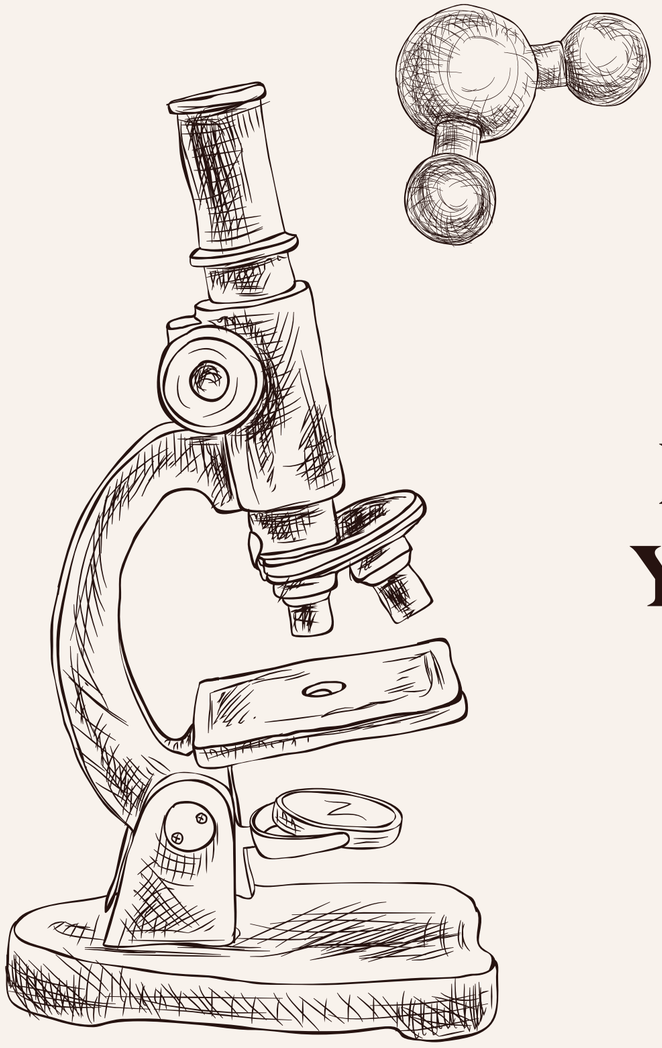
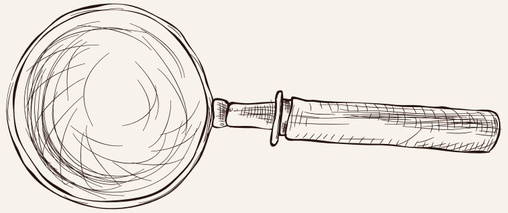


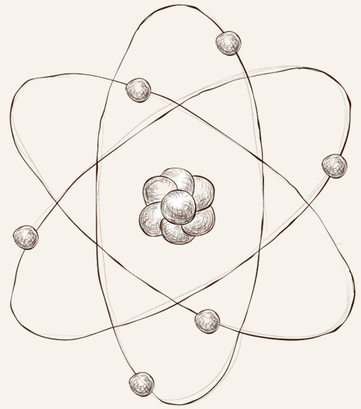
ICB5777 - Physiopathology of Infectious Diseases

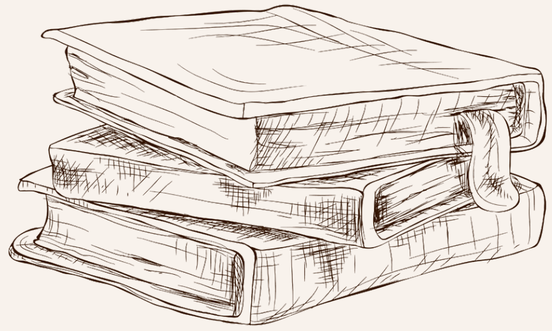
Module I

FEVER:

MALARIA, DENGUE, YELLOW FEVER AND TYPHOID FEVER







Presented by :

Jonathan Braga Moreira Bezerra

Lívia Moreno Lemuchi

Murilo Henrique Ozório Leite

Thais Pailo de Carvalho

INTRODUCTION

Common sense

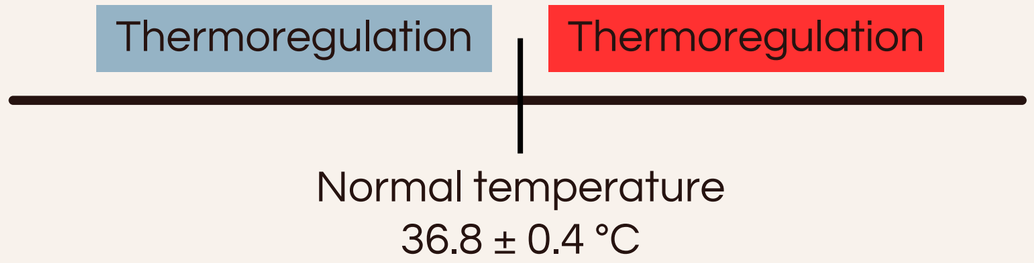
- Fever = Disease
- Fever has to end whatever it costs!
- Fever is an increase in body temperature

Reality

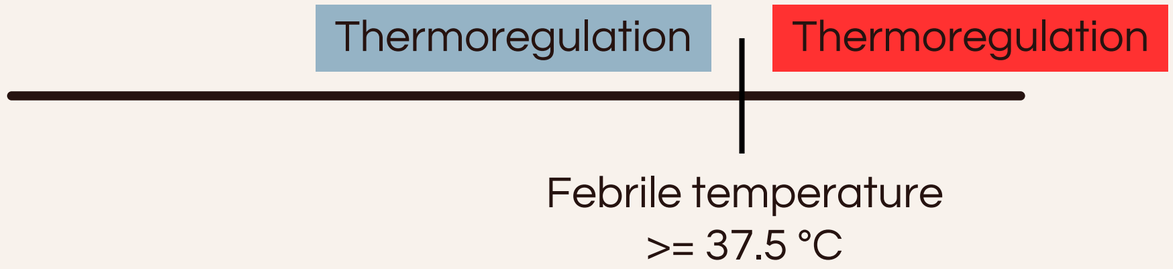
- Fever is an evolutive mechanism
- Elevated body temperature is an indispensable component of the febrile response, it is not synonymous with fever
- Orchestrated by endocrine, neurological, immunological and behavioural mechanism
- Fever is accompanied by various sickness behaviours, changes in metabolic and physiological characteristics
- Important to the pathogenesis, clinical presentation and outcome of many diseases

FEVER MECHANISM

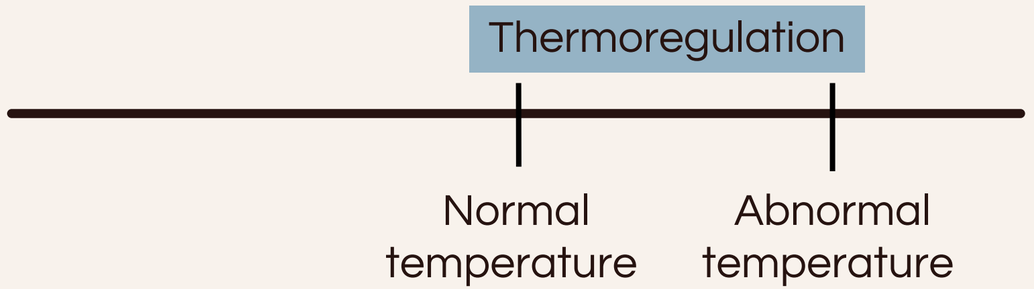
Normal situation



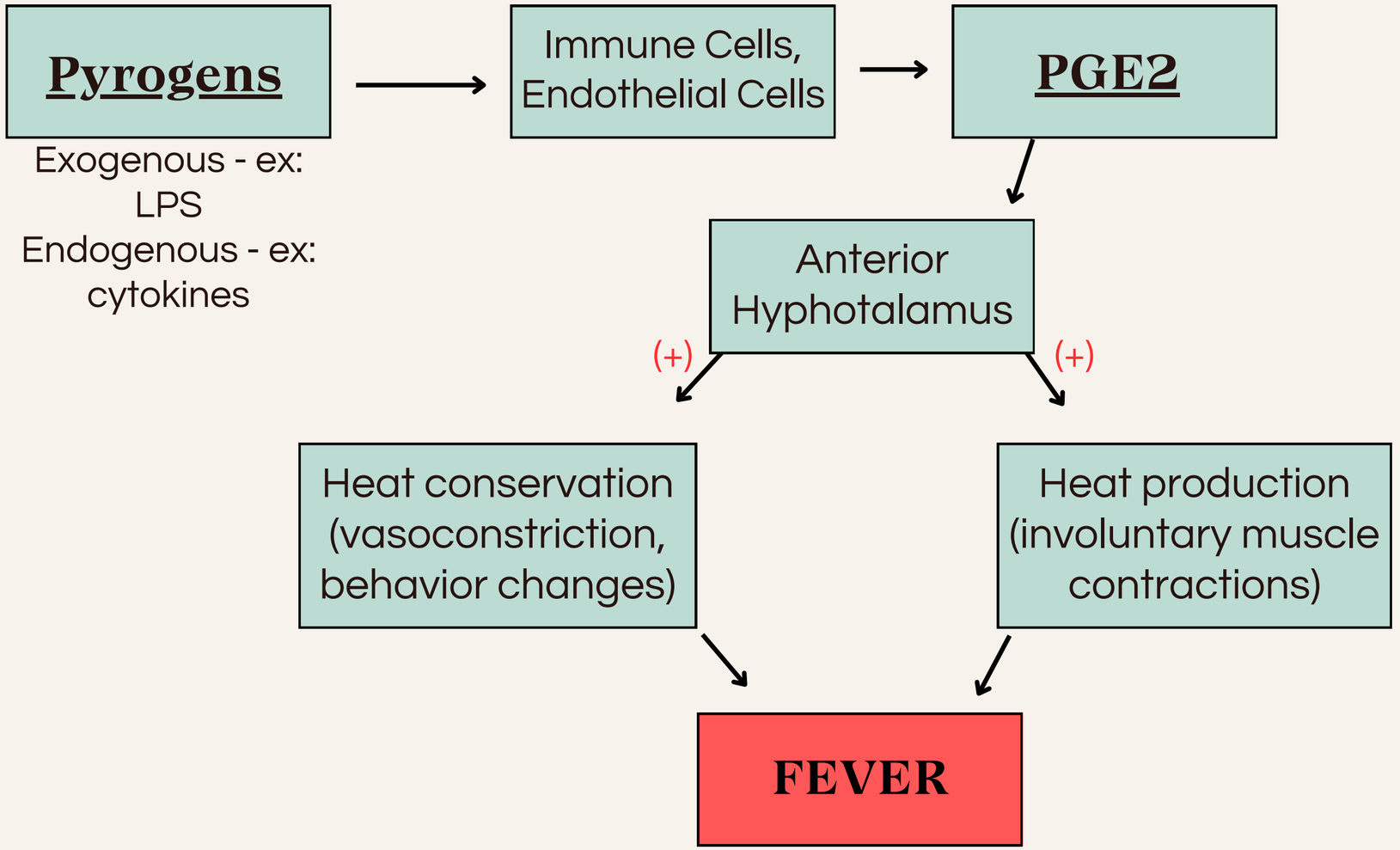
Fever situation



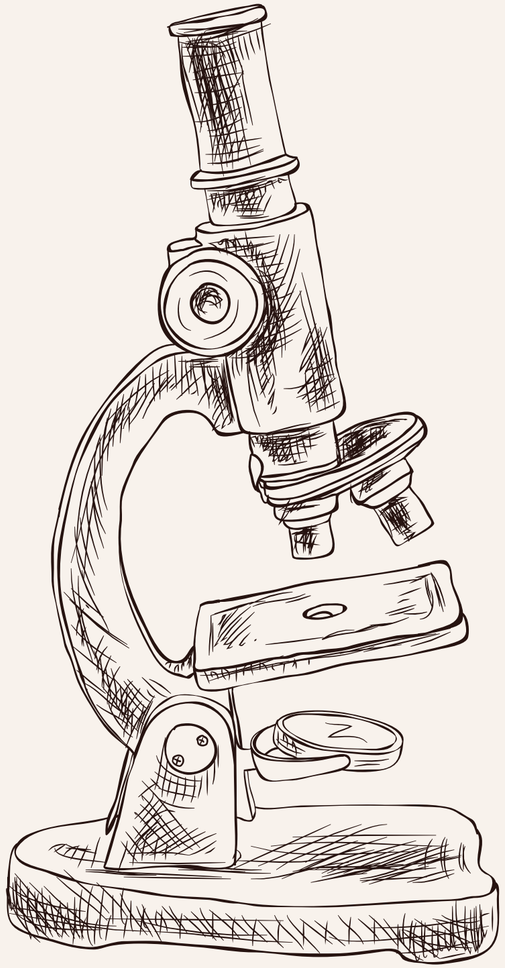
Heatstroke situation

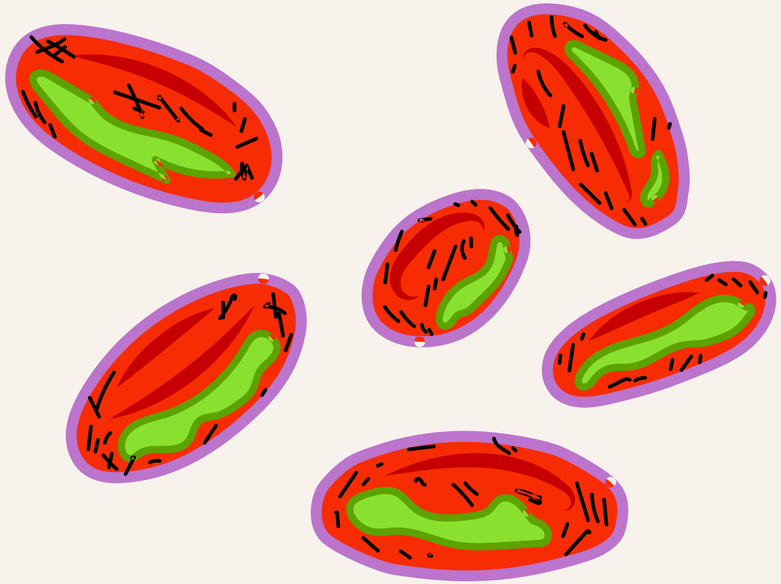


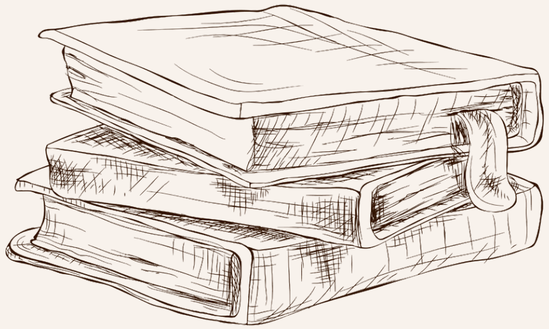
FEVER MECHANISM



MALARIA

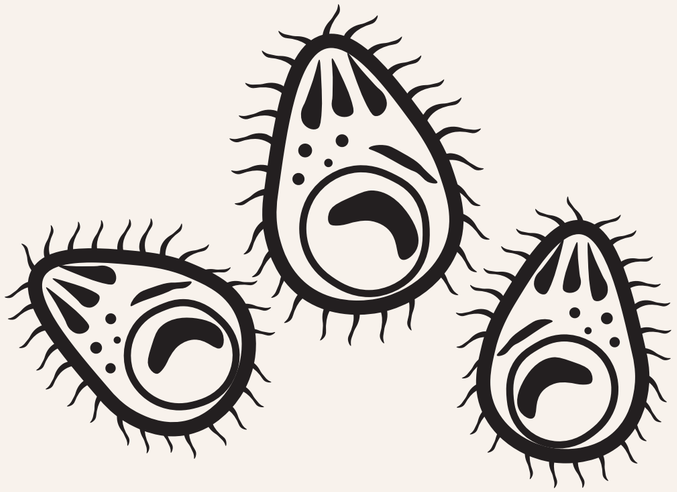






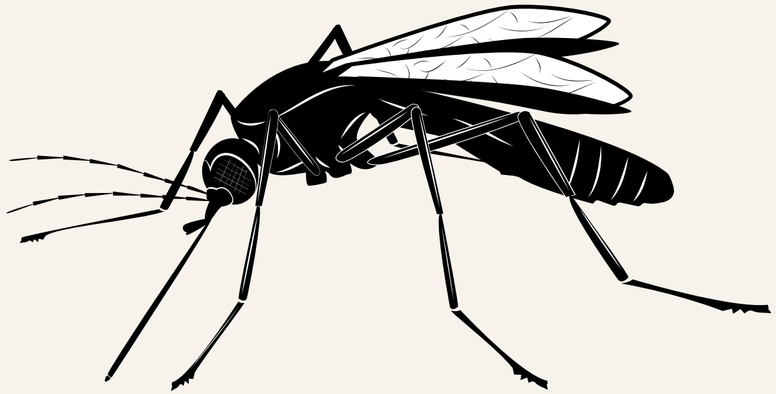
MALARIA

Vectorial parasitic diseases transmitted by infected female Anopheles mosquitoes genus caused by protozoans of Plasmodium genus.



