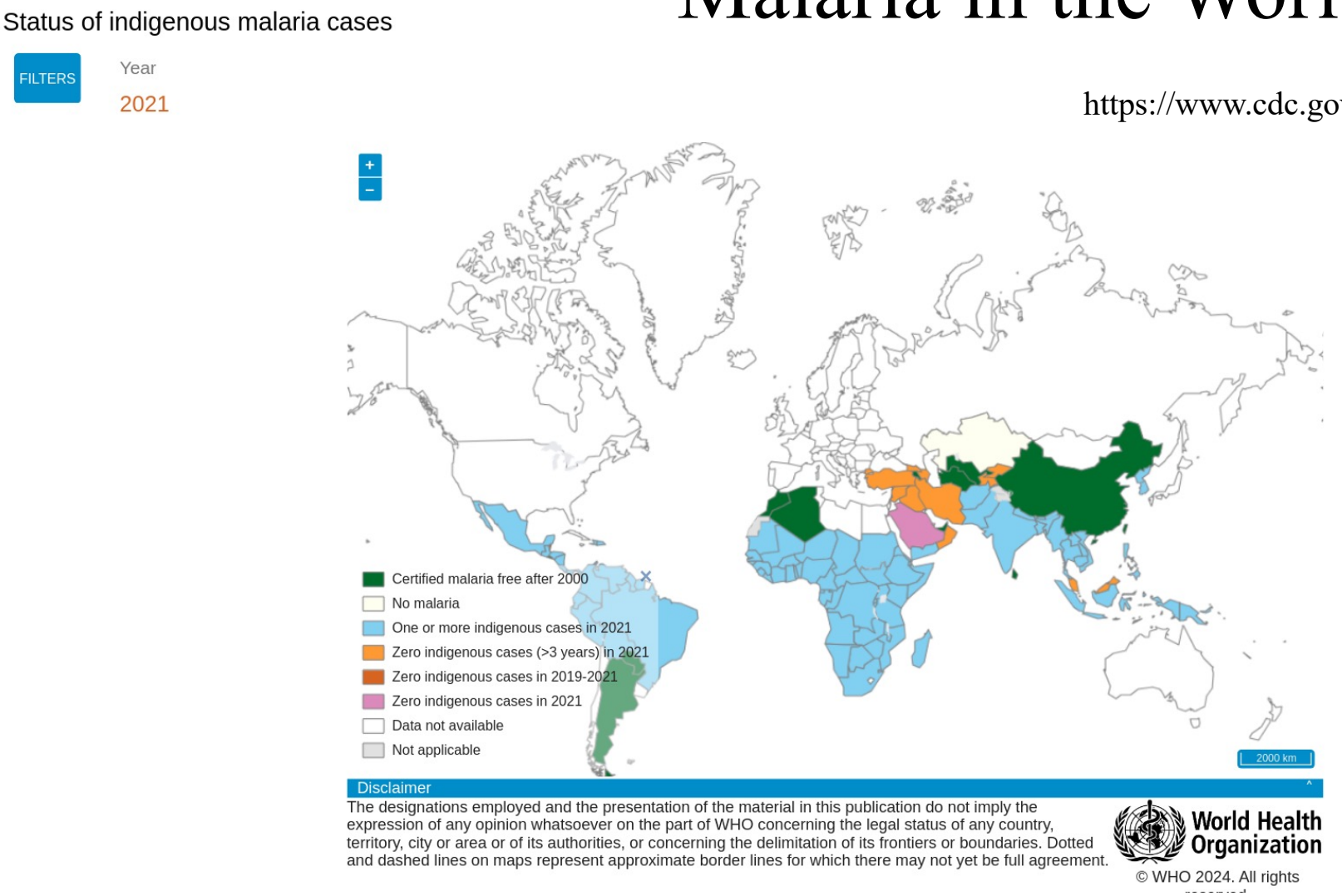
Malaria History

Malaria is an ancient disease and still one of the leading causes of mortality in the world.

- Nobel prize 1902: **Ronald Ross** demonstrated that malaria is transmitted in a cycle from human to human by mosquitoes
- Nobel Prize 1907: **Charles Laveran** proposed in 1890 that malaria was caused by a protozoan organism, Plasmodium.
- Nobel Prize 1948: **Paul Müller** discovered DDT and its use on insects was crucial in the worldwide campaign to eradicate malaria.
- Nobel Prize 2015: **Tu Youyou** extracted artemisinin from wormword and this drug improved malaria outcome for millions.

Wormwood

Malaria in the World



Approximately 3.2 billion people are at risk of malaria. **In 2022, estimated 249 million malaria cases across** 84 countries **with 608,000 malaria deaths.** Sub-Saharan Africa had 94% of malaria cases and 95% of malaria deaths. Children under the age of 5 account for 80% of deaths.

Malaria

Epidemiology

Malaria is one of the leading causes of death from infectious disease, especially in children under 5 and >90% of deaths occur in sub-Saharan Africa

WHY?

