

Malaria

Kemi Keshinro

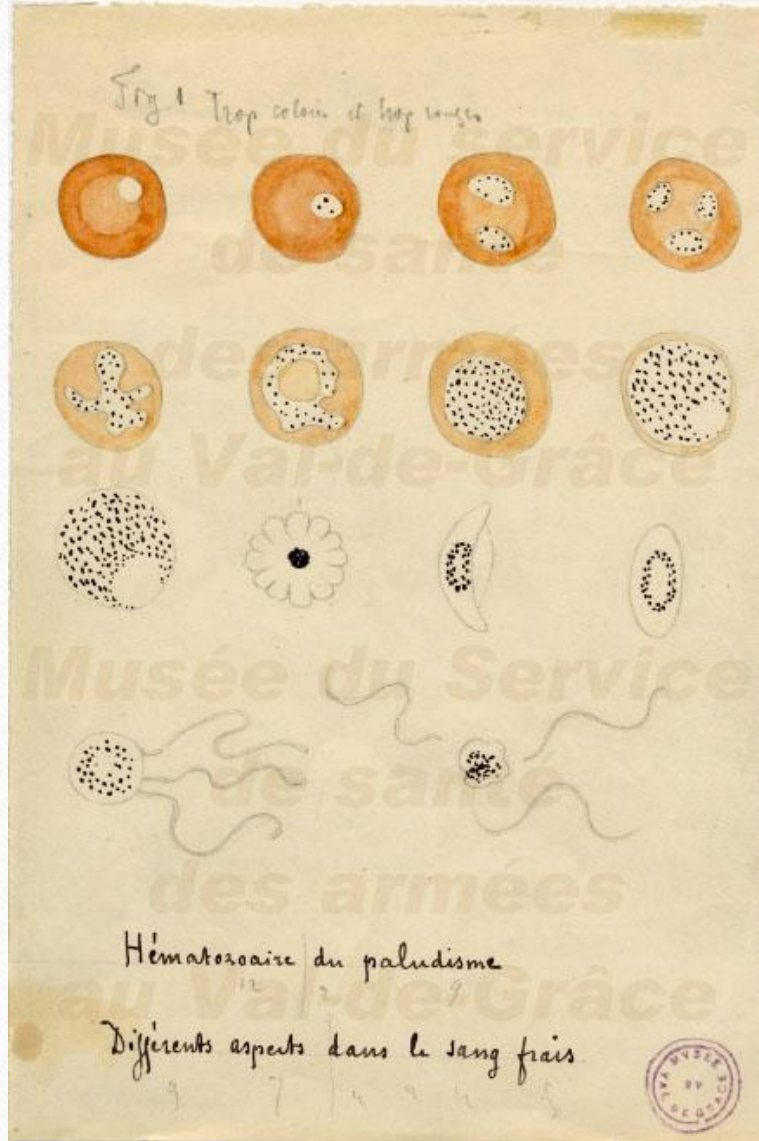
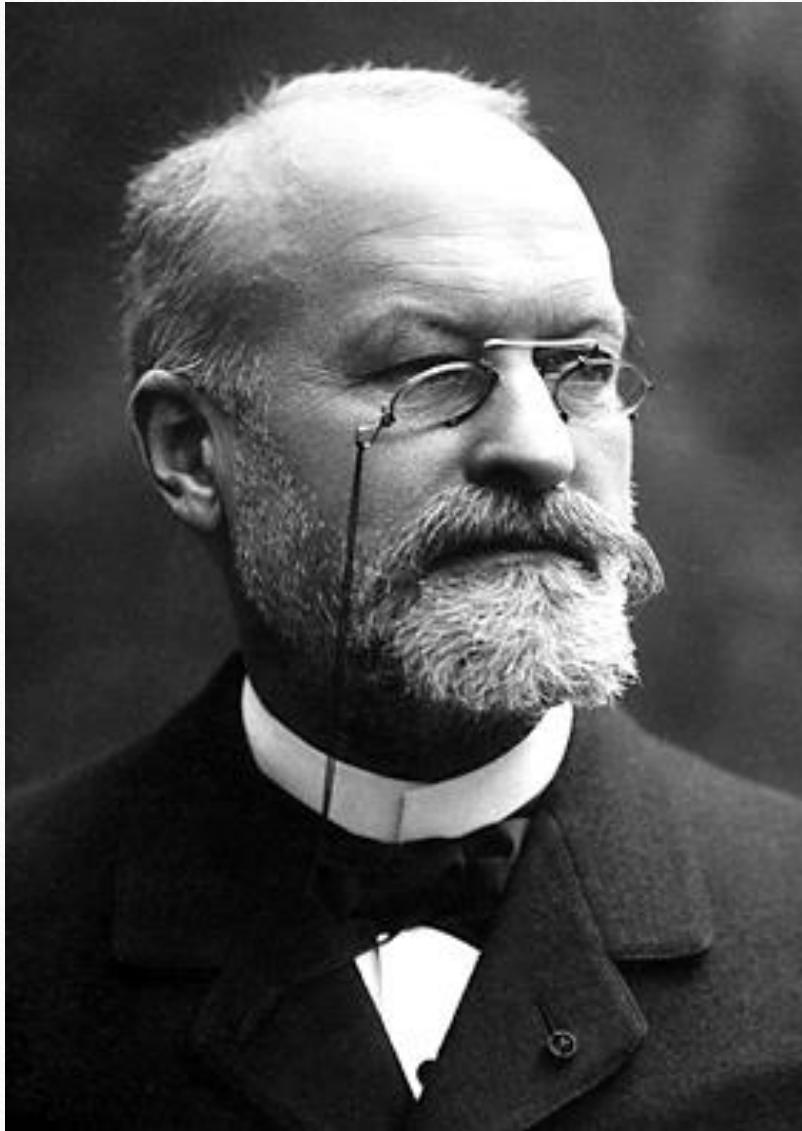
PGY4 Internal medicine/Pediatrics

Key Facts

- Malaria is a life-threatening disease caused by parasites that are transmitted to people through the bites of infected female mosquitoes.
- About 3.2 billion people – almost half of the world's population – are at risk of malaria.
- Young children, pregnant women and non-immune travelers from malaria-free areas are particularly vulnerable to the disease when they become infected.
- Sub-Saharan Africa carries a disproportionately high share of the global malaria burden. In 2015, the region was home to 89% of malaria cases and 91% of malaria deaths.