Currently, there 5 etiological agents associated with malaria in humans:

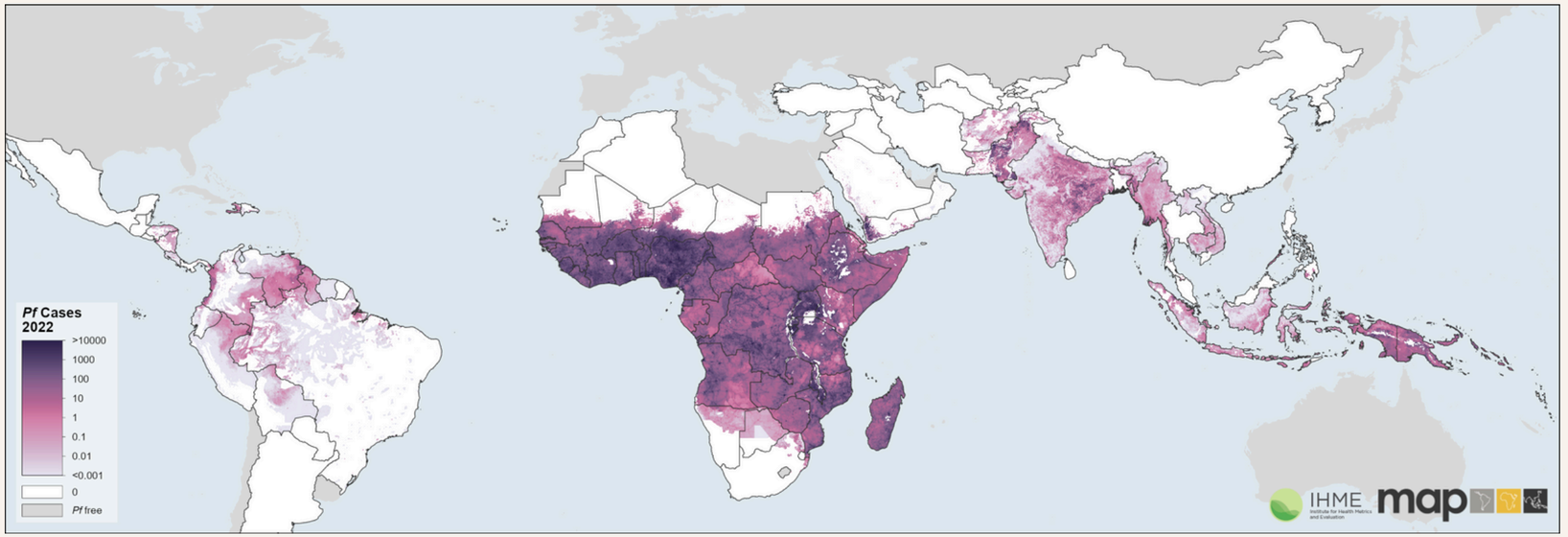
- P. falciparum
- P. vivax
- P. malariae
- P. ovale subspecies
- P knowlesi* (zoonotic)



Concerning with other 200 zoonotic species, specially P. simium and P. cynolmogi

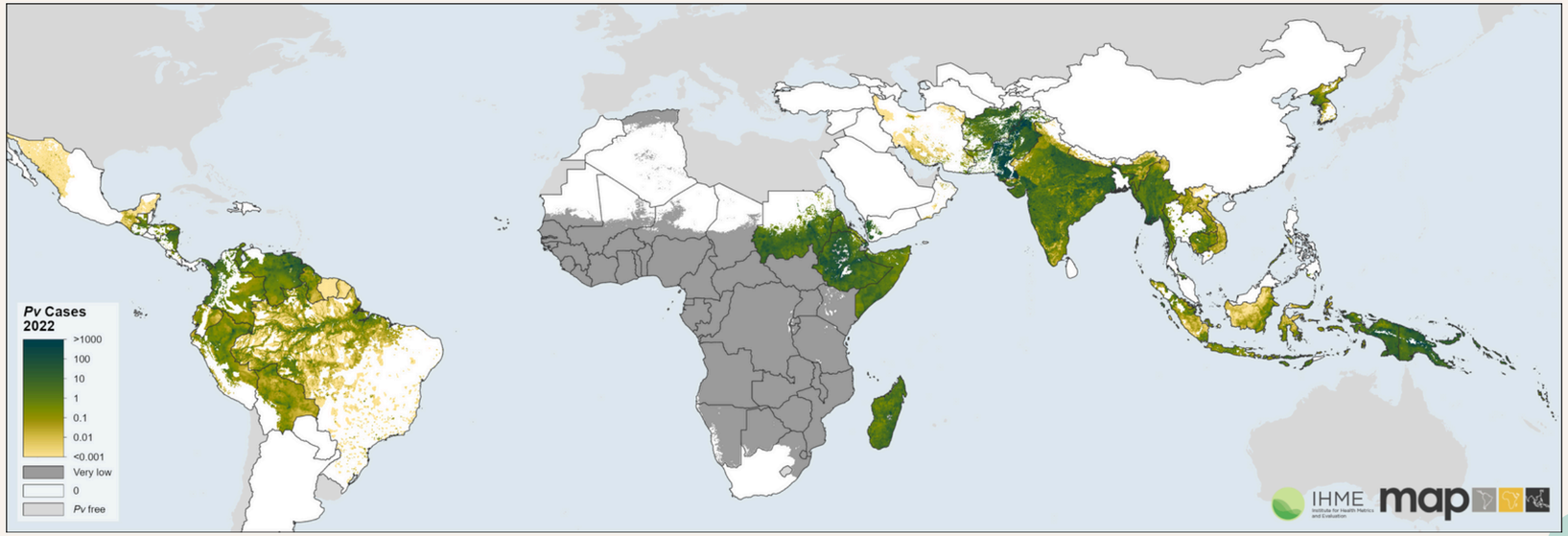
Garcia, 2010; Kantele et al, 2011; White et al, 2014

EPIDEMIOLOGY

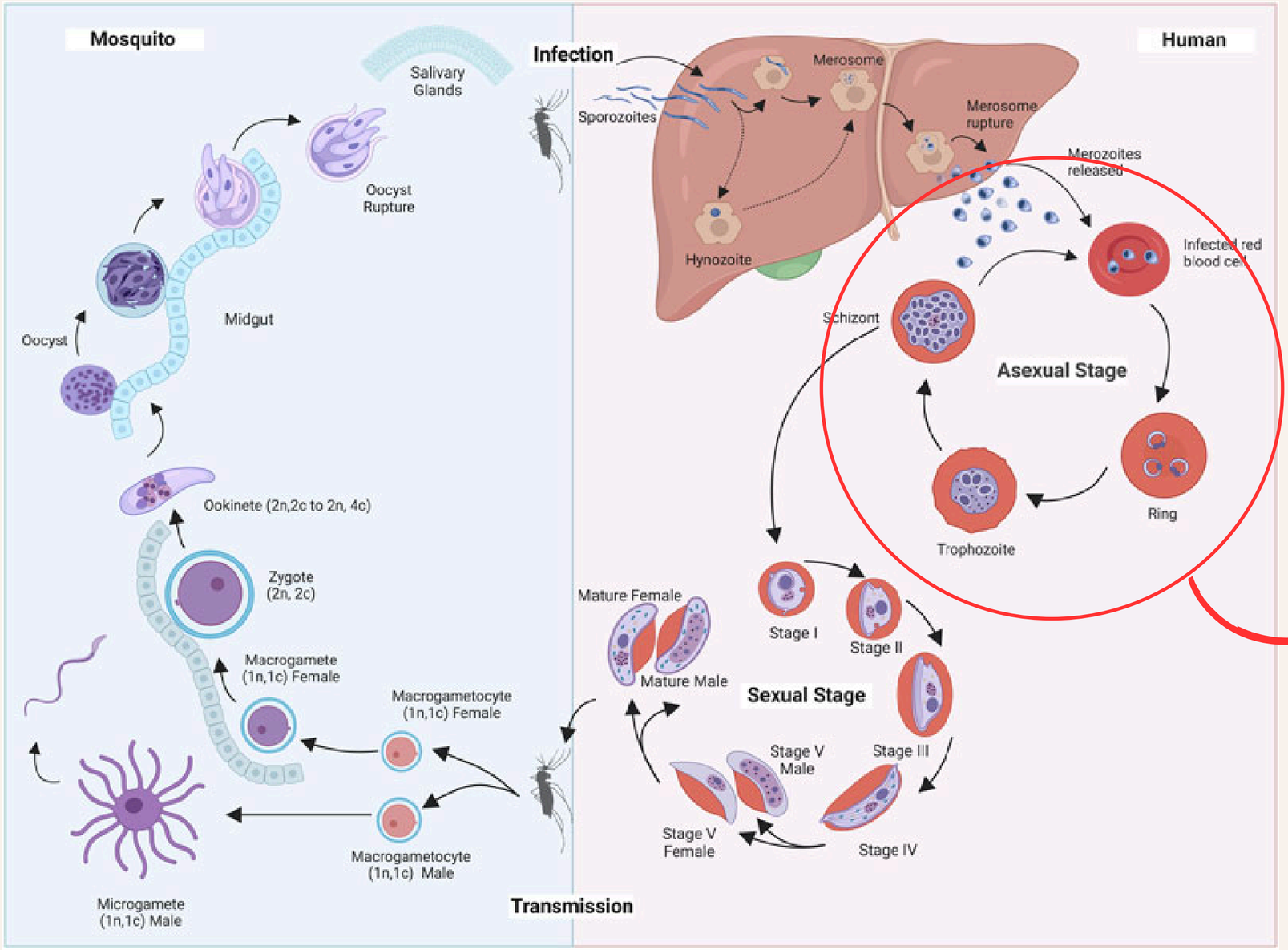


Clinical cases of P. falciparum in 2022

Clinical cases of P. vivax in 2022



LIFE CYCLE OF *PLASMODIUM*



Metaxenic cycle;

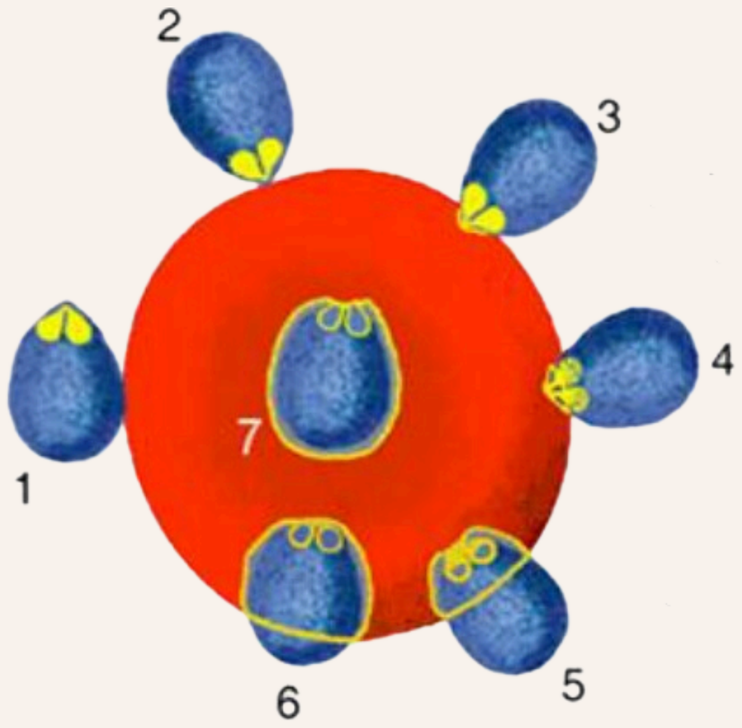
<u>P. vivax</u> had a latent form in host liver: hypnozoite;

Symptomatic detection by fever on erytrocitic stage.

Plasmodium species infects differentially Red Blood Cells (RBCs) by cytoadhesion

Chahine et al, 2022; CDC, 2024

PLASMODIUM Invasion



Invasion is an important way to differentiate Plasmodium infection and progression

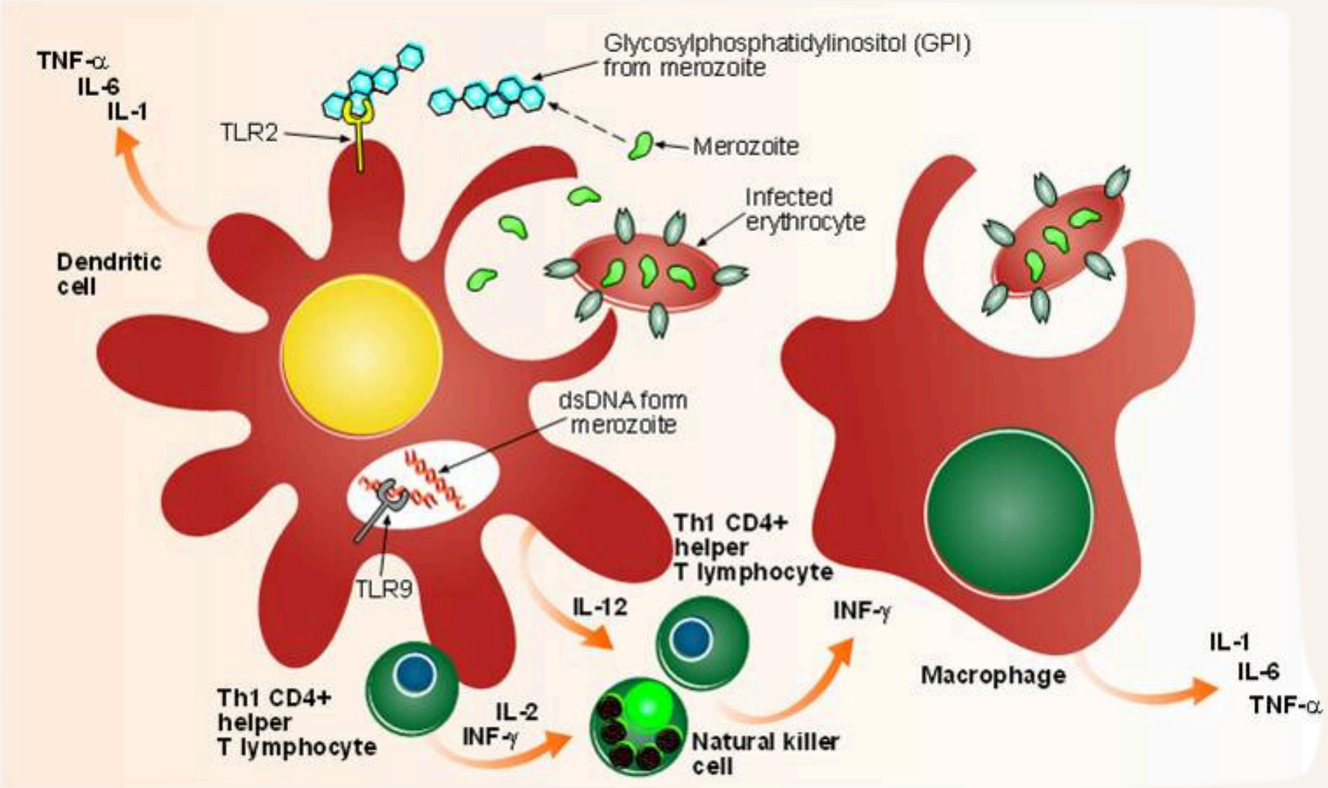
E.g, P. falciparum recognizes distinct many host receptors.

P. vivax recognizes reticulocytes and Duffy host receptors

On PVM (7), merozoites divides until guides to PVM and RBC lysis

Grau et al., 1992;

Pathogenesis of Malaria Fever

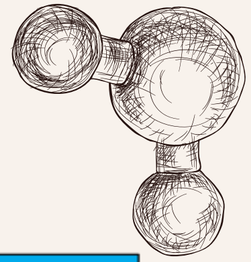


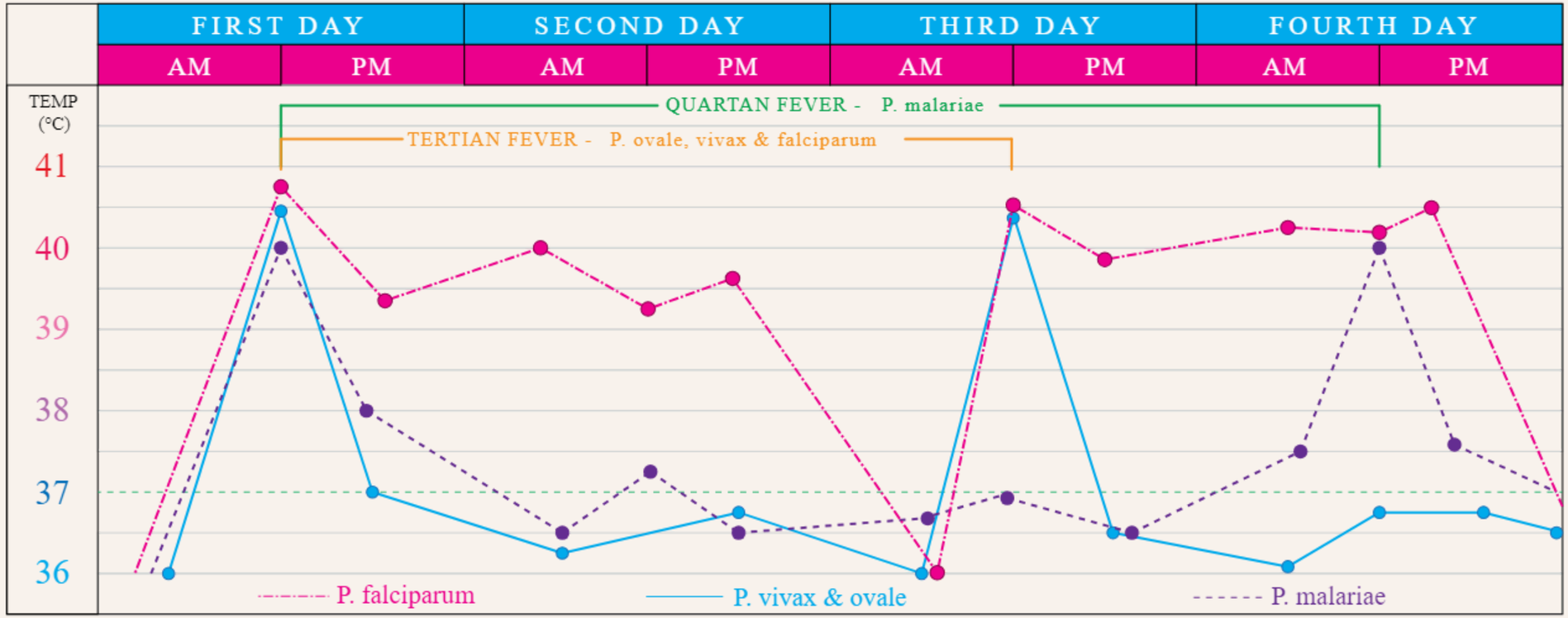
Immunogical detection by innate response cells recognition of merozoite's parasitaemia, var genes (mainly P.falciparum), antigenical debries (hemozoin and GPI);

