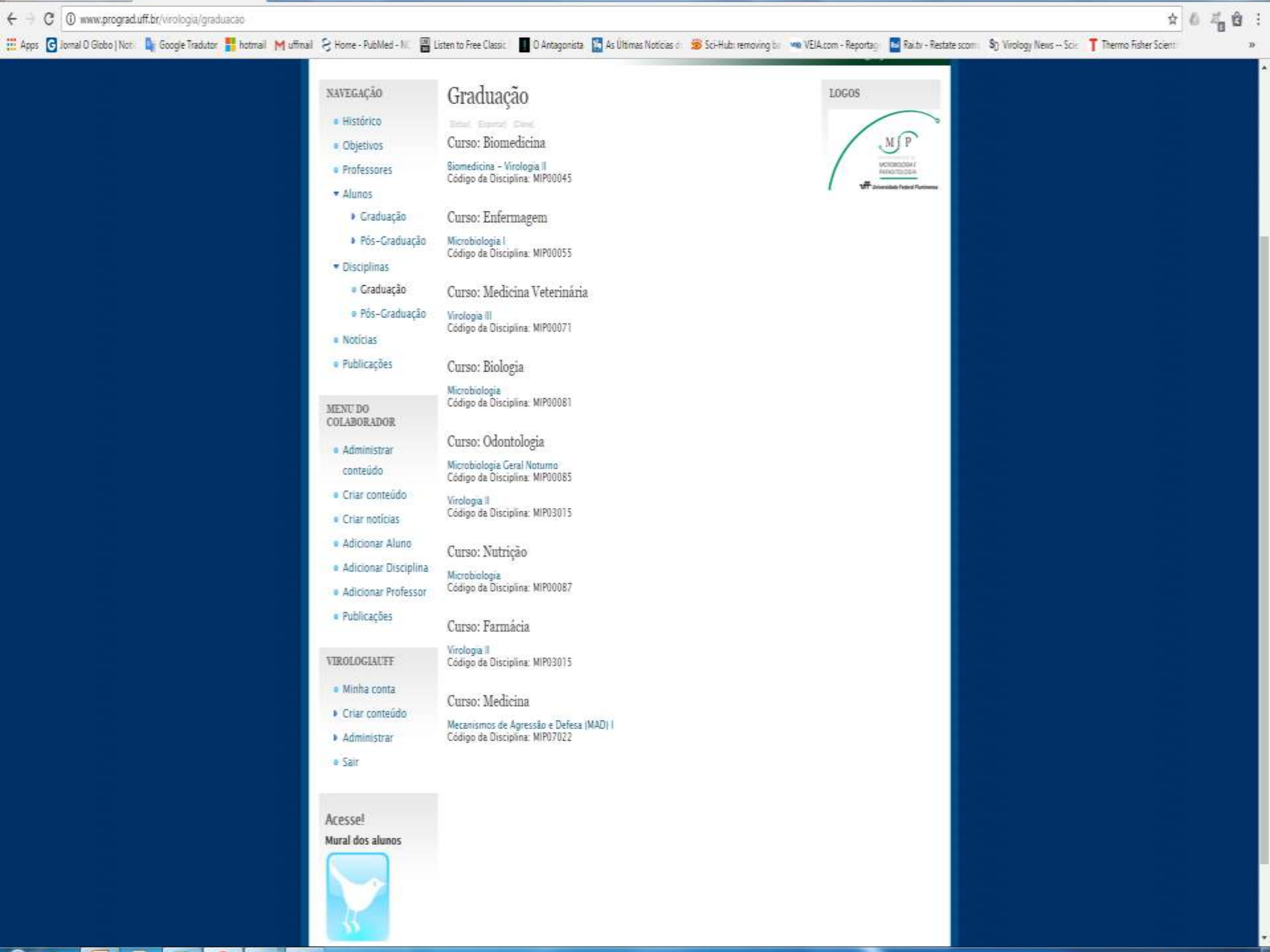
Patogênese Viral I: Conceitos gerais e Mecanismos de Emergência de Patógenos

Rafael Brandão Varella
Prof. Adjunto de Virologia
Departamento de Microbiologia e Parasitologia
UFF



Graduação

Curso: Biomedicina

Biomedicina - Virologia II
Código da Disciplina: MIP00045

Curso: Enfermagem

Microbiologia I
Código da Disciplina: MIP00055

Curso: Medicina Veterinária

Virologia III
Código da Disciplina: MIP00071

Curso: Biologia

Microbiologia
Código da Disciplina: MIP00081

Curso: Odontologia

Microbiologia Geral Noturno
Código da Disciplina: MIP00085

Virologia II
Código da Disciplina: MIP03015

Curso: Nutrição

Microbiologia
Código da Disciplina: MIP00087

Curso: Farmácia

Virologia II
Código da Disciplina: MIP03015

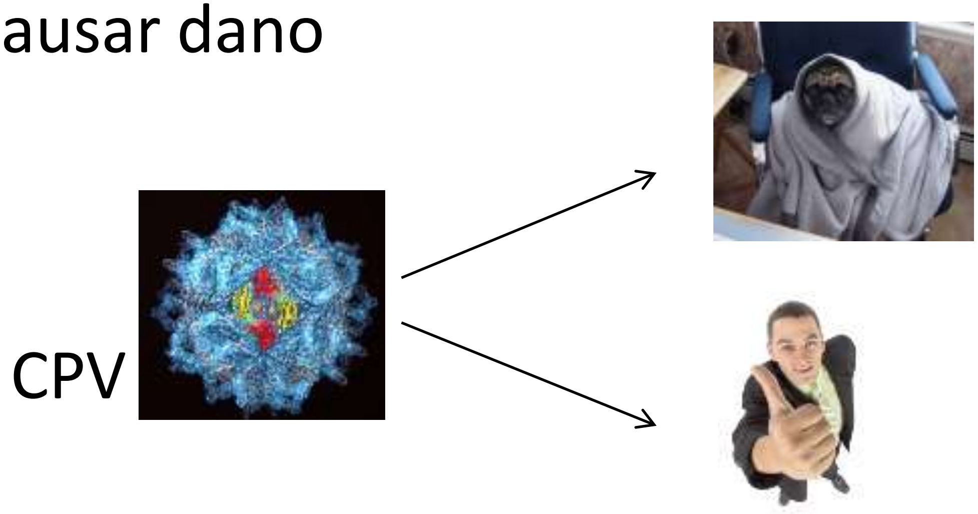
Curso: Medicina

Mecanismos de Agressão e Defesa (MAD) I
Código da Disciplina: MIP07022

Patogênese

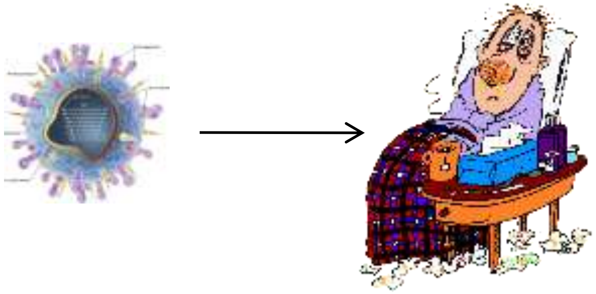
“processo ou mecanismo de desenvolvimento de uma doença”

- Patogenicidade: capacidade do vírus em infectar o hospedeiro e causar dano

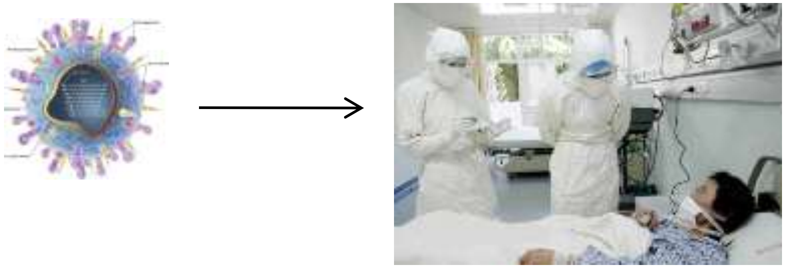


- Virulência: capacidade relativa de causar dano

HCoV



SARS



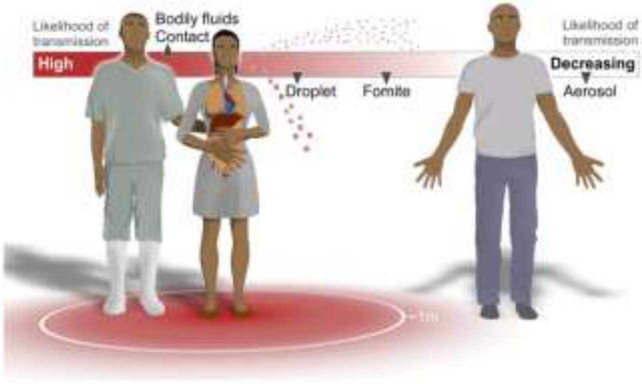
Fatores virais relevantes para o sucesso da infecção:

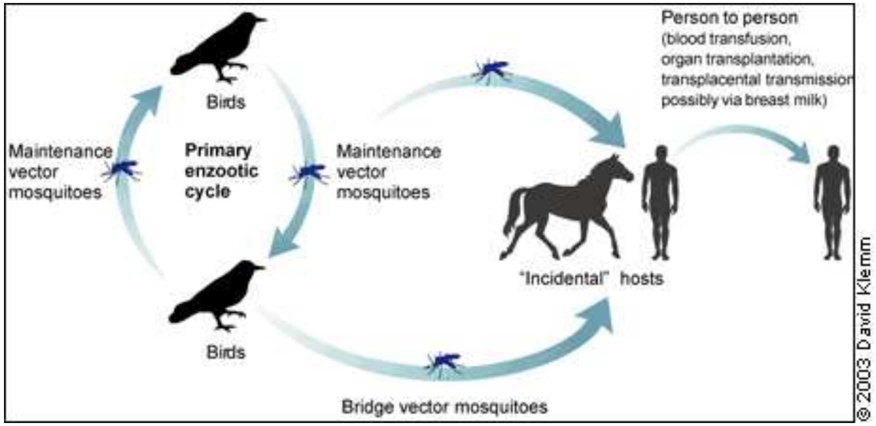
1. **Inóculo viral (conc. de vírus; propriedades do vírus)**