Trivial Facts

- Mal'aria is an Italian word which means bad air
- Gin and Tonic originated from treatment of malaria, British soldiers in India were treated with quinine mixed with water (Tonic) mixed with Gin.
- Four times, the Nobel Prize in Physiology or Medicine has been awarded for work associated with malaria: to Sir Ronald Ross (1902), Charles Louis Alphonse Laveran (1907), Julius Wagner-Jauregg (1927), and Paul Hermann Müller (1948).
- Two important currently used antimalarial drugs are derived from plants whose medicinal values had been noted for centuries: artemisinin from the Qinghaosu plant (*Artemisia annua*, China, 4th century) and quinine from the cinchona tree (*Cinchona* spp., South America, 17th century).



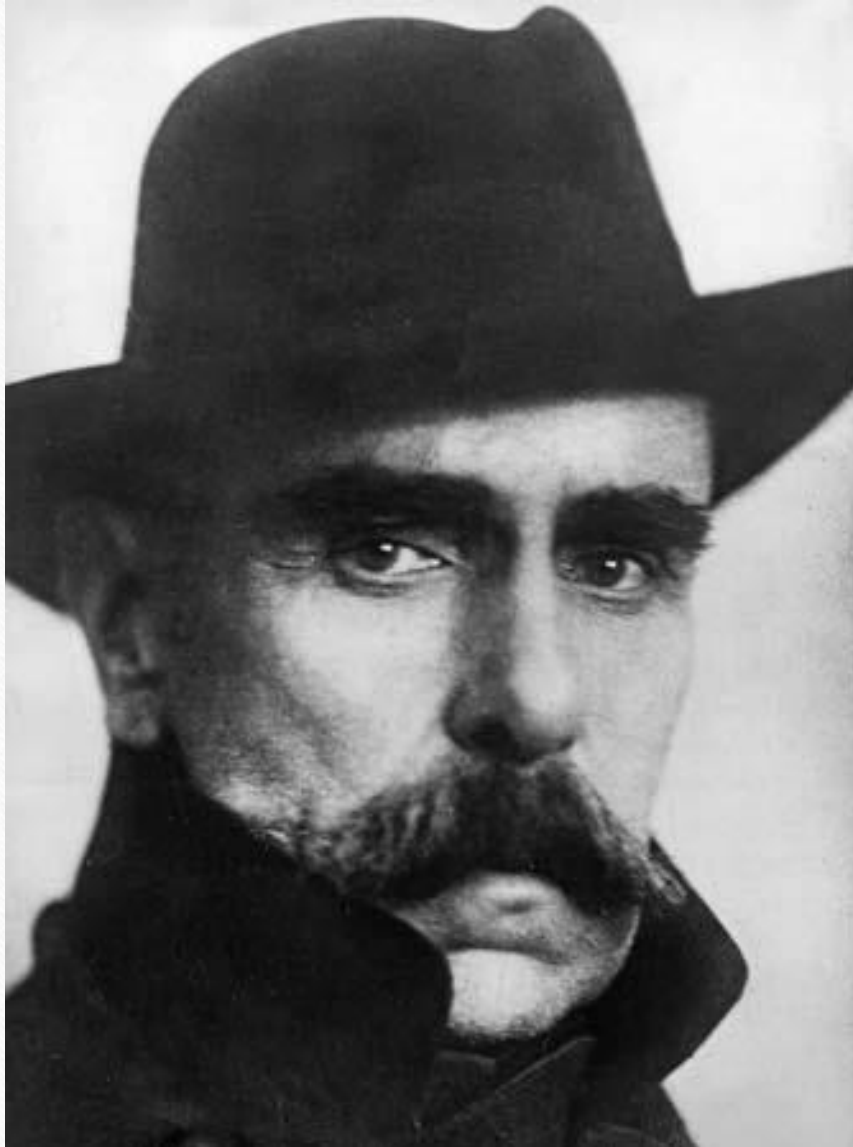
Dr. Alphonse Laveran

Won Nobel Prize in Physiology or Medicine in 1907 for his discoveries of parasitic protozoans as causative agents of infectious diseases such as malaria and trypanosomiasis



Sir Donald Ross

He was awarded the 1907 Nobel Prize for Physiology or Medicine for discovering that Mosquitos are vectors for Malaria.



Julius Wagner-Jauregg

Won the Nobel Prize in Physiology or Medicine in 1927. His Nobel award was "for his discovery of the therapeutic value of malaria inoculation in the treatment of dementia paralytica"



Paul Hermann Müller

He was awarded the Nobel prize in Physiology or Medicine in 1948 for his 1939 discovery of insecticidal qualities and use of DDT.

Transmission

- Malaria is transmitted by the bite of an infective female *Anopheles* mosquito.
- Because the malaria parasite is found in red blood cells of an infected person, malaria can also be transmitted through blood transfusion, organ transplant, or the shared use of needles or syringes contaminated with blood.
- Malaria may also be transmitted from a mother to her unborn infant before or during delivery ("congenital" malaria).

Disease Burden

- Between 2000 and 2015, malaria incidence fell by 37% globally; during the same period, malaria mortality rates decreased by 60%. An estimated 6.2 million malaria deaths have been averted globally since 2000.
- Sub-Saharan Africa continues to carry a disproportionately high share of the global malaria burden. In 2015, the region was home to 89% of malaria cases and 91% of malaria deaths.
- In areas with high transmission of malaria, children under 5 are particularly susceptible to infection, illness and death; more than two thirds (70%) of all malaria deaths occur in this age group. Between 2000 and 2015, the under-5 malaria death rate fell by 65% globally, translating into an estimated 5.9 million child lives saved.