DCs and activated macrophages are the main cells to inducing fever by proinflammatory cytokines;

Adaptative response acts on free merozoites and infected RBCs respectly by antibodies production and CD8+ cytotoxic response

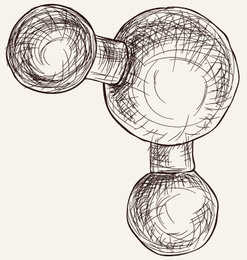
Malaria Fever

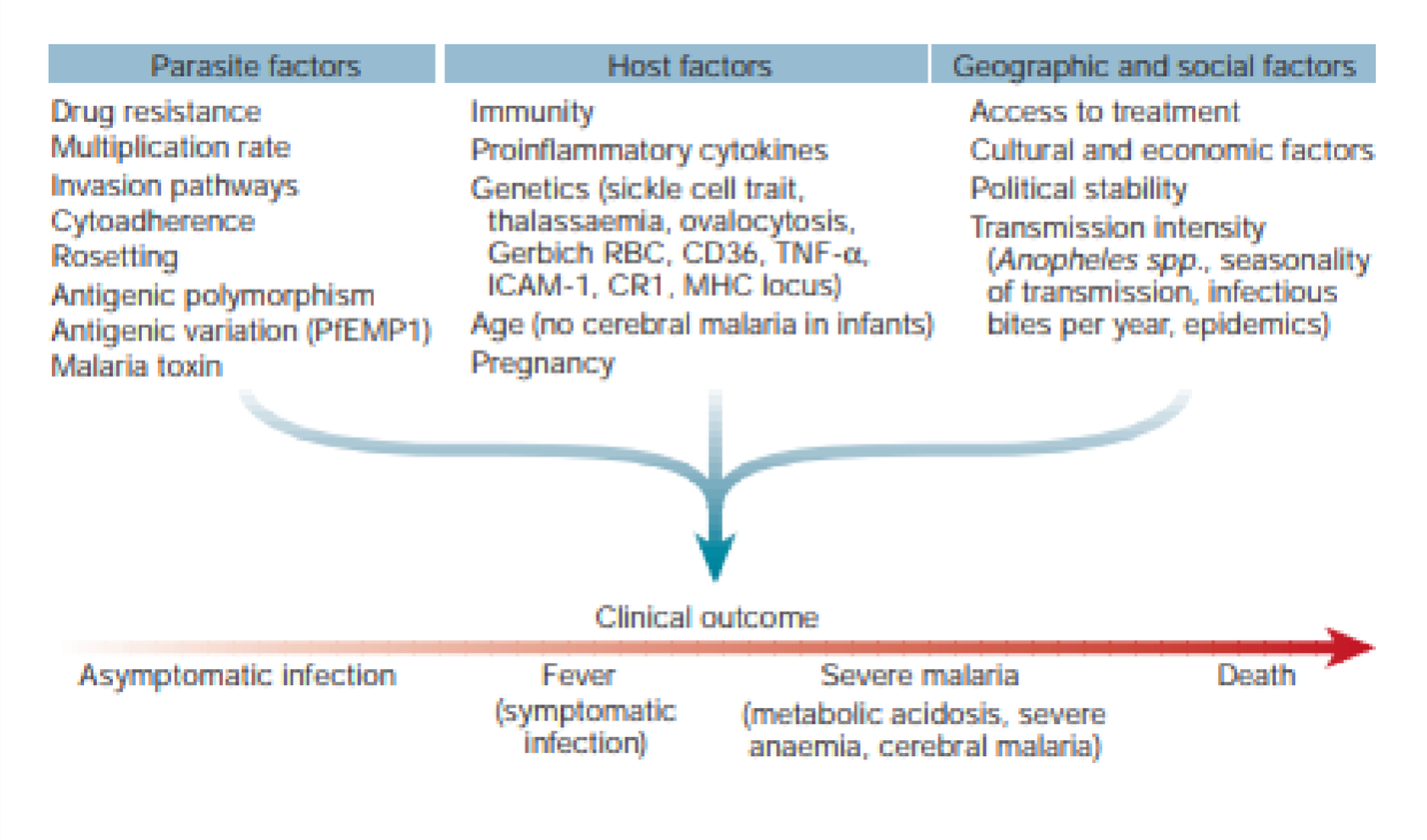




Fever pattern of distinct Plasmodium

Factors to malaria progression





Miller et al., 2006

Progression to Severe Malaria

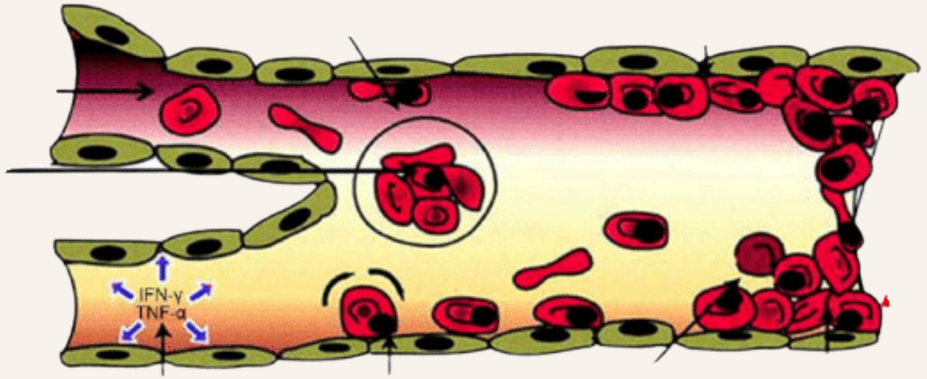
Adaptive response is not effective by tools of evasion or infection routes

Expression of var and rif genes

Non treated individues

CD36 and ICAM-1 alteration on infected RBCs on P.falciparum infection drives cytoadherence and rosetting of infected/non-infected RBCs on specificic endotellium vessels

P.vivax can turns erytrochtes more flexible, avoiding spleen RBCs removal



↓

Edema, anemia and endotellium dysfunction

Udomsangpetch et al., 2002; Li et al., 2016, Hadjailou et al., 2023

Progression of Severe Malaria

RBCs and MNC cytoadherence

Endothellium activation

Edema

CM

Cognitive impairment

P. falciparum

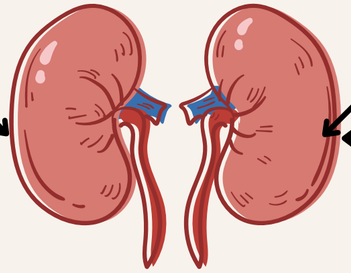
P. vivax

P. malariae

P. knowlesi

Leucocyte influx

Respiratory dysfunction



P. ovale

Renal failure

Souza et al. 2016

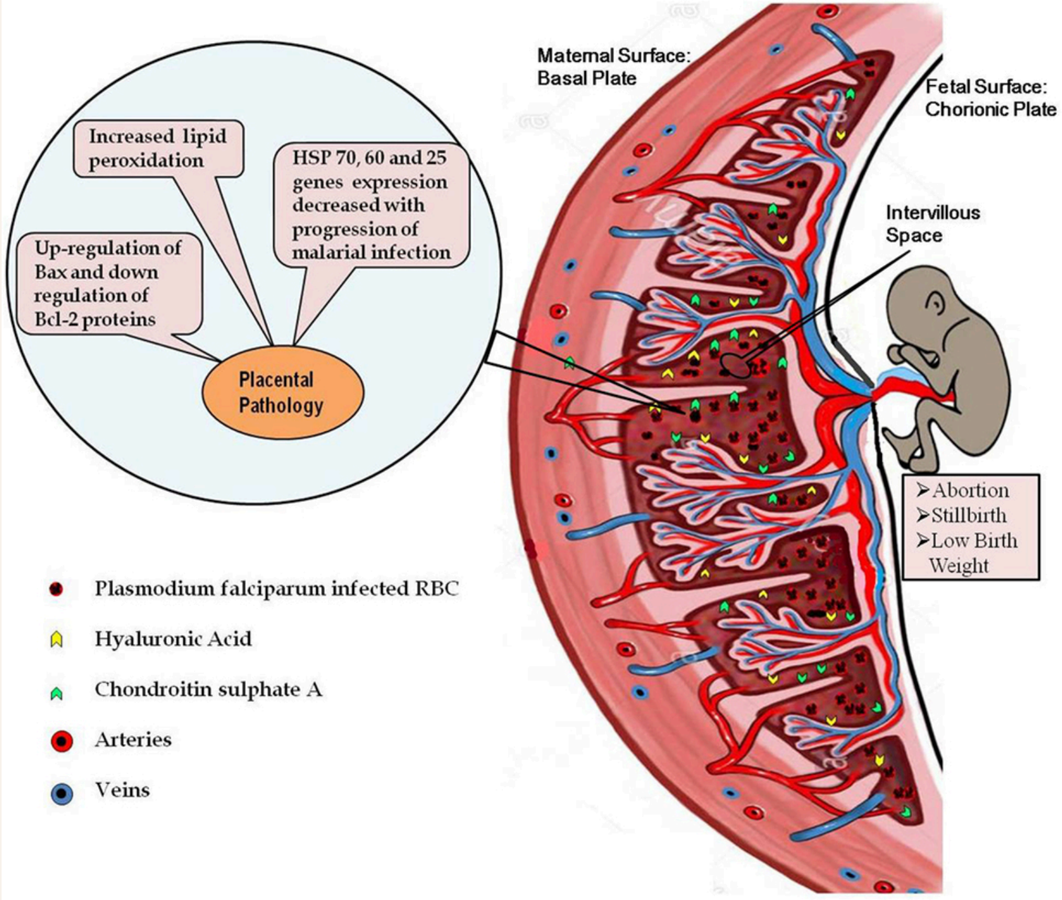
Placental malaria characteristic

Related to P. falciparum infection on first and second pregnancy

Absence of general fever, only by localizated fever

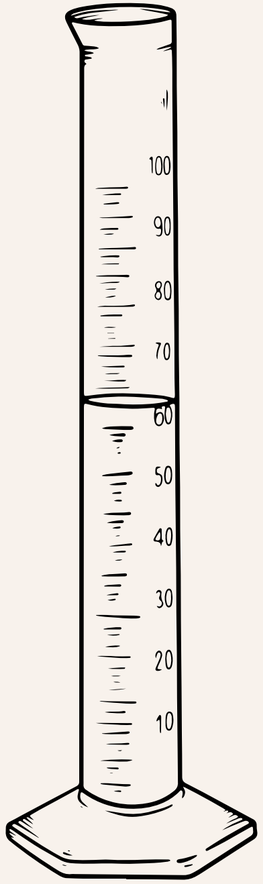
Cytoadhrence guides to excessive apoptosis

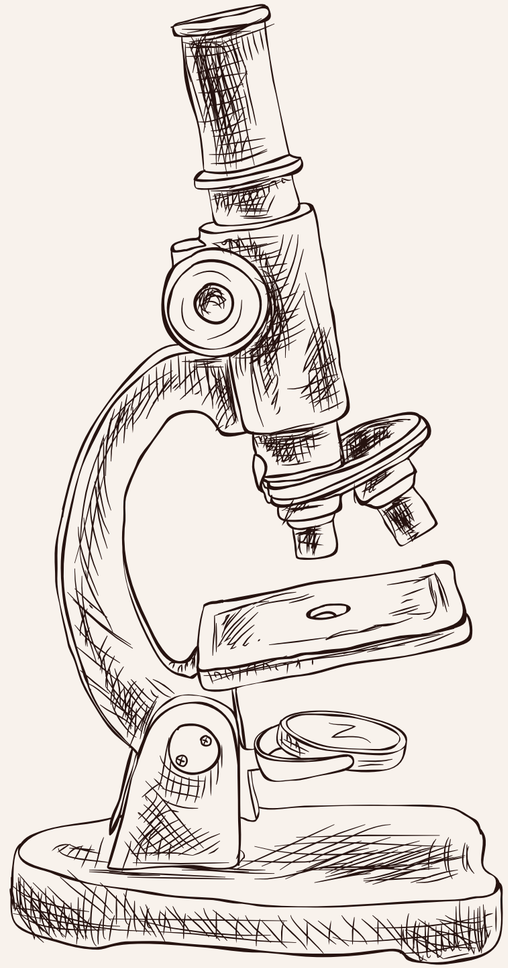
If non diagnosed and treated, the fetus/baby could be aborpted



Schofield et al. 2005. Sharma & Shukla, 2017

DENGUE

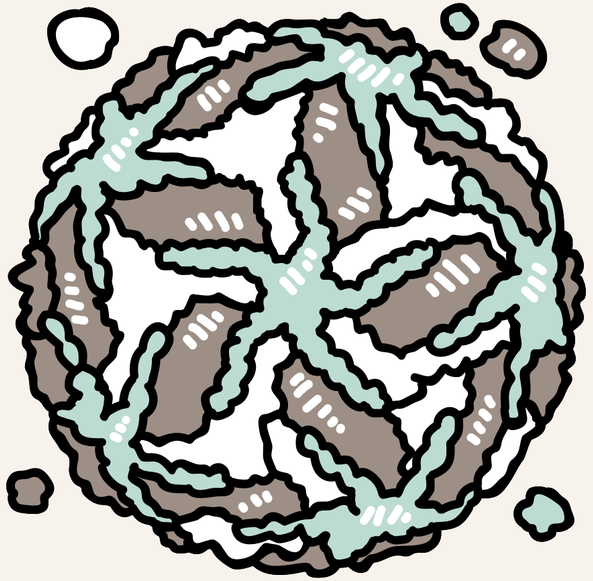




DENGUE

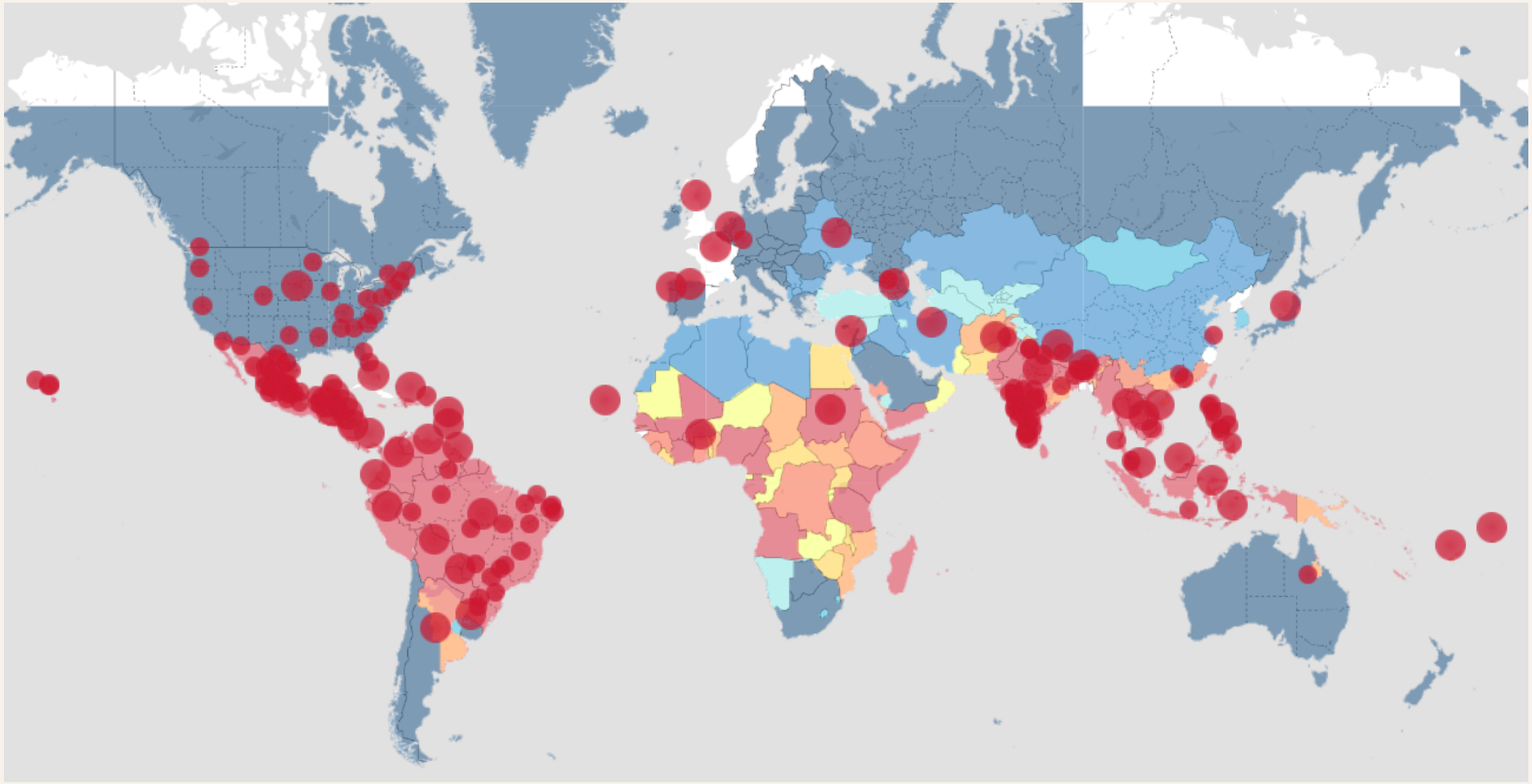
Viral diseases transmitted by infected female Aedes aegypti mosquitoes genus caused by Dengue virus (DENV).

