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Malaria

BSc Immunity & Infection

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Parasitism

Classical definition: A relationship between two organisms (type of symbiosis) in which one organism benefits at the other organism's expense.

OR

The close association of two or more dissimilar organisms where the association is harmful to at least one.

OR …

All imply that that **one** of the partners **benefits** and the **other** is **harmed.**

H**arm** is difficult to quantify → some parasitic relationships may be considered as (a) mutualism (the two associates cannot survive without one another) or (b) commensalism (no harm exerted in either direction).

Better definition/description (Crofton, 1971):

- Ecological relationship between two different organisms, the parasite and the host.
- Parasite is physiologically or metabolically dependent upon its host.
- Reproductive potential of the parasite exceeds that of its hosts.
- Heavily infected hosts killed by their parasites.
- Over-dispersed frequency distribution of parasites within the host population: the parasite population is not evenly distributed amongst the host population nor is it randomly distributed, but some hosts have a lot of parasites while most have very few.

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Special considerations in parasite immunology

- Host cell tissue specificity, migration, sequestration
- Complex host – pathogen interactions: immune evasion or avoidance mechanisms, host physiology vs. immune response
- Parasite diversity (genetic variability within species, populations)
- Variable antigen load (intensity of infection and multiplication)
- Pathology – usually host mediated
- Concomitant immunity (persistent parasitic infections regulate immunity to other infections)

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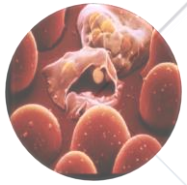
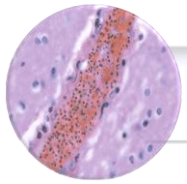
Immune evasion mechanisms



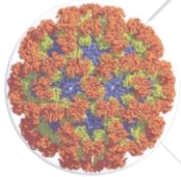
Intracellular parasitism:

- Primitive evasion mechanism
- Abs bind to free parasite stages, but cannot access parasites inside the host cells
- Plasmodium invades RBC that have no or little MHC, and thus escape antigen presentation and CTLs



Adherence to endothelial cells:

- Protects parasite from entering the spleen and liver, thus destruction



Antigenic diversity/polymorphism:

- Different antigens are expressed at different stages
- Polymorphisms of antigens (mutated alleles) evades recognition. Antigens able to elicit immune responses, in fact show extensive polymorphisms – diverse genotypes
- **Problems with vaccine development**
- **Affects mostly T cell recognition as TCR recognition is based mostly on primary structure**

Molecular smokescreen:

- Many antigens have many tandem repeats providing immunodominant B cell epitopes
- Especially antigens that do not elicit good protective immunity
- A way to mislead immunity

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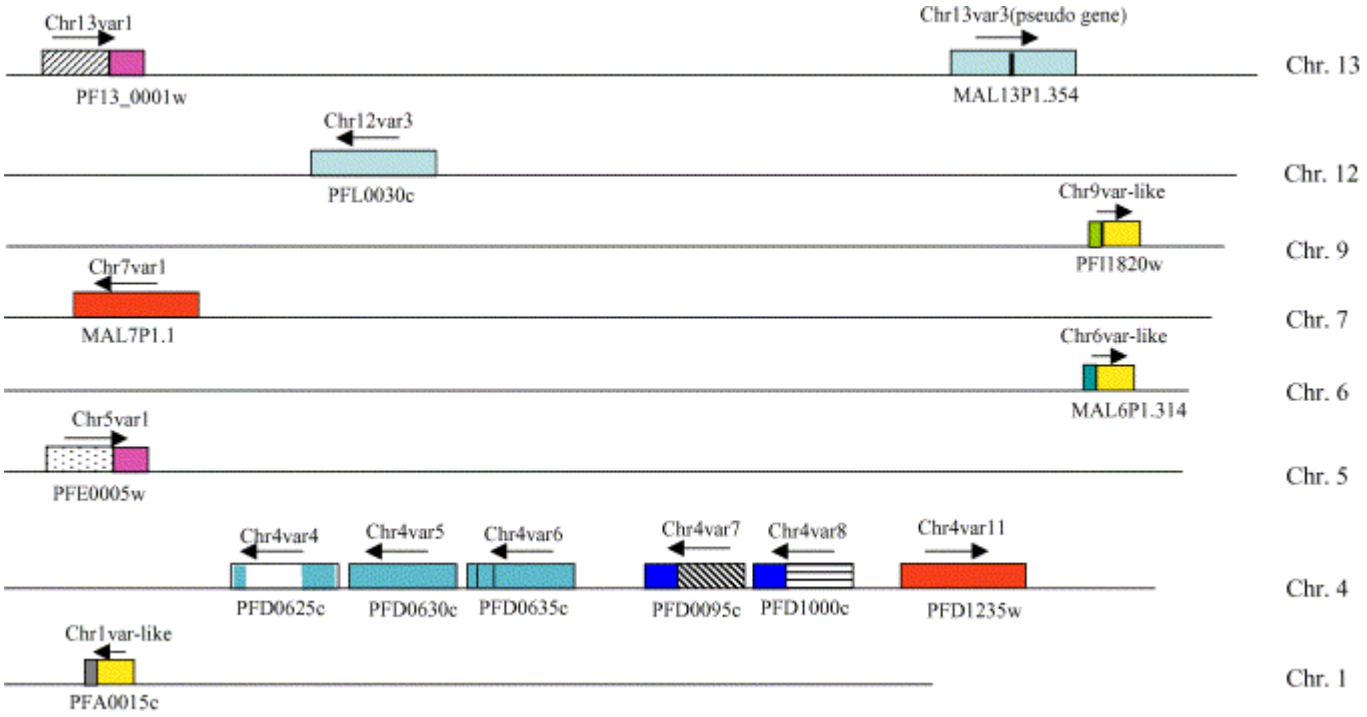
Antigenic variation in *Plasmodium falciparum*

PfEMP1 is one of the most abundant parasite proteins on the surface of infected RBC, and thus favorable for antibody production and accessible to antibodies

It evolved distinct immune evasion mechanisms

The var gene encoding PfEMP1 is present at various locations (approx 50) in the genome and the parasite can switch expression between different loci



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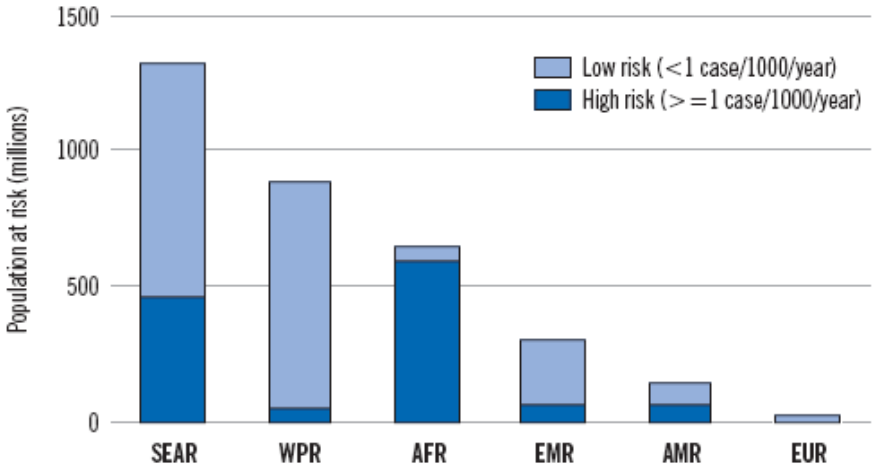
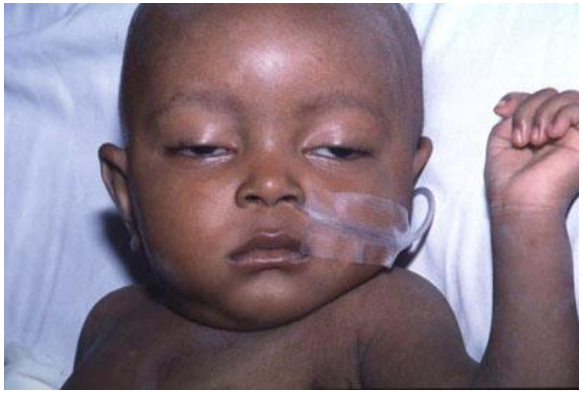
Malaria