- socioeconomic conditions are a contributing factor.
- in some heavy-burden countries, treating malaria accounts for up to 40% of public health expenditures.
- the vector--- *"the long lifespan and strong human-biting habit of the African mosquito vector species is the main reason why more than 85% of the world's malaria deaths are in Africa."*

WHO Fact Sheet No94. http://www.who.int/mediacentre/factsheets/fs094/en/index.html

Mosquito vector

Anopheles is the only mosquito genus capable of spreading malaria and only the female transmits malaria.

In many places, transmission is seasonal, with the peak during or just after the rainy season based on increased mosquito replication in standing water.

20 species of Anopheles worldwide can transmit Plasmodium parasites, but certain species transmit better, especially night biter species like *Anopheles gambiae.* In addition, *A. gambiae* preferentially bites humans.

History of Malaria

Malaria in the United States

- Malaria is primarily a disease of the tropics now, but in the late 1800s malaria was endemic in New England and a major cause of morbidity in Civil War. There were 600,000 cases in the US in 1914 primarily in Louisiana and Florida.
- There are species of *Anopheles (A. albimanus, A. freeborni*) that are capable of transmitting malaria present in Southern part of US.

- The US CDC says there are 1,700 **imported** cases of malaria each year in the United States. Most cases are from travelers where they acquired infections in regions with malaria transmission.

History of Malaria
Mosquito vector control
Fred Soper DDT

- *A. gambiae* was found in Brazil in 1930.
- Soper was brought in to eliminate *A. gambiae* but only after a bad epidemic in 1938--this was before DDT. They would use diesel oil and Paris green to spray in water.
- DDT discovered in 1939 during WWII. Fred Soper saw the potential in DDT after WWII. DDT was the first insecticide that when applied to houses could kill mosquitoes for up to a month.

Malaria eradication
Global Campaign 1947- 1955

- Combined systematic spraying of DDT to kill mosquitoes and treatment of infected patients with chloroquine.
- The eradication campaign was very effective in some countries e.g., Sri Lanka went from 1 million cases in 1955 to just 18 cases in 1963.
- The campaign cost (1955-1963) was ~$430 million.
- However, eradication in sub-Saharan Africa was never fully implemented.

Malaria eradication
End of First Global Malaria Campaign

- **Financial issues**

The cost was high and in 1963 the US Congress withdrew funding.

- **Drug resistance**

Chloroquine resistance of the Plasmodium species began to occur and spread.

- **Problems with DDT**
  - Widespread use of DDT in agriculture led to widespread DDT resistance.
  - DDT was found to be a devastating environmental pollutant causing severe damage to wildlife.
  - Complication occurred from DDT damaging an array of non-harmful insects.

Malaria eradication
Global Malaria Control Strategy in 1990s

- New idea of "control" rather than eradication.

- Prompt treatment for all episodes of disease

(within 24 hours of the onset of symptoms if possible)

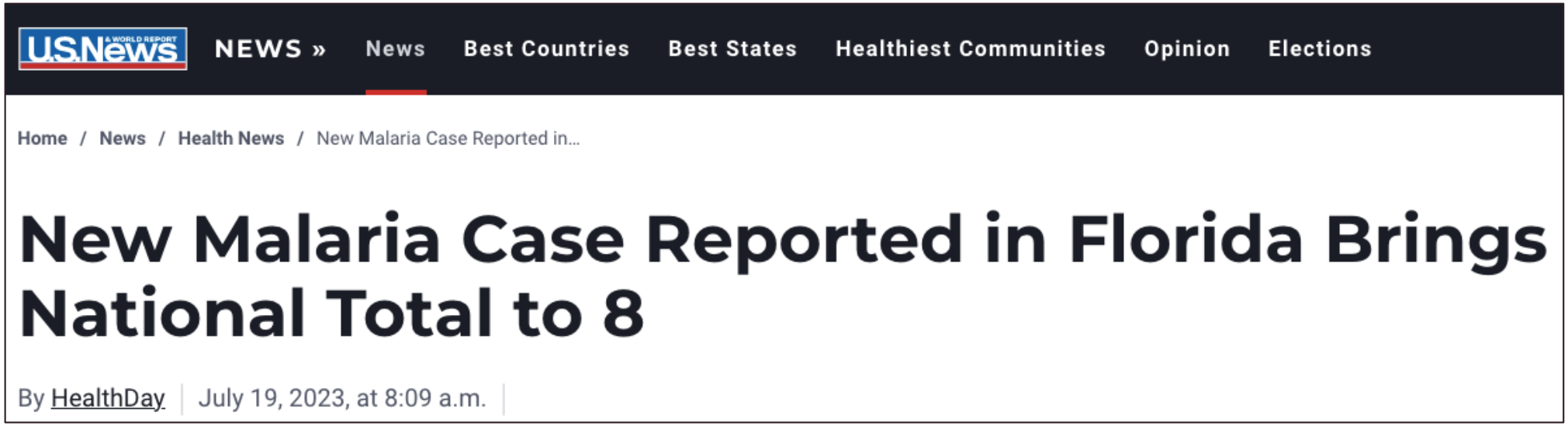
- Bednet use combined with insecticides.

- Indoor residual spraying to kill mosquitoes that rest on the walls and roofs of houses.

