0420115 - Pathophysiology of Infectious Diseases

FEVER

MALARIA
YELLOW FEVER
TYPHOID FEVER
DENGUE

Isabella Teobaldo Ramos - Maria Clara Teles - Mariana Mayumi Teramoto

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INTRODUCTION

Fever = regulated, temporary rise in core temperature (≈ 2–4 °C) triggered by infection.

Fever ≠ uncontrolled hyperthermia

The fever response is a hallmark of **infection** and **inflammatory** disease.

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FOUR CARDINAL SIGNS OF INFLAMMATION

- PAIN
- REDNESS
- SWELLING
- HEAT

3

"A COLD SHOWER IS THE BEST WAY TO BRING DOWN A FEVER."

"FEVER MEDICINES CURE THE ILLNESS."

"IF YOU BREAK THE FEVER, YOU'RE CURED."

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❌ RAPID COOLING CAN CAUSE SHIVERING, WHICH MAY ACTUALLY RAISE CORE TEMPERATURE.

❌ ANTIPYRETICS RELIEVE THE SYMPTOM OF FEVER BUT DO NOT TREAT ITS UNDERLYING CAUSE.

❌ FEVER MAY RESOLVE WHILE THE DISEASE PROCESS IS STILL ONGOING

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IN REALITY....

There is mounting evidence that the increase in core body temperature of 1°C to 4°C that occurs during fever is associated with **improved survival** and the **infection clearance.**

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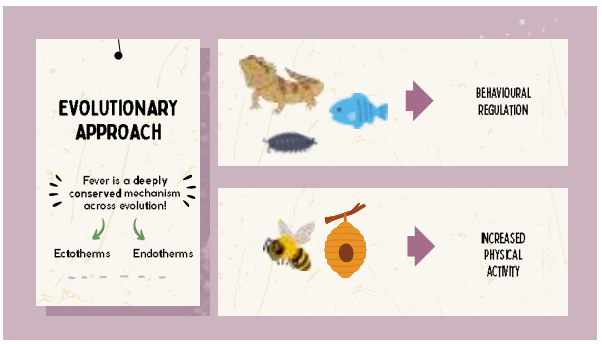
EVOLUTIONARY APPROACH
Fever is a deeply conserved mechanism across evolution!
Ectotherms
Endotherms
BEHAVIOURAL REGULATION
INCREASED PHYSICAL ACTIVITY

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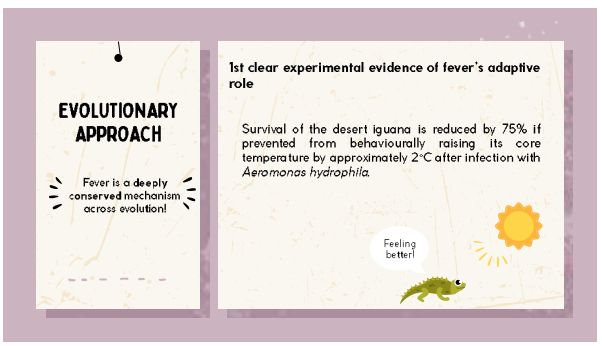
EVOLUTIONARY APPROACH
Fever is a deeply conserved mechanism across evolution!
1st clear experimental evidence of fever's adaptive role
Survival of the desert iguana is reduced by 75% if prevented from behaviourally raising its core temperature by approximately 2°C after infection with *Aeromonas hydrophila*.
Feeling better!

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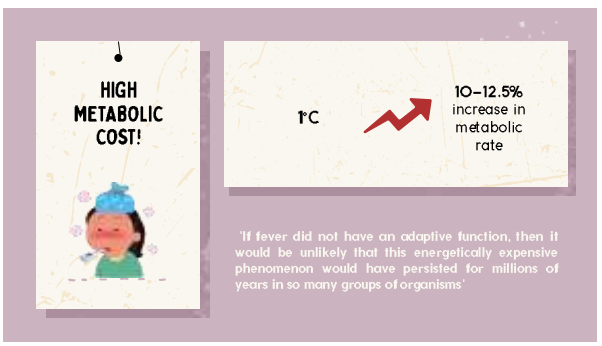
HIGH METABOLIC COST!
1°C
10–12.5% increase in metabolic rate
'If fever did not have an adaptive function, then it would be unlikely that this energetically expensive phenomenon would have persisted for millions of years in so many groups of organisms'