Caused by protozoan parasites of the genus *Plasmodium*. Fivespecies infect humans by entering the bloodstream: *Plasmodium falciparum*, which is the main cause of severe clinical malaria and death; *Plasmodium vivax*; *Plasmodium ovale*; *Plasmodium malariae;* and *Plasmodium knowlesi*. Inoculation of parasite sporozoites occurs via the bite of infected blood-feeding female mosquitoes of the genus *Anopheles*. In humans, the parasites multiply exponentially in the liver, releasing merozoites that develop and multiply in red blood cells. With a bite, mosquitoes ingest *Plasmodium* gametocytes, which undergo another reproductive phase inside the mosquito before being injected into another human host.

Fig. 3.2 Number of people estimated to be at low and high risk of malaria, by WHO region, 2006





POPULATION AT RISK (MILLIONS)	POPULATION	% ANY RISK
Africa	774	84
Americas	895	15
Eastern Mediterranean	540	55
Europe	887	2
South-East Asia	1 721	77
Western Pacific	1 763	50
World	**6 581**	**50**

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The malaria burden

2009 WHO Report

- ½ of world's population at risk
- 250 million people infected
- 800,000 people killed, 90% in Africa
- $12bn annual losses

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Our history is tightly associated with malaria

Alexander the Great
(356-323 BC)

Tutankhamen
(1341-1323 BC)

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Mal-aria: a disease caused by bad air

La Malaria (1850-1851) oil on canvas by Hebert (1817-1908)

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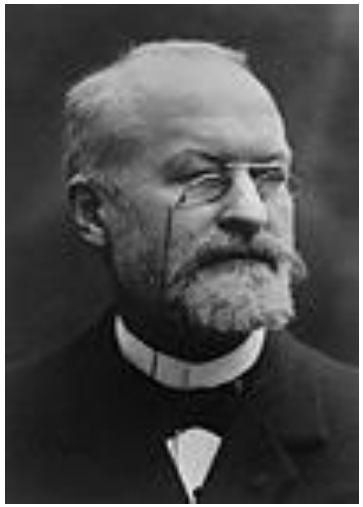
The discovery of Plasmodium

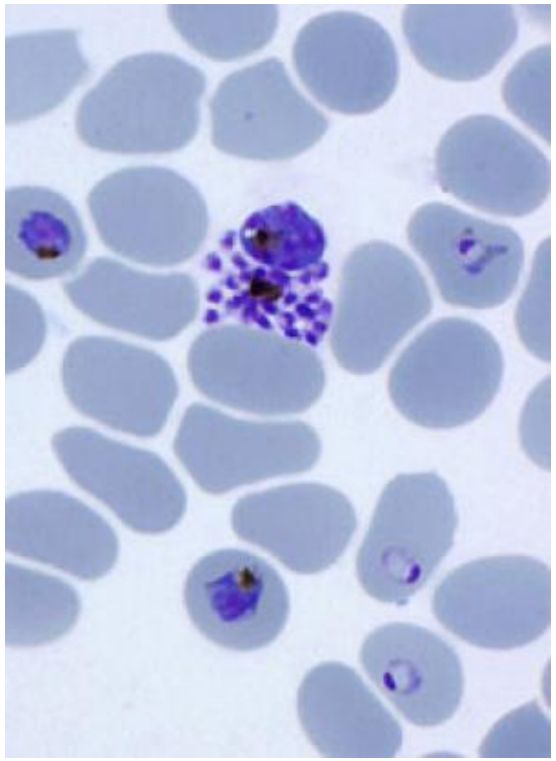


Alphonse Laveran
1845-1922

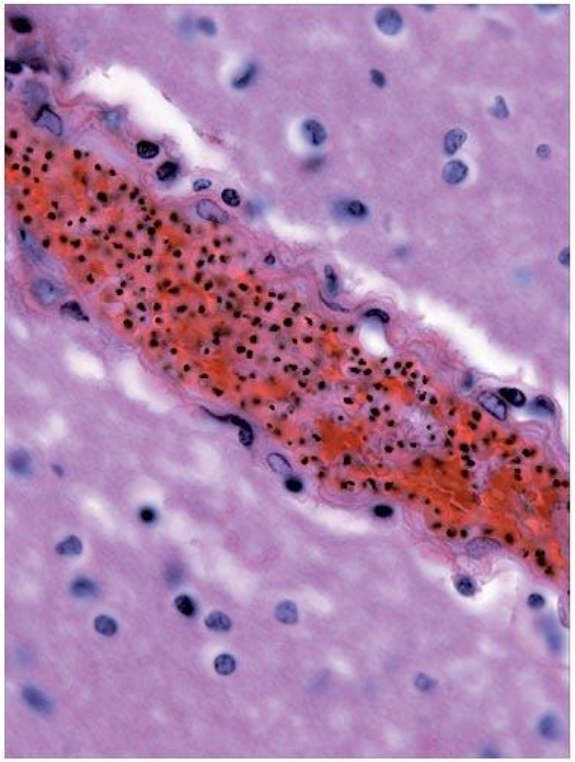
Identified Plasmodium as the cause of malaria in 1880

Camillo Golgi
1843-1926

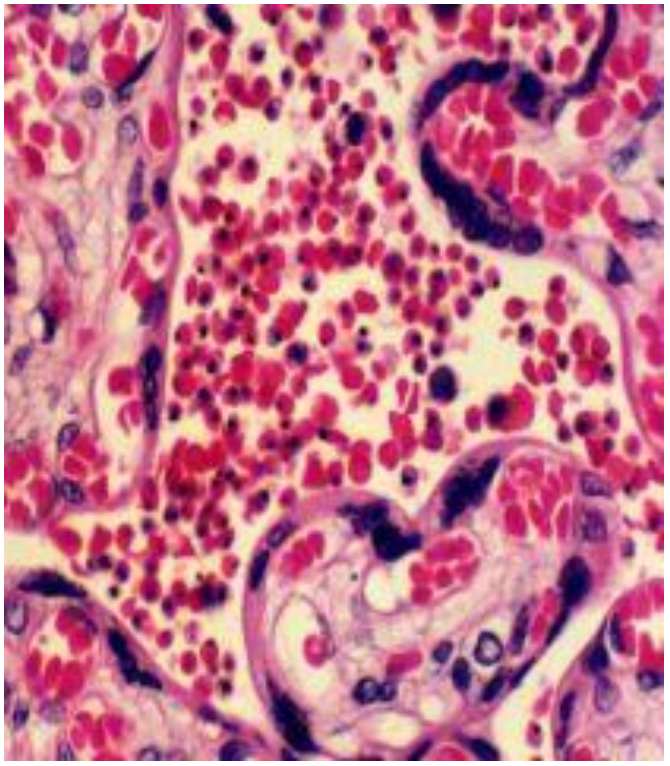
The cause of the disease



Infected RBCs - anaemia



Cerebral malaria



Placental malaria

Unicellular protozoan parasites of the genus Plasmodium:
P. falciparum, P. vivax, P. malariae, P. ovale, P. knowlesi