Plasmodium

- Plasmodium Falciparum
- Plasmodium Vivax
- Plasmodium Ovale
- Plasmodium Malariae
- Plasmodium Knowlesi
 - Zoonotic Transmission



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The Deadliest Parasite: *Plasmodium Falciparum*

- > 90% of disease burden in sub-Saharan Africa
- Africa's leading cause of mortality (20%) in children age 0 to 5 years
- Main cause of clinical and severe malaria and death

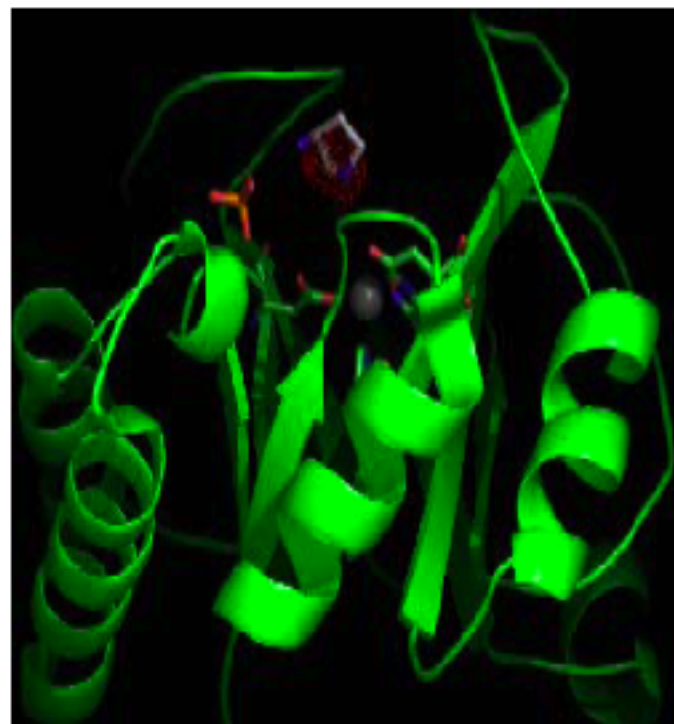
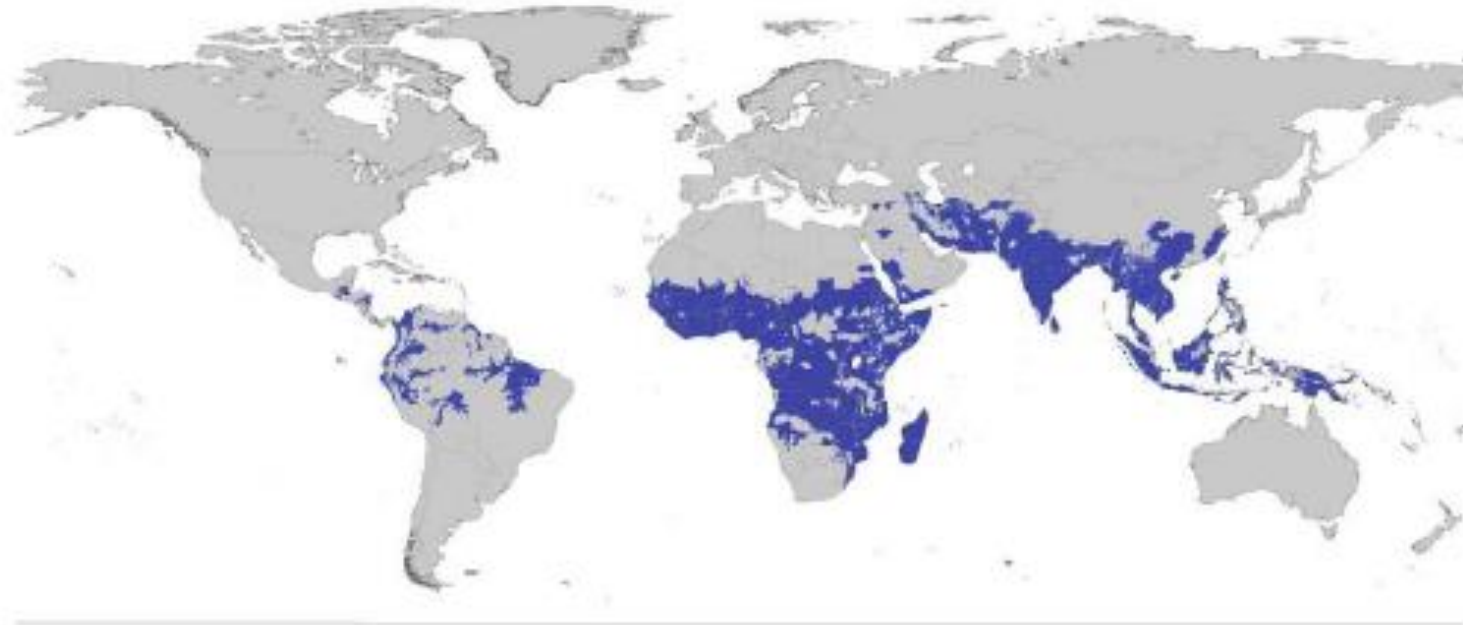


Image: *Plasmodium falciparum*
from Medical Structural Genomics
of Pathogenic Protozoa

Plasmodium Falciparum

- *P. falciparum* is the most prevalent malaria parasite on the African continent. It is responsible for most malaria-related deaths globally.
- It is the reason malaria why malaria is the number 3 cause of death from infectious disease in children under 5 year in Africa.
- Pregnant women have increased susceptibility to *P. falciparum* malaria; in malaria-endemic countries, *P. falciparum* contributes to 8-14% of low birth weight, which in turn decreases the chance of a baby's survival.