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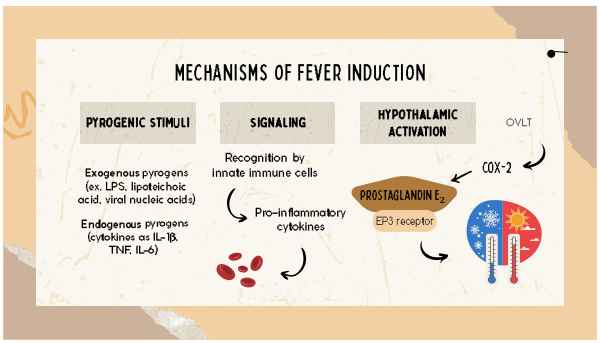
MECHANISMS OF FEVER INDUCTION
PYROGENIC STIMULI
SIGNALING
HYPOTHALAMIC ACTIVATION
OVLT
Recognition by innate immune cells
COX-2
Exogenous pyrogens (ex. LPS, lipoteichoic acid, viral nucleic acids)
PROSTAGLANDIN E_2
Pro-inflammatory cytokines
EP3 receptor
Endogenous pyrogens (cytokines as IL-1β, TNF, IL-6)

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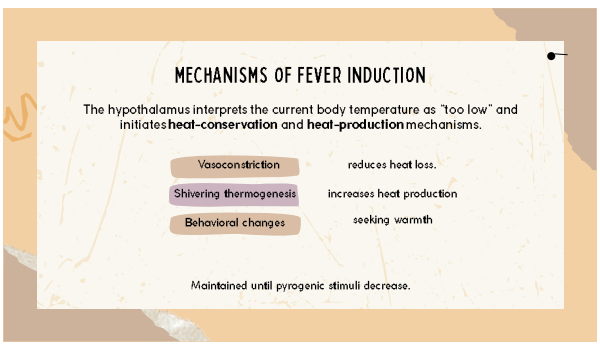
MECHANISMS OF FEVER INDUCTION
The hypothalamus interprets the current body temperature as "too low" and initiates **heat-conservation** and **heat-production** mechanisms.
Vasoconstriction
reduces heat loss.
Shivering thermogenesis
increases heat production
Behavioral changes
seeking warmth
Maintained until pyrogenic stimuli decrease.

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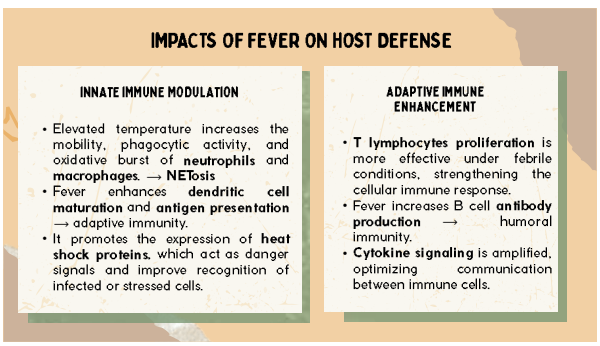
IMPACTS OF FEVER ON HOST DEFENSE
INNATE IMMUNE MODULATION
• Elevated temperature increases the mobility, phagocytic activity, and oxidative burst of **neutrophils** and **macrophages**. → **NETosis**
• Fever enhances **dendritic cell maturation** and **antigen presentation** → adaptive immunity.
• It promotes the expression of **heat shock proteins**, which act as danger signals and improve recognition of infected or stressed cells.
ADAPTIVE IMMUNE ENHANCEMENT
• **T lymphocytes proliferation** is more effective under febrile conditions, strengthening the cellular immune response.
• Fever increases B cell **antibody production** → humoral immunity.
• **Cytokine signaling** is amplified, optimizing communication between immune cells.

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ANTIPYRETICS

Paracetamol, aspirin, ibuprofen

Most antipyretics **block COX-2** → ↓ PGE_2 → setpoint returns to normal.

↳ Routine suppression with antipyretics may delay pathogen clearance.

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MALARIA

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MALARIA

CASES

263 million

DEATHS

597.000 in 83 countries worldwide.

Epidemiology (2023):

- In 2023, the Sub-Saharan African region had 94% of malaria cases (246 million) and 95% (569.000) of malaria deaths;
- Children under 5 years of age accounted for approximately 76% of all malaria deaths in the Region.

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ESTIMATED NUMBER OF MALARIA CASES

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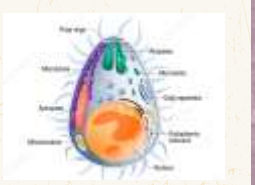
PATHOGEN 'Etiological agent'

Among all species of the genus Plasmodium, 5 species are responsible for infections in humans:

- Plasmodium falciparum
- Plasmodium vivax
- Plasmodium ovale
- Plasmodium knowlesi → Southeast Asia, the monkey malaria species

PLASMODIUM



Malaria is a protozoal disease!!!

