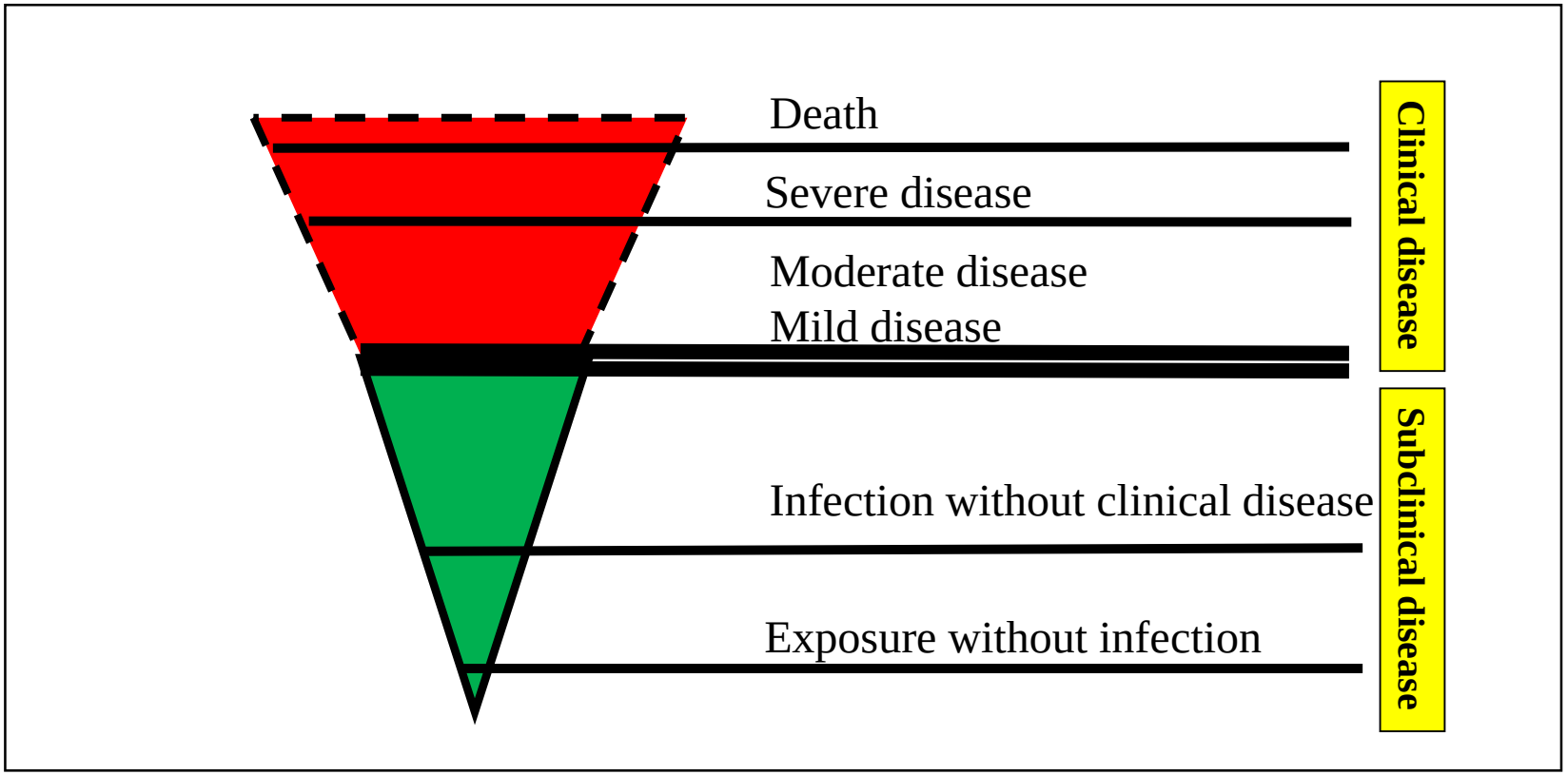

Virus
Host

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*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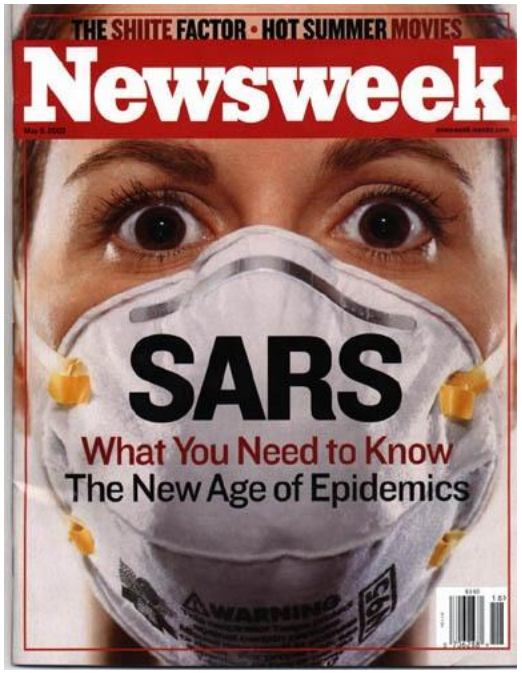
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Emergence of viral infections may be due to:

- the spread of a new agent
- reappearance (or re-emergence) of a known infection after a decline in incidence

Possible sources of “new viruses”

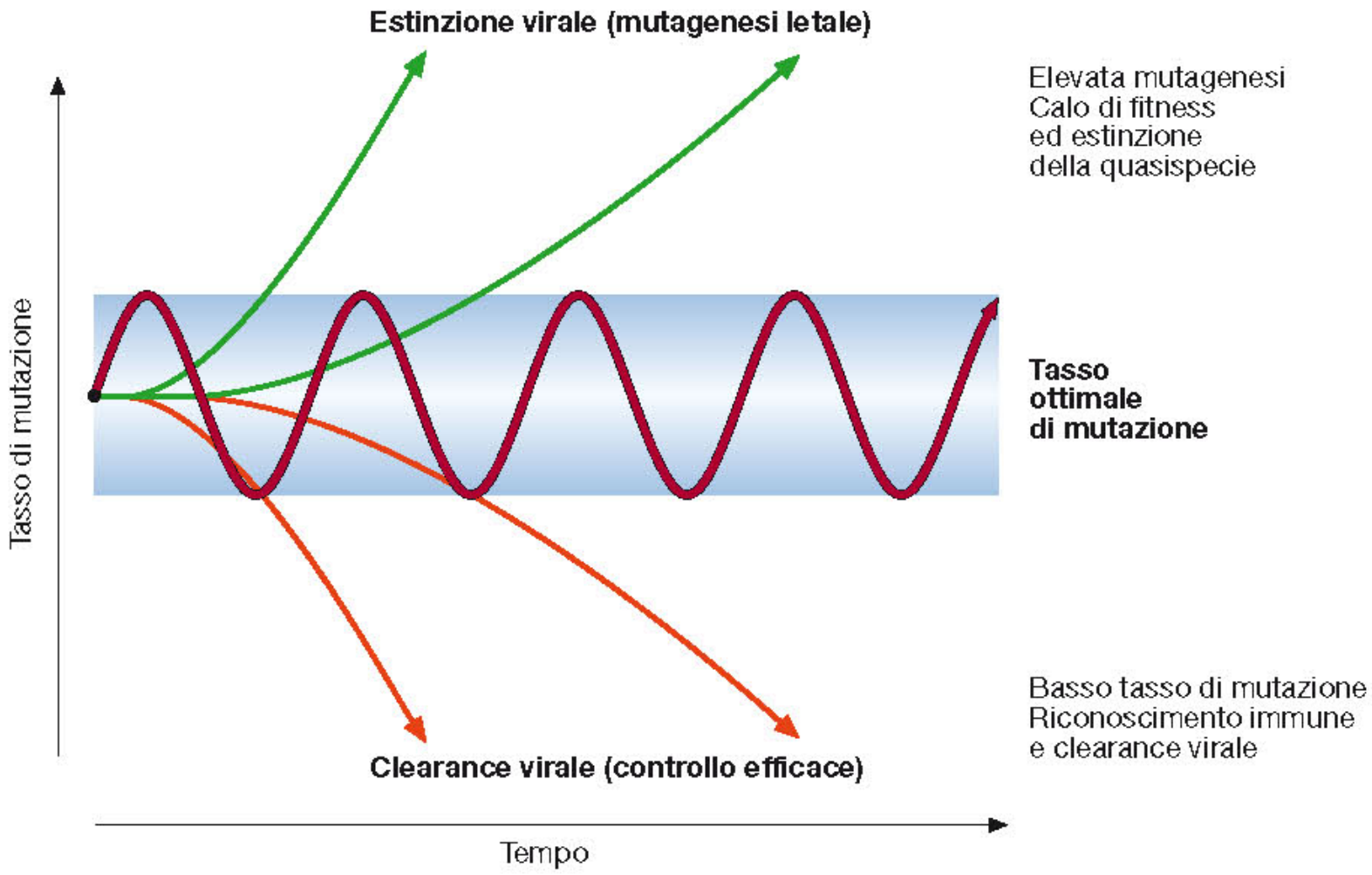
- *De novo* evolution
- “Viral Traffic”