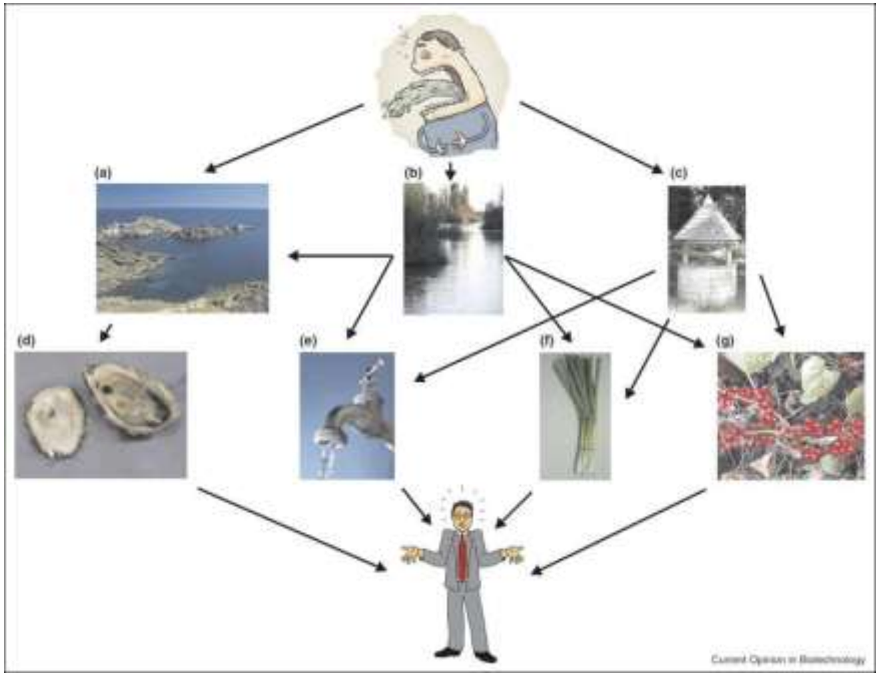
2. **Tropismo (susceptibilidade e permissividade)**

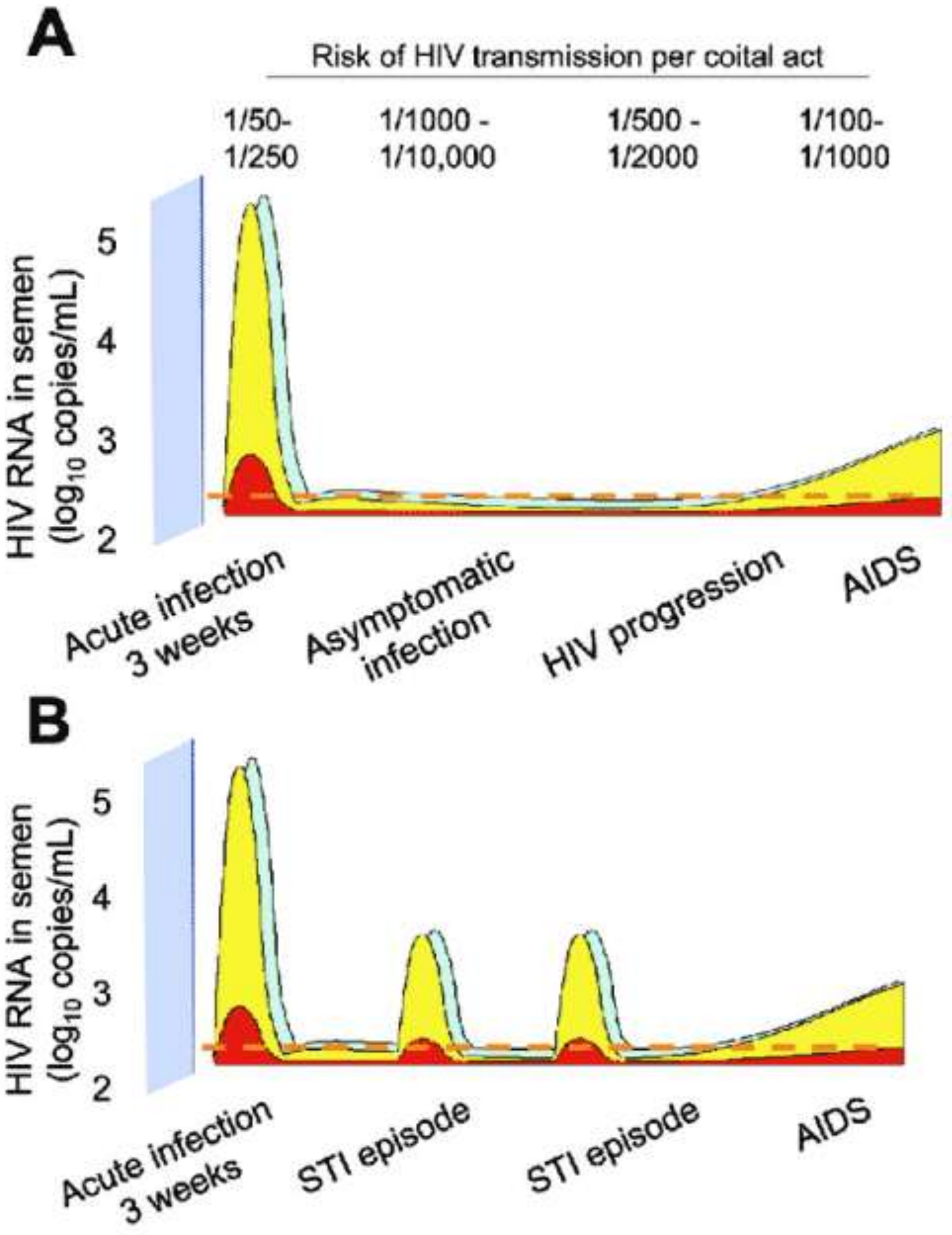
3. **Evasão das defesas do hospedeiro**

TRANSMISSÃO

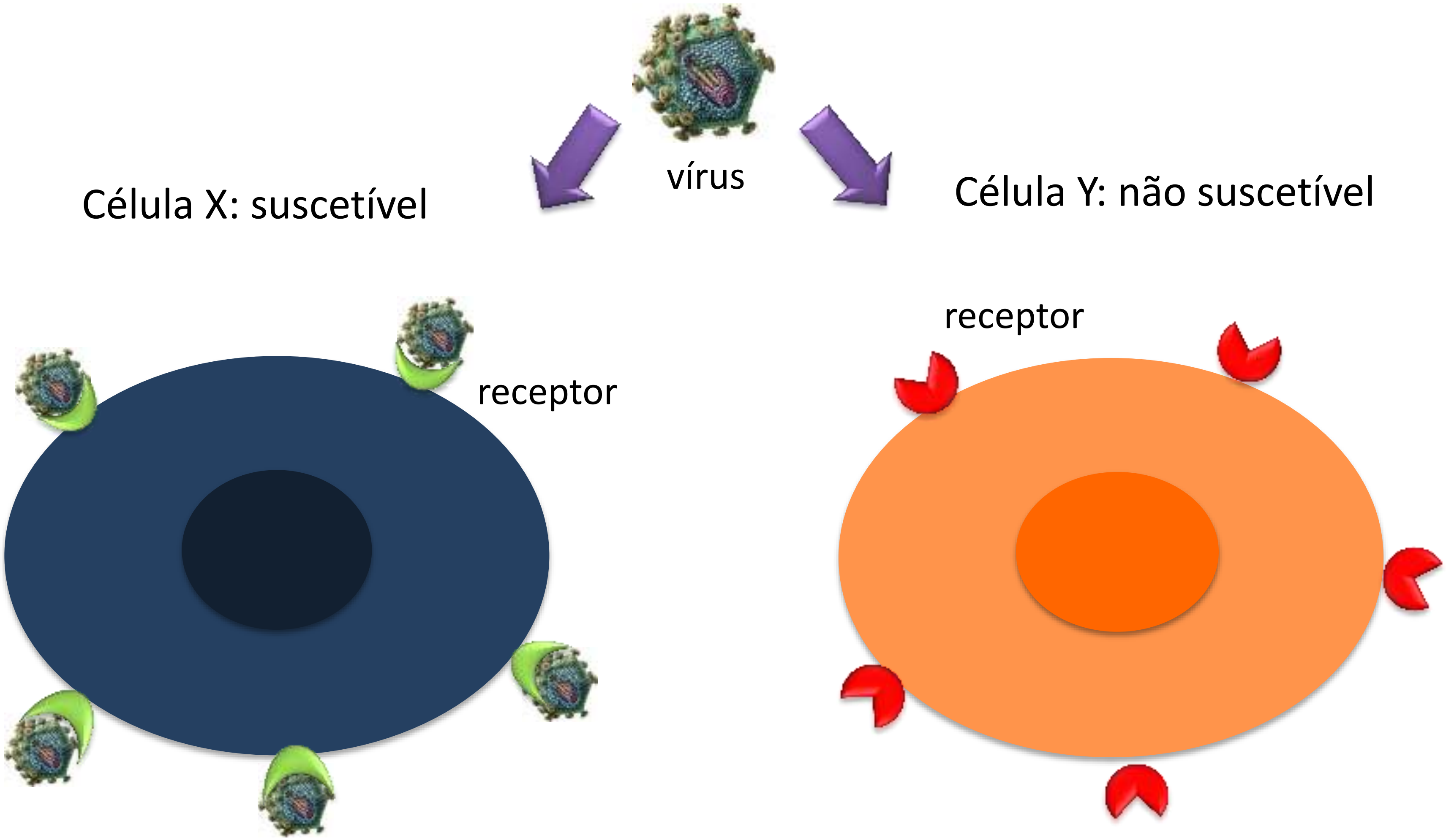







A
Risk of HIV transmission per coital act
1/50- 1/250
1/1000 - 1/10,000
1/500 - 1/2000
1/100- 1/1000
HIV RNA in semen ($\log_{10}$ copies/mL)
5
4
3
2
Acute infection 3 weeks
Asymptomatic infection
HIV progression
AIDS
B
HIV RNA in semen ($\log_{10}$ copies/mL)
5
4
3
2
Acute infection 3 weeks
STI episode
STI episode
AIDS

- Presença do receptor determina o espectro de hospedeiros, o tropismo do vírus e a patogenia



vírus

Célula X: suscetível

Célula Y: não suscetível

receptor

receptor

Fatores não-virais relevantes para a infecção:

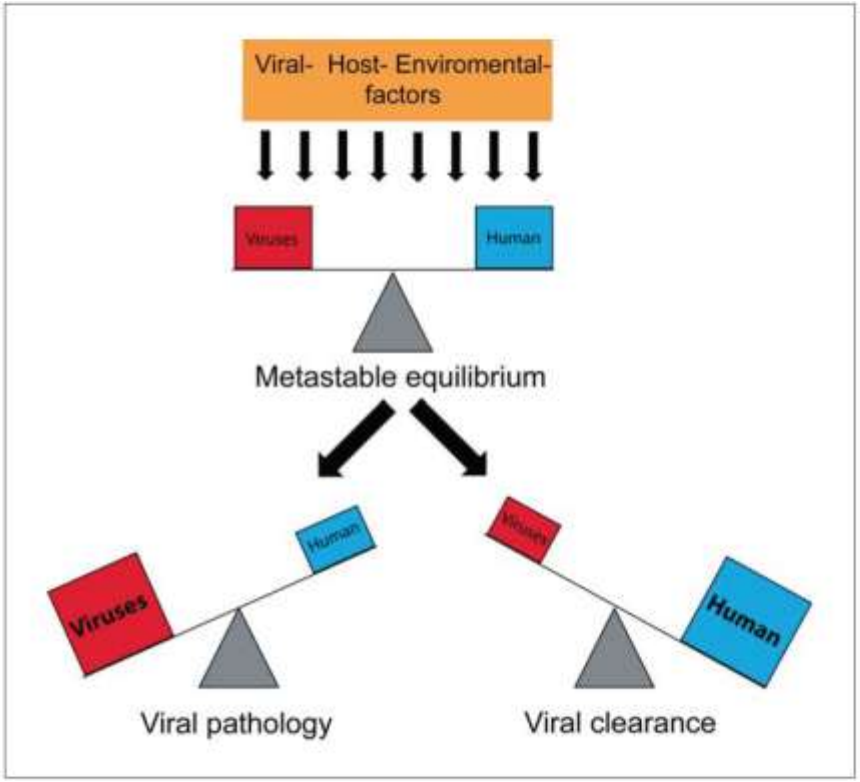
1. **Idade**

2. **Estado nutricional**

3. **Status imune**

4. **Genética**

- Pressão seletiva mútua: equilíbrio dinâmico



Mutações?
Recombinações?
Imunidade?