Distribution of Plasmodium falciparum



Plasmodium Vivax

- *P. vivax* has a wider geographical distribution than *P. falciparum* because it can develop in the *Anopheles* mosquito vector at lower temperatures, and can survive at higher altitudes and in cooler climates.
- It also has a dormant liver stage (known as a hypnozoite) that can activate months after an initial infection, causing a relapse of symptoms.
- Although *P. vivax* can occur throughout Africa, the risk of infection with this species is quite low there because of the absence in many African populations of the Duffy gene, which produces a protein necessary for *P. vivax* to invade red blood cells.
- *P. vivax* is estimated to have been responsible for 13.8 million malaria cases globally in 2015, and accounted for approximately half the total number of malaria cases outside Africa.
- More than 80% of *P. vivax* malaria cases are estimated to occur in three countries (Ethiopia, India and Pakistan).

Distribution Of Plasmodium vivax

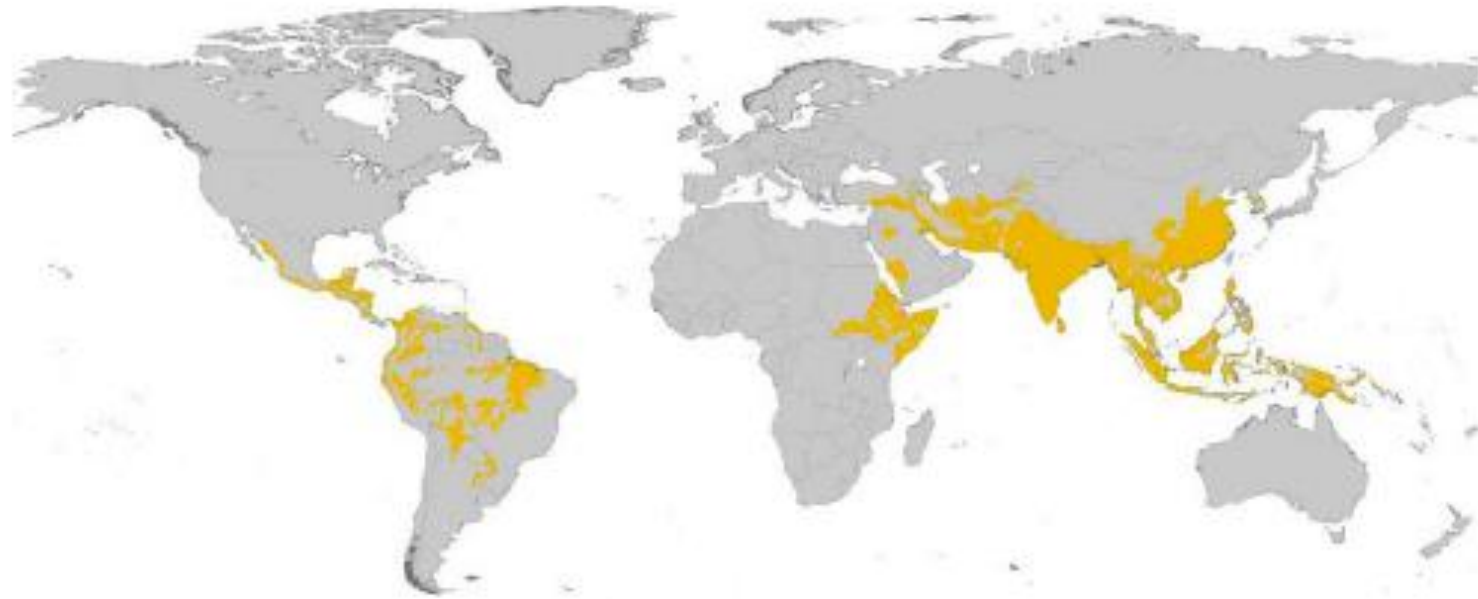


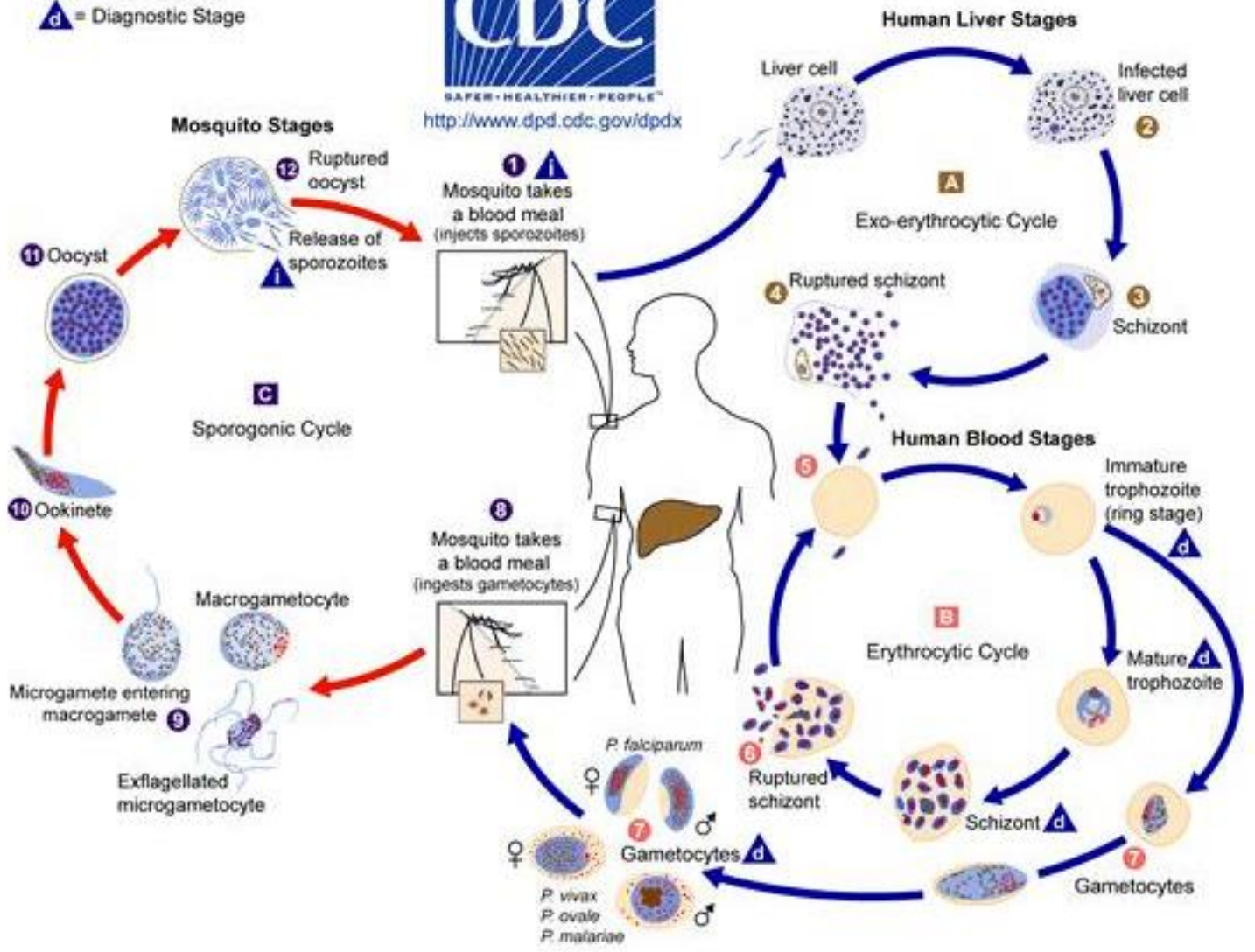
Table of differences between the various types of parasites that cause malaria