Currently, there are 4 DENV serotypes that can cause dengue in humans ⟶ DENV1, DENV2, DENV3 and DENV4



EPIDEMIOLOGY

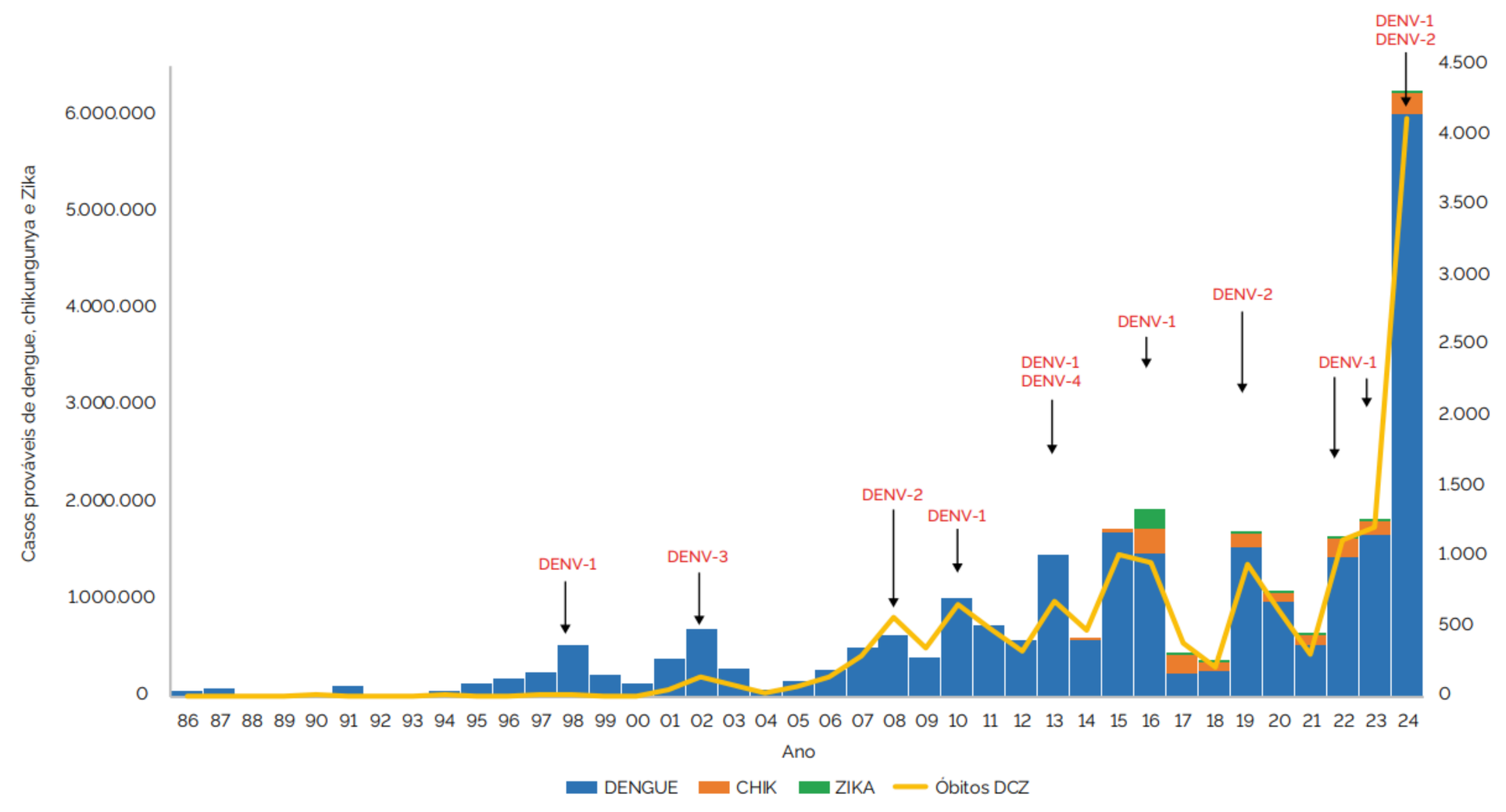
Endemic to tropical and sub-tropical regions, especially in Latin America
Now, is reaching North America and Europa too



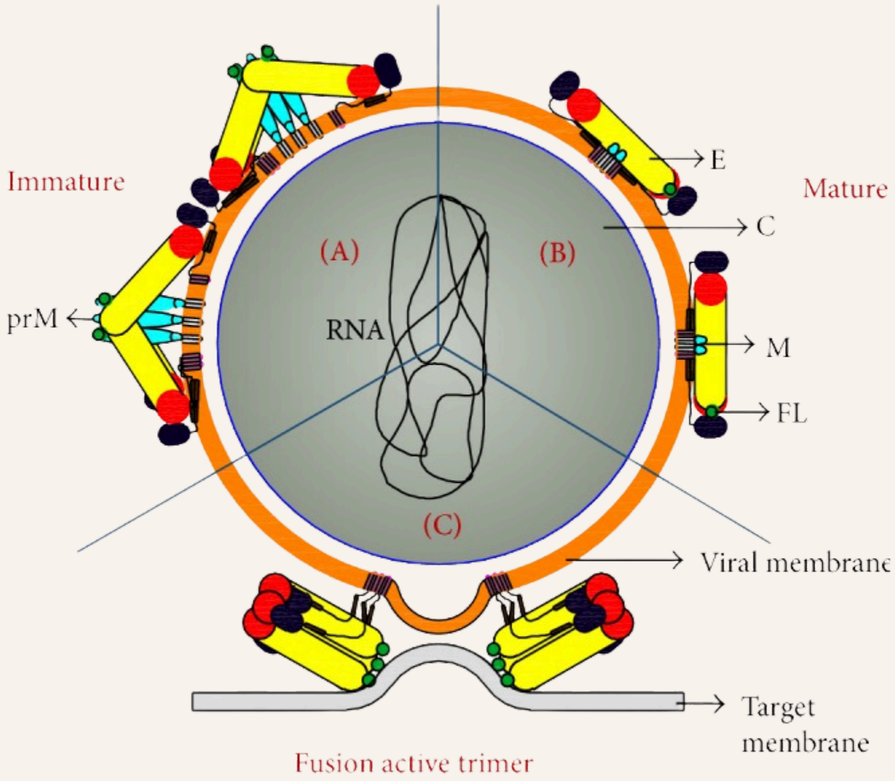
https://www.healthmap.org/dengue/en/

EPIDEMIOLOGY

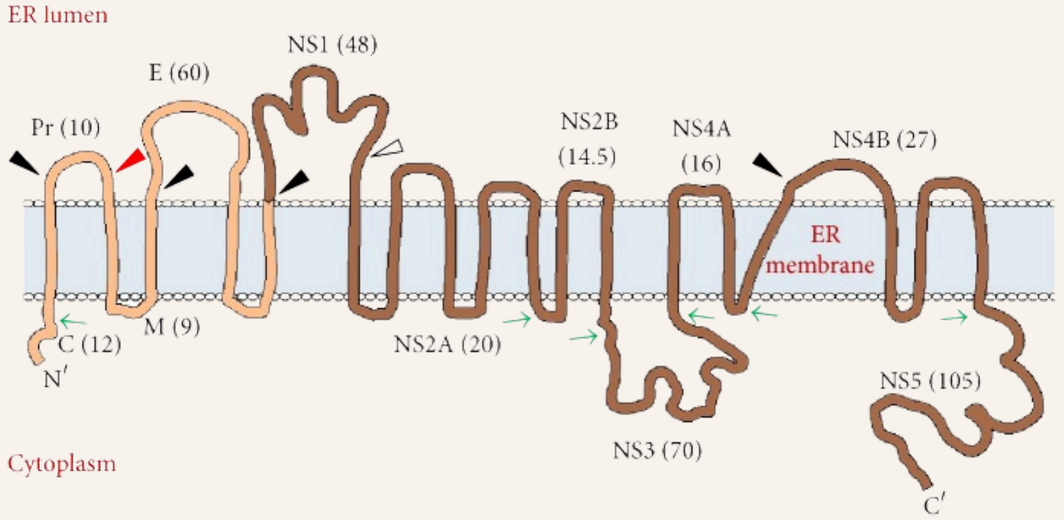
Historical series of probable cases



DENGUE VIRUS



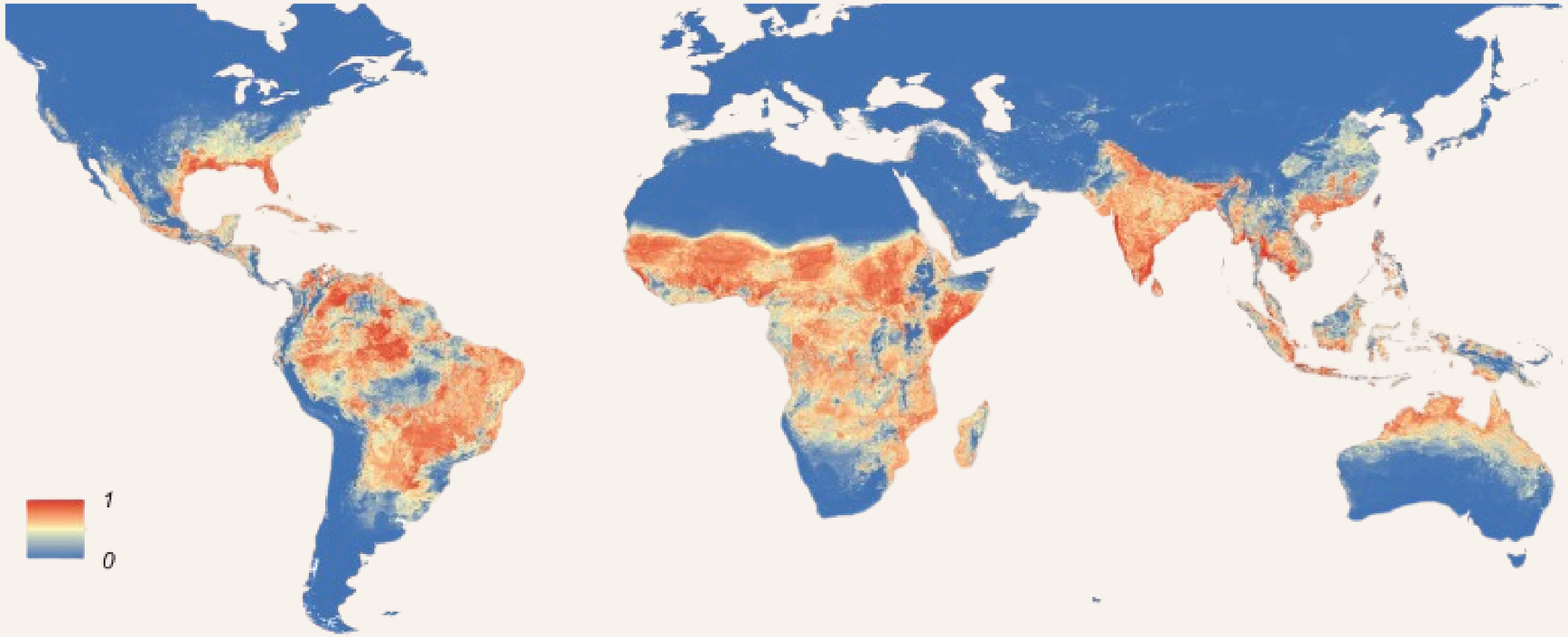
Khetarpal N, et al, 2016



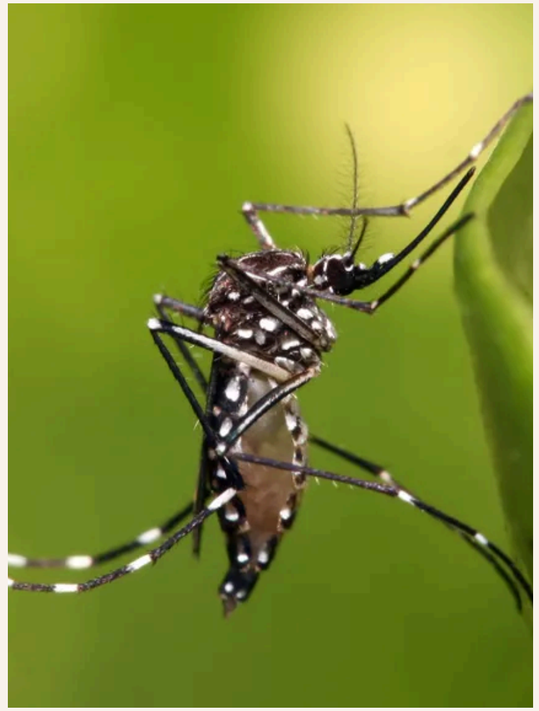
- Family of Flaviviridae, genus Flavivirus
- RNA genome of ~11kb
- 3 structural proteins:
  - Capsid (C)
  - Premembrane (prM)
  - Envelope (E)
- 7 nonstructural proteins

DENGUE VECTOR

Global map of the predicted distribution of Ae. aegypti



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4493616/

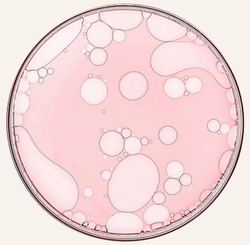


- Aedes aegypti
  - transmit DENV, yellow fever virus and chikungunya

THE SYMPTOMS

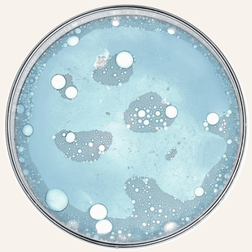
- **Asymptomatic**

The patient does not exhibit any clinical manifestations



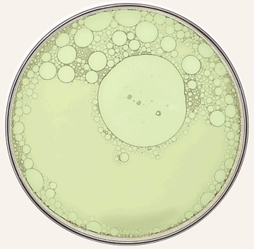
- **Dengue Hemorrhagic Fever (DHF)**

DF symptoms along with thrombocytopenia, hemorrhagic manifestations and plasma leakage The critical phase is usually reached at the end of febrile illness, marked by rapid decrease in temperature and often accompanied by circulatory disturbances including plasma leakage, hemoconcentration, and thrombocytopenia



- **Dengue Fever (DF)**

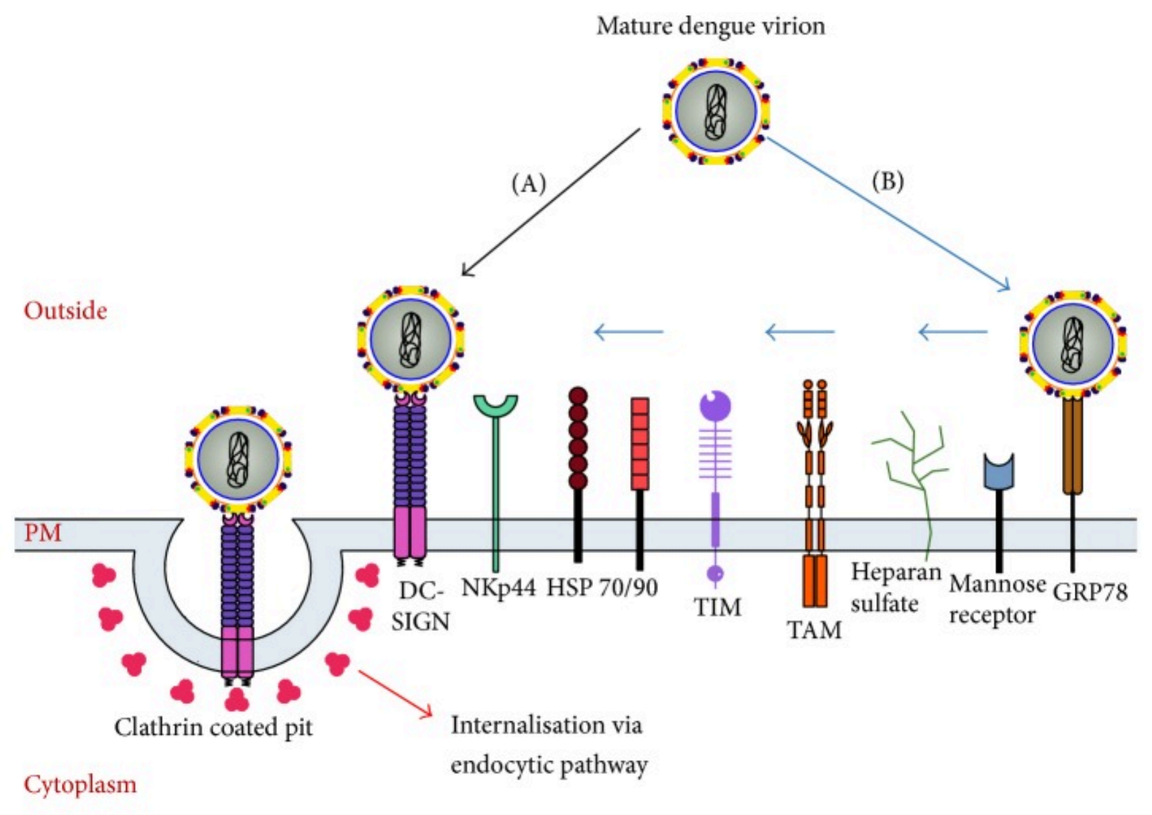
Self-limiting fever, lasting usually for 5-7 days, sometimes can be debilitating during the acute illness stage and the clinical features of DF vary according to the age of the patient. Usualyy patients apresent headache, retroorbital pain, myalgia, arthralgia, nausea, vomiting, and petechiae



- **Dengue Shock Syndrome (DSS)**

Critical plasma loss, a rapid, weak pulse with narrowing pulse pressure, cold clammy skin, and restlessness. The patient may die within 12–24 h of going into shock or recover rapidly with volume replacement therapy.