VECTOR

Mosquitoe Anopheles (female)

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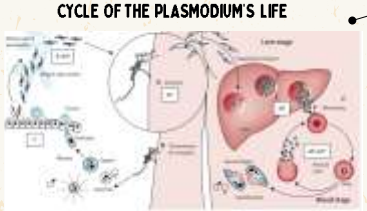
CAUSES AND MECHANISMS THAT LEAD TO THE DEVELOPMENT OF MALARIA

Etiopathogenesis

CYCLE OF THE PLASMODIUM'S LIFE



White et al. (2014)

Hepatic Phase: Sporozoites rapidly migrate to the liver, where they invade hepatocytes and undergo a process of asexual multiplication.

A distinctive feature of P. vivax and P. ovale infections is the formation of hypnozoites

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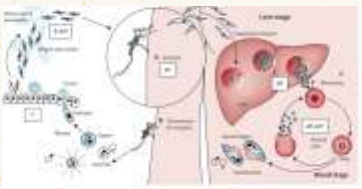
CAUSES AND MECHANISMS THAT LEAD TO THE DEVELOPMENT OF MALARIA

Etiopathogenesis

CICLE OF THE PLASMODIUM'S LIFE



White et al. (2014)

Erythrocytic Phase: Rupture of the hepatic schizont releases merozoites into the bloodstream, which then invade erythrocytes, initiating the asexual cycle in the blood → rupture of erythrocytes
It is at this stage that clinical disease manifests: sweats, chills, headache, vomiting, diarrhea and...

FEVER

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PERIODIC FEVERS

FISHER et al., 2021

1. Fever is the most distinctive symptom of malaria;
2. Periodic Fever is directly linked to the cyclical release of parasites into the bloodstream during the rupture of red blood cell schizonts;

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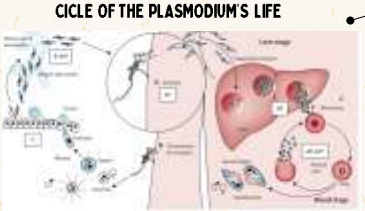
CAUSES AND MECHANISMS THAT LEAD TO THE DEVELOPMENOF MALARIA

Etiopathogenesis

CICLE OF THE PLASMODIUM'S LIFE



White et al. (2014)

A portion of the parasites in the blood stage differentiate into longer-lived sexual forms, the gametocytes, which are essential for the transmission of malaria to the vector → Anopheles

The other portion will reinfect the erythrocytes (red blood cells) and start the periodic fever cycle again.

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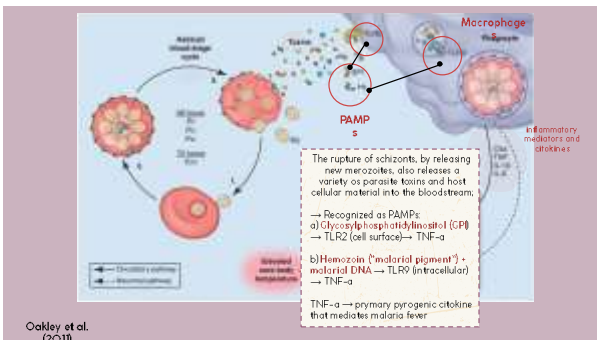
Macrophage
PAMP
s
inflammatory
mediators and
cytokines
The rupture of schizonts, by releasing new merozoites, also releases a variety os parasite toxins and host cellular material into the bloodstream;
→ Recognized as PAMPs:
a) Glycosylphosphatidylinositol (GPI) → TLR2 (cell surface)→ TNF-a
b) Hemozoin ("malarial pigment") + malarial DNA → TLR9 (intracellular) → TNF-a
TNF-a → prymary pyrogenic citokine that mediates malaria fever
Oakley et al.

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THINK ABOUT IT!
Is fever suppression beneficial in this context?

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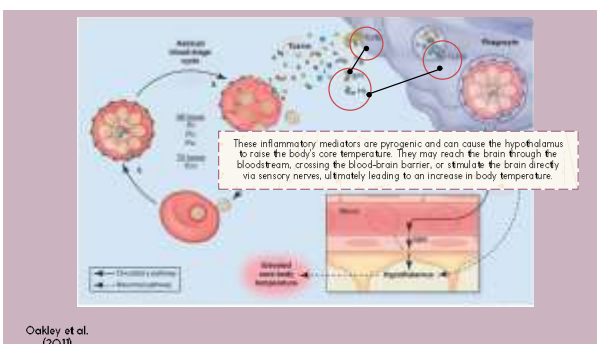
These inflammatory mediators are pyrogenic and can cause the hypothalamus to raise the body's core temperature. They may reach the brain through the bloodstream, crossing the blood-brain barrier, or stimulate the brain directly via sensory nerves, ultimately leading to an increase in body temperature.
Oakley et al.

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FEVER AND MALARIA
WHY THIS SYMPTOM IS SO IMPORTANT TO UNDERSTAND THIS DISEASE?

Fever isn't just a passive marker of this disease, but also an active element that directly influences the biology of the parasite and the progression of the pathology.