Plasmodium type	Type that causes malaria	Endemic area	Febrile seizures period	Involvement and severity
Falciparum	tropical malaria	In all endemic areas	Irregular Crisis	Very serious It can cause death if not treated quickly and effectively.
Vivax	tertian malaria	South America and Asia	Every 2 days	Grave, but with a delayed onset.
malariae	quartan malaria	South America and Asia	Every 3 days	Moderate, less frequently.
Ovale	tertian malaria	Africa	Every 2 days	Moderate, less frequently.
Knowlesi	It is mistaken with quartan malaria	Malaysia, Thailand and Cambodia	Every 24 hours	It can cause death if not treated quickly and effectively.

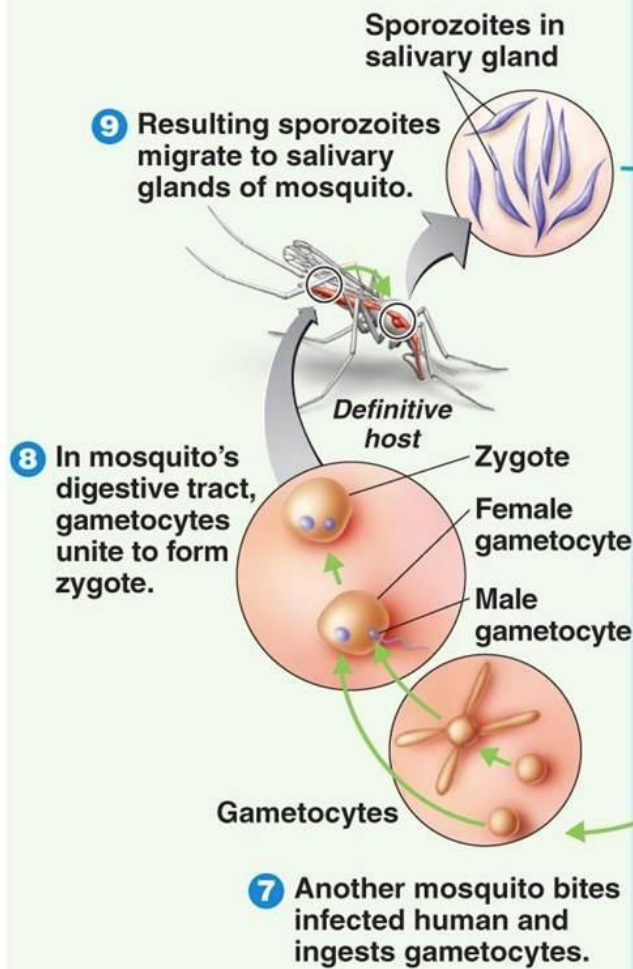
i = Infective Stage
d = Diagnostic Stage