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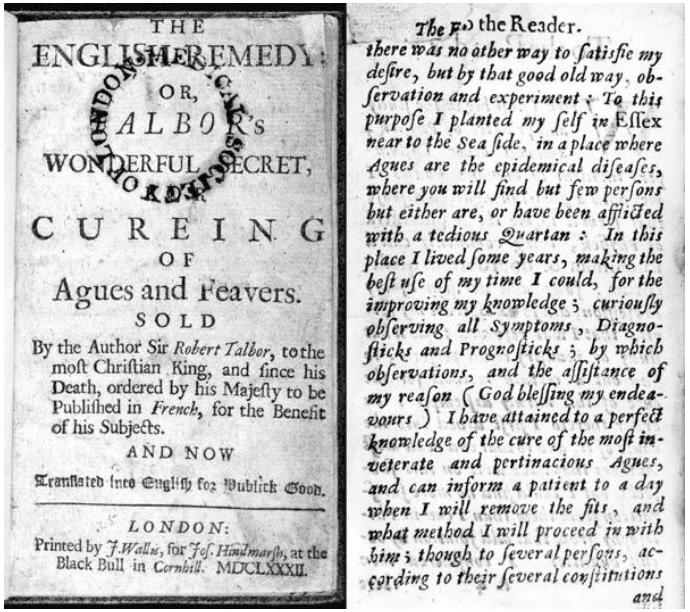
Quinine bark: the Jesuit's powder



THE
ENGLISH REMEDY:
OR,
ALBOR's
WONDERFUL SECRET,
CUREING
OF
Agues and Feavers.
SOLD
By the Author Sir *Robert Talbor*, to the most Christian King, and since his Death, ordered by his Majesty to be Published in *French*, for the Benefit of his Subjects.
AND NOW
Translated into English for Publick Good.

LONDON:
Printed by *J. Wallis*, for *Jos. Hindmarsh*, at the Black Bull in *Cornhill*. MDCLXXXII.

The [illegible] *to the Reader.*

there was no other way to satisfie my desire, but by that good old way, observation and experiment: To this purpose I planted my self in Essex near to the Sea side, in a place where Agues are the epidemical diseases, where you will find but few persons but either are, or have been afflicted with a tedious Quartan: In this place I lived some years, making the best use of my time I could, for the improving my knowledge; curiously observing all Symptoms, Diagnosticks and Prognosticks; by which observations, and the assistance of my reason (God blessing my endeavours) I have attained to a perfect knowledge of the cure of the most inveterate and pertinacious Agues, and can inform a patient to a day when I will remove the fits, and what method I will proceed in with him; though to several persons, according to their several constitutions and

Quinine bark (Quinine): oldest antimalariar drug, known in Europe since mid 17th Century (Talbor, London 1682) as Jesuits' powder, but had bad side effects

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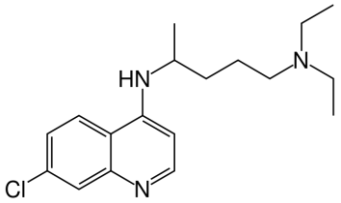
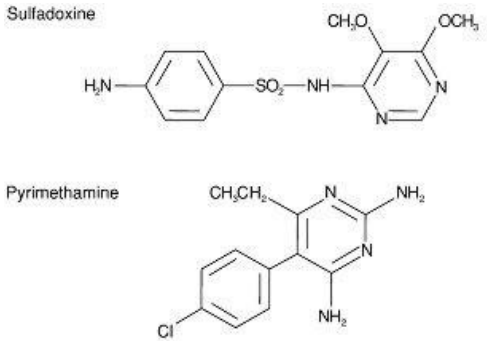
The history of drugs and resistance

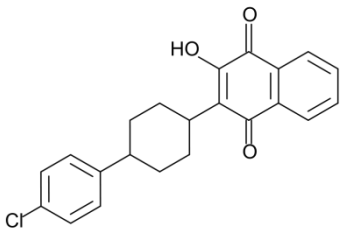


Chloroquine

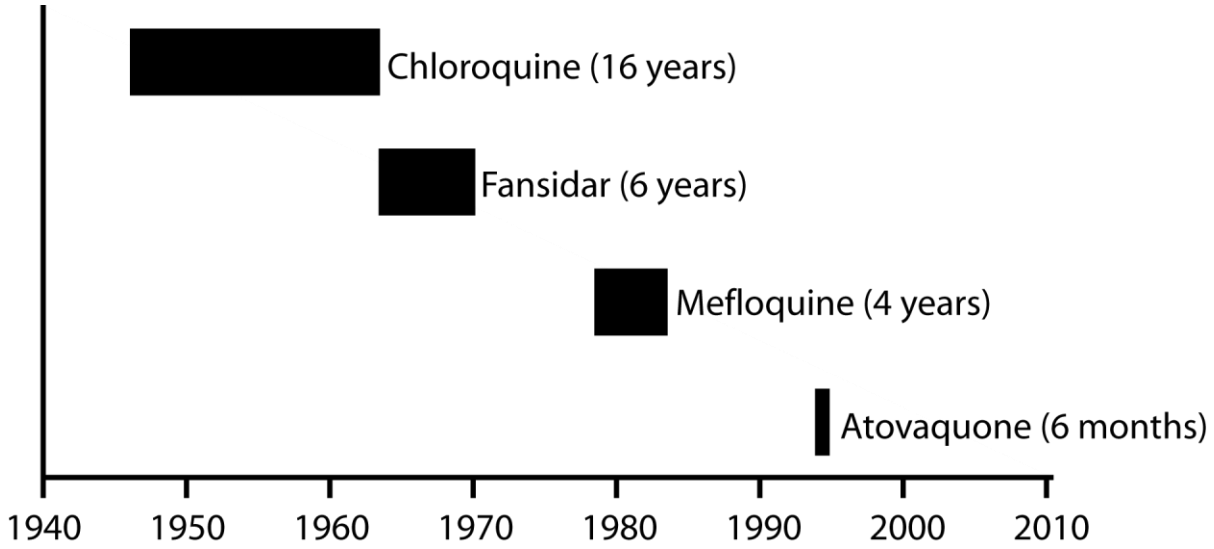


Fansidar

Mefloquine (Lariam)



Atovaquone (Malarone)