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RECENT STUDIES HAVE SHOWN THAT FEVER (38–40 °C) INCREASES AND SPEEDS UP THE STICKING OF PLASMODIUM FALCIPARUM-INFECTED RED BLOOD CELLS TO BLOOD VESSEL WALLS, EVEN IN YOUNG RING STAGES THAT NORMALLY DO NOT STICK.

Fever + Pfalciparum → move the PfEMP1 protein move to the surface of iRBCs

PfEMP1 → CD36 and ICAM-1 (endothelial cells receptor)

- Depending on the receptor → iRBCs can get stuck in small vessels in specific organs → block capillaries, reduce blood flow, and cause cerebral malaria

Rosetting: iRBC link to others RBCs around → forms a rosette-shaped cluster

More parasites get trapped in organs → disease more severe

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EFFECTS OF FEVER ON PLASMODIUM FALCIPARUM:

In vitro growth: High temperatures (e.g., 41°C) reduce parasite survival in culture.

In vivo development: recurrent fevers can accelerate the intraerythrocytic cycle. Fever → favor the synchronization of parasites in the asexual stage

Molecular changes: downregulation of replication pathway genes → reduced growth and replication

Modulates the expression of GPI → potentially reduzing inflammation

AND MORE ...

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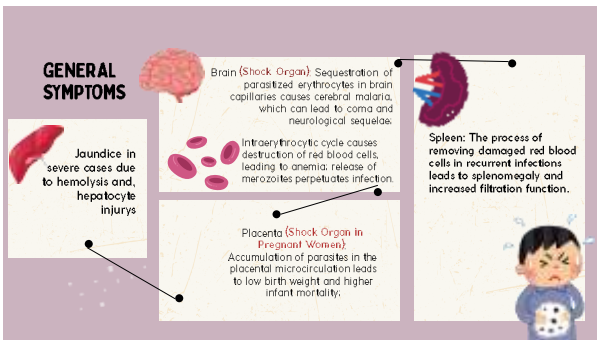
GENERAL SYMPTOMS
Jaundice in severe cases due to hemolysis and, hepatocyte injurys
Brain (Shock Organ): Sequestration of parasitized erythrocytes in brain capillaries causes cerebral malaria, which can lead to coma and neurological sequelae.
Intraerythrocytic cycle causes destruction of red blood cells, leading to anemia; release of merozoites perpetuates infection.
Placenta (Shock Organ in Pregnant Women): Accumulation of parasites in the placental microcirculation leads to low birth weight and higher infant mortality.
Spleen: The process of removing damaged red blood cells in recurrent infections leads to splenomegaly and increased filtration function.

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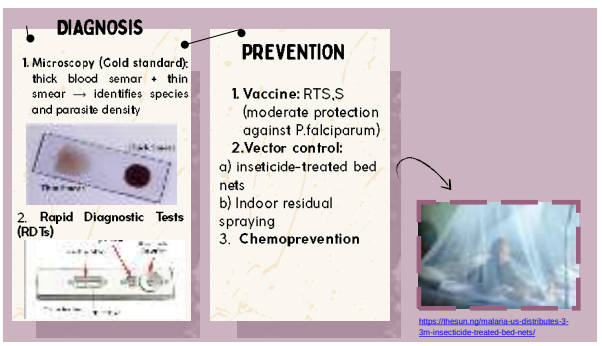
DIAGNOSIS
1. Microscopy (Gold standard): thick blood semar + thin smear → identifies species and parasite density
2. Rapid Diagnostic Tests (RDTs)
PREVENTION
1. Vaccine: RTS,S (moderate protection against P.falciparum)
2.Vector control:
a) inseticide-treated bed nets
b) Indoor residual spraying
3. Chemoprevention
https://thesun.ng/malaria-us-distributes-3-3m-insecticide-treated-bed-nets/

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CHALLENGES
Inseticide resistance and growing drug resistance
HOW???

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The parasite has the capacity of alternate the expression of different genes ***var*** of his repertory → presenting different antigen phenotypes → avoid the recognizing and depuration by antibodies generated earlier by the host

CHALLENGES

Insetícide resistance and growing drug resistance

HOW???

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YELLOW FEVER

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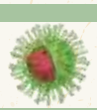
MAIN FEATURES

Transmission	Severity	Distribution
Viral disease transmitted by mosquito bites	Severe symptoms in 15–20% of cases	Endemic in tropical regions



Yellow fever, caused by a *Flaviviridae* virus, has two transmission cycles. The sylvatic cycle wich circulates between monkeys and forest mosquitoes and the urban cycle involving *Aedes aegypti* and humans.