Conceitos de emergência viral e reemergência de patógenos; tipos, origens e consequências.

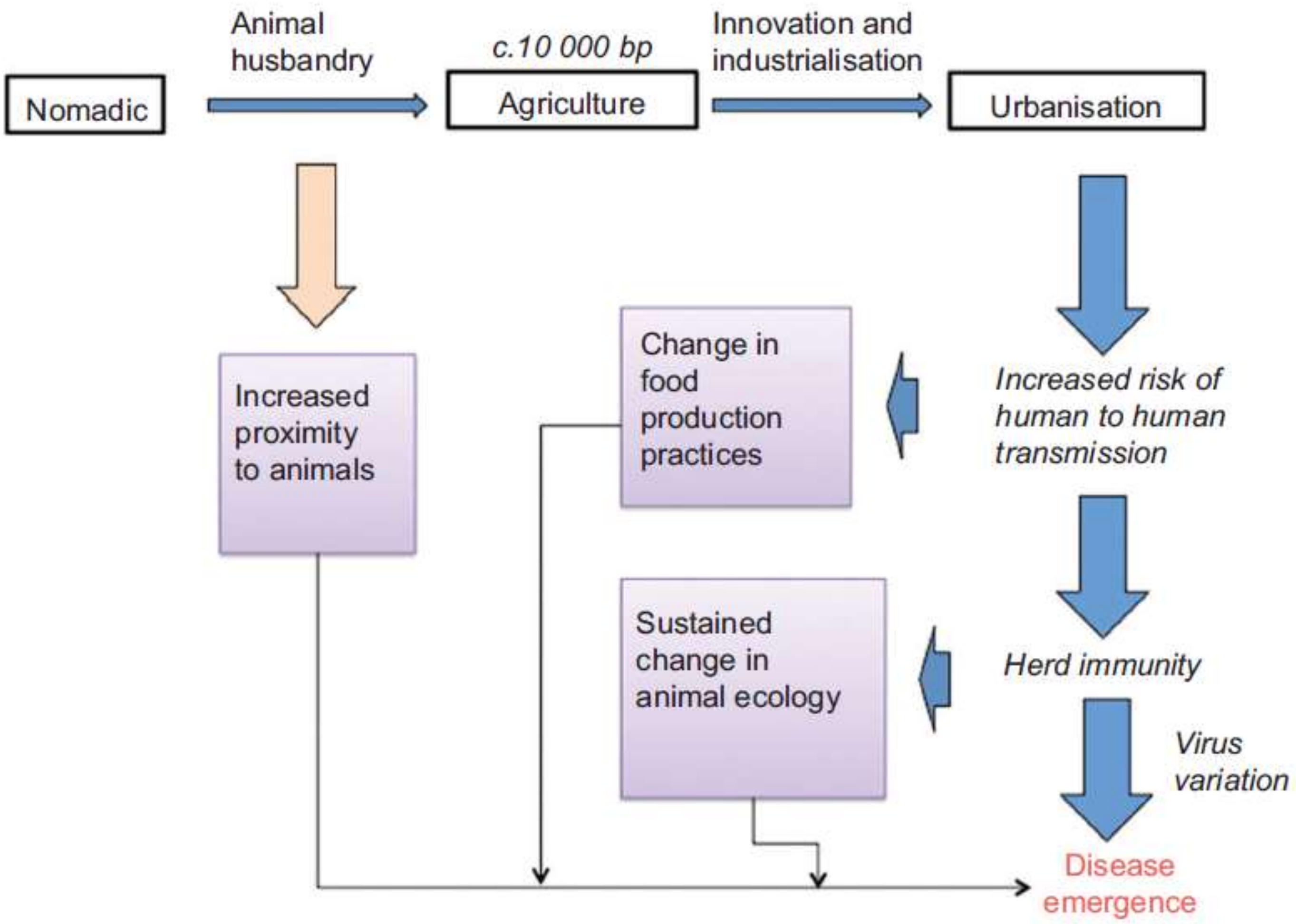


Figure 1 Disease emergence pathways and responses to zoonotic infections.

- O surgimento de novas viroses são dependentes dos seguintes fatores:

- **Capacidade adaptativa do patógeno**
- **Comportamento humano/animal**
- **Fatores ambientais**

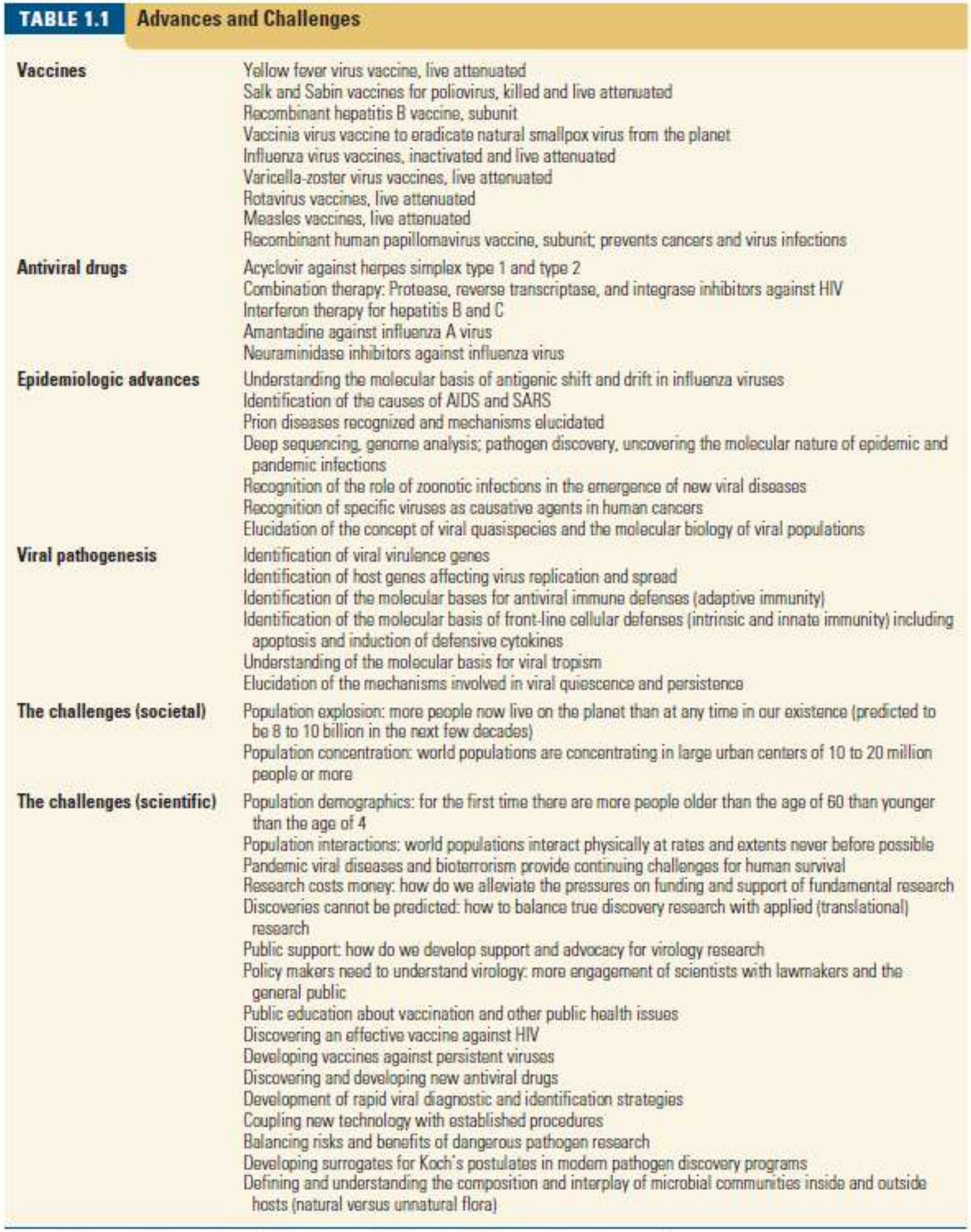


TABLE 1.1 **Advances and Challenges**

Vaccines	Yellow fever virus vaccine, live attenuated Salk and Sabin vaccines for poliovirus, killed and live attenuated Recombinant hepatitis B vaccine, subunit Vaccinia virus vaccine to eradicate natural smallpox virus from the planet Influenza virus vaccines, inactivated and live attenuated Varicella-zoster virus vaccines, live attenuated Rotavirus vaccines, live attenuated Measles vaccines, live attenuated Recombinant human papillomavirus vaccine, subunit; prevents cancers and virus infections
Antiviral drugs	Acyclovir against herpes simplex type 1 and type 2 Combination therapy: Protease, reverse transcriptase, and integrase inhibitors against HIV Interferon therapy for hepatitis B and C Amantadine against influenza A virus Neuraminidase inhibitors against influenza virus
Epidemiologic advances	Understanding the molecular basis of antigenic shift and drift in influenza viruses Identification of the causes of AIDS and SARS Prion diseases recognized and mechanisms elucidated Deep sequencing, genome analysis; pathogen discovery, uncovering the molecular nature of epidemic and pandemic infections Recognition of the role of zoonotic infections in the emergence of new viral diseases Recognition of specific viruses as causative agents in human cancers Elucidation of the concept of viral quasispecies and the molecular biology of viral populations
Viral pathogenesis	Identification of viral virulence genes Identification of host genes affecting virus replication and spread Identification of the molecular bases for antiviral immune defenses (adaptive immunity) Identification of the molecular basis of front-line cellular defenses (intrinsic and innate immunity) including apoptosis and induction of defensive cytokines Understanding of the molecular basis for viral tropism Elucidation of the mechanisms involved in viral quiescence and persistence
The challenges (societal)	Population explosion: more people now live on the planet than at any time in our existence (predicted to be 8 to 10 billion in the next few decades) Population concentration: world populations are concentrating in large urban centers of 10 to 20 million people or more
The challenges (scientific)	Population demographics: for the first time there are more people older than the age of 60 than younger than the age of 4 Population interactions: world populations interact physically at rates and extents never before possible Pandemic viral diseases and bioterrorism provide continuing challenges for human survival Research costs money: how do we alleviate the pressures on funding and support of fundamental research Discoveries cannot be predicted: how to balance true discovery research with applied (translational) research Public support: how do we develop support and advocacy for virology research Policy makers need to understand virology: more engagement of scientists with lawmakers and the general public Public education about vaccination and other public health issues Discovering an effective vaccine against HIV Developing vaccines against persistent viruses Discovering and developing new antiviral drugs Development of rapid viral diagnostic and identification strategies Coupling new technology with established procedures Balancing risks and benefits of dangerous pathogen research Developing surrogates for Koch's postulates in modern pathogen discovery programs Defining and understanding the composition and interplay of microbial communities inside and outside hosts (natural versus unnatural flora)