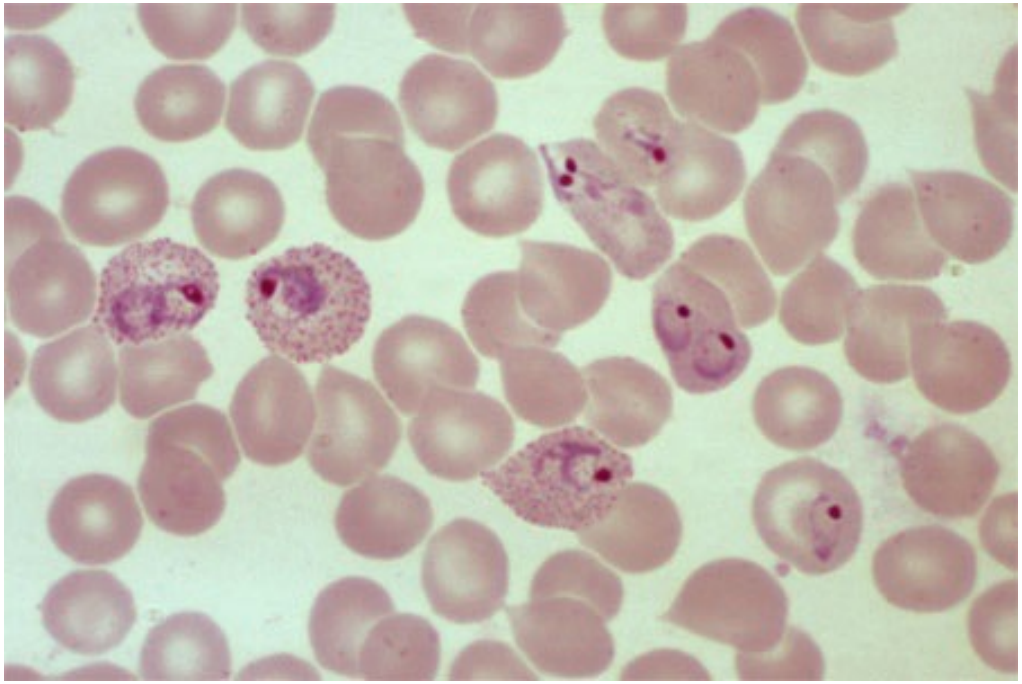
-WHO Fact Sheet No94. http://www.who.int/mediacentre/factsheets/fs094/en/print.html

Malaria US outbreak in June/July 2023

- The *Anopheles* mosquitoes have always been present, but few infected individuals and mosquito control have stopped any big outbreaks since 1951.
- There were only a total of 8 cases in Florida and Texas