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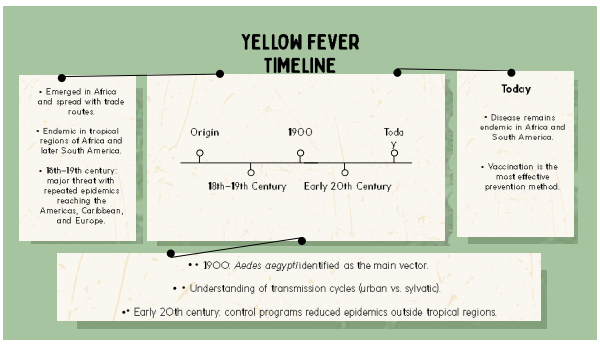
YELLOW FEVER TIMELINE
• Emerged in Africa and spread with trade routes.
• Endemic in tropical regions of Africa and later South America.
• 18th–19th century: major threat with repeated epidemics reaching the Americas, Caribbean, and Europe.
Origin
1900
Toda
18th–19th Century
Early 20th Century
Today
• Disease remains endemic in Africa and South America.
• Vaccination is the most effective prevention method.
• 1900: Aedes aegypti identified as the main vector.
• Understanding of transmission cycles (urban vs. sylvatic).
• Early 20th century: control programs reduced epidemics outside tropical regions.

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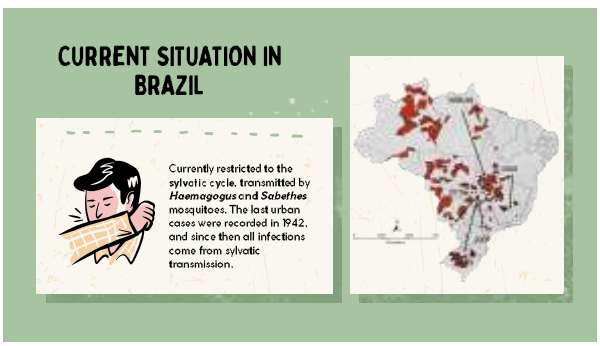
CURRENT SITUATION IN BRAZIL
Currently restricted to the sylvatic cycle, transmitted by Haemagogus and Sabethes mosquitoes. The last urban cases were recorded in 1942, and since then all infections come from sylvatic transmission.

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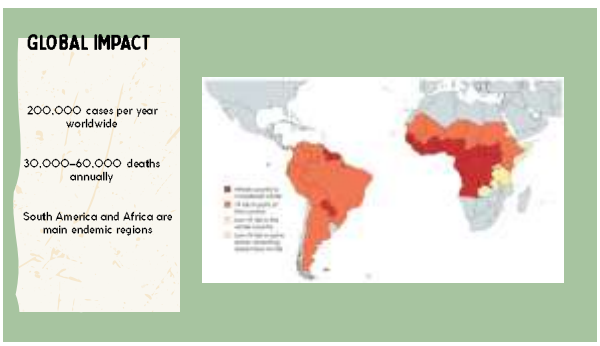
GLOBAL IMPACT
200,000 cases per year worldwide
30,000–60,000 deaths annually
South America and Africa are main endemic regions

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VECTOR

Yellow fever vector

The disease is transmitted by arthropod vectors, especially female mosquitoes from the genus ***Aedes aegypti***, ***Haemagogus***, and ***Sabethes***.

Transmission cycles

In the jungle cycle, humans are infected when sylvatic mosquitoes that fed on infected monkeys bite them. In the urban cycle, transmission occurs between humans via Aedes aegypti.
OBS.: transovarial transmission in the vectors

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Once ingested by the mosquito, the virus cannot be transmitted immediately. It must first replicate. This process occurs in stages.

REPLICATION

Beginning of replication

The virus settles in the mosquito's midgut, where it multiplies and then invades other tissues.

Dissemination

From the midgut, the virus spreads to other parts of the mosquito's body.

Arrival at the salivary glands

The virus reaches the mosquito's salivary glands, and it can now be transmitted to others

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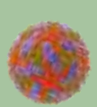
VIRUS



- Genus *Flavivirus* (family *Flaviviridae*)
- Arbovirus
- Positive-strand, single-strand RNA
- Size: 40–60 nm in diameter
- Shape: spherical, enveloped, with icosahedral symmetry

Three structural proteins (Capsid (C), Membrane (M), and Envelope (E)) and seven nonstructural (NS) proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5)

Narrow host range: infects non-human primates and humans

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CELL INFECTION MECHANISM

- Endossome
- NS – viral replication complex
- Free virions or enclosed in autophagosomes

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STAGES OF THE DISEASE

Febrile phase

abrupt onset
3-4 days
high fever and other symptoms

chills, severe headache, muscle pain, nausea and vomiting, fatigue and weakness.

Remission period

pacient improvment
hour to days
symptoms decrease

Severe phase

15% of the cases
fever returns and
symptoms worsen
could be fatal

Symptoms on the severe phase: jaundice, hemorrhages, kidney and liver failure, severe abdominal pain, delirium, seizures, and, in more severe cases, coma.