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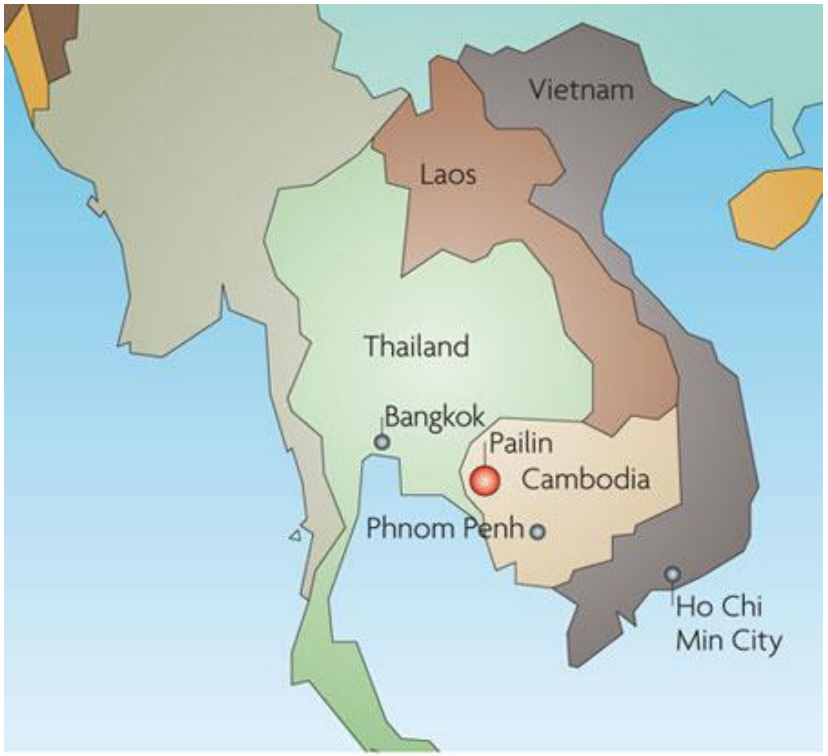
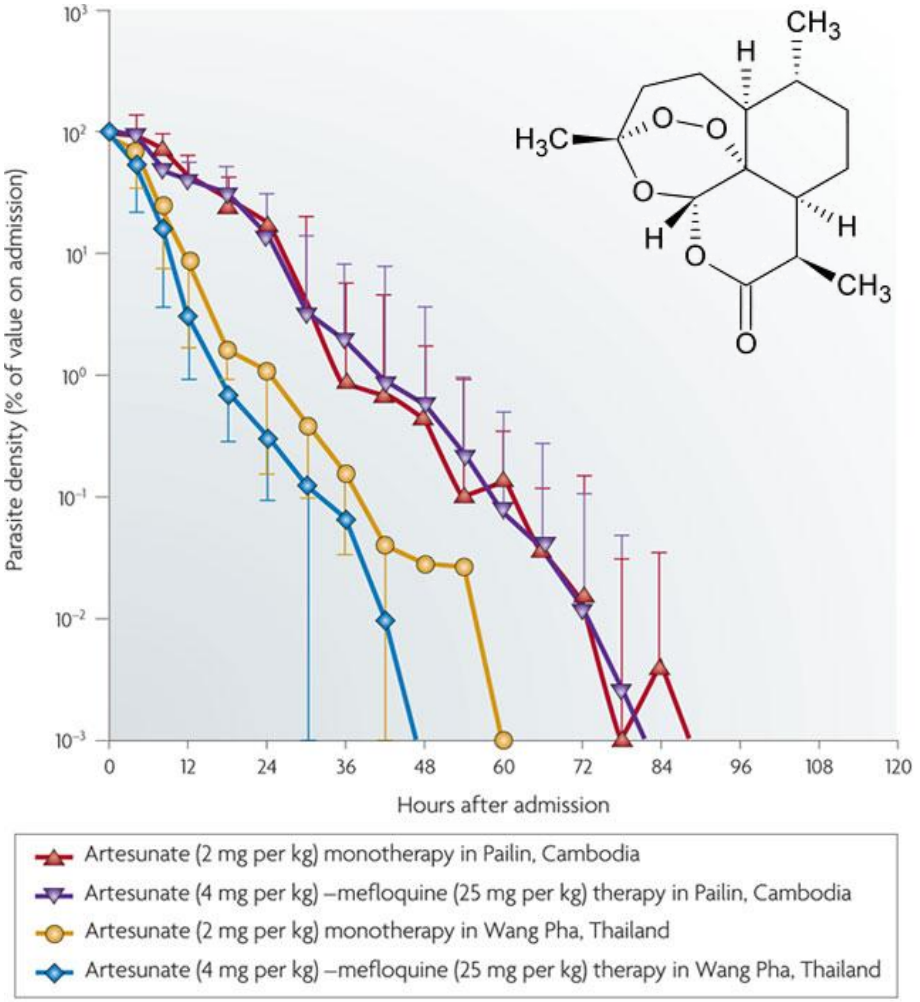
Artemisinin resistance – the clock is ticking



Nature Reviews | Microbiology

Dondrop et al (2010)



Resistance may be spreading into Africa

Nature Reviews | Microbiology

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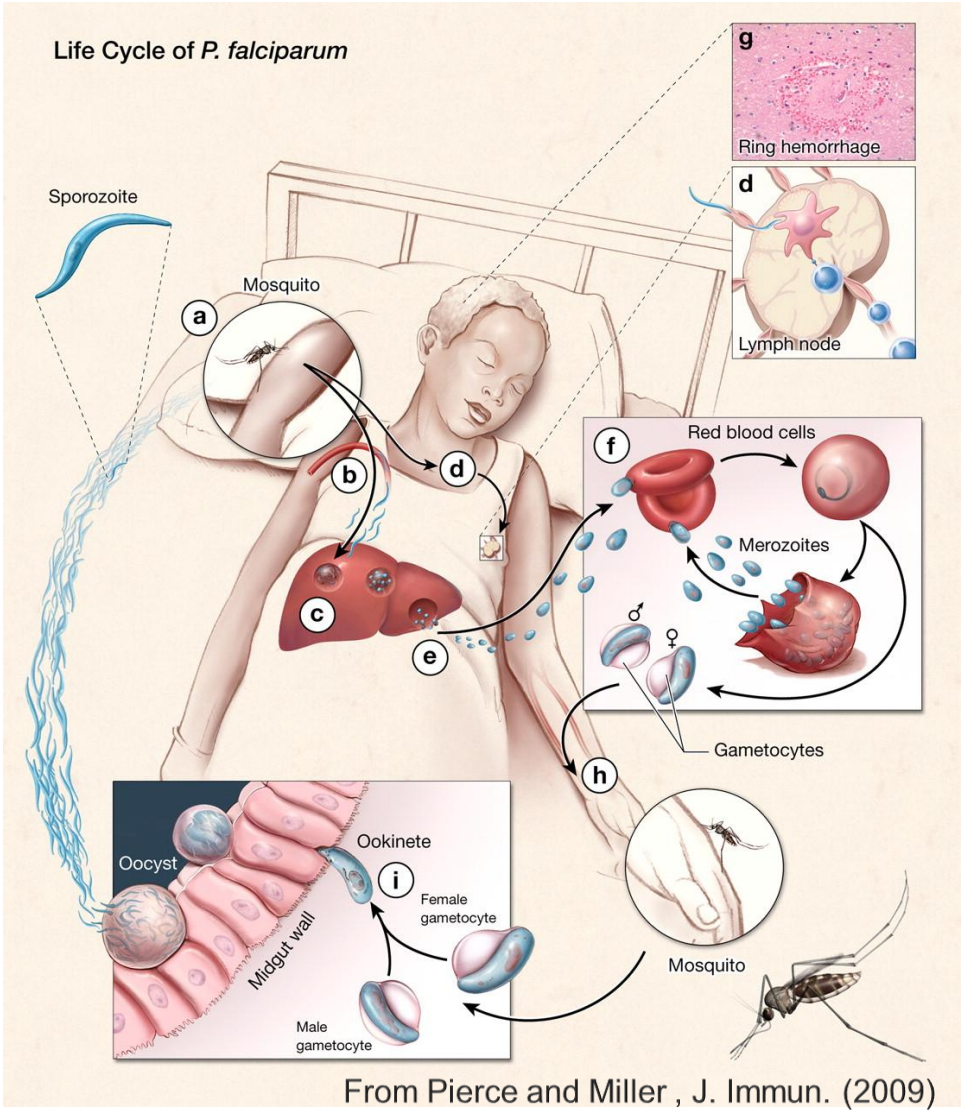
Malaria transmission cycle – the vector component