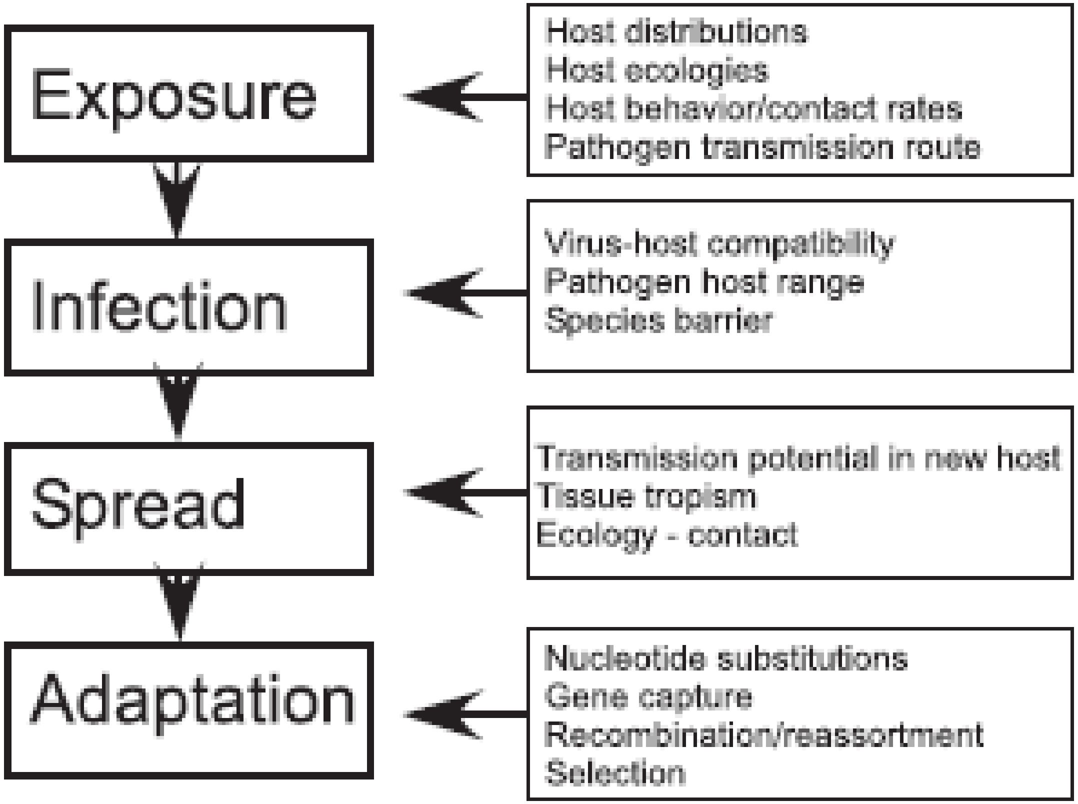
AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; SARS, severe acute respiratory syndrome.

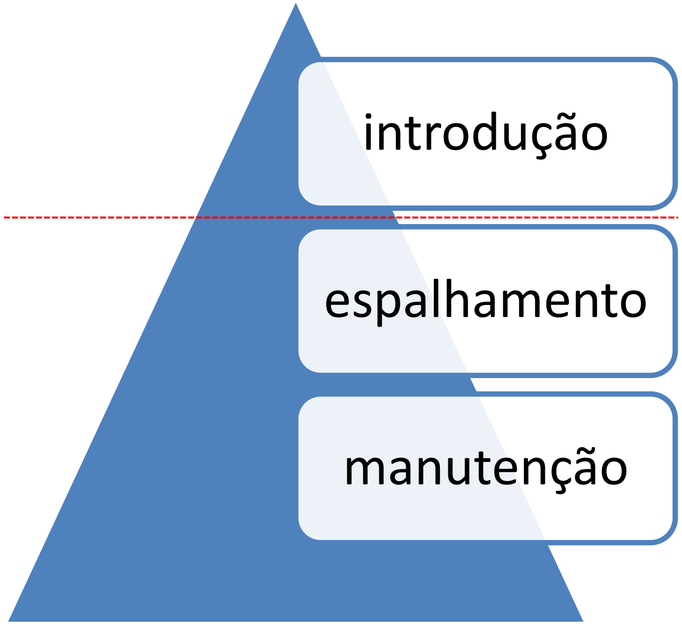
Table 1. Examples of pathogens considered to have emerged via a species jump

Pathogen	Original host	New host	Year reported	Refs
Transmissible spongiform encephalopathies				
BSE/vCJD	Cattle	Humans	1996	[53]
Viruses				
Rinderpest	Eurasian cattle	African ruminants	Late 1800s	[4]
Myxoma virus	Brush rabbit/Brazilian rabbit	European rabbit	1950s	[3]
Ebola virus	Unknown	Humans	1977	[54]
FPLV/CPV	Cats	Dogs	1978	[55]
SIV/HIV-1	Primates	Humans	1983	[2]
SIV/HIV-2	Primates	Humans	1986	[2]
Canine/Phocine distemper virus	Canids	Seals	1988	[56]
Hendra virus	Bats	Horses and humans	1994	[57]
Australian bat lyssavirus	Bats	Humans	1996	[57]
H5N1 influenza A	Chickens	Humans	1997	[32]
Nipah virus	Bats	Pigs and humans	1999	[57]
SARS coronavirus	Palm civets	Humans	2003	[58]
Monkeypox virus	Prairie dogs	Humans	2003[a]	[59]
Bacteria				
Escherichia coli O157:H7	Cattle	Humans	1982	[60]
Borrelia burgdorferi	Deer	Humans	1982	[15]
Fungi				
Phytophthora infestans	Andean potato	Cultivated potato	1840s	[8]
Cryphonectria parasitica	Japanese chestnut	American chesnut	Late 1800s	[9]

[a] Monkeypox was first reported in humans in 1970, but infections acquired from prairie dogs were not seen until 2003.

- A emergência de um patógeno é complexa, multifatorial, e depende dos seguintes eventos:



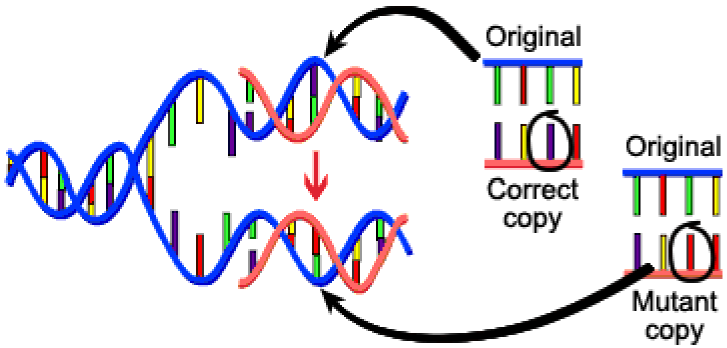

introdução

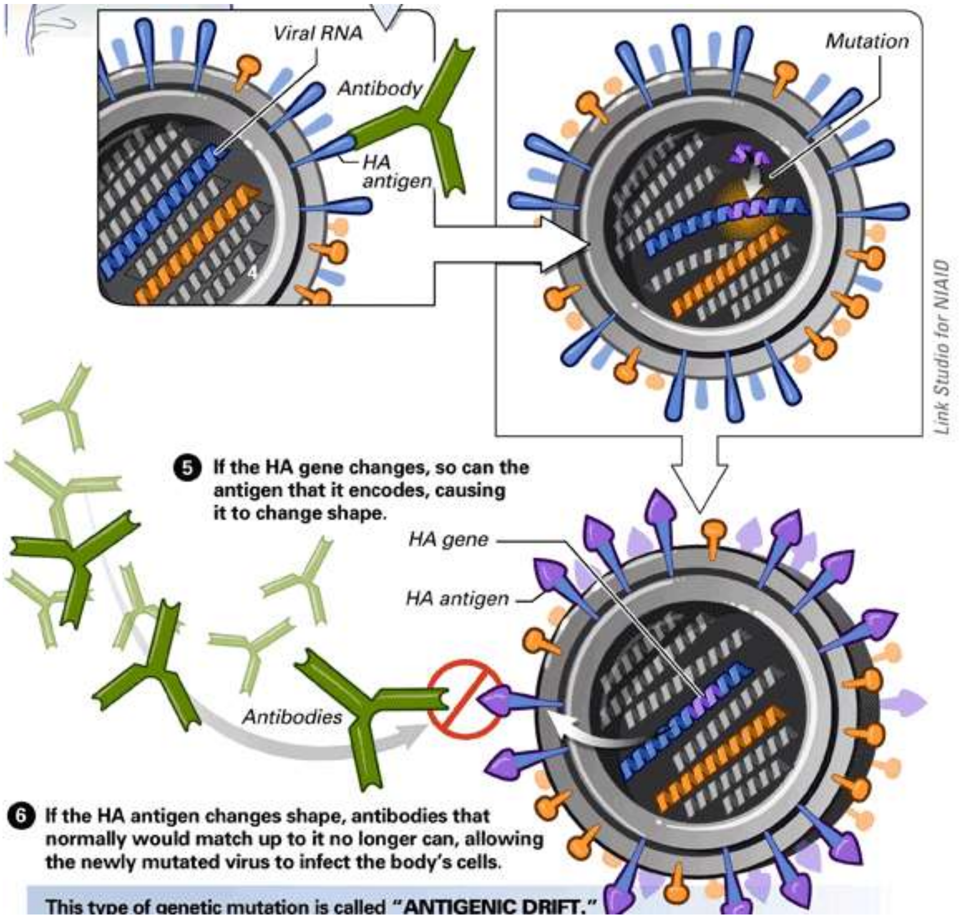
espalhamento

manutenção

Características dos MOs Relacionadas à emergência: Mutação, Recombinação e Rearranjo

Efeitos das mutações



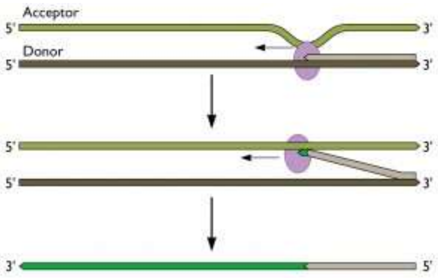


⑤ If the HA gene changes, so can the antigen that it encodes, causing it to change shape.

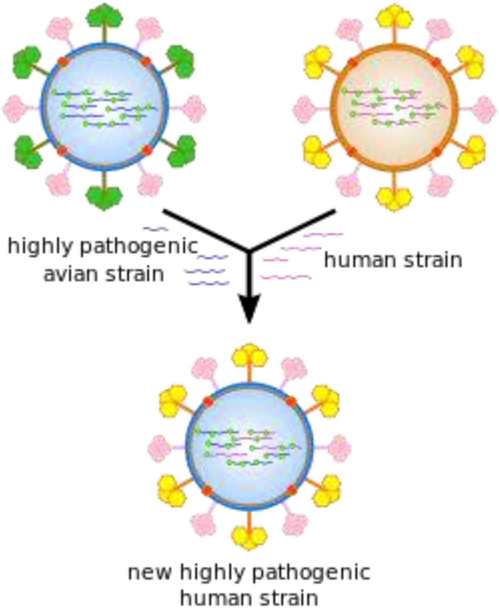
⑥ If the HA antigen changes shape, antibodies that normally would match up to it no longer can, allowing the newly mutated virus to infect the body's cells.