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PATHOGENESIS

1. Virus inoculation into the host
2. Replication in the lymph nodes and viremia
3. Spread to organs like liver, spleen, kidney and the myocardium
4. Death of the hepatocytes (hepatic necrosis) and the kidney cells (acute renal failure)

→ Hepatic tropism, intense replication

→ Main cause of jaundice and of hemorrhages, as the liver stops producing blood clotting factors.

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IMMUNE RESPONSE

Innate response

quick response
macrophages and dendritic cells
TNF-alfa, IL-6, IFN alfa and beta
NK cells

Adaptative response

slow and specific response
CD8+ T lymphocytes
CD4+ T lymphocytes

Antibodies

long-term protection
B lymphocytes neutralize

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PREVENTION

- Combating the vector mosquito
- Vaccines

The development of two live, attenuated YF vaccines in the 193Os, and their wide deployment in the 194Os, led to a further decline of the disease. Subsequently, there have been periodic upsurges of YF activity in endemic regions without routine immunization programs.

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TYPHOID FEVER

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EPIDEMIOLOGY

WORLDWIDE /YEAR

9.2 million cases
133,000 deaths
(WHO. Typhoid Fact Sheet. 2023)

Incidence peaks between the ages of 5 and 9.

Endemicity
- Africa
- Asia
- Latin America

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EPIDEMIOLOGY

Recently developed typhoid conjugate vaccines, improved surveillance and understanding of antimicrobial resistance patterns, and WASH initiatives have decreased the disease burden.

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Salmonella enterica

Serotype Typhi (S Typhi) } Enteric fever

Serotype Paratyphi A, B and C - Paratyphoid fever

INFECTIOUS AGENT

- Gram-negative;
- Facultative anaerobic bacillae.
- Exclusively human pathogens.
- Motile, with peritrichous flagella

Other Salmonella serotypes, collectively known as nontyphoidal Salmonella, typically cause gastroenteritis as the main symptom.

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TRANSMISSION

Transmission occurs via **fecal–oral route**.

Initially colonizes the small intestine, invades M cells of Peyer's patches, and disseminates via the bloodstream to the reticuloendothelial system (liver, spleen, bone marrow)

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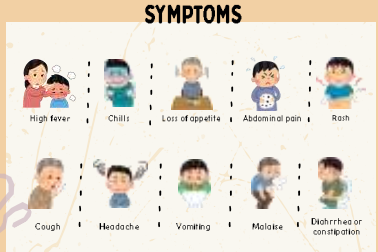
SYMPTOMS



Following an incubation period of **6 to 30 days**, enteric fever presents insidiously with the gradual onset of **fever** with **fatigue, anorexia, headache, malaise**, and **abdominal** symptoms. If treatment is delayed or inadequate, **meningitis, sepsis, or intestinal perforation** can occur.

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RISK FACTORS

Non-endemic countries	Travel and contact with travelers from an endemic country Exposure to food contamined by a chronic carrier
Endemic countries	Individual host factors; Environmental exposures; Climate and geographic factors.

- More severe in immunocomprimised patients.
  - HIV
  - glucocorticoid therapy
  - altered phagocyte function → malaria and sickle cell anemia
- Intake of antacids and antihistamines:
- "Damaged" gut flora:
  - broad-spectrum antibiotics
  - malnutrition
- Bad WASH conditions (state of water, sanitation, and hygiene);
- Climate change (floods, droughts, unsafe food/water).

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PATHOGENESIS

- **evasion** of stomach **acidity**;
- **invasion** of the **intestinal** epithelium;
- **dissemination** and intracellular **survival**;
- **excretion** and **transmission**;
- **antimicrobial resistance**.

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INGESTION AND INVASION

INCUBATION PHASE

SECONDARY BACTEREMIA

SHEDDING & TRANSMISSION

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INGESTION AND INVASION

1.Bacteria ingested via contaminated food/water.

2.Drinks/food buffer gastric acid → **bacteria reach distal ileum.**

3.S. Typhi **cross gut lining** through: enterocytes; M cells of Peyer's patches

T3SS

4.Engulfed by gut phagocytes → delivered to macrophages of lamina propria.