From Pierce and Miller , J. Immun. (2009)

- Dual lifecycle: asexual and sexual
- Mosquito is the definitive host (sexual)
- Passage through mosquito is obligatory
- Human malaria transmitted only by Anopheles mosquitoes

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Ross-MacDonald model of malaria transmission

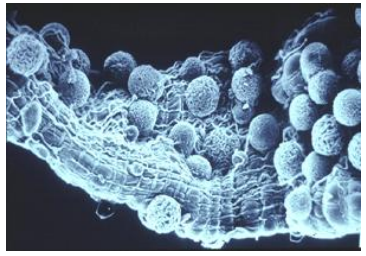
a = Mosquito biting rate

m = Mosquito-to-man ratio

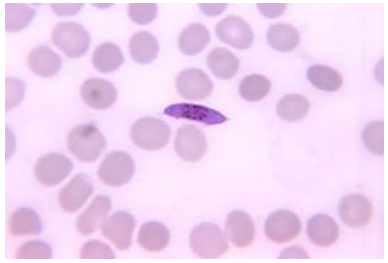
b = Proportion of infectious mosquitoes

$$R_0 = \frac{ma^2bp^n}{r(-\log_e p)}$$

n = Days taken for parasite in mosquitoes to become infective



r = Daily proportion of infected people who are not infectious to mosquito



p = Mosquito daily survival rate

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The discovery of the vector

Ronald Ross
1857-1932

Identified mosquitoes as the vectors of malaria in 1897

Battista Grassi
1854-1925

Showed that only certain mosquitoes can transmit malaria

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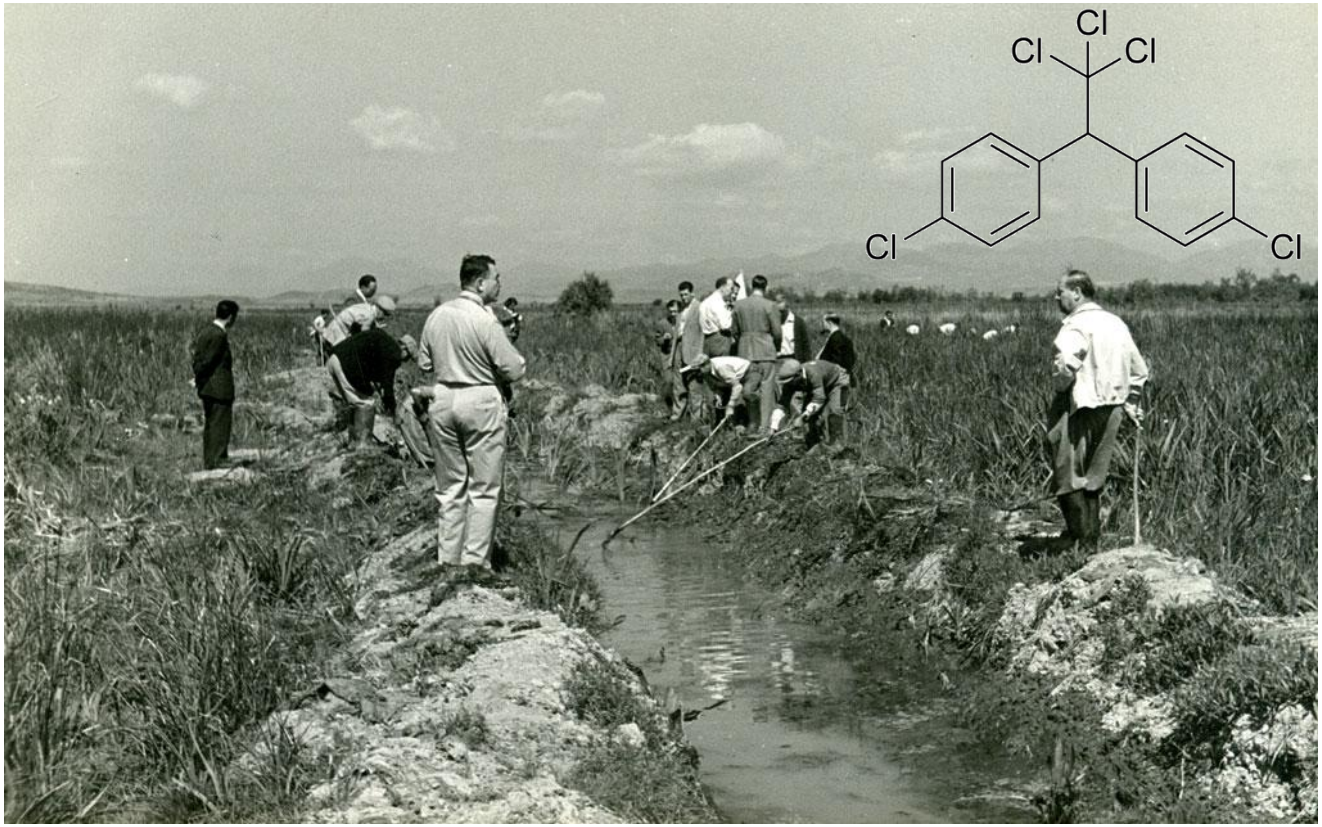
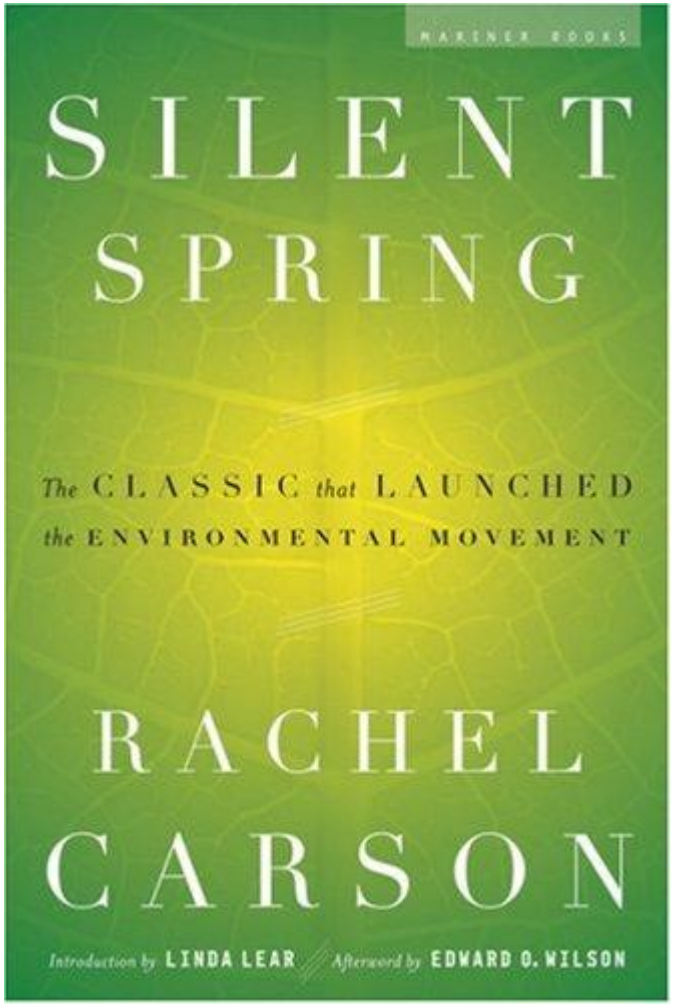
Malaria eradication - DDT