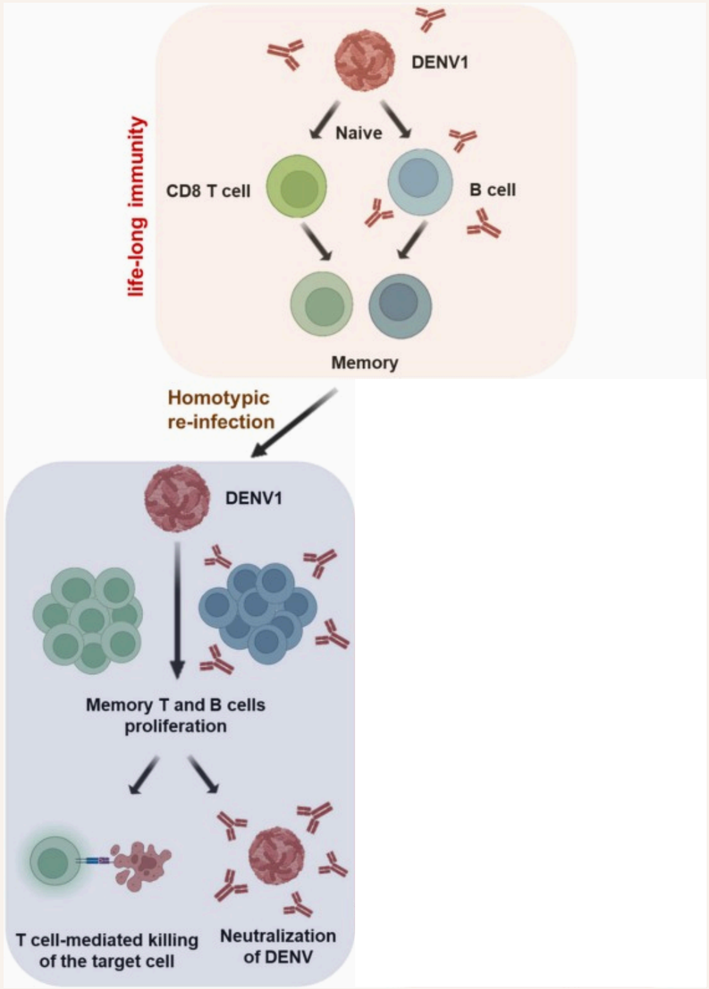
PATHOGENESIS



Kraemer MU et al, 2025

- Mosquitoes:
  - The primary targets the midgut epithelium, and then spreads to salivary glands
- Humans:
  - Infects and replicates in the cells of mononuclear lineage like monocytes, dendritic cells, macrophages and Langerhans cells
- Model of Flavivirus Cell Entry:
  - Attachment factors and primary receptors
  - Endocytic pathway
- Infection:
  - Lymph nodes
  - Viremia - liver, lungs, spleen and bone marrow

IMMUNE RESPONSE



Muhammad Bilal Khan et al, 2023

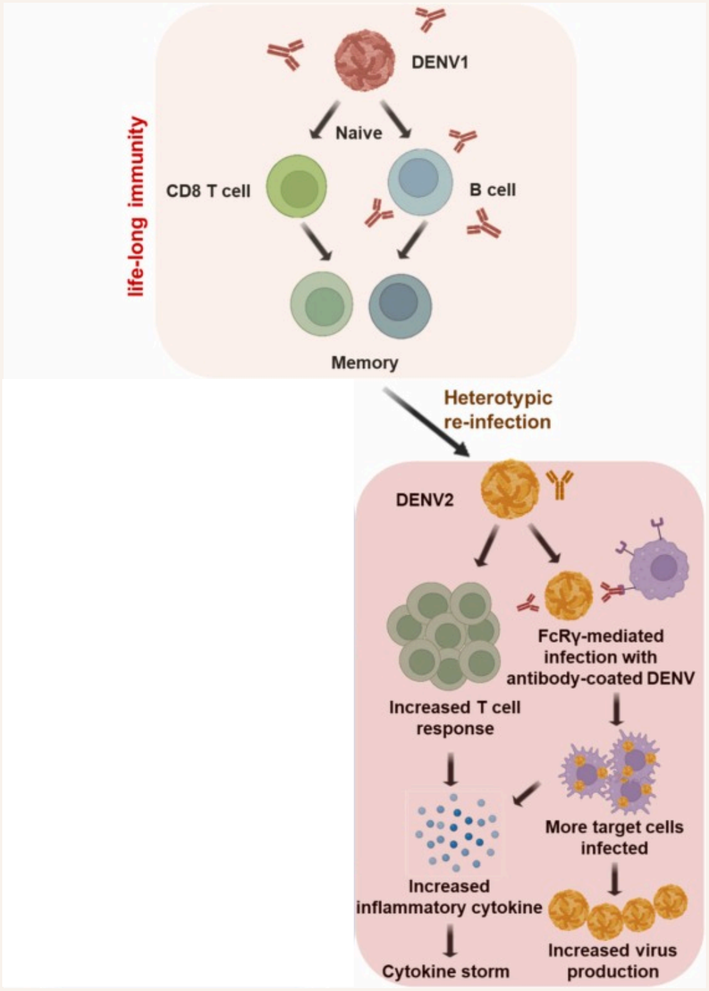
First Infection

- Macrophages and dendritic cells, detect the presence of the virus and release as IL-1β, IL-6 and TNF-α
- This infection is characterized by IgM and IgG high levels, against protein E
- IgM is transient, disappearing after 2-3 months after exposure, and IgG persists for the rest of life, but it do not give immunity to others serotypes

Second Homotypic Infection

- DENV is quickly neutralized by antibodies produced by immunological memory cells

IMMUNE RESPONSE

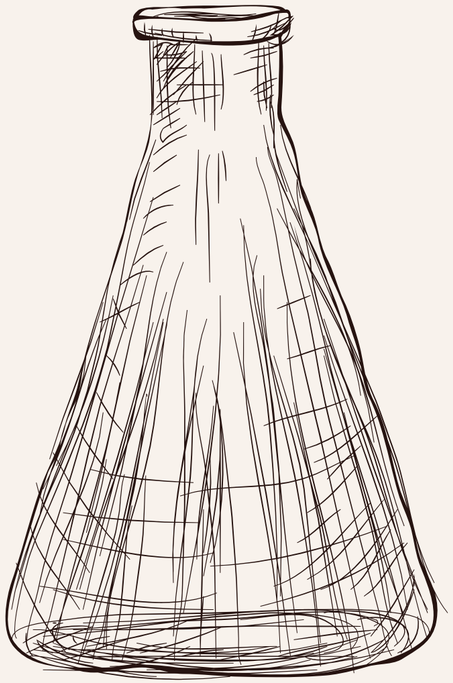


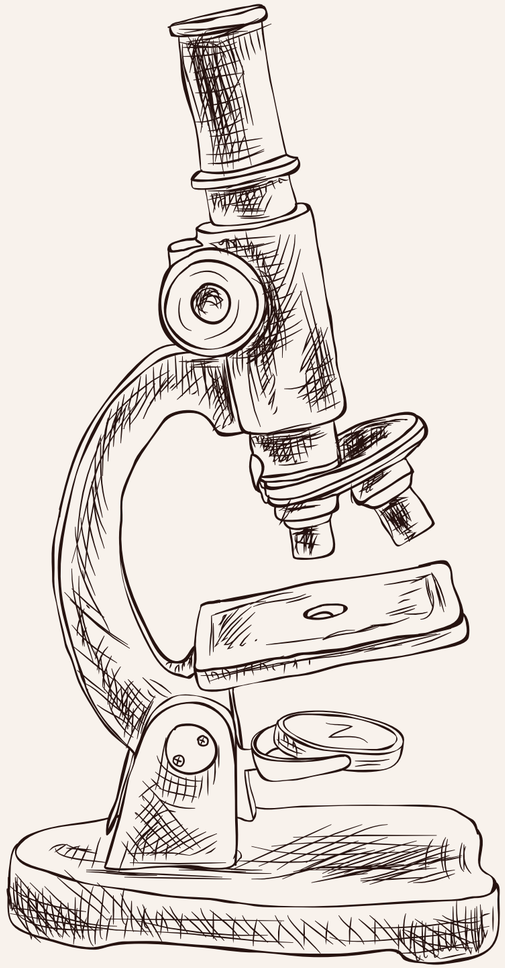
Muhammad Bilal Khan et al, 2023

Second Heterotypic Infection

- Normally causes DF, but 2-3% cases evolve to DHF, that can progress to DSS
- ADE:
  - Antibodies forms complexes with the DENV, promoting the virus's access to monocytes via Fc receptors, leading to an increase in viral load and disease severity
  - One hypothesis is that FcR-γ mediated entry suppresses the antiviral immune response
- Cross Reactive T Cells:
  - Produce high concentrations of pro- and anti-inflammatory cytokines
  - High plasmatic levels of IL-1β, IL-2, IL-4, IL-6, IL-7, IL-8, IL-10, IL-13, IL-18, TGF-1β, TNF-α e IFN-γ

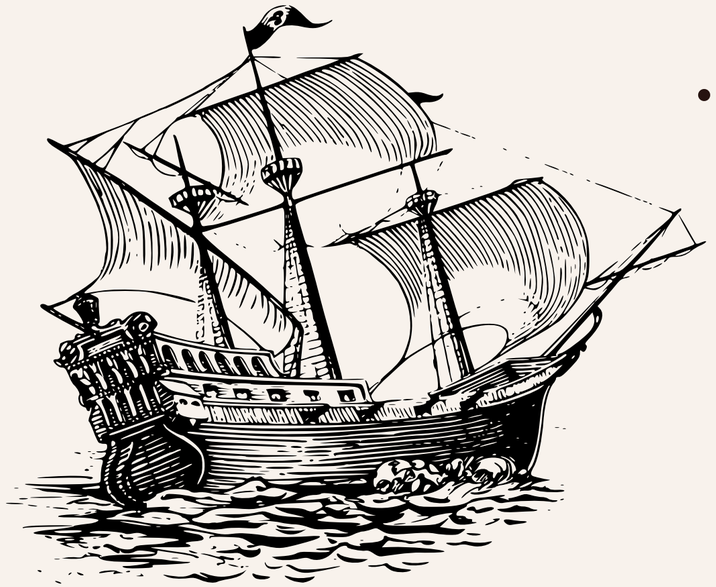
YELLOW FEVER



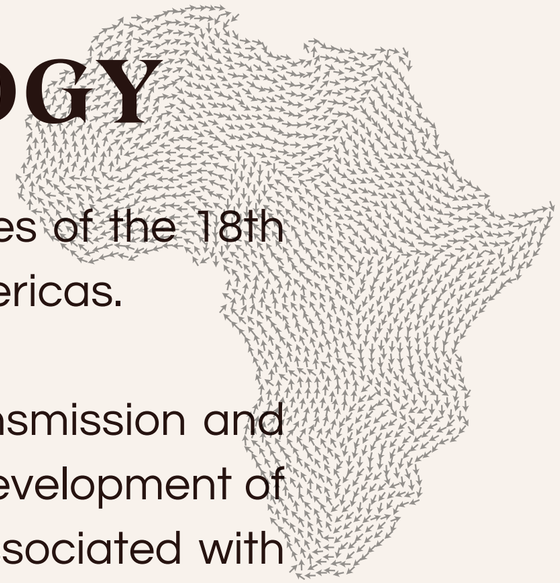


YELLOW FEVER

- Viral hemorrhagic fever
- Yellow fever virus, the prototype species in the Flavivirus genus (Flaviviridae family)
- Yellow eyes, jaundice
- Transmitted via mosquitoes of the Haemogogus, Sabethes and Aedes genera
- Origin in Africa

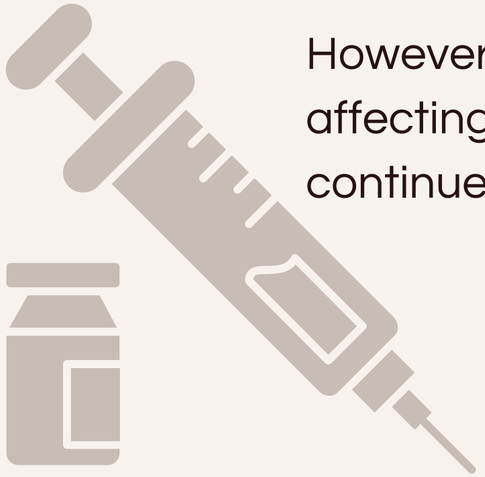


HISTORY AND EPIDEMIOLOGY



Yellow fever (YF) was one of the most dangerous infectious diseases of the 18th and 19th centuries, resulting in mass casualties in Africa and the Americas.

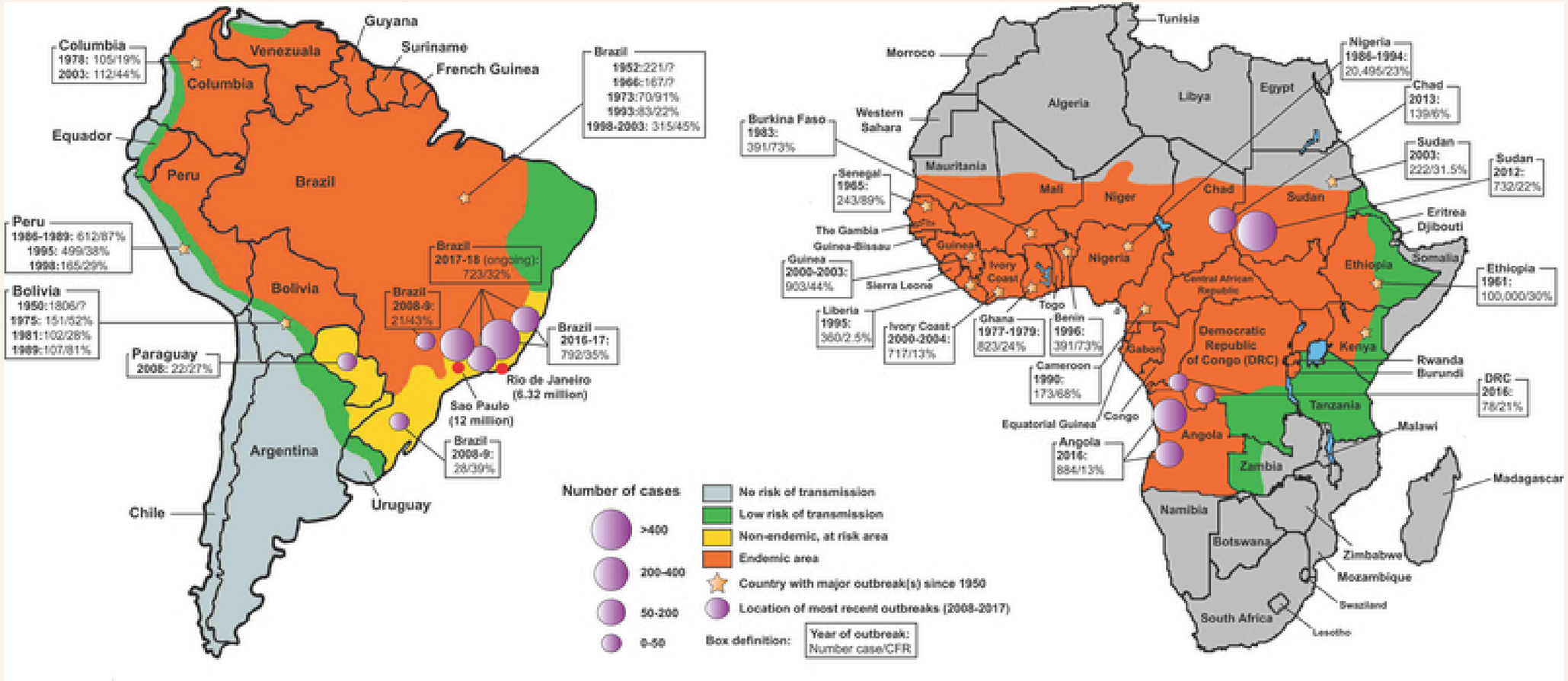
The discoveries (in 1900) that mosquitoes were responsible for transmission and that the disease was preventable by vector control, as well as the development of the YFV-17D vaccine (in the 1930s), have reduced both the fear associated with the disease and its medical impact, since the urban cycle was erradicated.



However, yellow fever remains an endemic and epidemic disease problem affecting thousands of people in tropical Africa and South America, and is a continued threat to people who travel to these regions without vaccination.