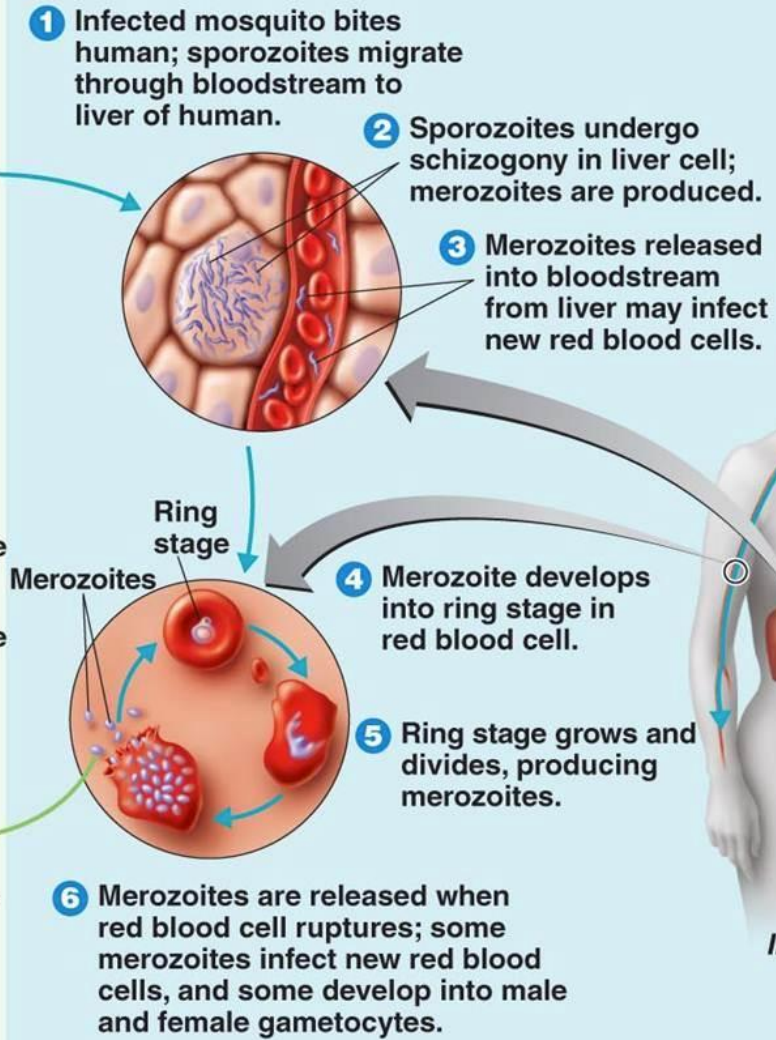
<http://www.dpd.cdc.gov/dpdx>

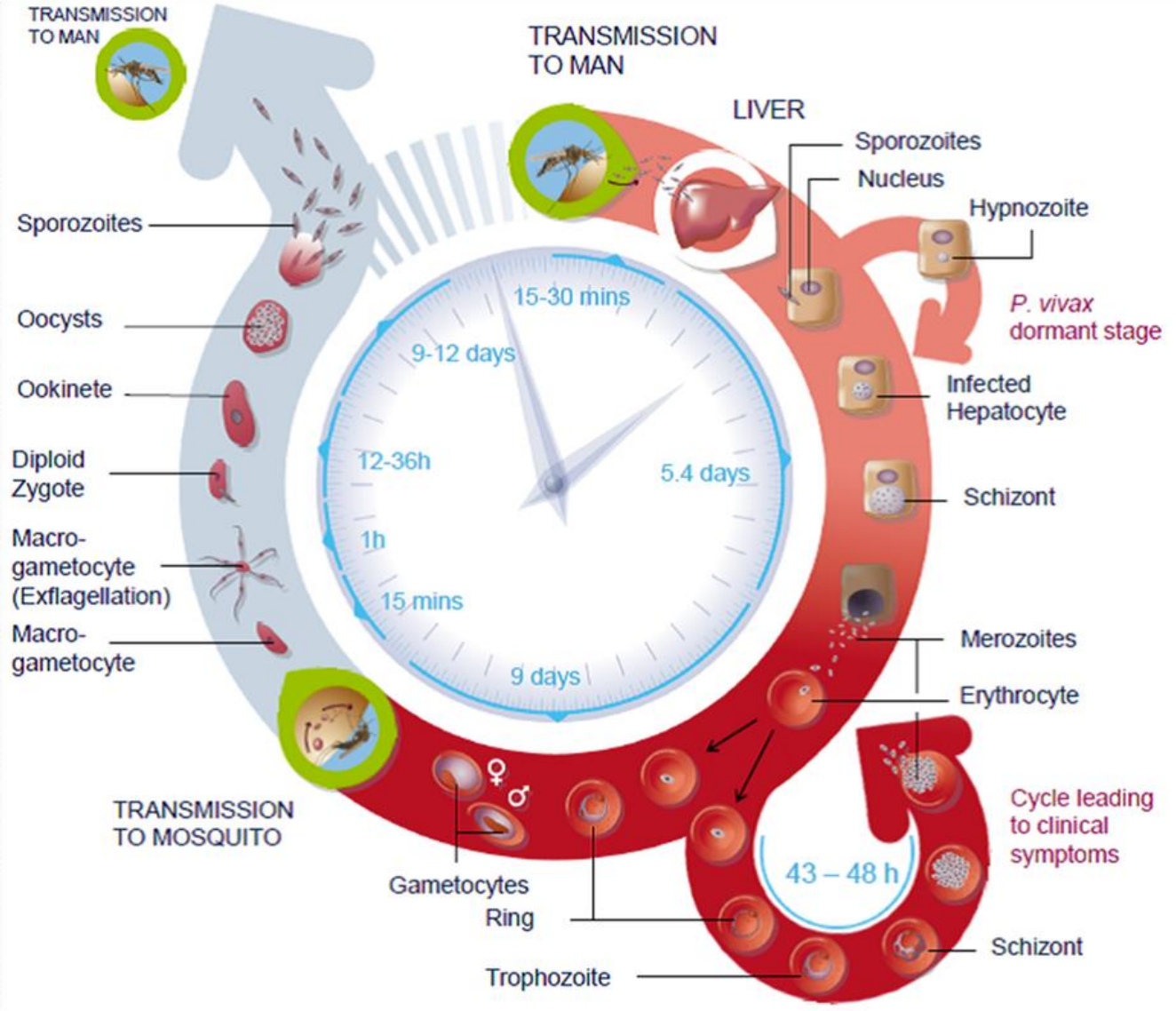


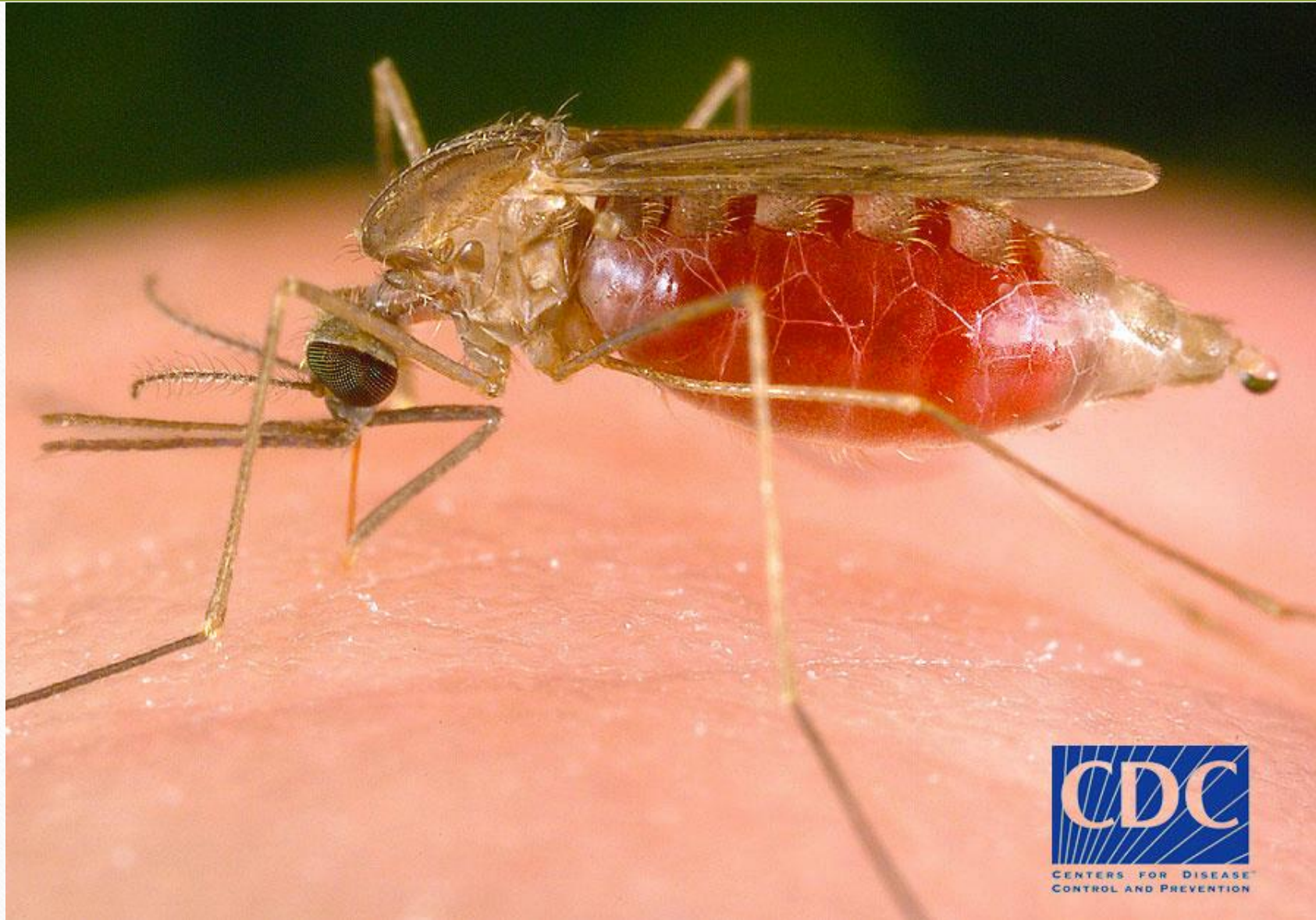
Sexual reproduction



Asexual reproduction







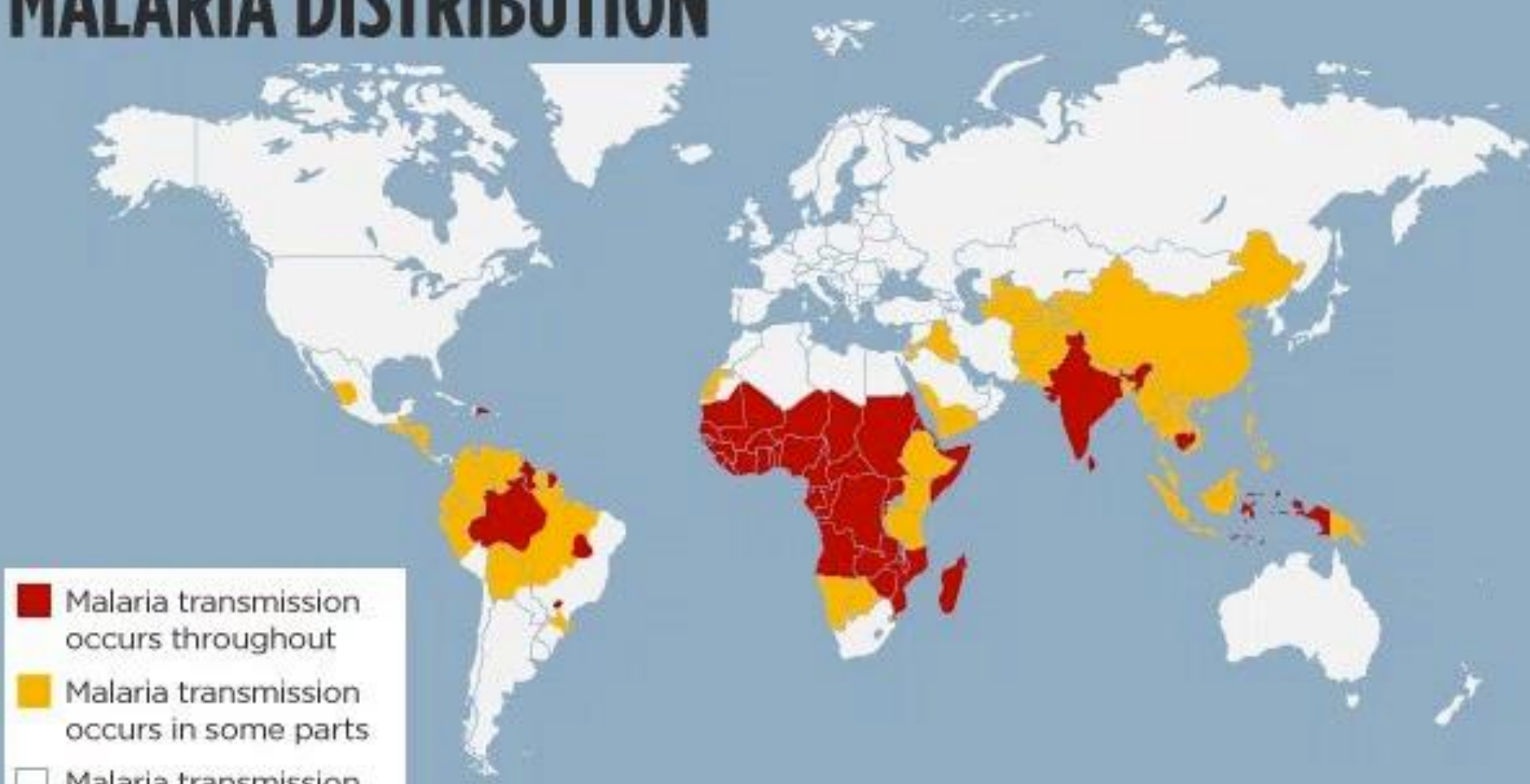


Anopheles

- | | | | |
|---------------------------|---|----------------------|-------------------|
| ○ No vector | ● funestus and arabiensis | ● melas | ● pulcherrimus |
| ● albimanus | ● funestus, arabiensis and gambiae s.s. | ● messeae | ● quadrimaculatus |
| ● annularis | ● funestus and gambiae s.s. | ● minimus | ● sacharovi |
| ● anthropophagus | ● gambiae s.s. | ● multicolor | ● sergentii |
| ● arabiensis | ● gambiae s.s. and funestus | ● nunez-tovari | ● sinensis |
| ● arabiensis and funestus | ● labranchiae | ● punctulatus group | ● stephensi |