Environmental management and DDT led to malaria eradication in Italy and later (by 1950's) the entire Europe

By 1980's close to worldwide malaria eradication

The disaster – Silent Spring



The persistence and concentration of DTT in food chain together and its toxic effects exacerbated by aggressive agricultural use led to the environmental movement (Silent Spring) and disastrous ban of DTT.

Excessive use also led to widespread mosquito resistance.

New insecticides too suffer from excessive agricultural use and development of mosquito resistance.

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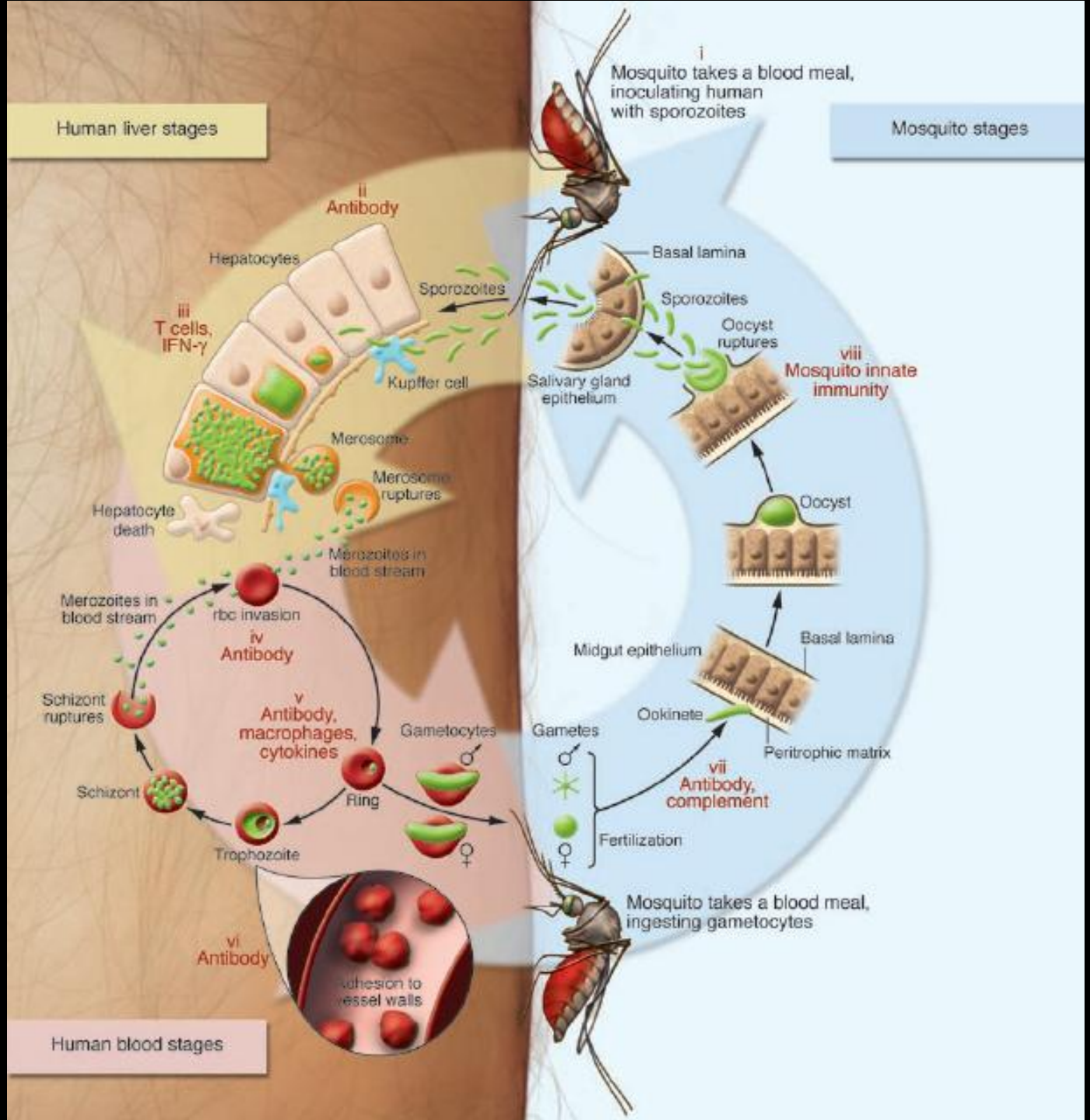
Bed nets are great but CANNOT be the solution

Insecticide impregnated bed nets (ITNs) one of the few remaining ways to control malaria (drastic decrease in the last years), but:

- mosquitoes already developed resistance to used insecticides
- they impose a massive pressure and change mosquito behaviour
- they cause lack of immunity


Human liver stages
Mosquito stages
i
Mosquito takes a blood meal, inoculating human with sporozoites
ii
Antibody
Hepatocytes
Sporozoites
iii
T cells, IFN-γ
Kupffer cell
Merosome
Merosome ruptures
Hepatocyte death
Merozoites in blood stream
Basal lamina
Sporozoites
Oocyst ruptures
viii
Mosquito innate immunity
Salivary gland epithelium
Oocyst
Midgut epithelium
Basal lamina
Ookinete
Peritrophic matrix
Gametes
vii
Antibody, complement
Fertilization
Merozoites in blood stream
rbc invasion
iv
Antibody
Schizont ruptures
v
Antibody, macrophages, cytokines
Gametocytes
Schizont
Ring
Trophozoite
Mosquito takes a blood meal, ingesting gametocytes
vi
Antibody
Human blood stages

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Malaria Pathogenesis

Symptoms commence when parasites engaged in erythrocytic cycle reach a level sufficient to generate a strong immune response, usually 1-2 weeks after infection.

Fever, the hallmark of malaria is caused by parasite-derived molecules released after synchronous schizont rupture of infected RBC activating **inflammatory cells e.g. macrophages**.

Temperatures **over 40°C** kill trophozoite and schizont stages.

Mediated by **secretion of** powerful pyrogenic cytokines such as IL-1 and **TNF-alpha**.

Erythrocytic cycle becomes **synchronized** – simultaneous rupture of infected RBC causes **periodic fever** (depending on parasite species, usually 48h) and associated symptoms and result in malaria paroxysm.

Reticuloendothelial system is activated to clear infected RBC – **splenomegaly**.

This in conjunction with **bone marrow suppression** cause **anemia**: haemolysis, haemoglobinuria, iron deficiency.