This type of genetic mutation is called **"ANTIGENIC DRIFT."**

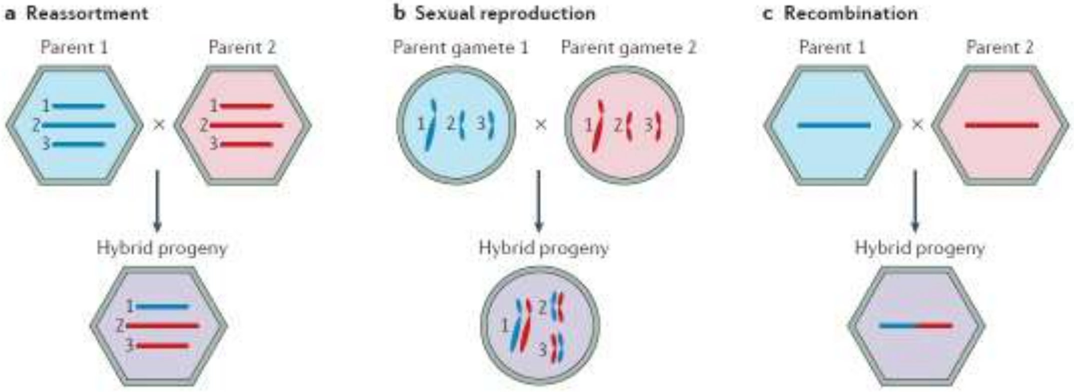
Efeitos de recombinação e rearranjo



Ex: SARS CoV, HIV



Ex: FluV, Rota



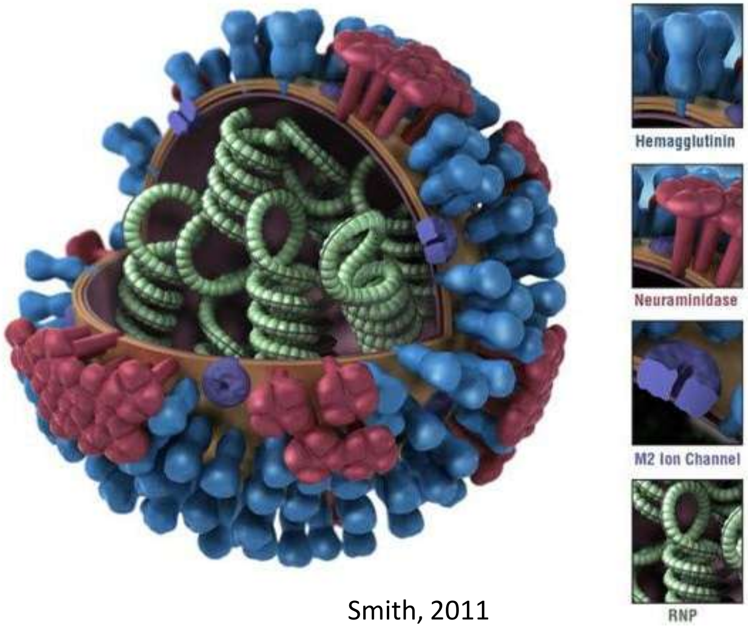
- A variação genômica dos vírus podem alterar a **patogenicidade**, influenciando o curso da infecção.

- Quais são as regiões afetadas pelas variações genéticas?

  - **Enzimas:** proteases; polimerases; fatores de transcrição e regulação gênicos; transporte de RNA e proteínas

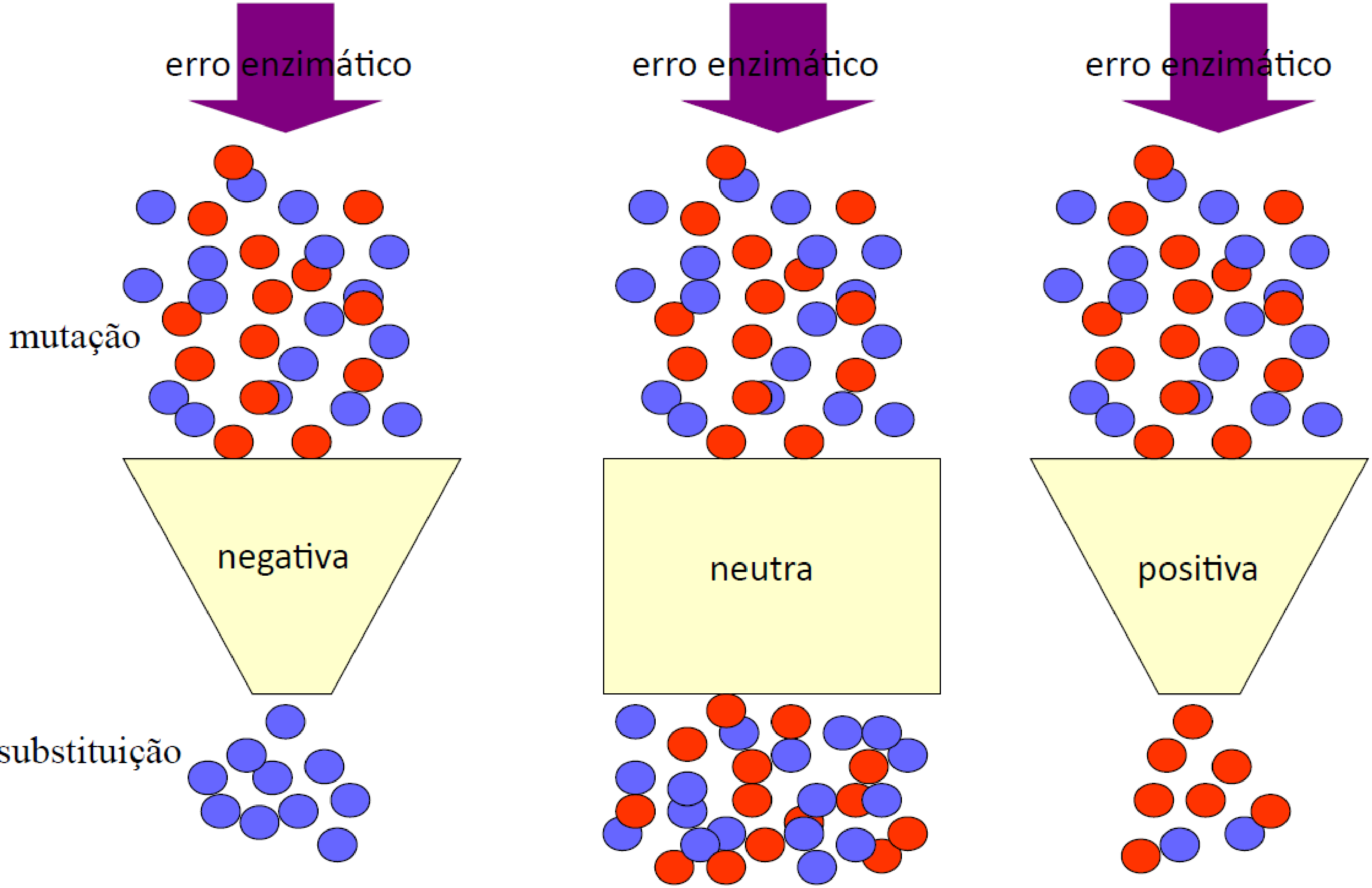
  - **Proteínas do envelope**

  - **Proteínas do capsídeo**



Smith, 2011

O filtro seletivo



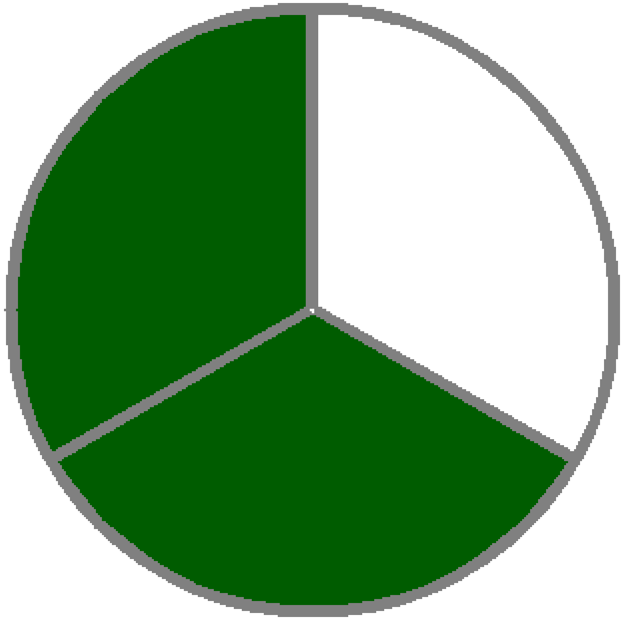
- Todos os vírus estão sujeitos a mutações, entretanto:

- Vírus RNA são muito mais susceptíveis: ausência de mecanismo de reparo (“proofreading”)

- Taxa de erro da RNApol: $10^{-3 \text{ a } -4}$ erros/nt
- Taxa de erro da DNApol: $10^{-9 \text{ a } -10}$erros/nt

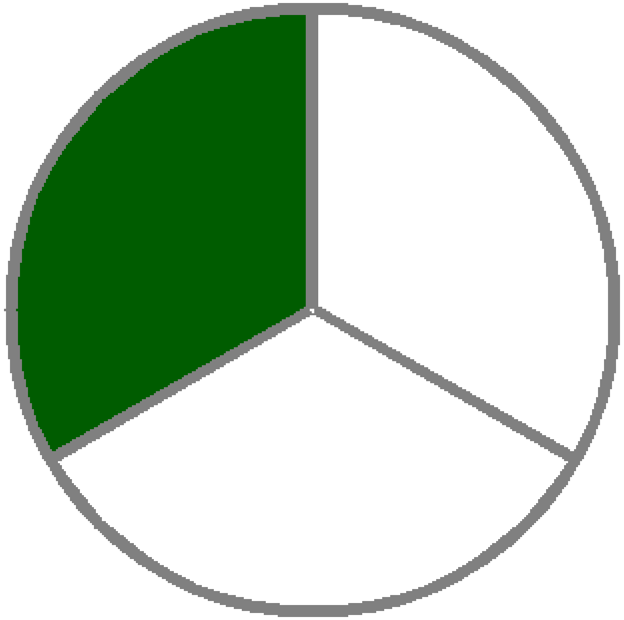
- Este fenômeno provoca diversas substituições, adições e deleções genéticas