EPIDEMIOLOGY

Endemic to tropical and sub-tropical regions of South America and Africa. Annually, there are approximately 80,000–200,000 YFV cases worldwide. The number of fatalities annually is commonly estimated as 30,000–60,000



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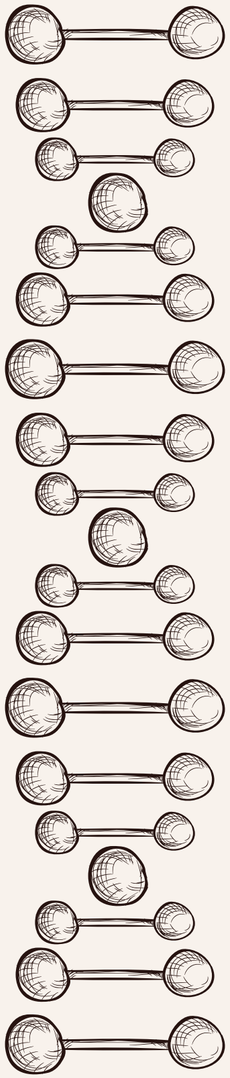
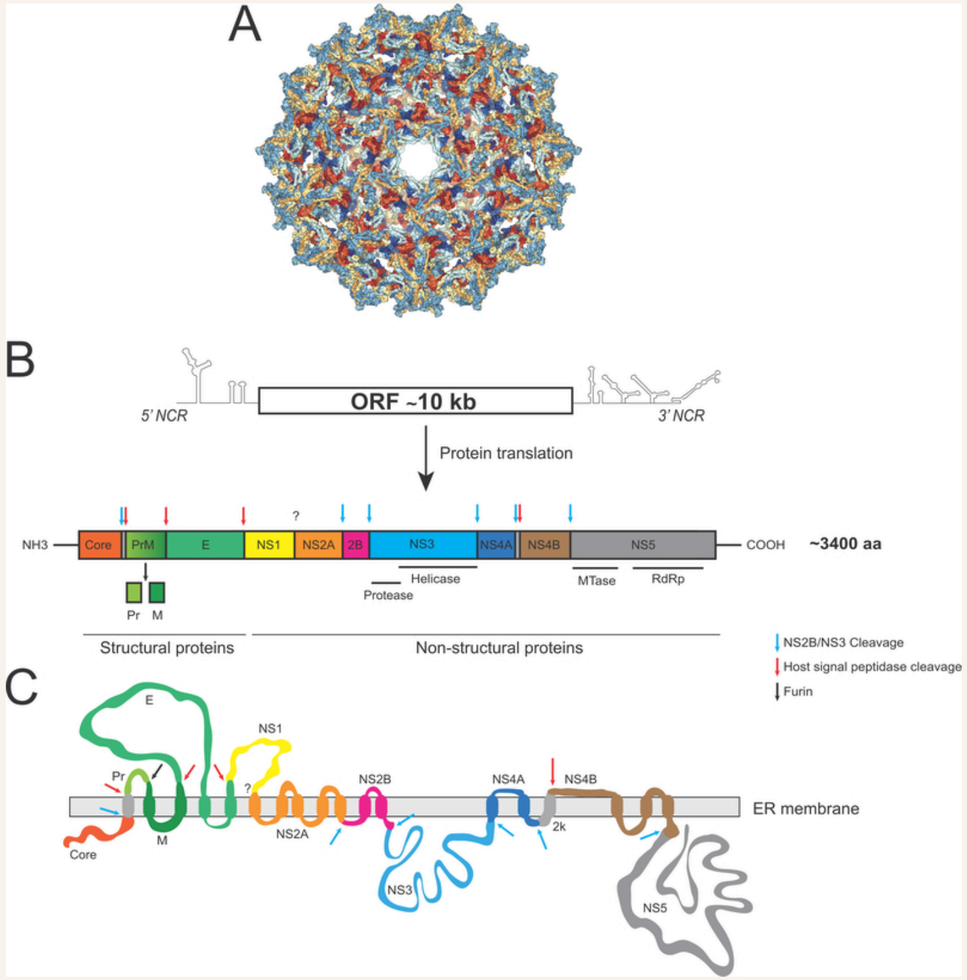


YFV CHARACTERISTICS

- positive-sense, single-stranded RNA virus
- enveloped virus
- 3 structurual proteins: C- core, PrM, E glycoprotein= viral coat
- 7 NS proteins



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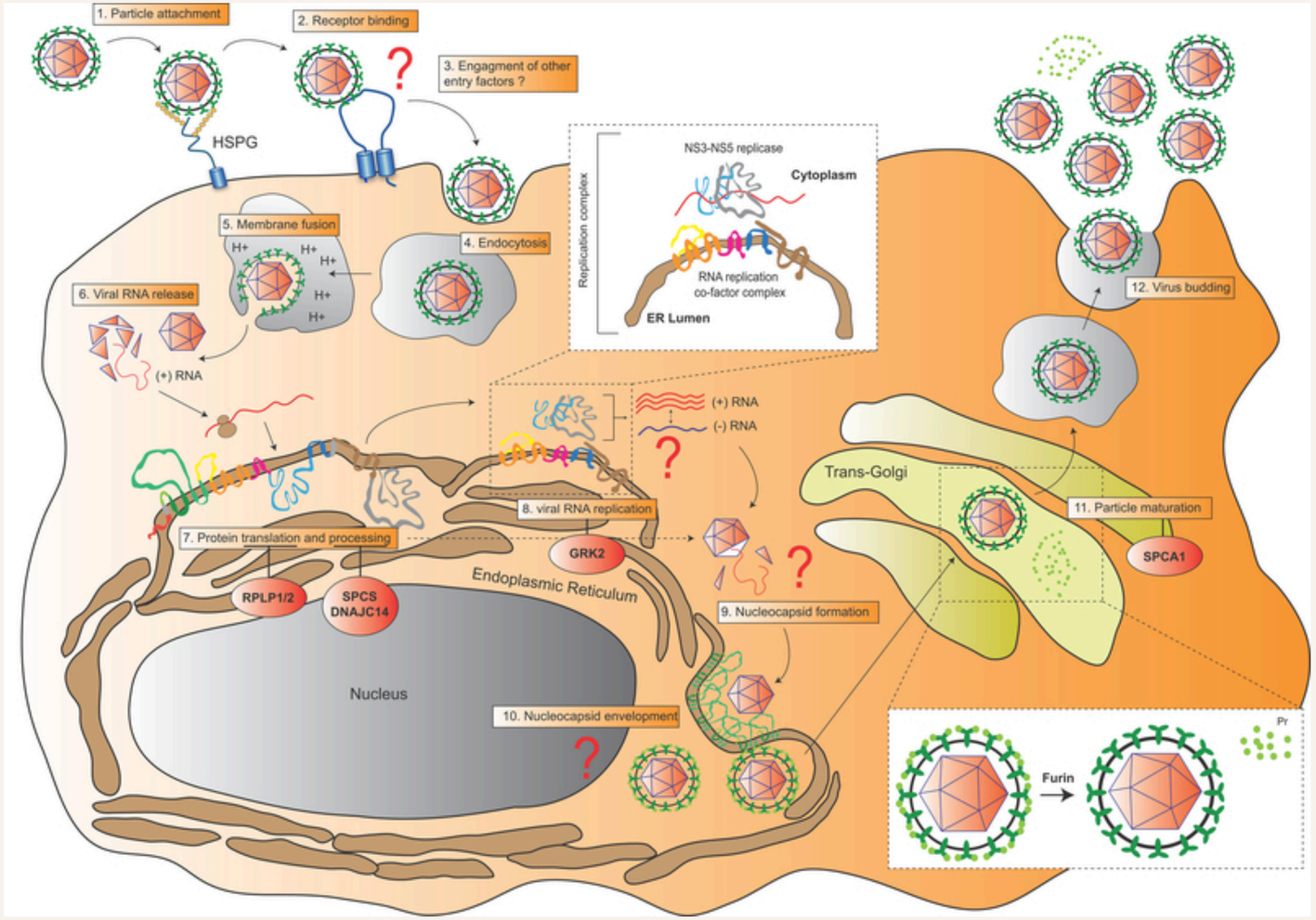
CELL INFECTION MECHANISM

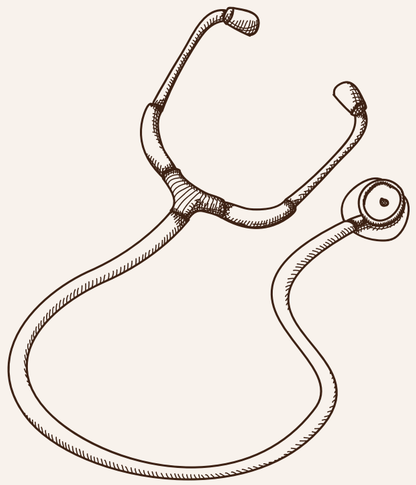


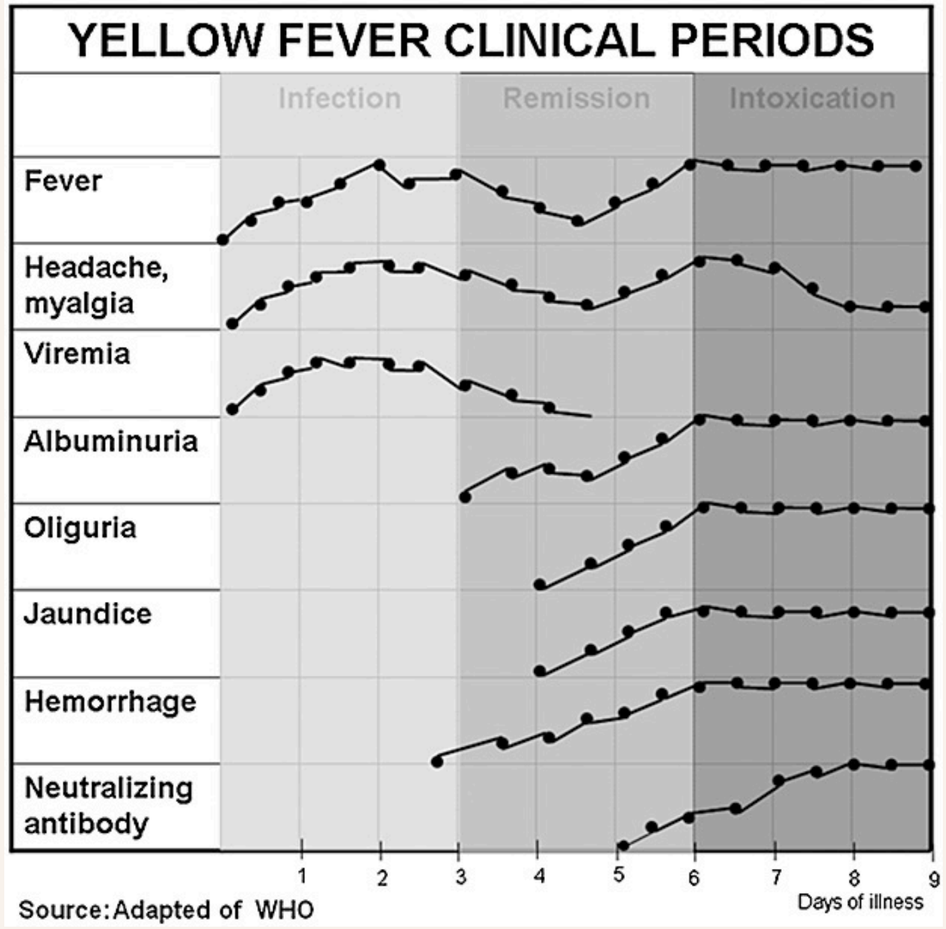
- neutralising antibodies against E
- NS3 --> cytotoxic T cells
- NS1 --> cytotoxic antibodies

Douam F, Ploss A. Yellow Fever Virus: Knowledge Gaps Impeding the Fight Against an Old Foe.Trends Microbiol. 2018

ILNESS STAGES

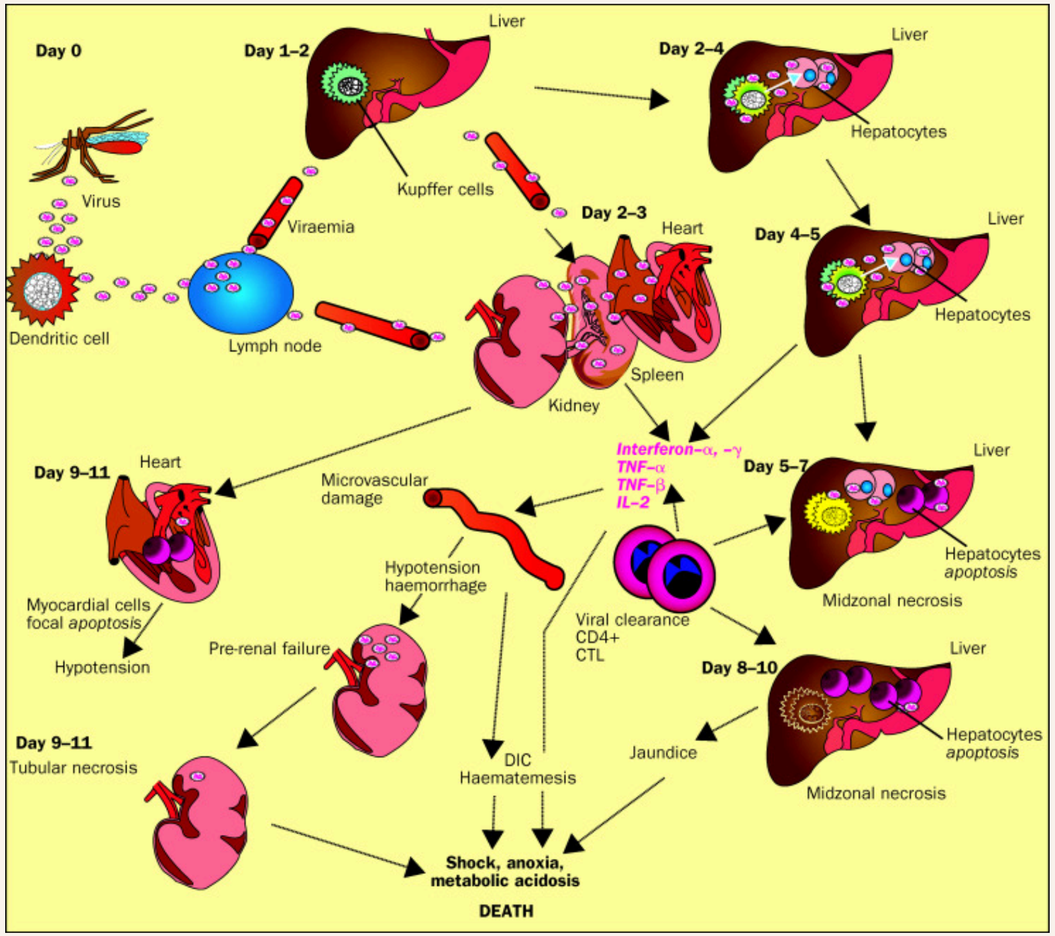
- Period of incubation (3-6 days aftes bite)
- Period of viremia or infection (3-5 days)
- Period of remission (12h-2 days)
- Period of intoxication (15–25% of people)





PATHOGENESIS

VISCEROTROPISM



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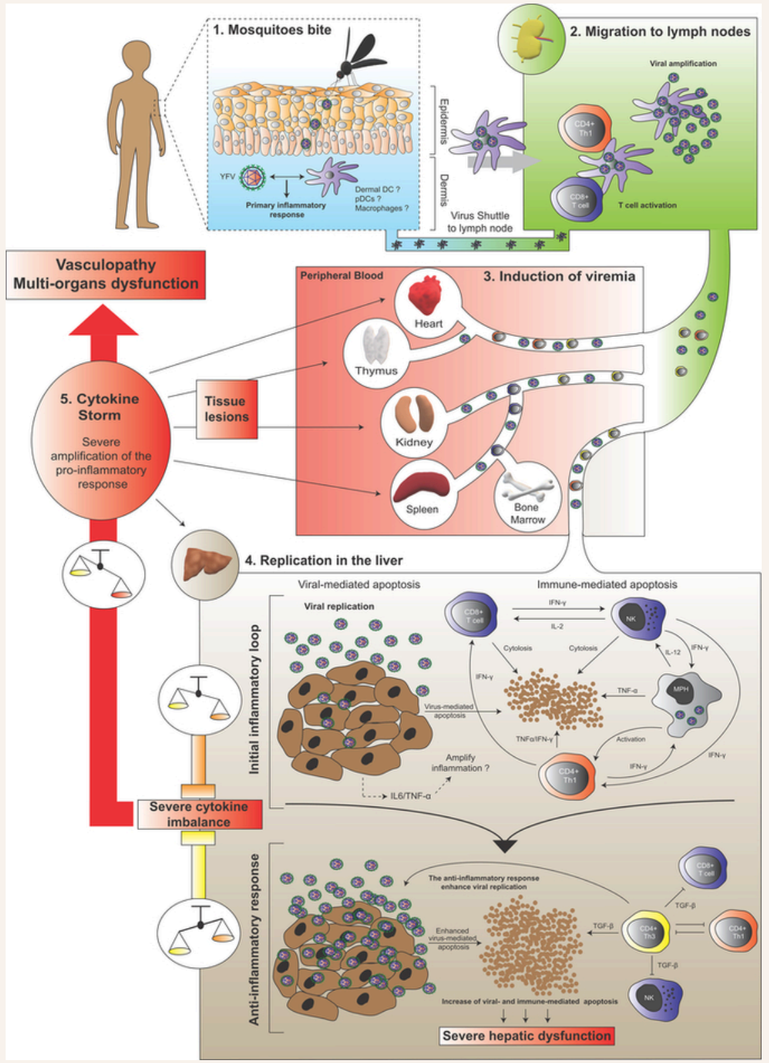
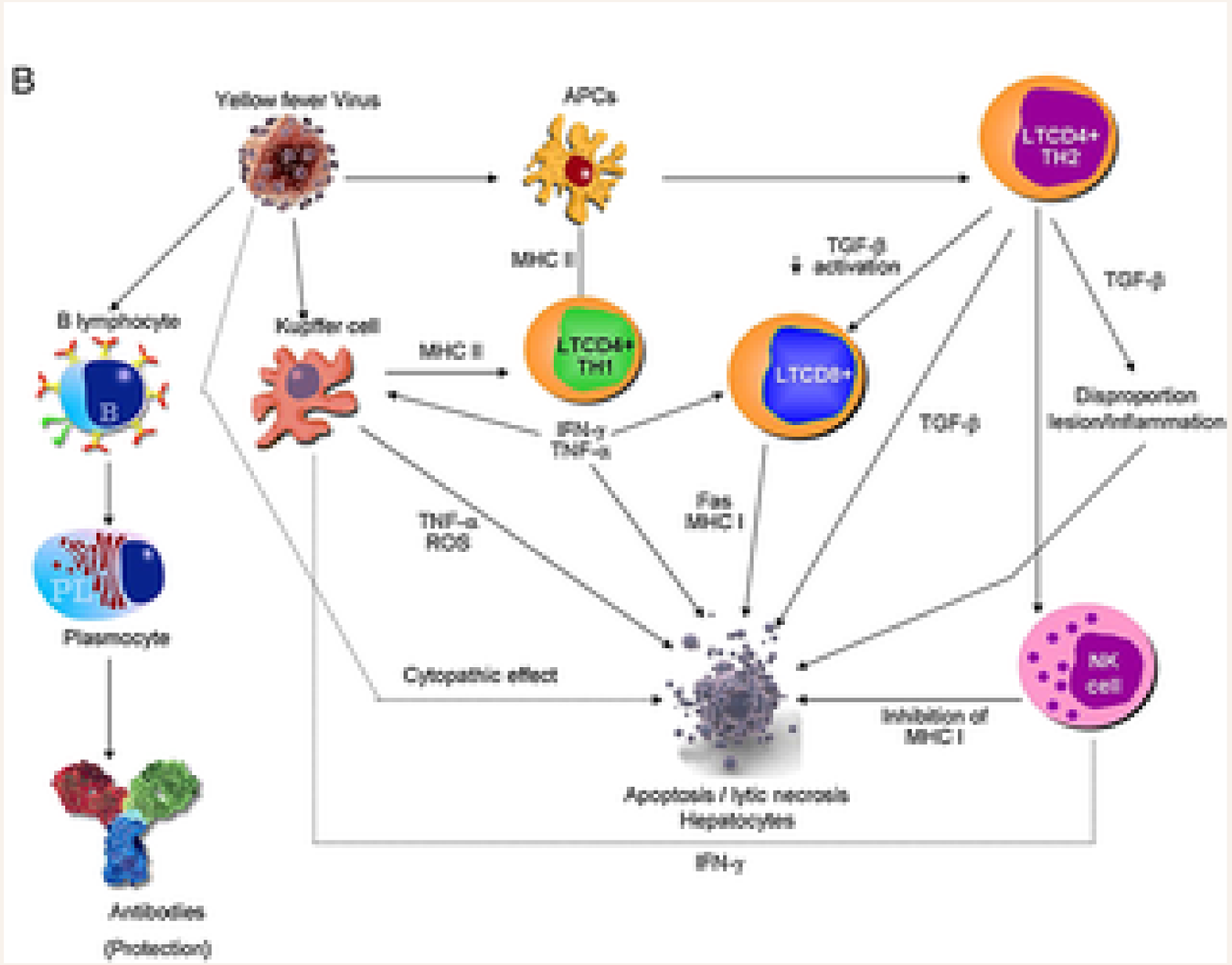