Malaria is an intracellular protozoan parasite

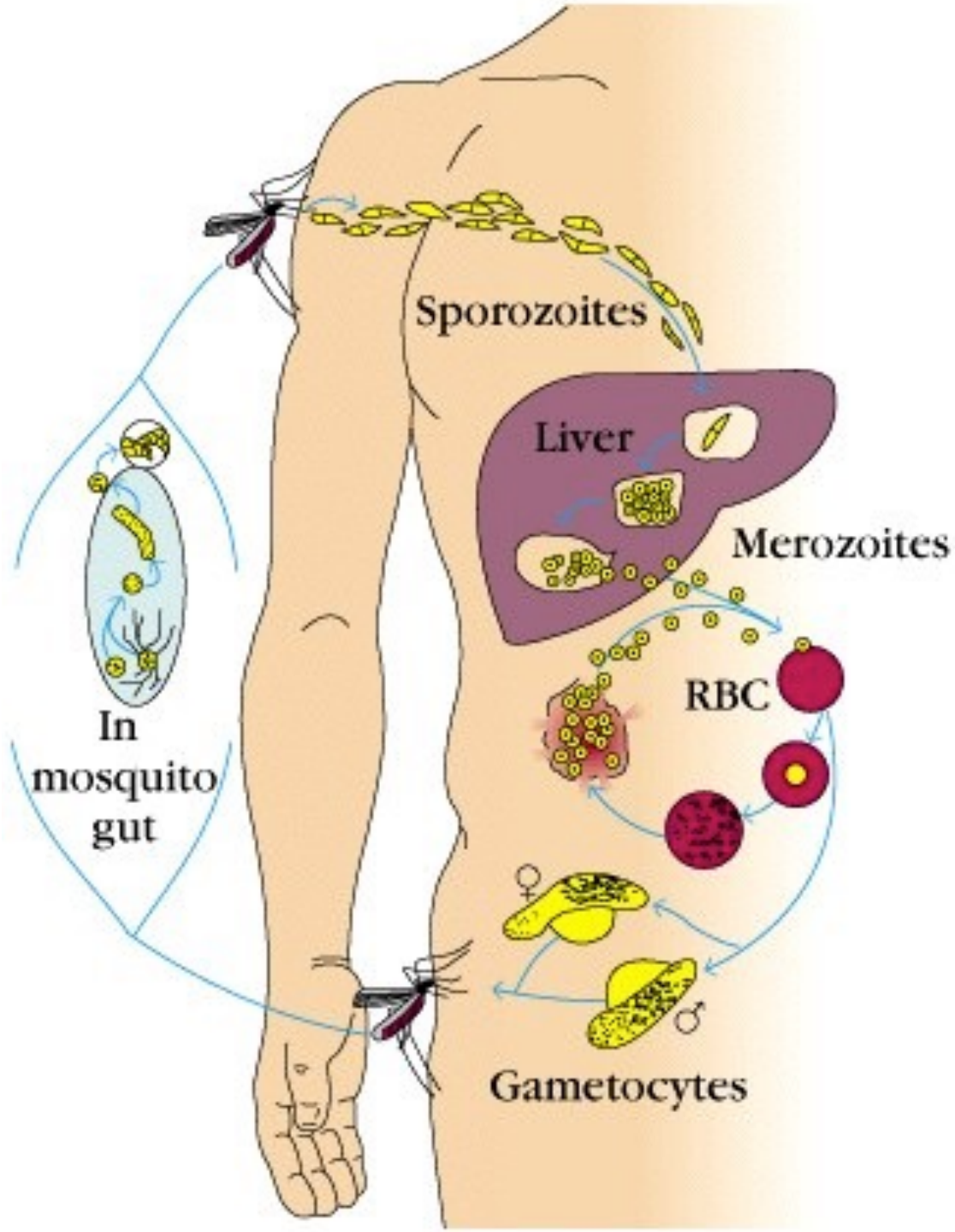


- Malaria is caused in humans by 4 species *Plasmodium vivax, P. falciparum, P. ovale, P. malariae*

There are many other species-specific *Plasmodium* (mouse or rodent malaria *P. berghei* used in animal model of malaria).

- Infects red blood cells (RBCs)--which makes parasites relatively easy to find in blood.
- By living in RBCs, the parasite evades key adaptive immune mechanism (CTLs).

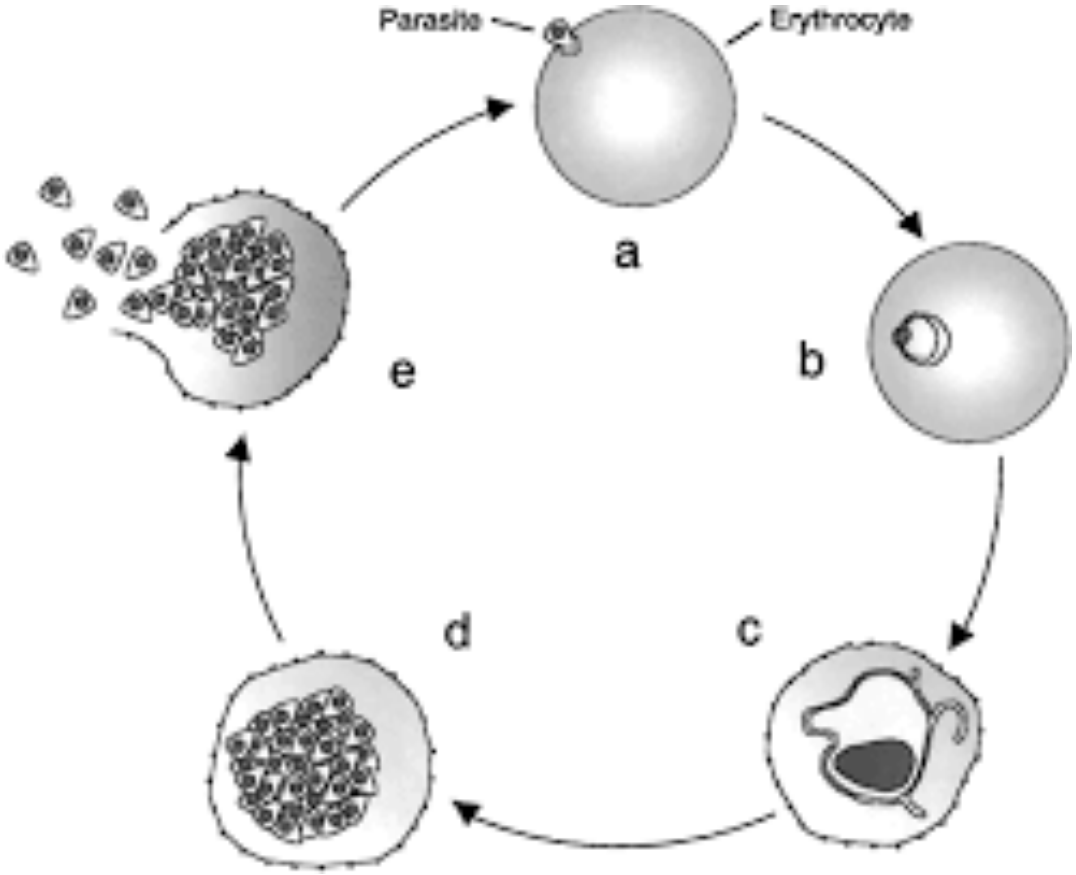
Malaria



- Sporozoites can infect liver cells within 10 minutes after mosquito bite Each infected cell can release 10-30,000 merozoites.
- First cycle in liver (7-14 days). Disease only commences once the parasite replicates in RBCs.

