Malaria

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Key facts
With an estimated 216 million cases annually among 3.3 billion people at risk, malaria is a leading cause of death and disease worldwide, particularly affecting children under 5 and pregnant women. More than 90% of the disease burden is in sub-Saharan Africa where climate conditions are favourable for the mosquito vector to thrive, but malaria continues to cause considerable morbidity in Asia and south America. Global efforts to roll out malaria control tools (facilitating access to effective treatment and insecticide treated bed nets, targeting vector resting and breeding sites) have helped to reduce the burden of malaria in some areas but sustainable control or elimination is going to be very difficult to achieve without an effective vaccine.

Malaria life cycle
Malaria is an intracellular parasite transmitted through the bite of a female Anopheles mosquito. Of the five Plasmodium species that are known to infect humans (P. falciparum, P. vivax, P. ovale, P. malariae and P. knowlesi) P. falciparum causes the majority of infections (and deaths). During a mosquito bite, sporozoites are released from the mosquito salivary glands into the host’s skin, enter the bloodstream, circulate to the liver and invade hepatocytes and differentiate. This is known as the pre-erythrocytic stage. At this time, the infection is not apparent clinically. After approximately one week, each infected liver cell will rupture, releasing as many as 30,000 merozoites into the bloodstream where they invade red blood cells (RBCs). Here, each parasite develops, maturing from rings to trophozoites to fully formed mature schizonts (each of which contains 16-20 merozoites) over a period of 44-72 hrs (depending on species). Eventually, the schizonts rupture to release more merozoites into the bloodstream where they invade new RBC, starting a new cycle. This is the erythrocytic or blood-stage of the infection. It is during the rupturing of the RBCs and the release of merozoites into the bloodstream that the acute clinical symptoms of malaria (fever, headache, nausea) are manifested. Severe malaria is caused by excessive RBC rupture (leading to anaemia), excessive inflammation, and accumulation of infected RBCs (iRBCs) in small blood vessels (leading to organ damage). A small proportion of merozoites develop into male and female gametocytes and are taken up by biting mosquitoes. Within the mosquito gut, fertilisation occurs, the zygote undergoes meiosis and thousands of sporozoites are produced, completing the cycle.

Immune response to the pre-erythrocytic stage
Naturally acquired immunity at this stage is not very effective, as evidenced by recurrent infections throughout life in residents of endemic areas. However, antibodies (Abs) are eventually developed against the most abundant surface protein on the sporozoite (the circumsporozoite protein), which trap sporozoites in the skin and reduce their invasion into liver cells by inhibiting their motility. Likewise, infected liver cells can be destroyed by Ab-dependent cellular cytotoxicity, or by the action of interferon-γ-producing CD4+ and CD8+ T cells, NK cells and γδ T cells, which induce final effectors such as nitric oxide. The circumsporozoite protein forms the basis of the first malaria vaccine to reach phase 3 clinical trials (RTS.S, developed by GSK): current data suggest that both Abs and CD4+ T cells contribute to the approx. 50% efficacy of this vaccine in preventing clinical malaria.

Immune response to the blood stages
Blood-stage infection is characterised by a pro-inflammatory cytokine response involving IL-1β, IL-6, IFNγ, TNFα and IL-12, which enhances phagocytosis and killing of iRBCs by macrophages. However, overproduction of these cytokines contributes to malarial pathology and down regulation of inflammation (by IL-10 and TGF-β) once parasitaemia is under control, is required to prevent severe disease. Phagocytosis of iRBC is augmented by their opsonisation by cytotoxic Abs binding to parasite antigens exported to the RBC surface. However, these antigens are highly polymorphic and undergo clonal antigenic variation, meaning that effective opsonisation (or prevention of iRBC sequestration in blood vessels) may only develop after many and varied malaria infections. Antigens expressed on merozoites are also polymorphic but Abs against conserved or semi-conserved epitopes can inhibit merozoite invasion of RBC. Complement-fixing Abs against gametocyte and gamete antigens can prevent the establishment of infection in the mosquito and thereby block malaria transmission.