TH1 CD4+

TH3 CD4+

Douam F, Ploss A. Yellow Fever Virus: Knowledge Gaps Impeding the Fight Against an Old Foe.Trends Microbiol. 2018

IMMUNE RESPONSE



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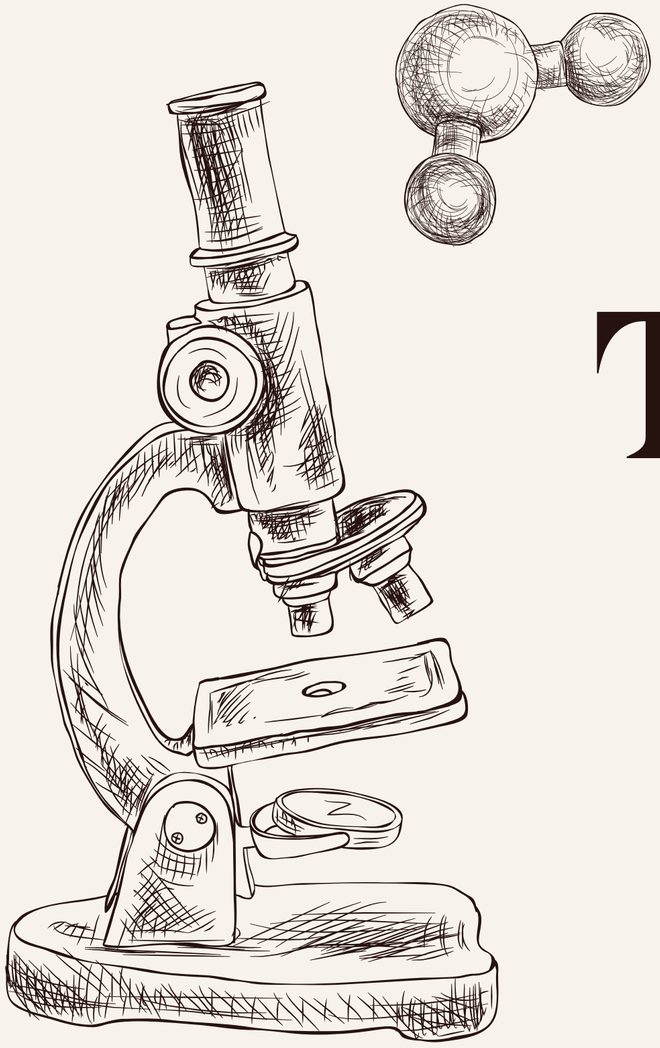
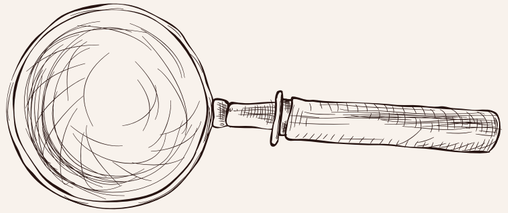
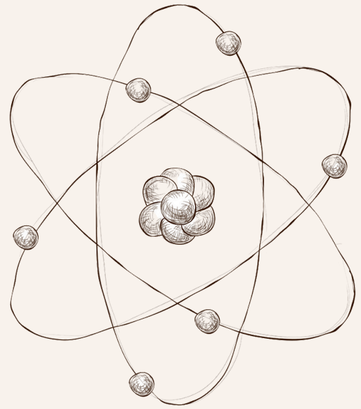
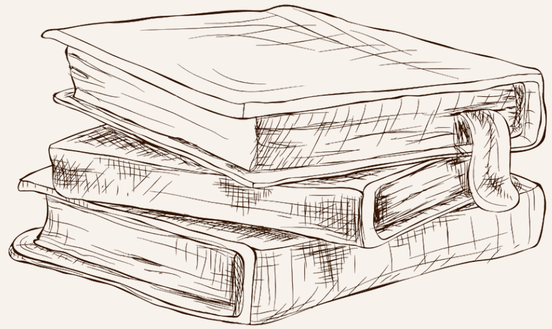


Fisiopatologia das doenças infecciosas

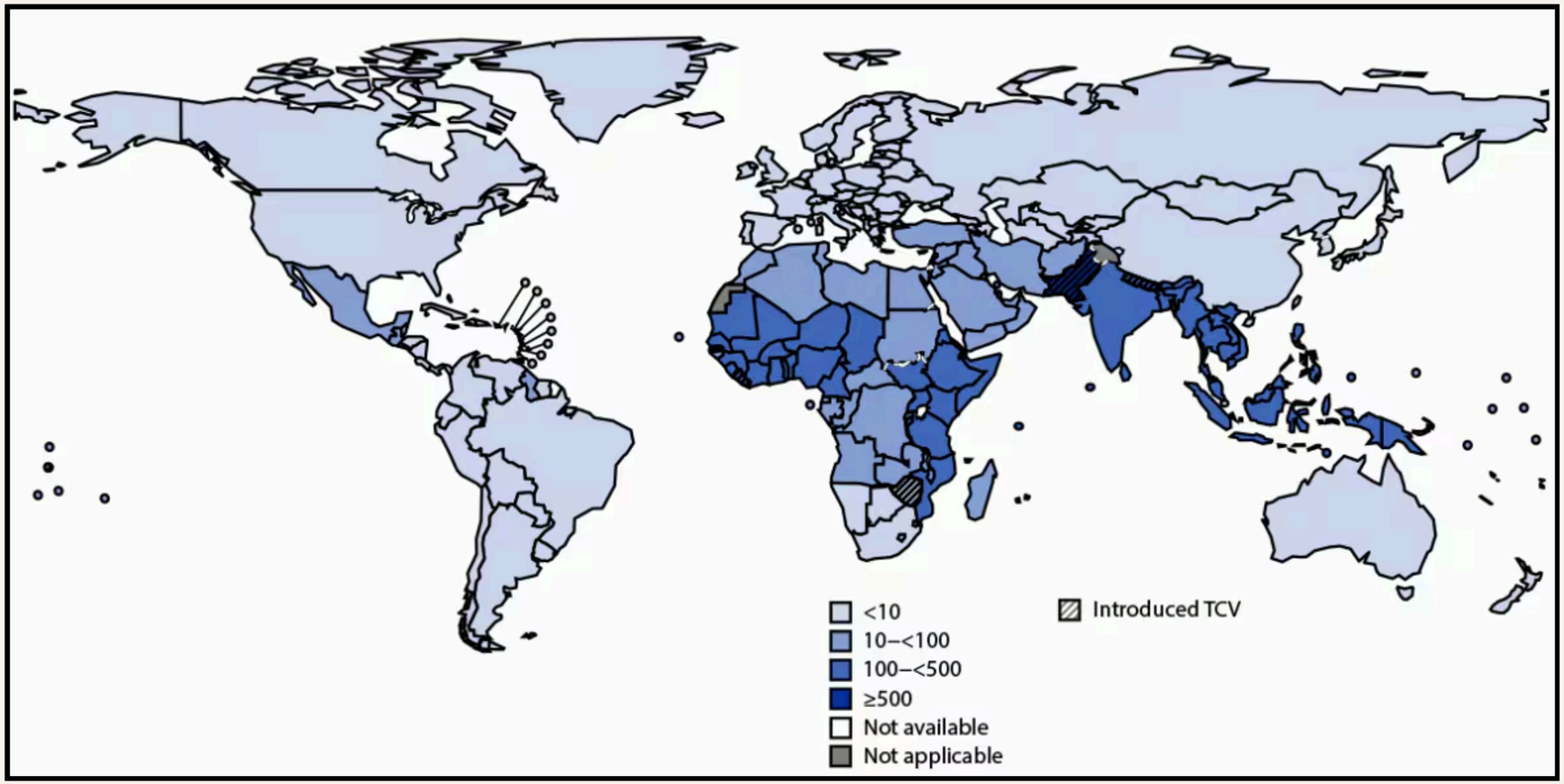
TYPHOID FEVER







S.TYPHI EPIDEMIOLOGY



https://pubmed.ncbi.nlm.nih.gov/36795626/

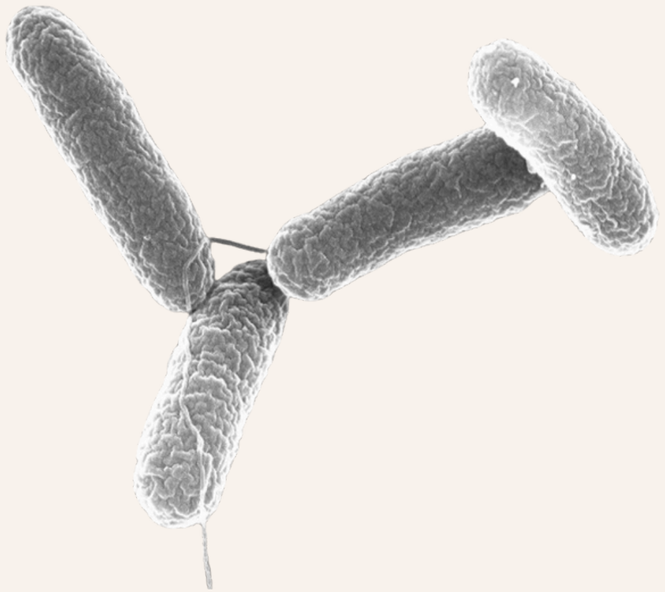
S.TYPHI EPIDEMIOLOGY

An estimated 11–21 million typhoid fever cases and 148,000–161,000 associated deaths occurred in 2015. The World Health Organization (WHO) recommends safe, effective typhoid conjugate vaccines (TCV) for typhoid fever control.

Population-based and modeling studies confirm high typhoid incidence in the WHO South-East Asian, Eastern Mediterranean, and African regions. Since 2018, five countries have introduced TCV into their national routine immunization schedule.

S.TYPHI CHARACTERISTICS

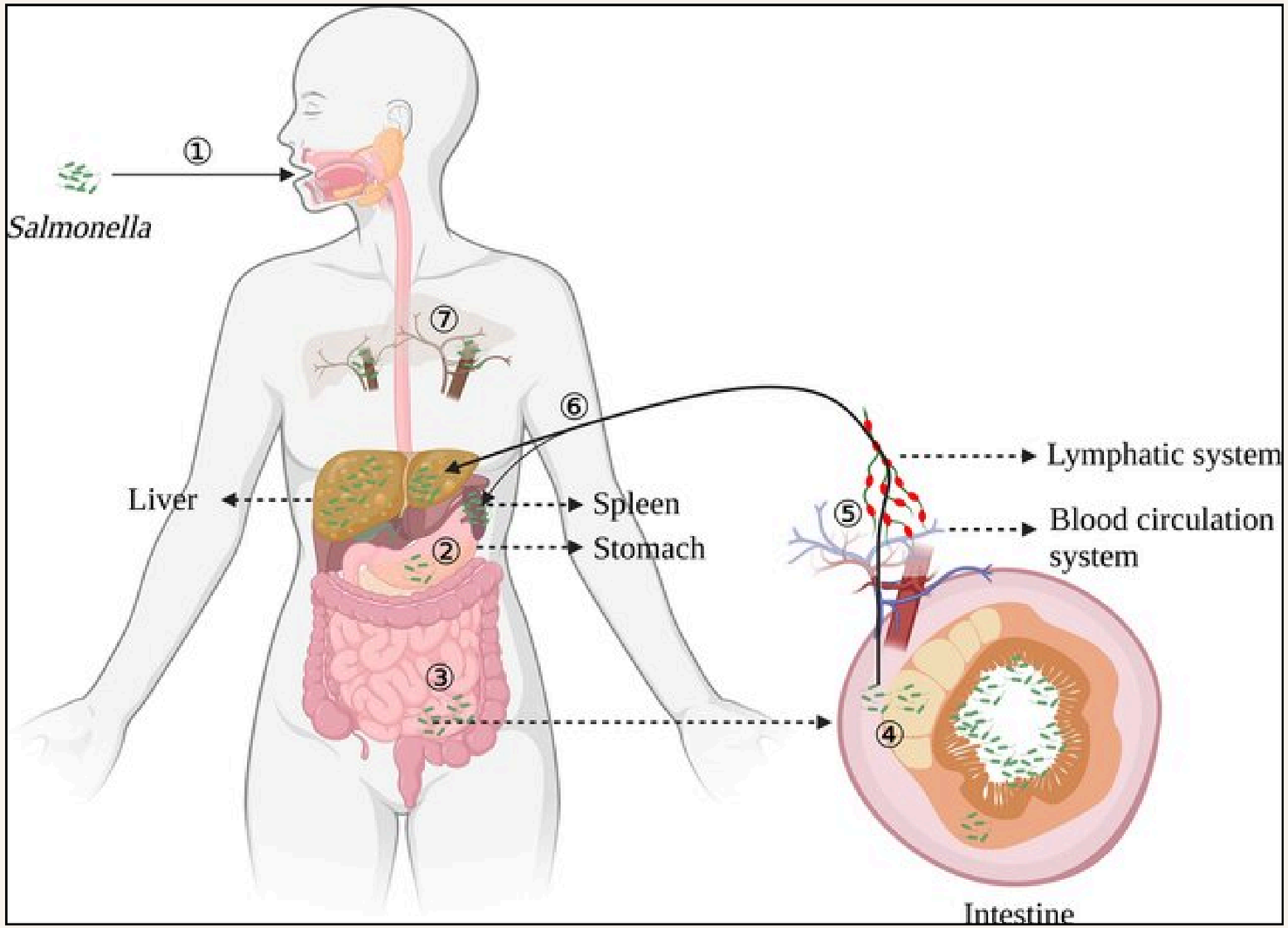
- Gram-negative
- Aerobic
- Flagellated
- Fast-growing bacillary bacteria.



SYMPTOMS

Typhoid fever caused by S.Typhi has nonspecific clinical features, including symptoms such as malaise, which can complicate the diagnosis.