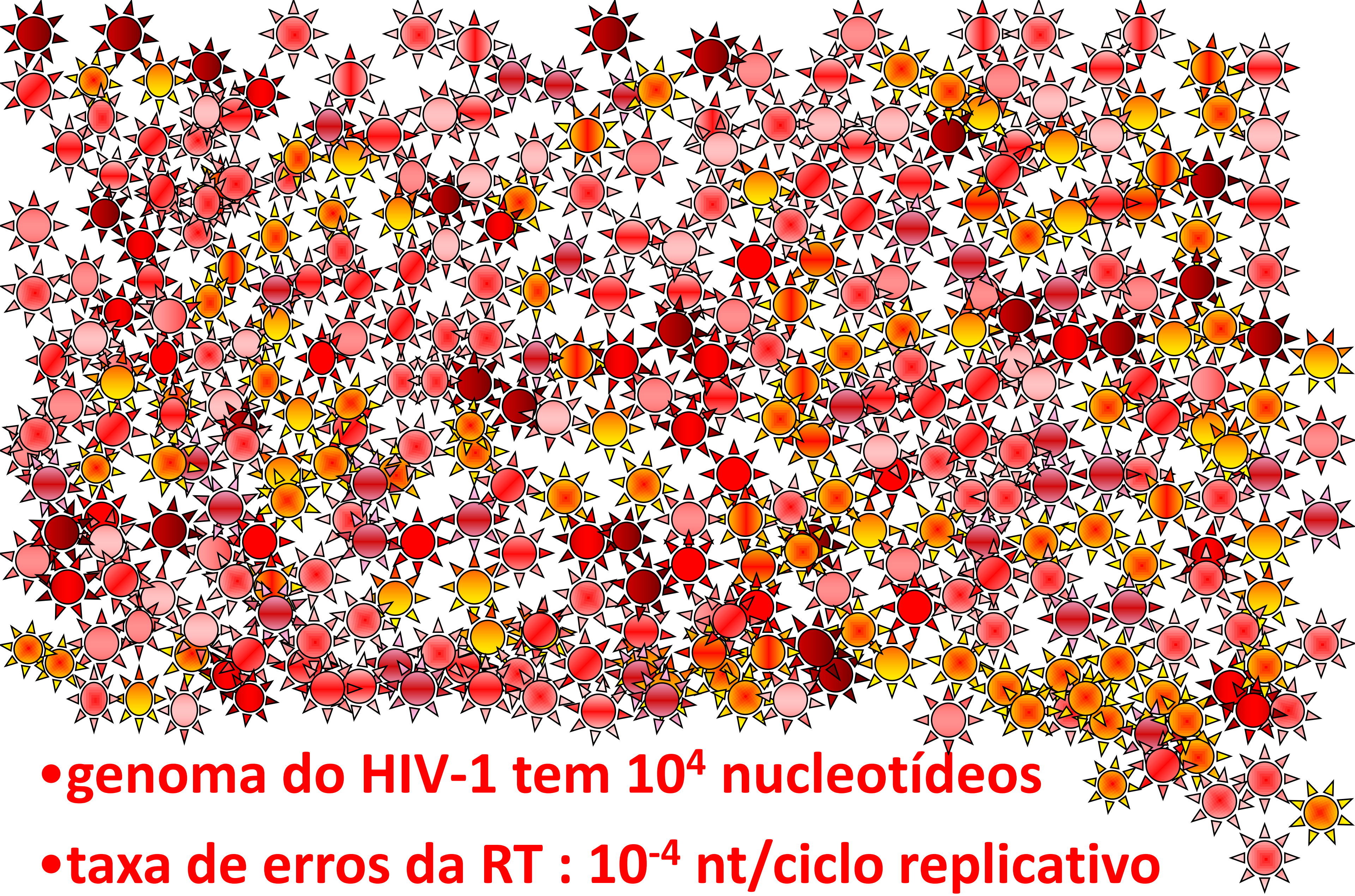
2/3 das infecções são causadas por vírus



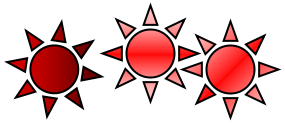
e

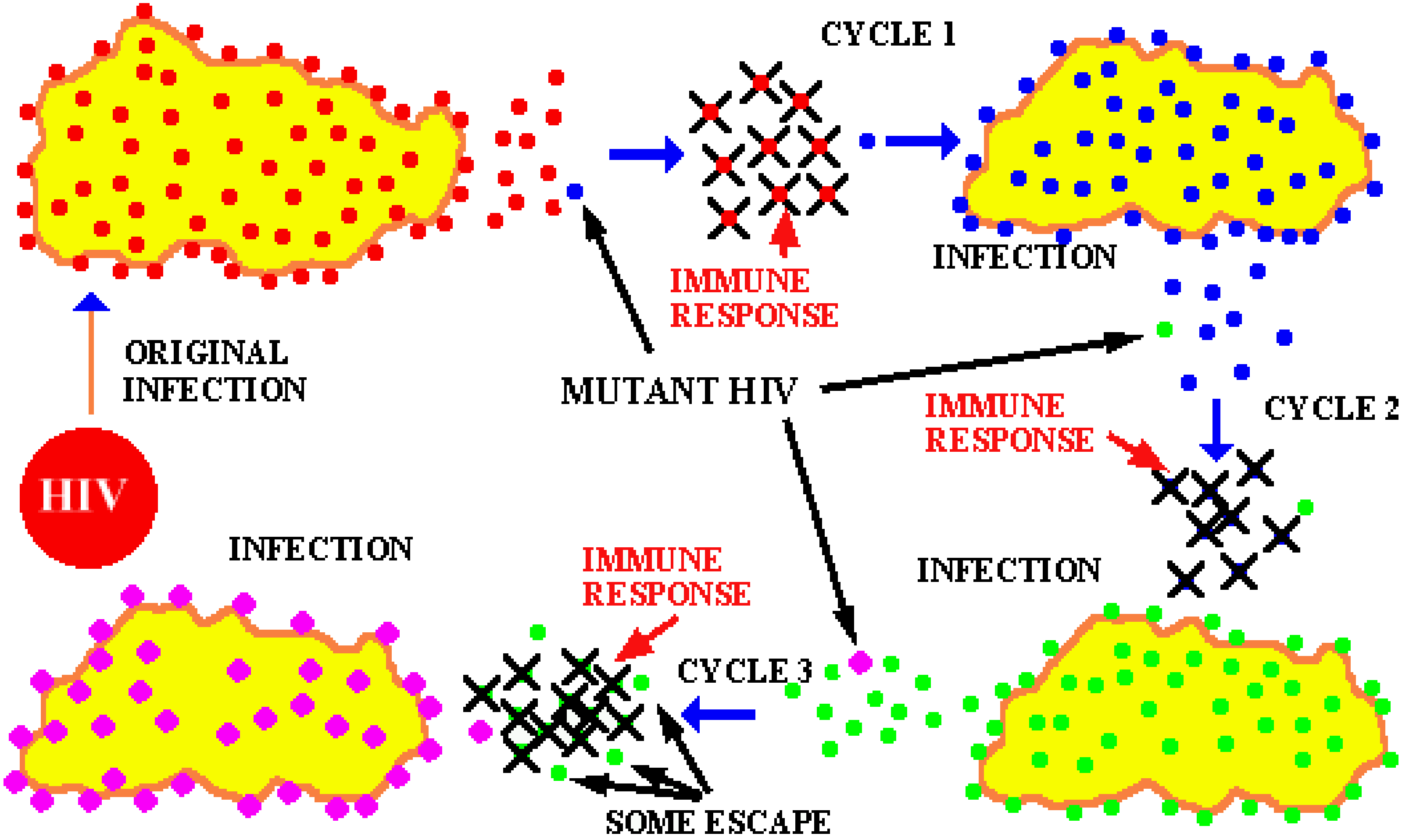
1/3 das doenças emergentes são causadas por vírus RNA

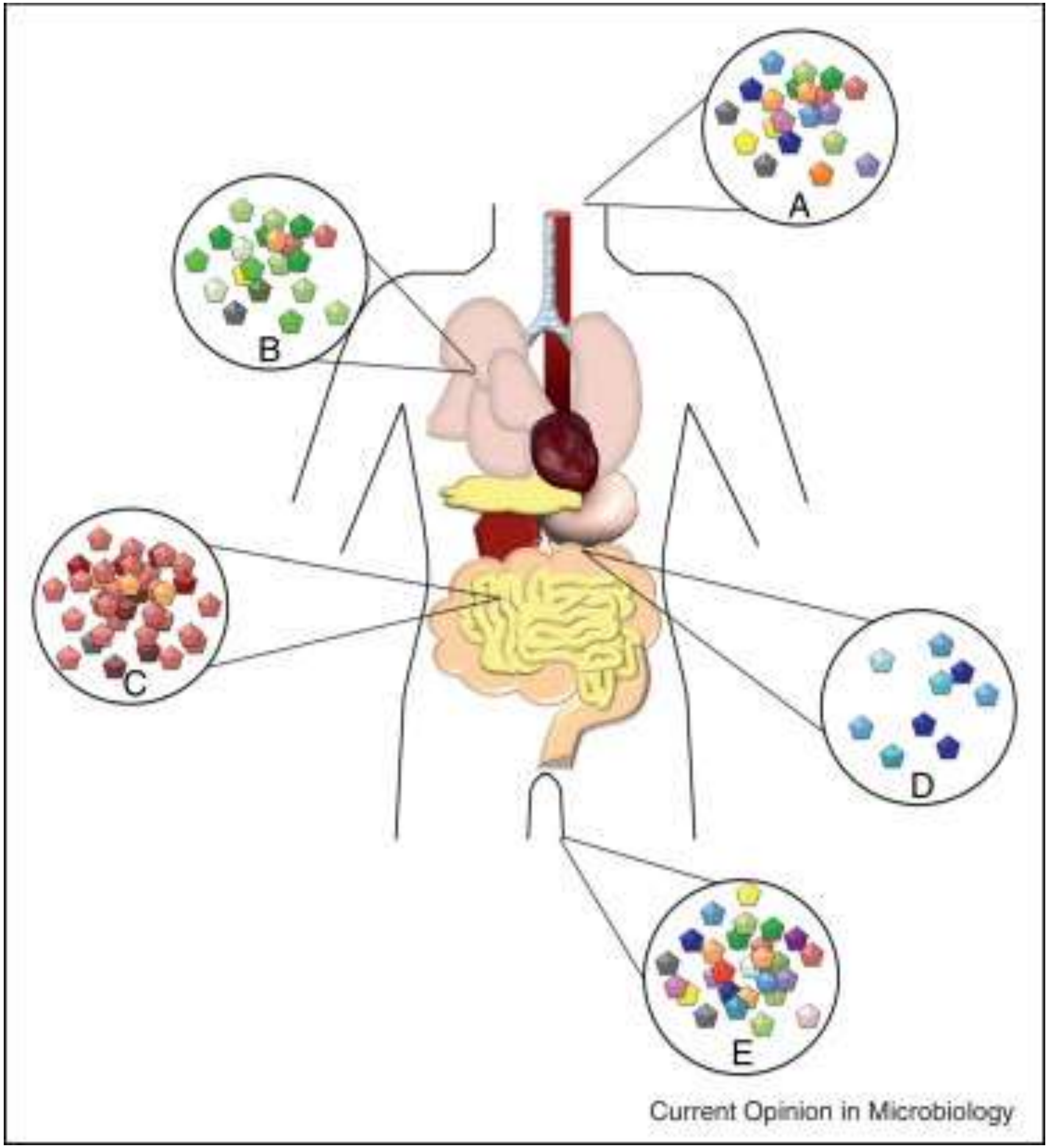




- genoma do HIV-1 tem 10^4 nucleotídeos
- taxa de erros da RT : 10^{-4} nt/ciclo replicativo
- Portanto: pelo menos 1 mutação/vírus