Merozoite Form

- Merozoites can have many rounds of replication in RBCs.
- *P. falciparum* parasites can infect as many as 60% of the RBCs.
- Each time merozoites are released they cause systemic inflammation and fever.



Malaria Disease is from merozoite form

- Infected individuals have **cyclic fevers** with the release of parasites from RBCs every 48-72 hours. Cytokines from the lysed RBCs trigger fever.

- Malaria can cause severe anemia based on loss of RBCs.

Clinical Aspects

Diagnosis: The symptoms are very similar to other infections but easy to diagnose by examining peripheral blood smear under microscope.
P.vivax/*ovale*/*malariae* cause characteristic spiking fevers with a 48-72 hr periodicity. But *P.falciparum* can be distinguished from other species in blood smears: *P. falciparum* is usually associated with multiple infected cells/smear.

Mortality: In endemic areas almost 100% of children have yearly symptomatic malaria but only 1-2% have severe complications usually cerebral malaria. *P.falciparum* causes most deaths from malaria brain infections where cerebral malaria has a mortality of 20%. Infection triggers an inflammatory responses that can result in neurological damage or death.

Immune Response to Malaria

- **Innate immunity.** Parasites eliminated by phagocytosis and C' activation outside cells
- **Adaptive Immunity.** Complicated immune response to Malaria with different antigens expressed by different morphological forms in liver and RBCs.
  - **Abs to sporozoites** before liver and **CTL** against liver infected cells.
  - T helper cells and B cells provide **antibody** triggered lysis to kill infected **RBCs.**

Why is Malaria such a successful pathogen?

- Very well-adapted for humans and no animal reservoir.

- Also evolved for transmission only in *Anopheles* mosquito.

- Gametocytes represent sexual stage where they can infect mosquitoes. After being taken up into gut, the sporozoites replicate throughout the mosquito and after 2-weeks the sporozoites enter the salivary glands of the mosquito.

- Plasmodium parasites are very good at evading immune response.

Malaria
Partial immunity and immune evasion

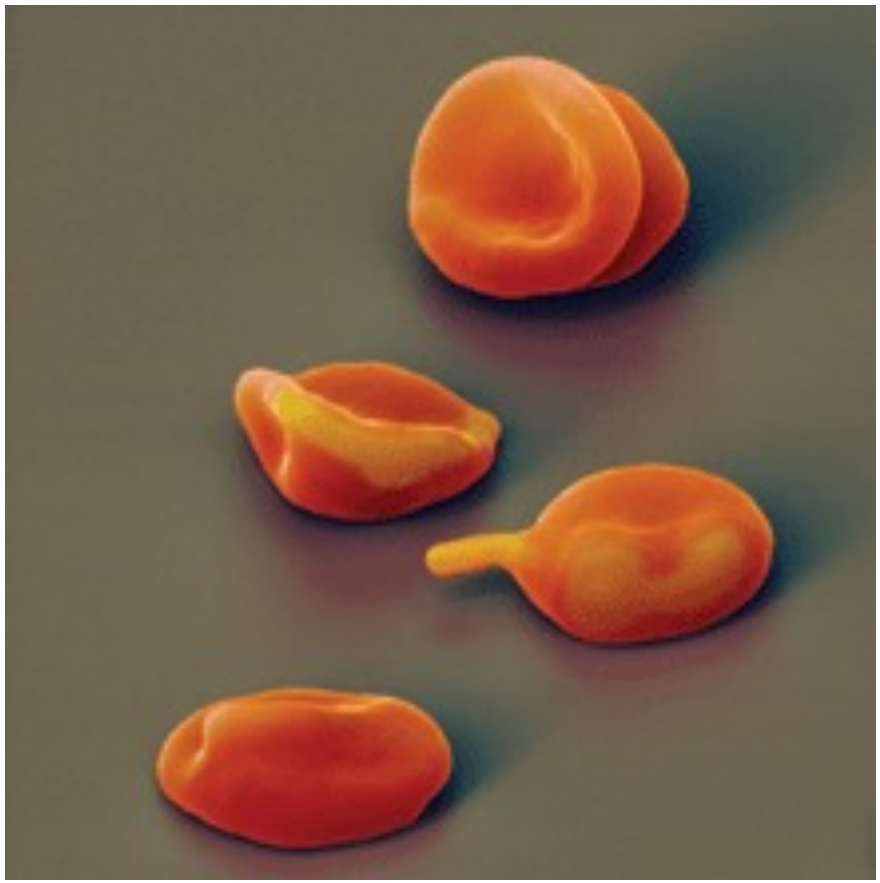
What is "partial" immunity?

In endemic areas, partial immunity is usually found in individuals >15 years of age. This partial immunity can reduce symptoms but if parasite replicates in blood, mosquito transmission still occurs.