- Local pain: in the abdomen or muscles
- In the gastrointestinal tract: constipation, diarrhea, bloating, nausea, bleeding, blood in the stool or vomiting
- In the body: fever, chills, fatigue, malaise or loss of appetite
- Also common: headache, muscle weakness, internal bleeding, irritation with small red spots, skin irritation or weight loss

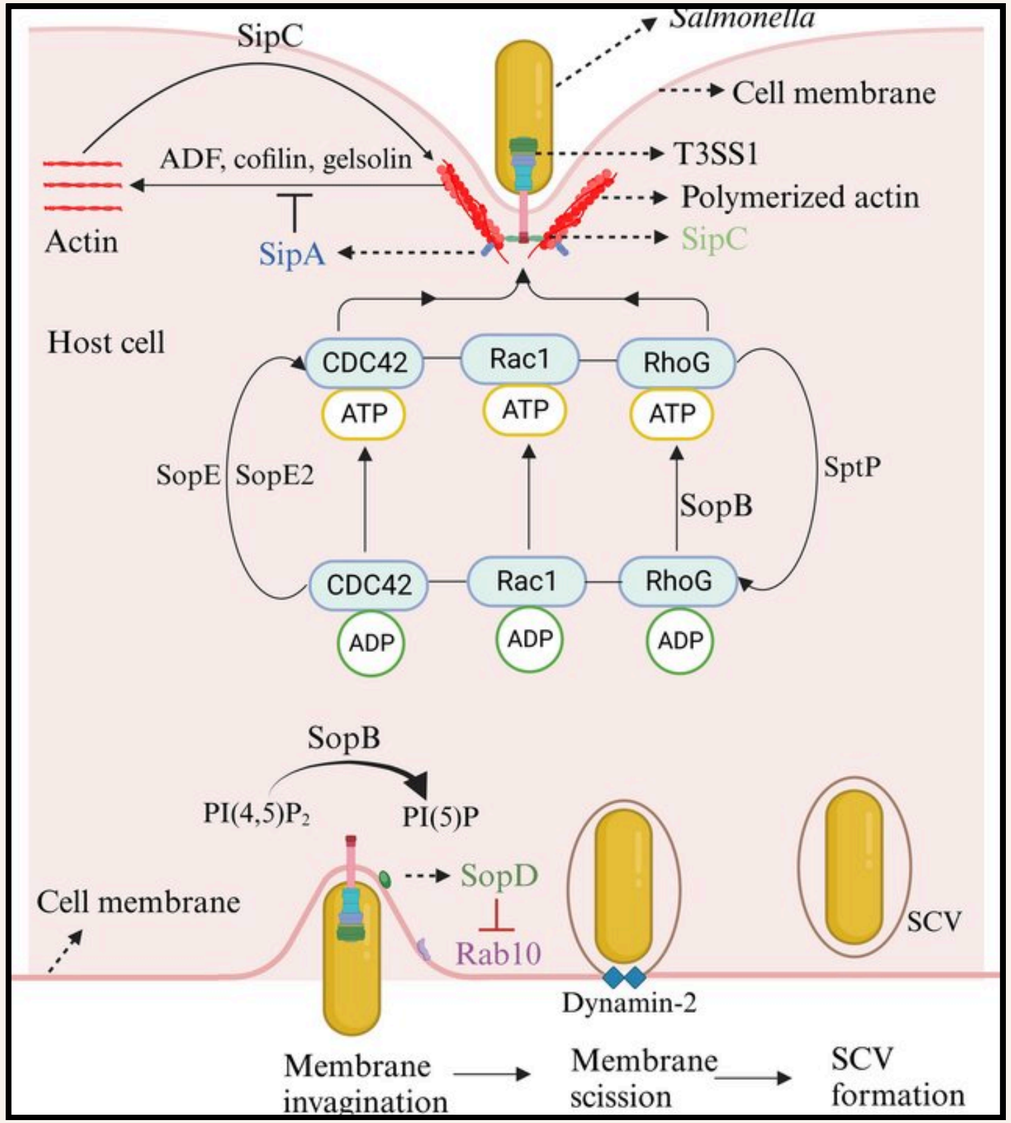


INFECTION CICLE BY S. TYPHI IN THE HOST

https://www.researchgate.net/publication/375113336_Strategies_adopted_by_Salmonella_to_survive_in_host_a_review

INFECTION MECHANISMS

Salmonella effectors secreted by its T3SS1 protein complex promote the invasion of host cells



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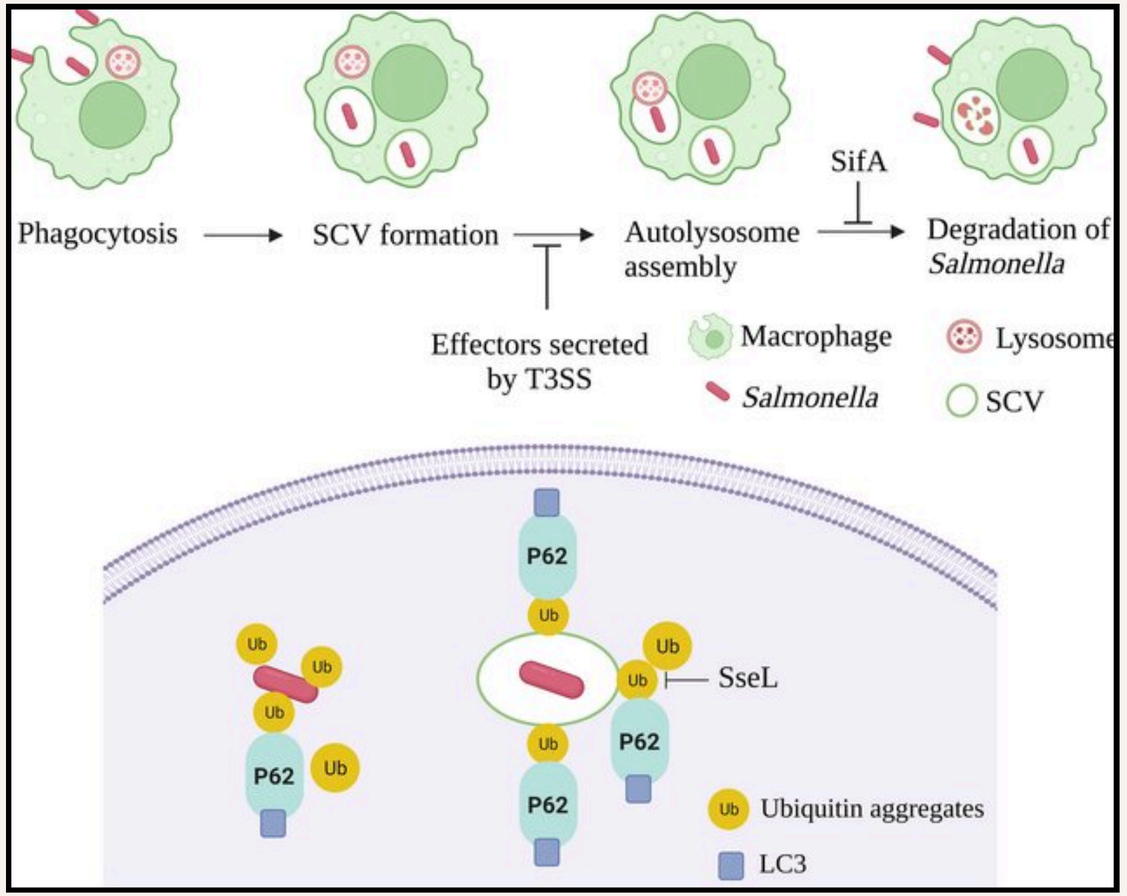
INFECTION MECHANISMS

Salmonella inhibits the autophagic clearance of host cells



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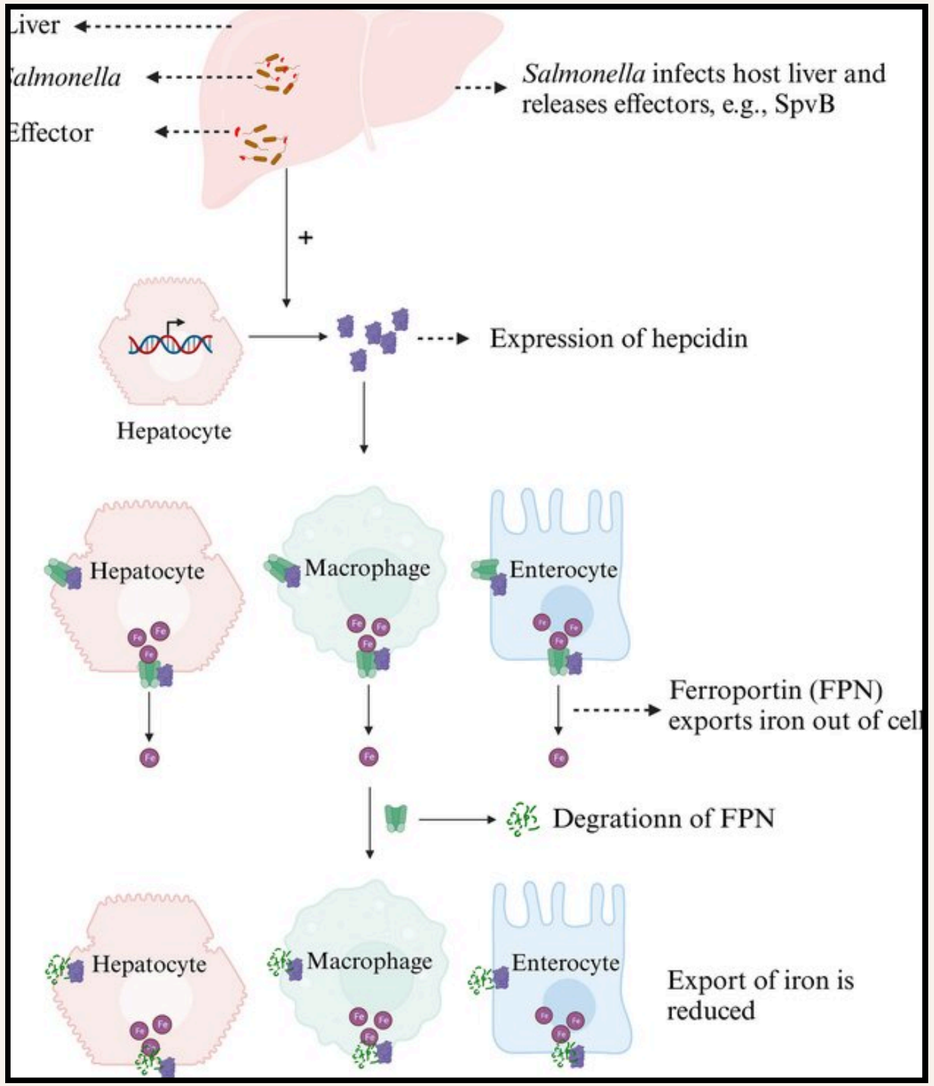
INFECTION MECHANISMS

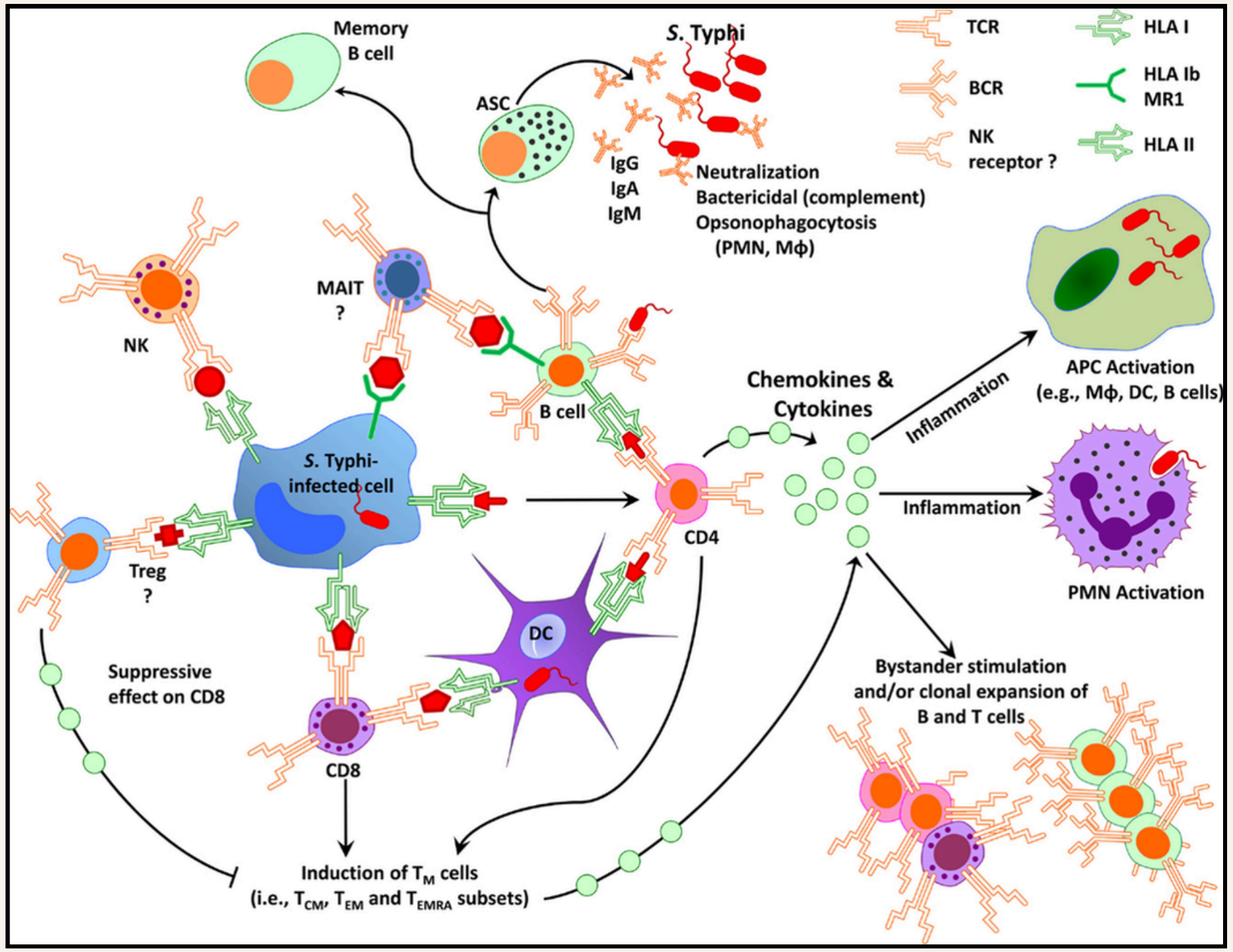
Salmonella infection upregulates hepcidin production by host cells to inhibit iron export and promote intracellular replication



https://www.researchgate.net/publication/375113336_Strategies_adopted_by_Salmonella_to_survive_in_host_a_review

IMMUNOLOGICAL MECHANISMS

Simple diagram of immunity to S. Typhi in humans.



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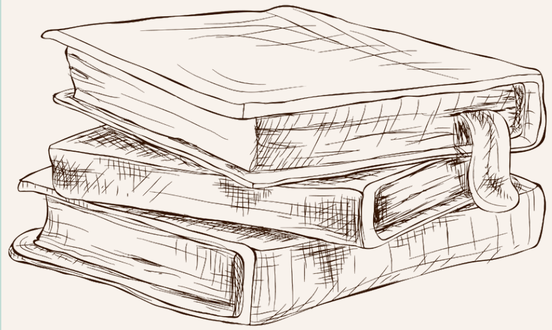
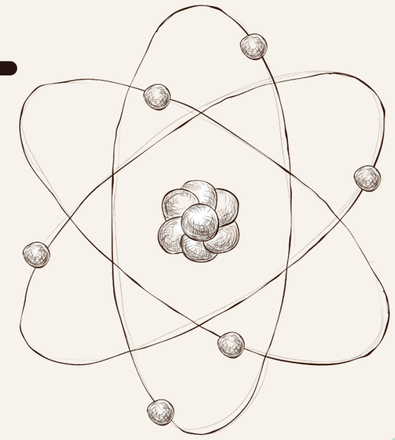


COMPARISON OF FEVERS



DISEASES	Malária	Dengue	Yellow Fever	Typhoid Fever
Duration	8-30 days	5-7 days	3-5 days	3-4 weeks (if untreated)
Body temperature	40°C to 41°C	39° to 40°C	39°C	39° to 40°C
Patterns	Intervaled fever (tertian or quartian)	✗	✗	✓
Pyrogens	Endogenous: TNF-α, IL-1 and IL-6 Exogenous: Hemozoin and GPI	IL-1 and IL-6	TNF-α	IL-1 and IL-6

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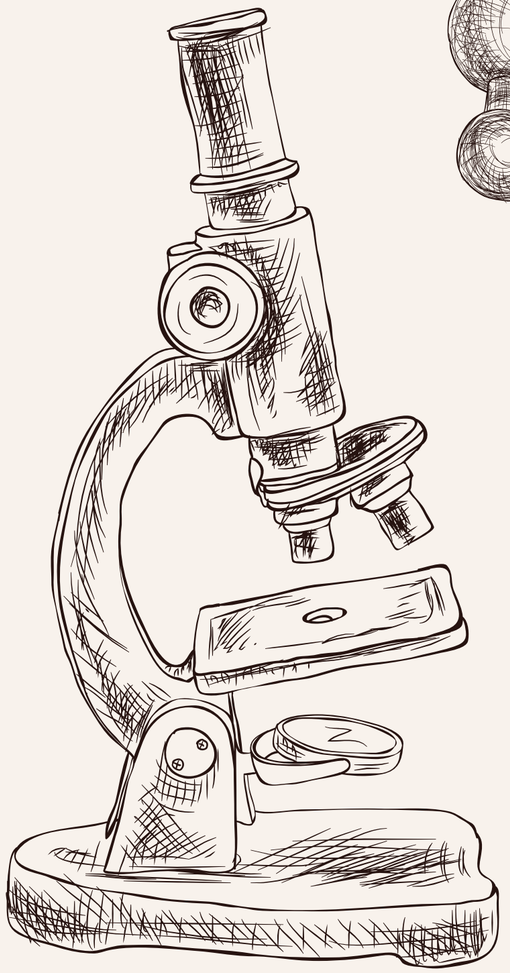

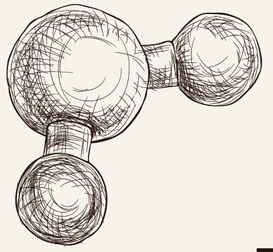

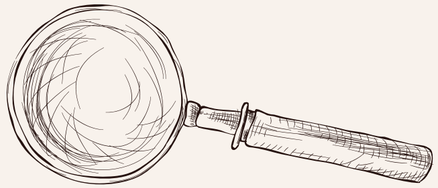

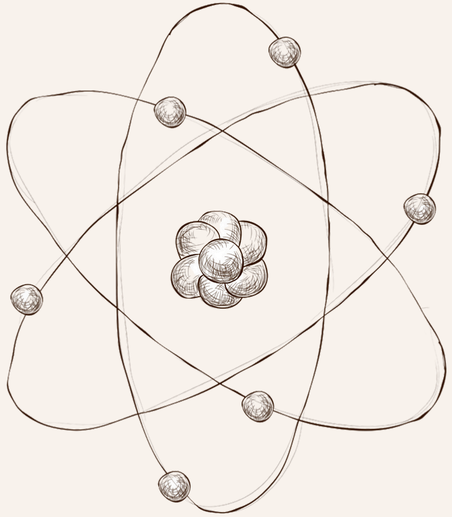

Thank you!

Do you have any questions?