- 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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- De novo evolution
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- New virus or new variant
- Interspecies transfer from the “zoonotic pool”
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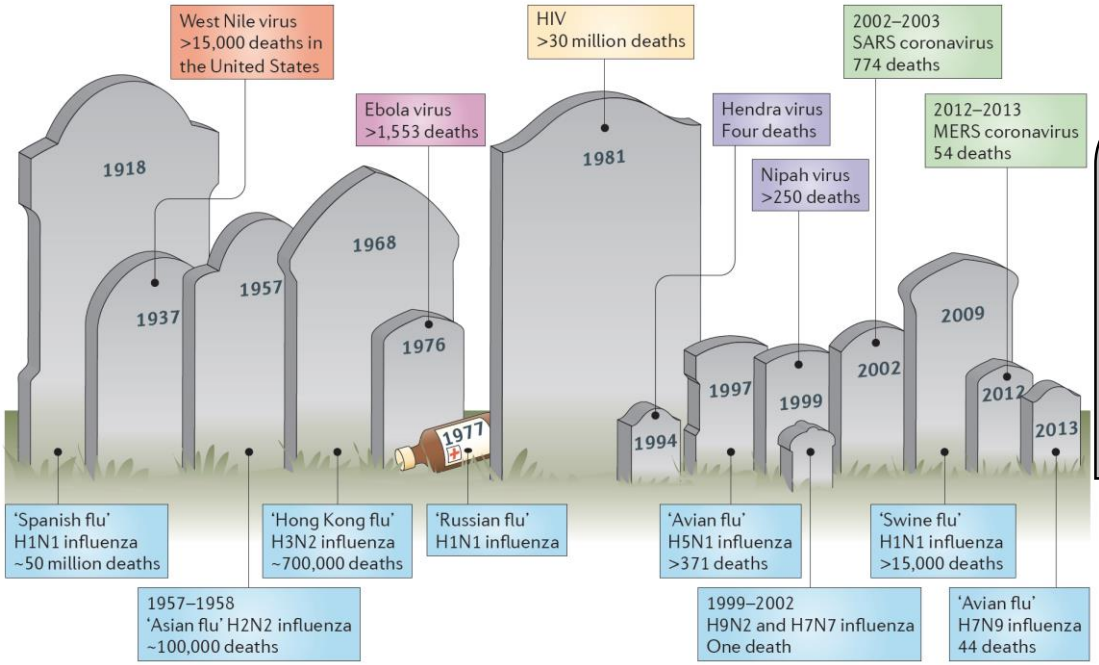
Emerging infectious disease: Examples of viral diseases likely originated by spillover events