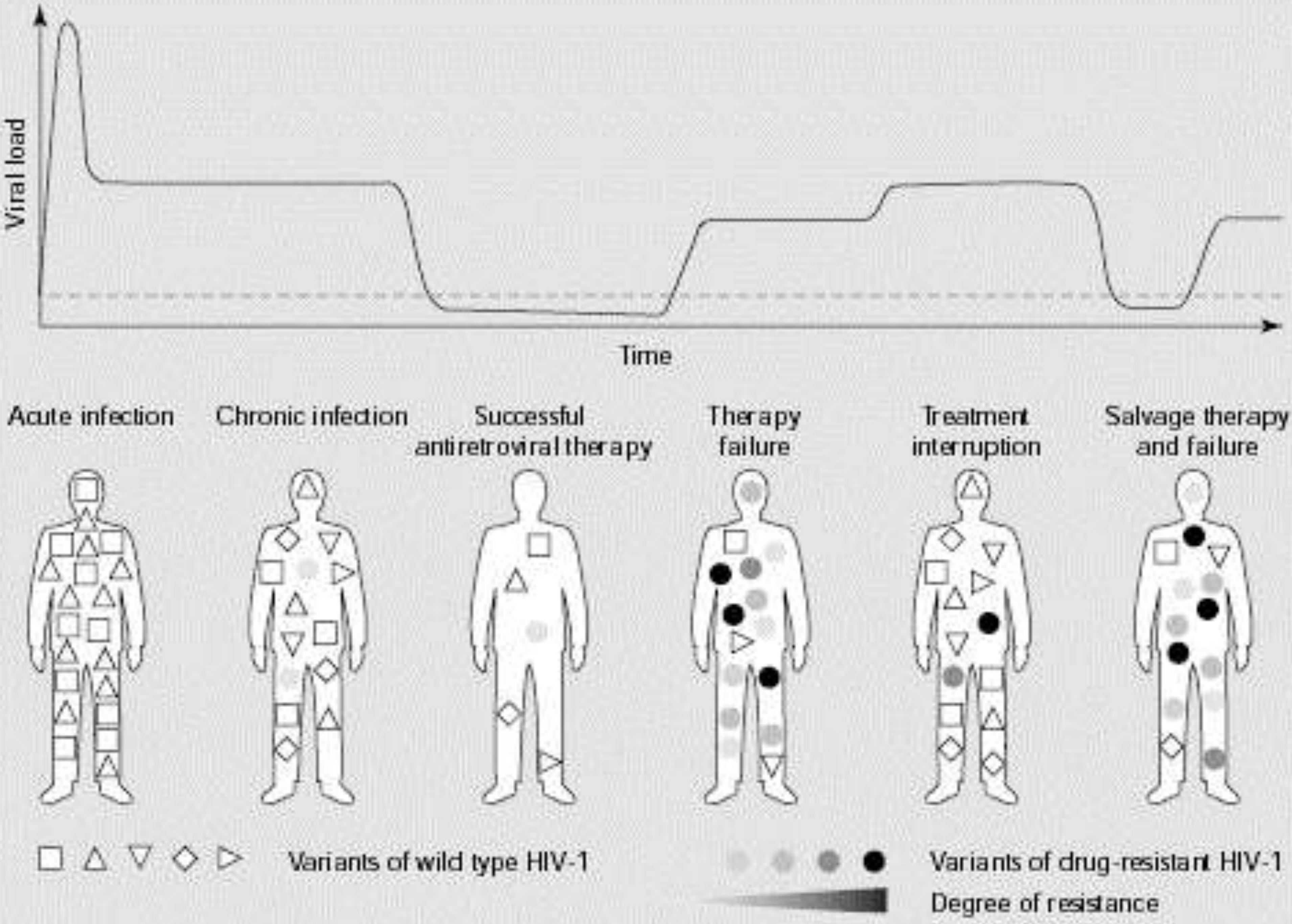


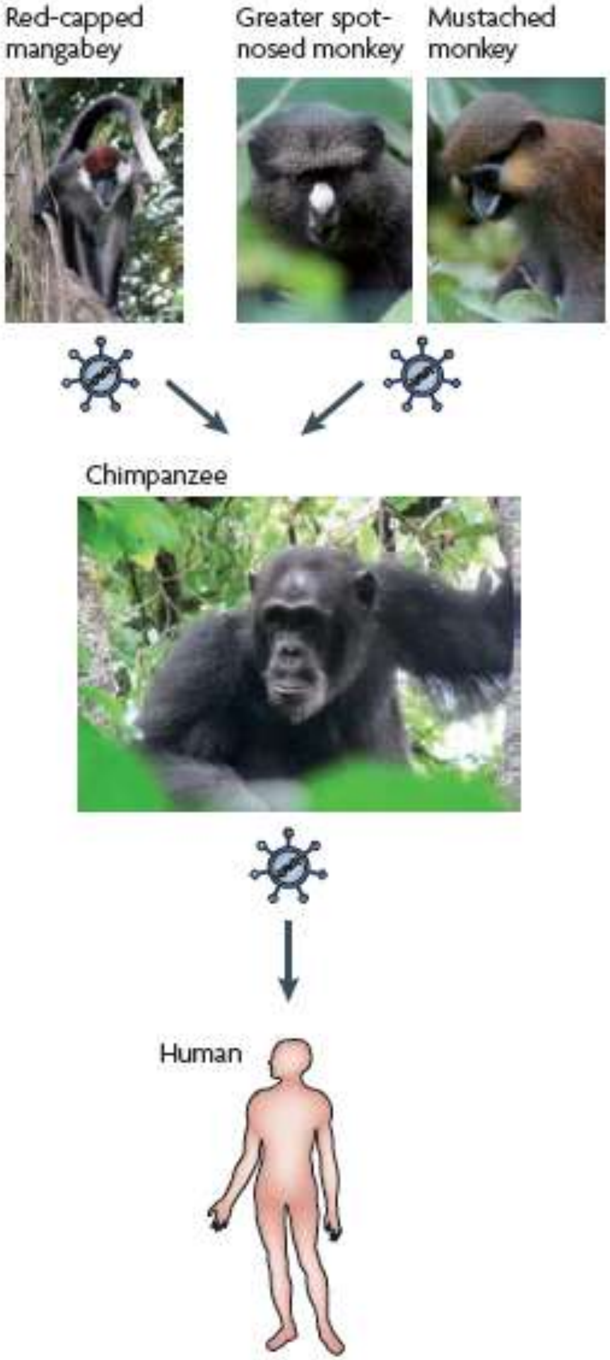

CYCLE 1
INFECTION
IMMUNE RESPONSE
ORIGINAL INFECTION
MUTANT HIV
HIV
IMMUNE RESPONSE
CYCLE 2
INFECTION
IMMUNE RESPONSE
INFECTION
CYCLE 3
SOME ESCAPE


A
B
C
D
E
Current Opinion in Microbiology

- CONSEQUêNCIAS:

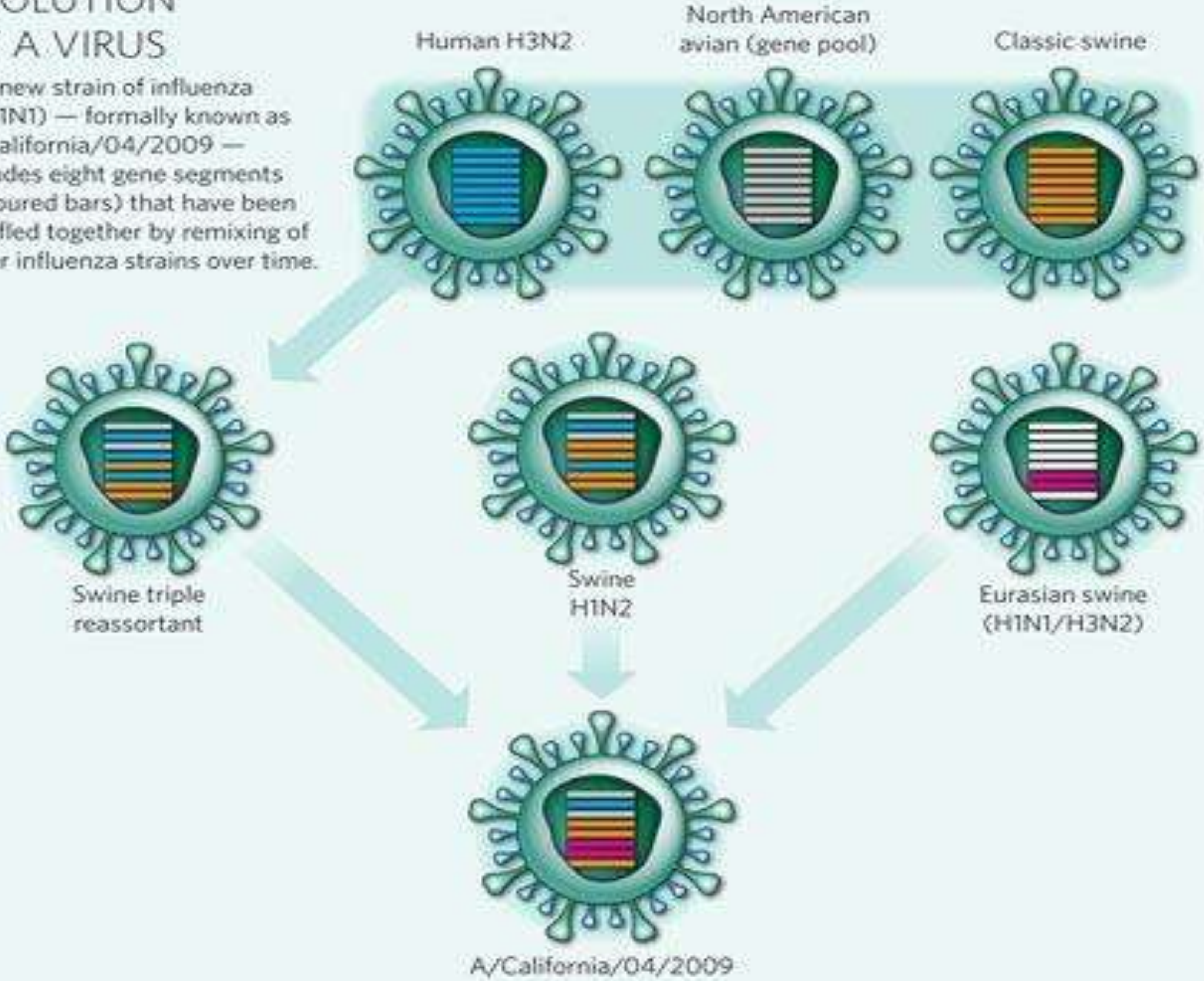
- Manutenção de infecção permanente (HIV)
- Resistência a drogas e vacinas (Influenza, HCV, HIV)
- Quebra de barreiras inter-espécies (Parvovírus, Influenza, Sarampo, Doença Vesicular Suína...)
- Emergência ou re-emergência de viroses


Viral load
Time
Acute infection
Chronic infection
Successful antiretroviral therapy
Therapy failure
Treatment interruption
Salvage therapy and failure
□ △ ▽ ◇ ▷ Variants of wild type HIV-1
● ● ● ● Variants of drug-resistant HIV-1
Degree of resistance


Red-capped mangabey
Greater spot-nosed monkey
Mustached monkey
Chimpanzee
Human

EVOLUTION OF A VIRUS

The new strain of influenza A(H1N1) — formally known as A/California/04/2009 — includes eight gene segments (coloured bars) that have been shuffled together by remixing of other influenza strains over time.