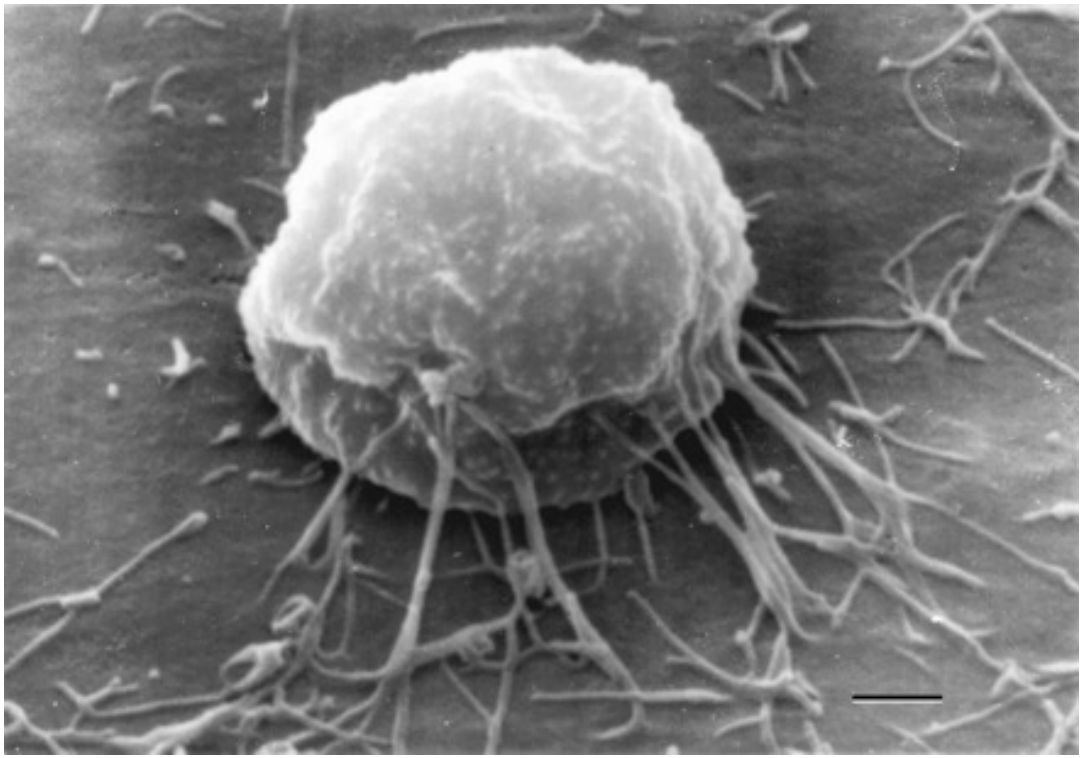
How does malaria evade antibodies?

Parasite expresses key antigens on the surface of infected RBCs and can change these surface antigens.

Malaria



Yellow stained plasmodium parasites in RBCs.



Infected RBC with knobs.

Immune evasion
Changes in surface antigens=knobs

- Malaria evades immunity by the expression of variant surface antigens (**VSAs**) that are the primary targets of antibodies on the surface of *P. falciparum* infected RBCs.
- The key family of VSAs are *Plasmodium falciparum* erythrocyte membrane protein 1 (**Pfemp1**) antigens encoded by 60 genes.
- These VSAs, especially Pfemp1 proteins, provide binding of infected RBCs to the vascular endothelium. By binding in the small blood vessels of the body, the infected RBCs evade degradation in the spleen and liver.
- The ability of *P. falciparum* to CHANGE the expression of these VSAs is an important form of **antigenic variation** that makes it difficult for people to develop more than partial immunity.

Anti-malarial Drugs

Original drug was Chloroquine this is a quinine compound very similar to what is found in tonic water.

Choloroquine was established as an effective and safe antimalarial in 1946. Chloroquine is thought to inhibit heme-polymerization, leading to heme-toxicity to the parasites. But great resistance by the parasites was detected 1970s.

Many other drugs (mostly targeting heme) have been developed and used since the 1970s.

However, drug resistance by plasmodium parasites has been found against all of them. But many of these drugs are widely used and are very useful for most malaria infections.

Malaria Prevention
Non-medical

Mosquito control.

Pyrethroid-insecticide (**permethrin**) treated **bednets** are a non-medical solution that is affordable and effective.

In one large trial, malaria deaths in children <12 months of age were reduced by 22%.

Natural resistance to Malaria

1. Individuals who are heterozygous for HbS (sickle cell hemoglobin) have some protective advantage against malaria. The mechanism by which HbA/S heterozygosity protects against malaria is unclear, it may be that infected cells tend to sickle under low oxygen tension conditions which allows for increased removal of sickle infected cells.
NOTE** in uninfected heterozygous individuals only a few percent of cells are sickled.
Recent study conducted in Kenya determined that sickle cell trait provides 60% protection against overall mortality primarily during 2-16 months of age. As a result, the frequency of sickle cell carriers (heterozygous) can be up to 25% in endemic areas.

2. Blood type has also been identified through epidemiology studies as potentially protective against malaria. May be that uninfected O type red blood cells are less likely to "rosette—form clump of RBCs" to prevent killing.