5.Recognition via TLR-4/5 ⟶ release of IL-8 ⟶ recruits T cells and neutrophils

6.S. Typhi minimizes inflammation by:

- **a. Vi capsular antigen** → masks PAMPs, **suppresses neutrophil activation.**
- **b.** ↓ **Flagellin expression**

INCUBATION PHASE

SECONDARY BACTEREMIA

SHEDDING & TRANSMISSION

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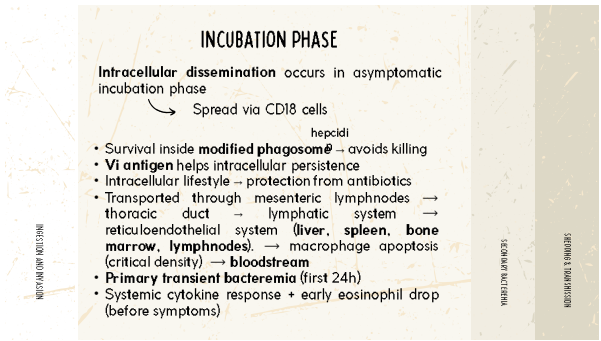
INCUBATION PHASE
SECONDARY BACTEREMIA
SHEDDING & TRANSMISSION
INCUBATION PHASE
Intracellular dissemination occurs in asymptomatic incubation phase
Spread via CD18 cells
hepcidi
• Survival inside modified phagosome → avoids killing
• Vi antigen helps intracellular persistence
• Intracellular lifestyle → protection from antibiotics
• Transported through mesenteric lymphnodes → thoracic duct → lymphatic system → reticuloendothelial system (liver, spleen, bone marrow, lymphnodes). → macrophage apoptosis (critical density) → bloodstream
• Primary transient bacteremia (first 24h)
• Systemic cytokine response + early eosinophil drop (before symptoms)

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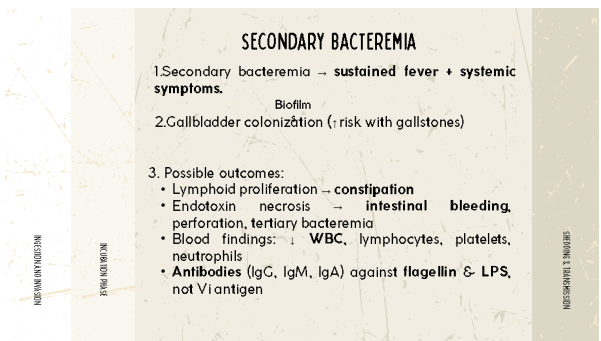
INGESTION & INVASION
INCUBATION PHASE
SECONDARY BACTEREMIA
SHEDDING & TRANSMISSION
SECONDARY BACTEREMIA
1.Secondary bacteremia → sustained fever + systemic symptoms.
Biofilm
2.Gallbladder colonization (↑ risk with gallstones)
3. Possible outcomes:
• Lymphoid proliferation → constipation
• Endotoxin necrosis → intestinal bleeding, perforation, tertiary bacteremia
• Blood findings: ↓ WBC, lymphocytes, platelets, neutrophils
• Antibodies (IgG, IgM, IgA) against flagellin & LPS, not Vi antigen

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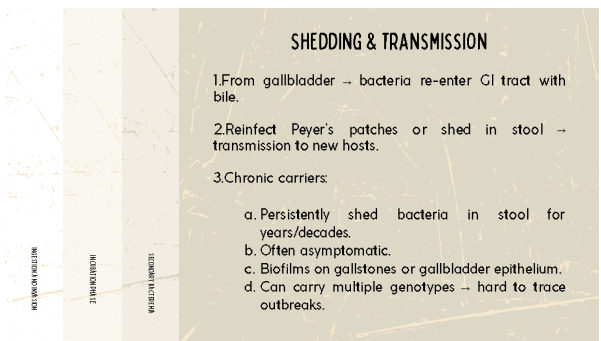
INGESTION & INVASION
INCUBATION PHASE
SECONDARY BACTEREMIA
SHEDDING & TRANSMISSION
1.From gallbladder → bacteria re-enter GI tract with bile.
2.Reinfect Peyer's patches or shed in stool → transmission to new hosts.
3.Chronic carriers:
a. Persistently shed bacteria in stool for years/decades.
b. Often asymptomatic.
c. Biofilms on gallstones or gallbladder epithelium.
d. Can carry multiple genotypes → hard to trace outbreaks.

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TREATMENT

Antibiotic therapy is the mainstay of treatment for enteric fever.

Delayed treatment → higher risk of complications and severe disease

Empiric Antibiotic Treatment

- Fluoroquinolones (ciprofloxacin) – first line in areas without high resistance.
- Third-generation cephalosporins (ceftriaxone) – used in resistant areas and severe cases
- Azithromycin – oral option for uncomplicated cases.

If the initial antibiotic is effective, fever decreases over the following 3 to 5 days, and treatment is continued for the recommended interval. If fever persists for more than 5 days, a search for a persistent locus of infection or treatment with alternate antibiotics should be considered, based on bacterial susceptibility whenever possible.