Also **hepatic dysfunction** and **lactic acidosis** [(reduced tissue perfusion, anaerobic glycolysis (host and parasite)]

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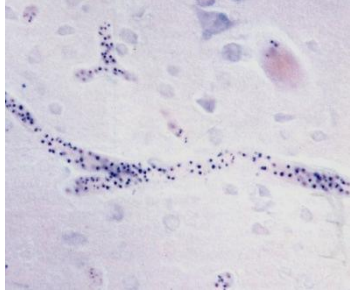
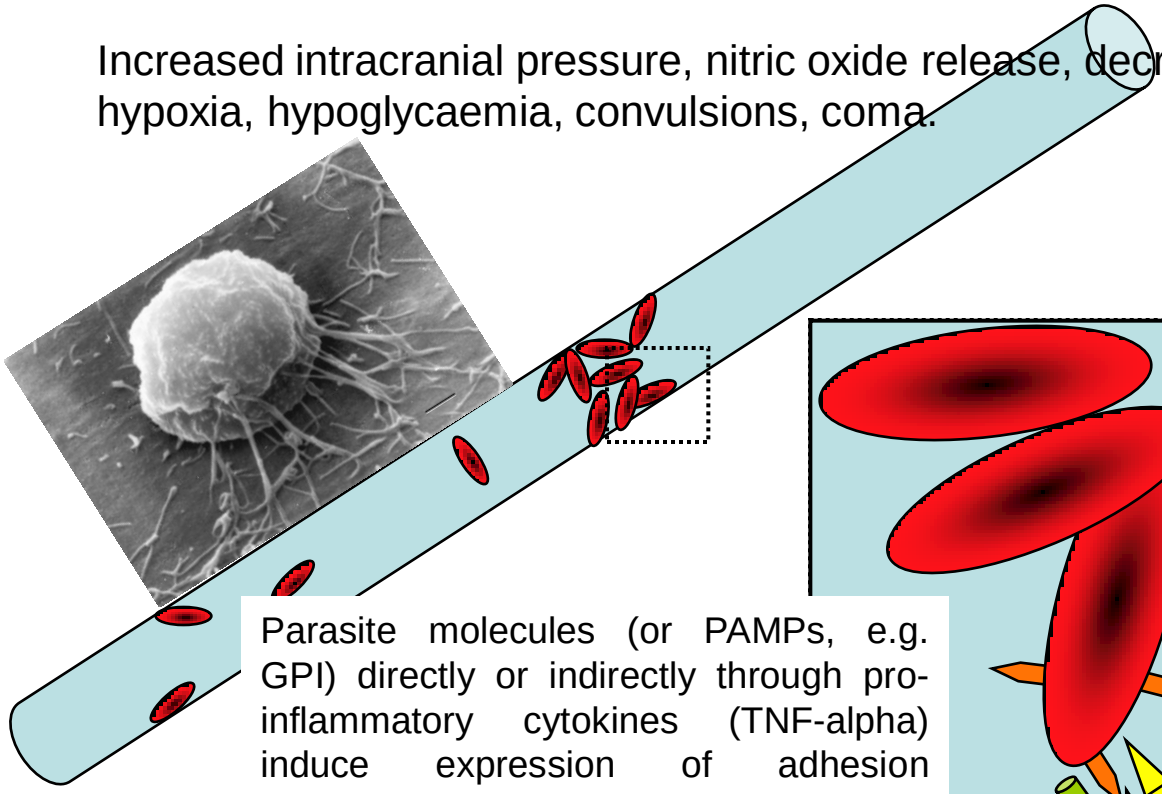
Cerebral malaria



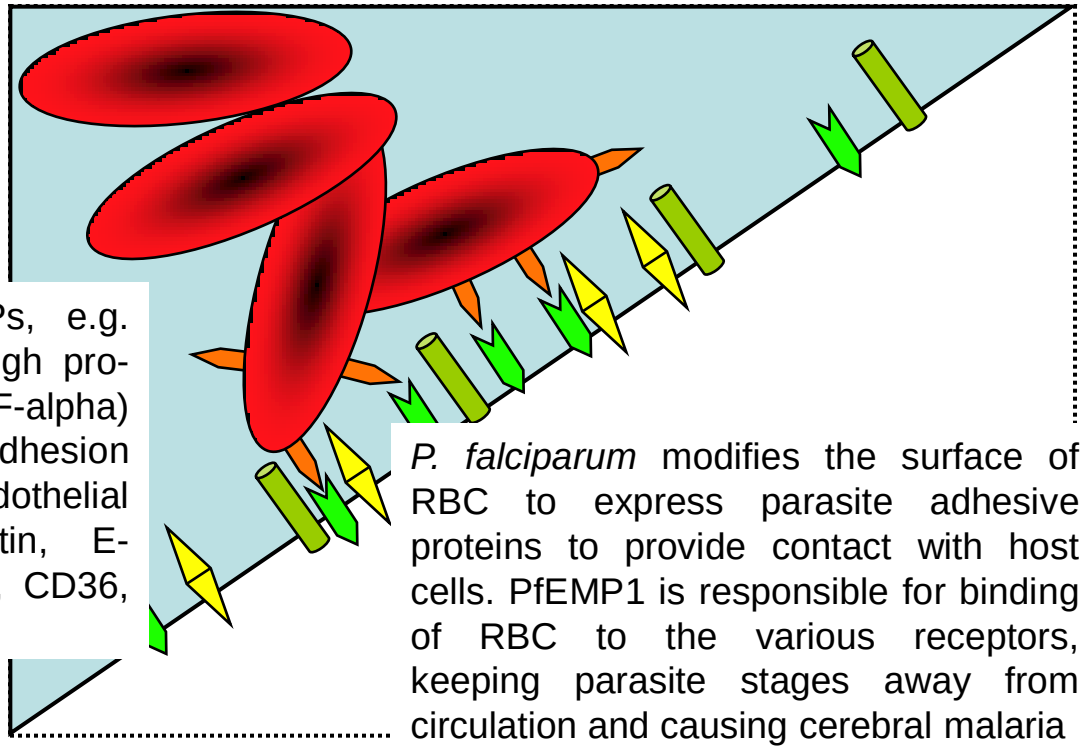
The major cause of death of people infected with *P. falciparum*.

The result of **occlusion of brain microvessels** sequestered with infected RBC.

Increased intracranial pressure, nitric oxide release, decreased cerebral perfusion, hypoxia, hypoglycaemia, convulsions, coma.



Parasite molecules (or PAMPs, e.g. GPI) directly or indirectly through pro-inflammatory cytokines (TNF-alpha) induce expression of adhesion molecules on surface of endothelial cells, e.g. ICAM-1, P-selectin, E-selectin, beta-integrin, VCAM-1, CD36, ELAM-1 etc…



P. falciparum modifies the surface of RBC to express parasite adhesive proteins to provide contact with host cells. PfEMP1 is responsible for binding of RBC to the various receptors, keeping parasite stages away from circulation and causing cerebral malaria