SARS-CoV- 2
774,834,251 Cases
7,007,007 Deaths
(March 3, 2024
(source WHO)

2019



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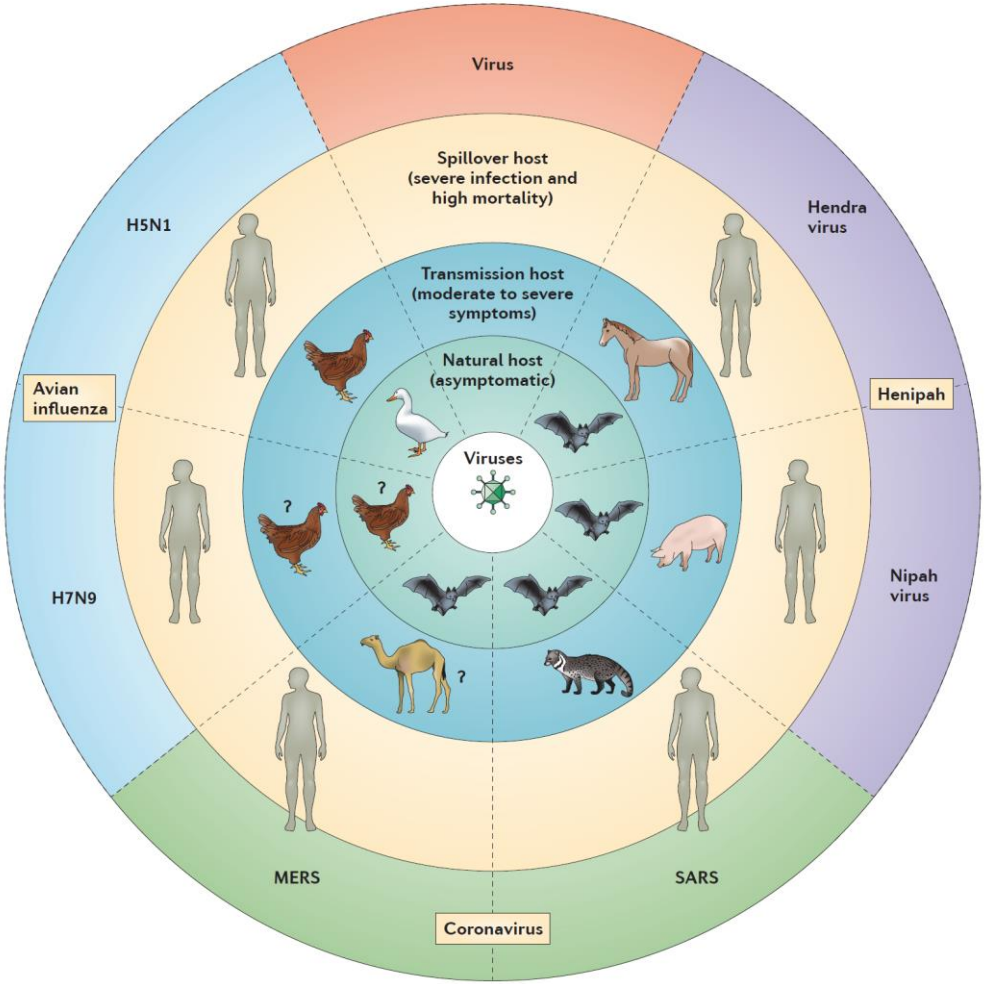
Studying immunity to zoonotic diseases in the natural host — keeping it real