Human H3N2

North American avian (gene pool)

Classic swine

Swine triple reassortant

Swine H1N2

Eurasian swine (H1N1/H3N2)

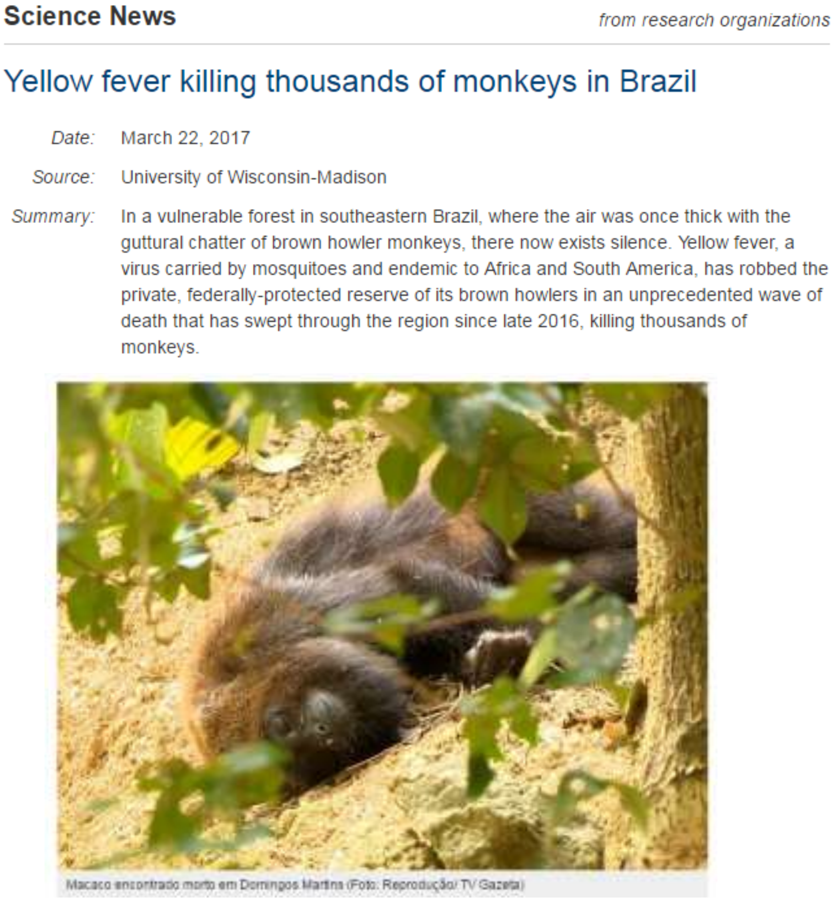
A/California/04/2009

Influência humana no processo de emergência de patógenos

Paying the price: the H5N1 influenza virus that caused avian flu was spread in Chinese markets.

- Facilidade de deslocamento humano;
- Era dos transplantes;
- Uso indiscriminado de antimicrobianos;
- Condições sócio-econômicas precárias;
- Problemas em vigilância epidemiológica;
- Modelos de criação animal;
- Deslocamento de animais de criação;

Destruição de áreas silvestres



Science News *from research organizations*

Yellow fever killing thousands of monkeys in Brazil

Date: March 22, 2017

Source: University of Wisconsin-Madison

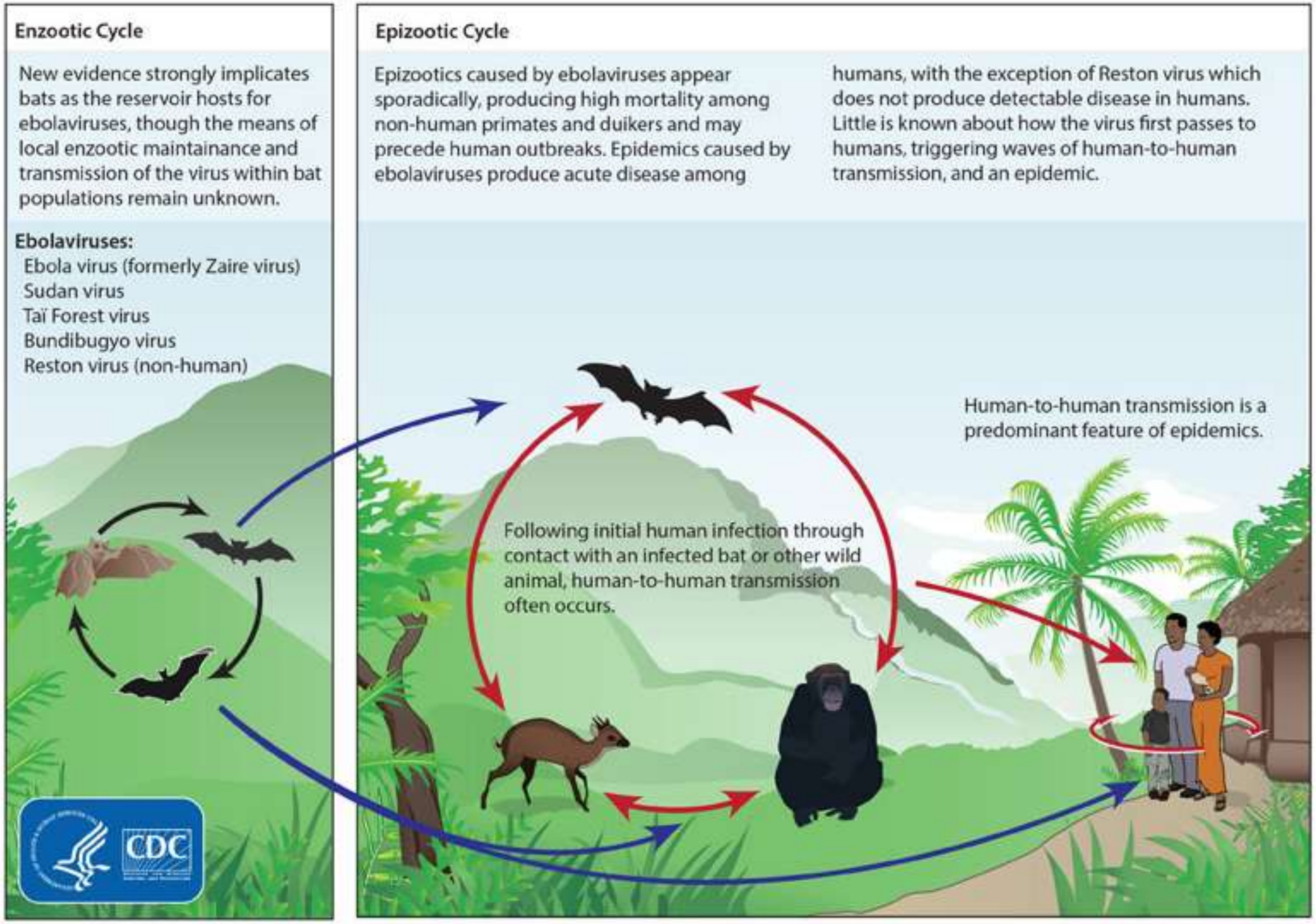
Summary: In a vulnerable forest in southeastern Brazil, where the air was once thick with the guttural chatter of brown howler monkeys, there now exists silence. Yellow fever, a virus carried by mosquitoes and endemic to Africa and South America, has robbed the private, federally-protected reserve of its brown howlers in an unprecedented wave of death that has swept through the region since late 2016, killing thousands of monkeys.

Macaco encontrado morto em Domingos Martins (Foto: Reprodução/ TV Gazeta)

"Sistemas ecológicos empobrecidos podem favorecer o crescimento das populações de mosquitos. Mosquitos infectados encontrando populações grandes de macacos em pedaços de mata atlântica isolados podem ser a origem destes surtos"

- Falta de corredores naturais entre as matas
- Aumento de endogamia
- Aumento da exposição de pessoas

Transmissão na natureza



Enzootic Cycle

New evidence strongly implicates bats as the reservoir hosts for ebolaviruses, though the means of local enzootic maintainance and transmission of the virus within bat populations remain unknown.

Ebolaviruses:

Ebola virus (formerly Zaire virus)
Sudan virus
Taï Forest virus
Bundibugyo virus
Reston virus (non-human)

Epizootic Cycle

Epizootics caused by ebolaviruses appear sporadically, producing high mortality among non-human primates and duikers and may precede human outbreaks. Epidemics caused by ebolaviruses produce acute disease among humans, with the exception of Reston virus which does not produce detectable disease in humans. Little is known about how the virus first passes to humans, triggering waves of human-to-human transmission, and an epidemic.

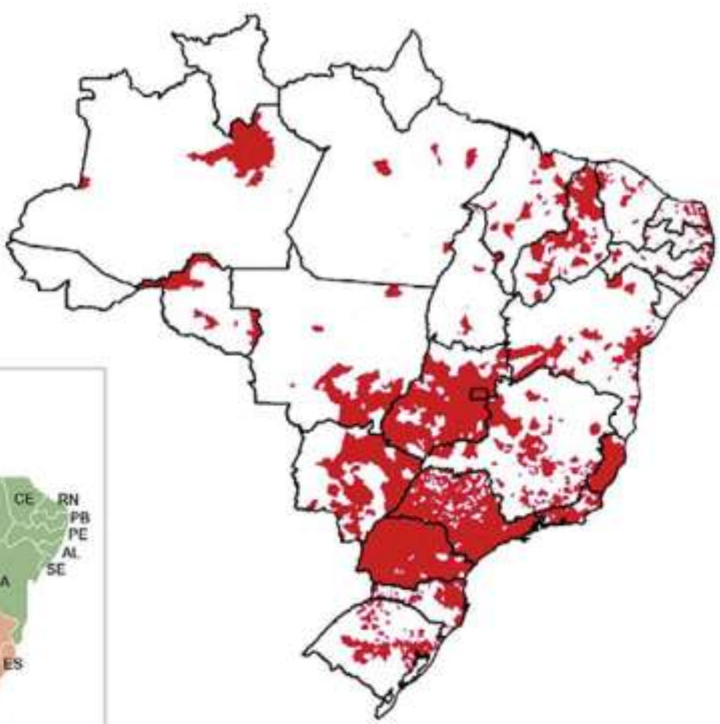
Following initial human infection through contact with an infected bat or other wild animal, human-to-human transmission often occurs.

Human-to-human transmission is a predominant feature of epidemics.

Influência ambiental/ecológica no processo de emergência de patógenos

- Processo migratório de aves selvagens;
- Alterações de temperatura e condições climáticas;
- Adaptabilidade de vetores a novos ambientes;
- Hospedeiros “supertransmissores”

Brazilian municipalities were *Aedes albopictus* was detected in 2011 and 2014



2011

2014