Natural resistance to Malaria

- Blood type has also been identified through epidemiology studies as potentially protective against malaria.
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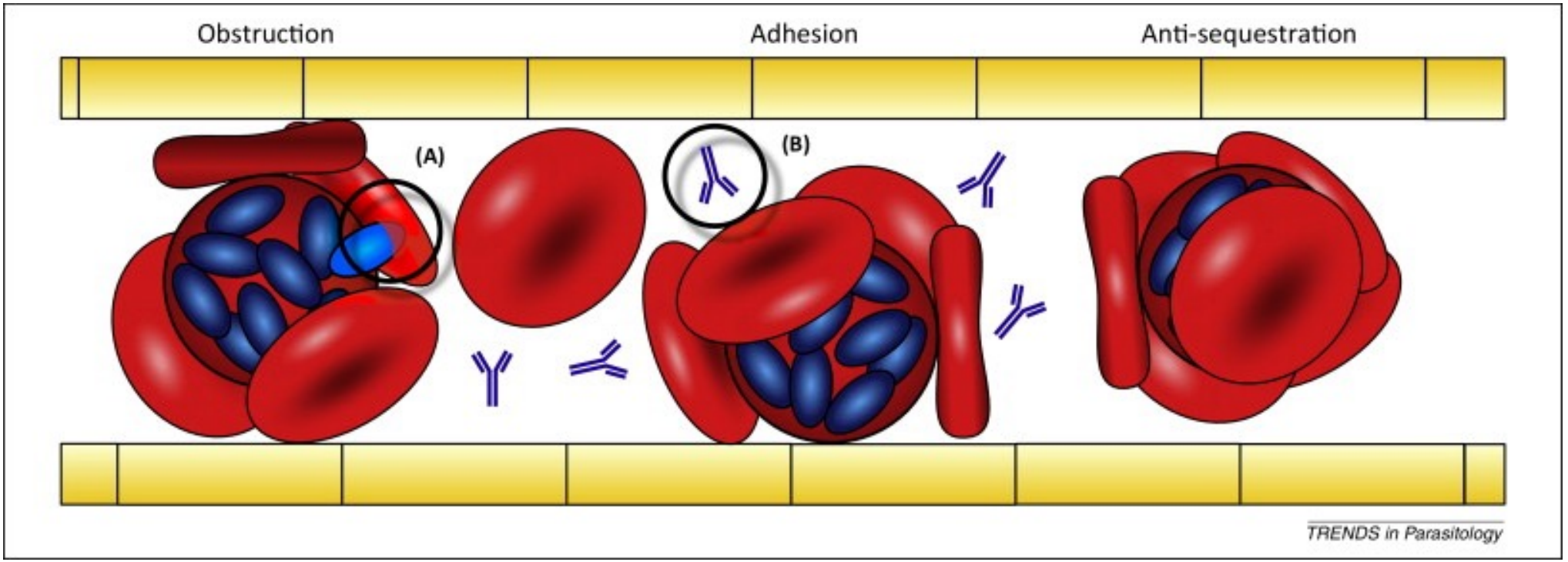
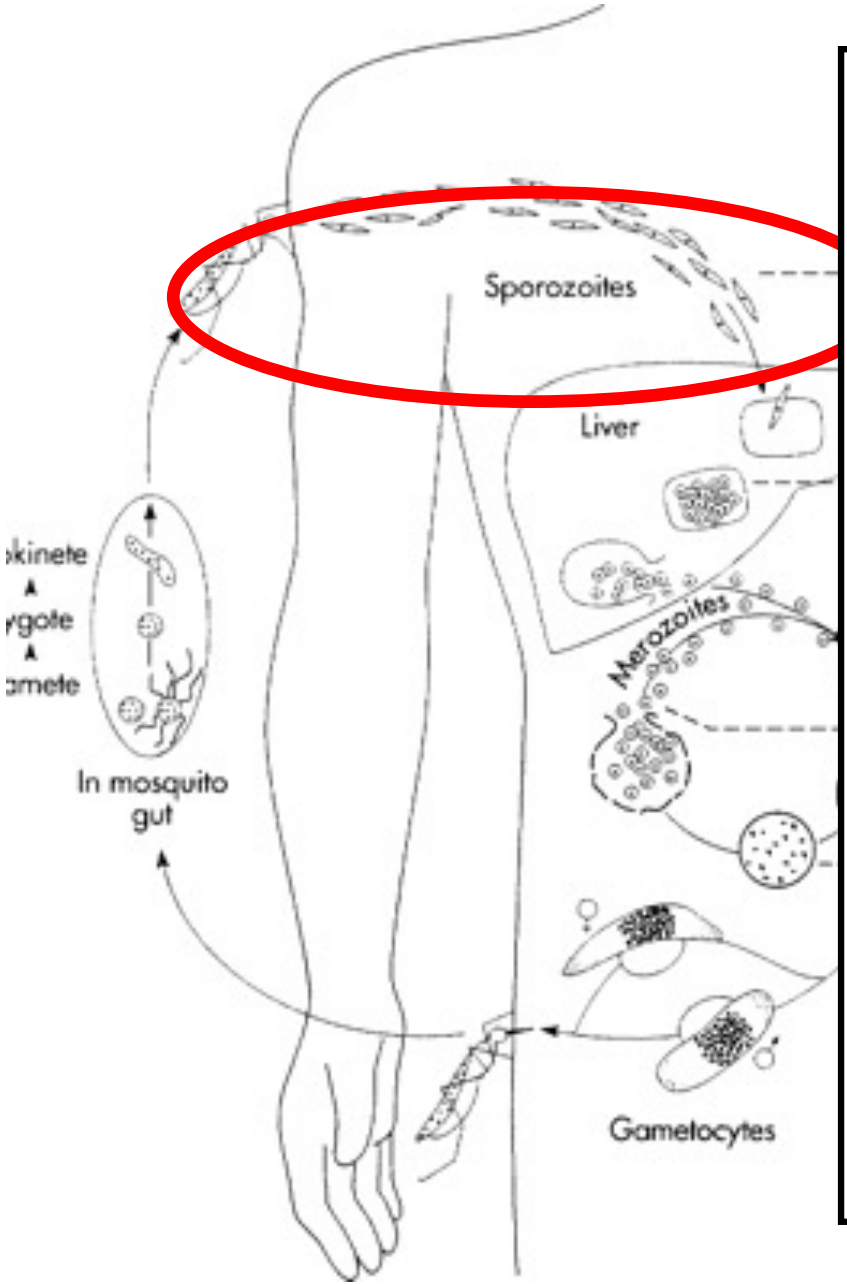