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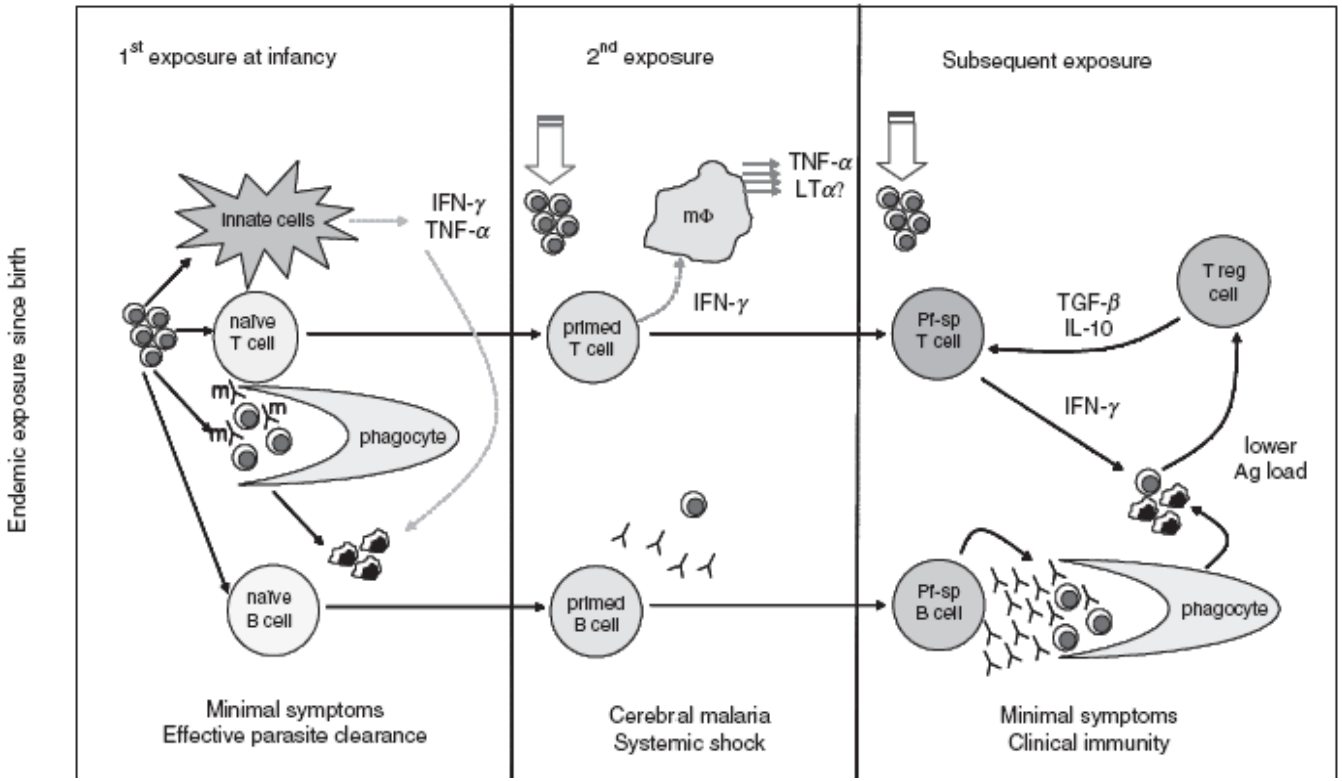
Immunity pattern to malaria in endemic regions



Primary infection in infants induces low levels of IFN-gamma and TNF-alpha (innate immunity) and primes T cells (adaptive immunity) - minimal clinical symptoms and usually parasites are cleared (abs or CTLs or fetal conditions)

On re-infection, great production of IFN-gamma which together with GPI boost production of TNF-alpha leading to increased risk for cerebral malaria and systemic shock

Subsequent infections are dealt with effectively by acquired immunity, reducing the parasite load and dampening the pro-inflammatory cytokine cascade (through TGF-beta and IL-10)

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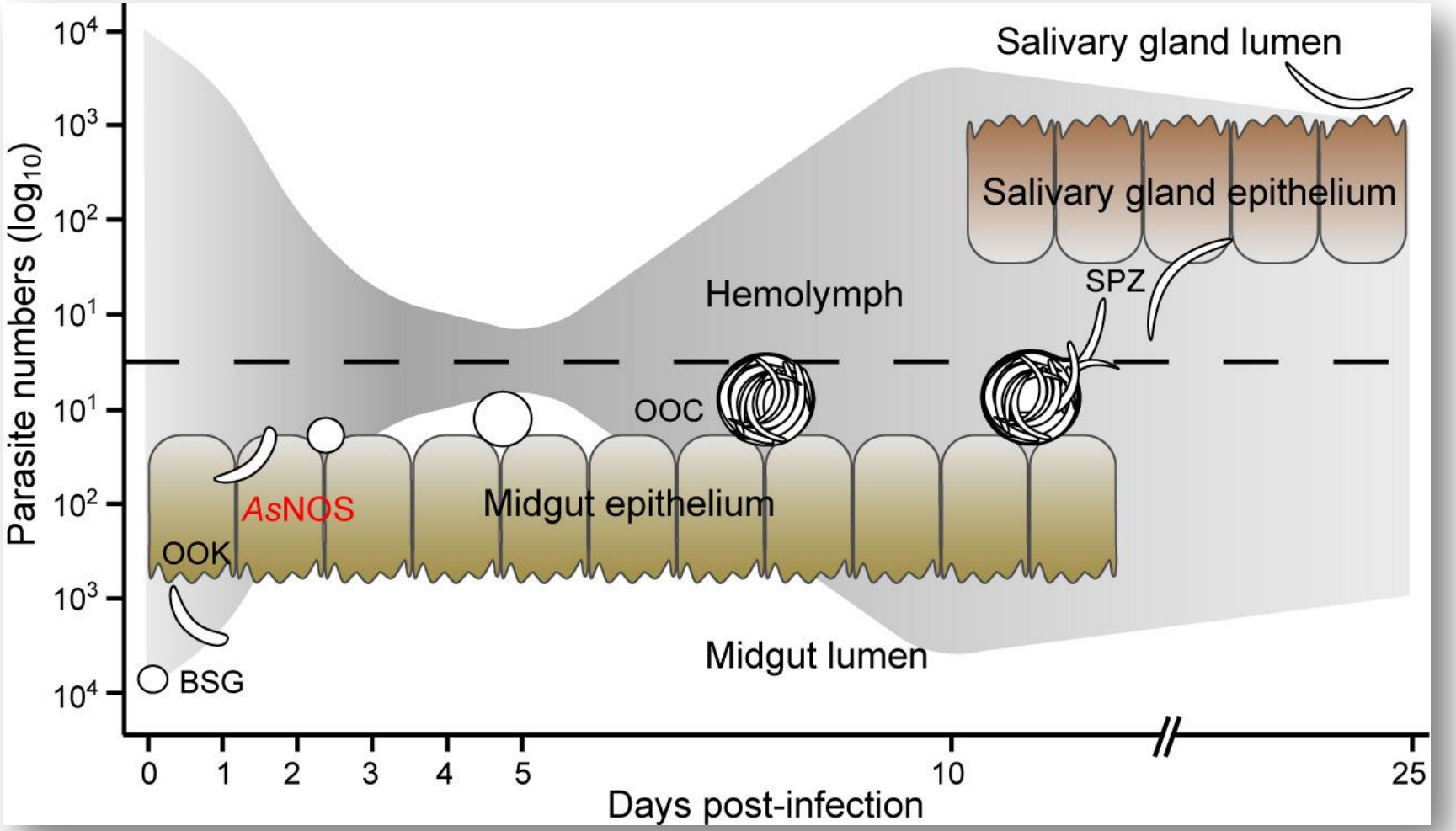
Plasmodium losses in the mosquito



Christophides, Cell Micro (2005)

Mosquito infection with malaria: a complex biological system that involves many organisms from diverse taxa