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DENGUE

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MAIN FEATURES

Transmission

Viral disease transmitted by mosquito bites

Distribution

Endemic in tropical regions

Dengue, caused by a virus from the family *Flaviviridae*, has four diferent serotypes DENV 1, DENV 2, DENV 3, DENV 4,

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EPIDEMIOLOGY

- Originating from Africa
- First epidemic recorded in the 80s
- 50-100mi people infected per year worlwide
- 6,6mi cases in Brazil last year, 6000 deaths

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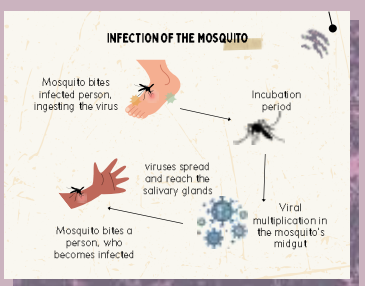
VECTOR

- Transmitted by the bite of female *Aedes aegypti*
- Cosmopolitan
- Transovarial transmission



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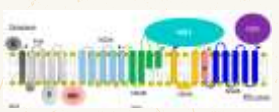
VIRUS

- Genus *Orthoflavivirus*
- Arbovirus
- Single-stranded, positive strand RNA
- Enveloped and icosahedral virus



Four serotypes: DENV-1, DENV-2, DENV-3, and DENV-4, genetically similar but with differences in their antigenic composition.

Three structural proteins (Capsid (C), Membrane (M), and Envelope (E)) and seven nonstructural (NS) proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5)

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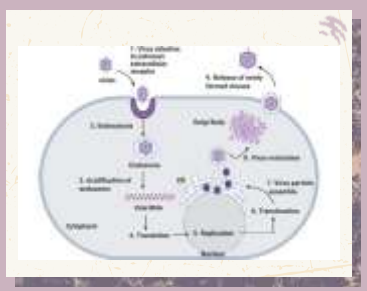
CELL INFECTION MECHANISM

- Endossome
- NS – viral replication complex
- Free virions released



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STAGES OF THE DISEASE

Febrile phase	Critical phase	Recovery phase
abrupt onset 2-7 days high fever and other symptoms	not every case 24-48h fever decrease "dengue shock"	symptom relief days to weaks

Severe and continuous abdominal pain, persistent vomiting, accumulation of fluid in body cavities, bleeding (bleeding from the nose, gums, or purple spots on the skin).

Symptoms such as headache, pain behind the eyes (retro-orbital pain), muscle and joint pain, extreme tiredness, nausea, vomiting and, in some cases, red spots on the body (rash) are common in the febrile phase

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PATHOGENESIS

1. Virus inoculation into the host
2. Replication in mononuclear and endothelial cells
3. Viremia and strong immune response, generating several symptoms
4. Increased vascular permeability: plasma leakage, fluid shock, and hemorrhage (thrombocytopenia)

→ Replication in organs like spleen, liver and lymfatic tissues

→ The virus reaches the bone marrow

→ Corticosteroids and NSAIDs interfere with the functioning of platelets in the blood

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IMMUNE RESPONSE

Innate response

quick response
macrophages and dendritic cells
TNF-alfa, IL-6, IFN alfa e beta

Adaptative response

slow and specific response
CD8+ T lymphocytes
CD4+ T lymphocytes

Antibodies

long-term protection
B lymphocytes neutralize

?

Antibody-Dependent Enhancement (ADE)

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ANTIBODY-DEPENDENT ENHANCEMENT (ADE)

A key mechanism in secondary infections.
If a person is infected a second time with a dengue serotype different from the first, the antibodies produced in the first infection may, instead of neutralizing the new virus, bind to it and facilitate its entry into immune cells, increasing viral replication and disease severity.

You can only get one type of DENV in your life, but you can have the 4 types of the virus

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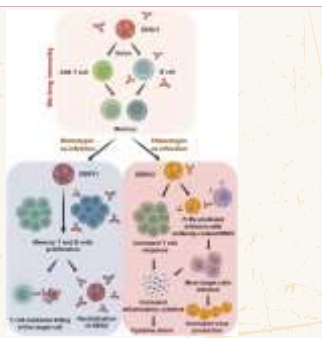
IMMUNE RESPONSE



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PREVENTION

- Combating the vector mosquito
- Vaccines

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COMPARISON OF FEVERS

Diseases	Malaria	Yellow Fever	Dengue	Typhoid Fever
Body Temperature	39°C to 41°C	39°C	39°C to 40°C	39°C to 40°C
Duration	8-30 days (depends on the Plasmodium genus)	3-4 days, second phase more severe: 7-10 days	2-7 days	1-3 weeks (if untreated)
Pyrogens	TNF-a and parasitic toxins: Hemozoin and GPI	TNF-a	IL-1 and IL-6	LPS, IL-1 and IL-6
Patterns	Periodic Fevers: Quotidian, Tertian and Quartan	✕	horse sadle	step-ladder fever

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THANK YOU!
ANY
QUESTIONS?

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