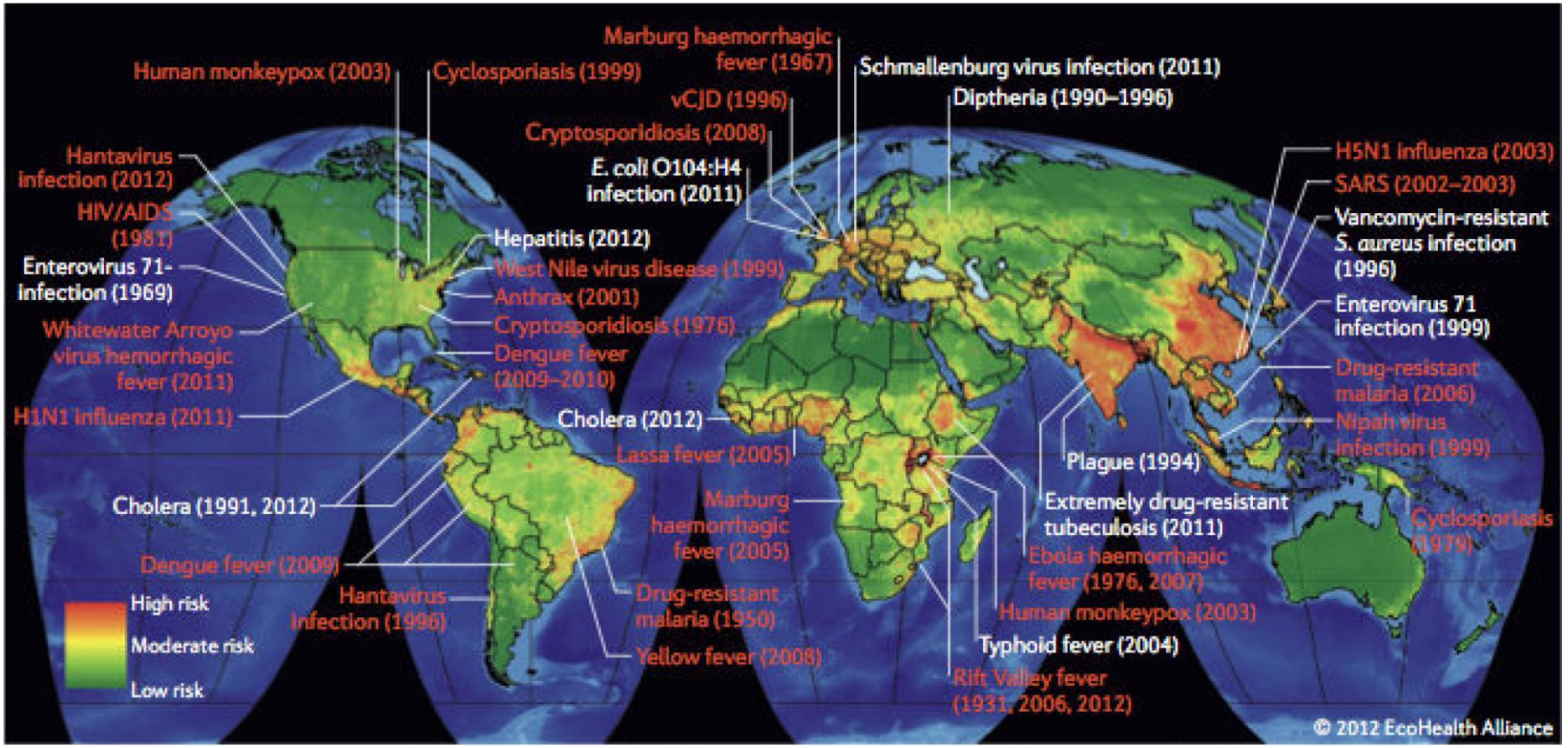
Andrew G. D. Bean[1], Michelle L. Baker[1], Cameron R. Stewart[1], Christopher Cowled[1], Celine Deffrasnes[1], Lin-Fa Wang[1,2] and John W. [illegible]



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



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