The functional significance of rosetting. Rosettes formed by Plasmodium falciparum-infected erythrocytes (IE) might lead to obstruction of blood flow (left IE), facilitate merozoite reinvasion following schizont rupture (A), and/or shield infected RBCs from antibodies (B).
OR the rosette may interfere with infected RBCs thus acting as host defense.

Christian W. Wang, Lars Hviid **Rifins, rosetting, and red blood cells.** Trends in Parasitology, Volume 31, Issue 7, 2015, 285–286.
http://dx.doi.org/10.1016/j.pt.2015.04.009

Recombinant Vaccine against Pre-liver stage



RTS,S is composed of a *P. falciparum* **circumsporozoite** protein fused with the **hepatitis B virus surface** antigen combined with a GlaxoSmithKline proprietary adjuvant.

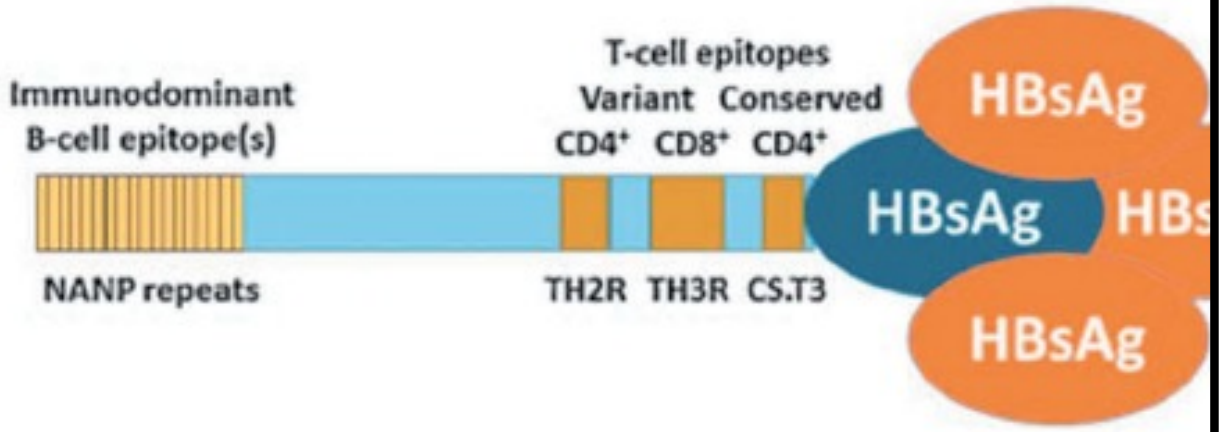
Phase III clinical trials found 50-56% reduction in first case of malaria when given to 5-17-month-old children.

RTS,S = 'R' for the central repeat region of Plasmodium (P.) falciparum circumsporozoite; the 'T' for the T-cell epitopes of the CSP; and the 'S' for hepatitis B surface antigen (HBsAg).

RTS,S is recommended by WHO and GAVI as of October 2021

- RTS,S has been in development since 1987.
- Requires 4 doses/immunizations for protection.
- Vaccine is ONE tool in combination with drugs and insecticide-treated nets to reduce malaria incidence.
- **Most significant was 30% reduction in cases of severe malaria.**
- Use of vaccine reduced the need for blood transfusions for severe malaria by 29%.

https://www.who.int/news/item/06-10-2021-who-recommends-groundbreaking-malaria-vaccine-for-children-at-risk
https://www.gavi.org/news/media-room/gavi-unitaid-and-global-fund-welcome-who-recommendation-worlds-first-malaria



Recombinant protein vaccine is composed of **18 B cell epitopes and 5 T cell epitopes** from Plasmodium circumsporozoite fused to HBV surface antigen (HBsAg). Unfused HBsAg self-assembles with fused into virus-like particles