| ● aquasalis | ● fluviatilis | ● pharoahensis | ● sundaicus |
| ● atroparvus | ● freeborni | ● pseudopunctipennis | ● superpictus |
| | ● barbirostris | | |
| | ● culicifacies | | |
| | ● dirus | | |
| | ● farauti | | |
| | ● flavirostris | | |
| | ● maculatus | | |
| | ● darlingi and marajoara | | |

MALARIA DISTRIBUTION

CNN



- Malaria transmission occurs throughout
- Malaria transmission occurs in some parts
- Malaria transmission is not known to occur

SOURCE: Centers for Disease Control

Mosquito

- In most cases, malaria is transmitted through the bites of female *Anopheles* mosquitoes. There are more than 400 different species of *Anopheles* mosquito; around 30 are malaria vectors of major importance. **All of the important vector species bite between dusk and dawn.** The intensity of transmission depends on factors related to the parasite, the vector, the human host, and the environment.
- Transmission is more intense in places where the mosquito lifespan is longer (so that the parasite has time to complete its development inside the mosquito) and where it prefers to bite humans rather than other animals. The long lifespan and strong human-biting habit of the African vector species is the main reason why nearly 90% of the world's malaria cases are in Africa.

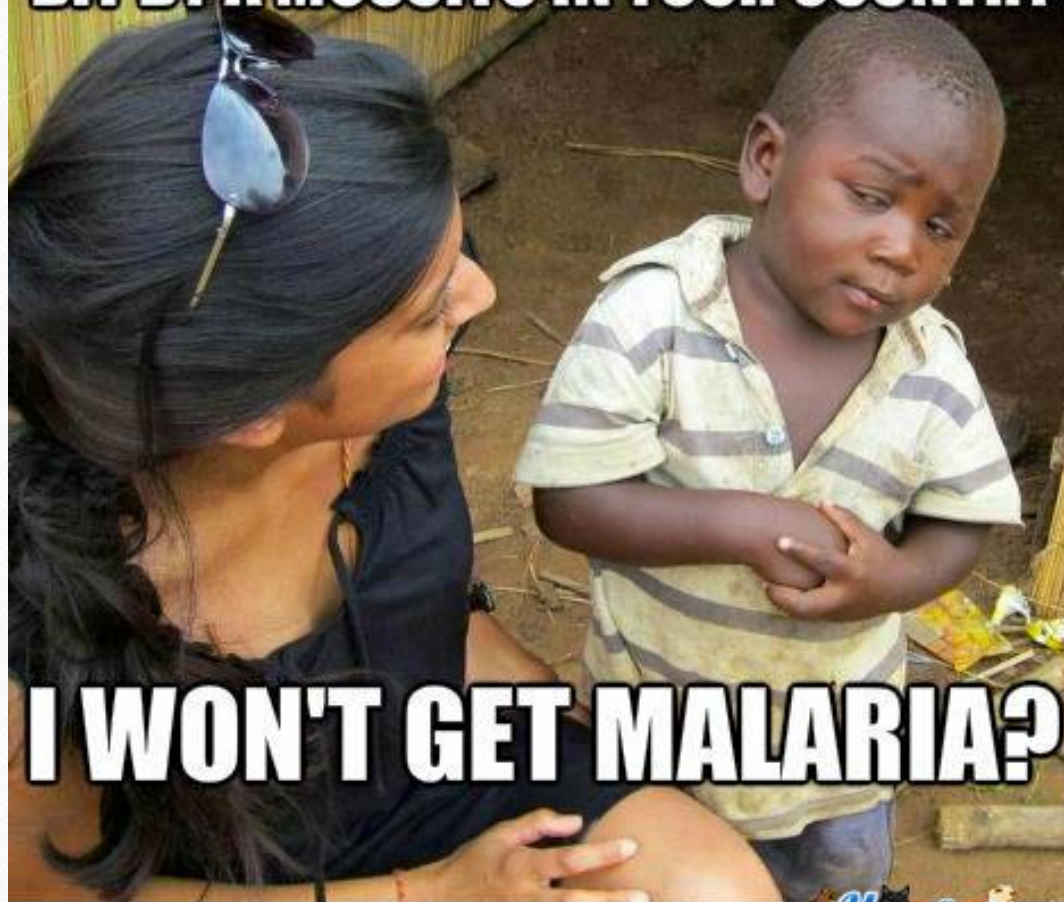
- One important behavioral factor is the degree to which an *Anopheles* species prefers to feed on humans (anthropophily) or animals such as cattle (zoophily).
- Anthropophilic *Anopheles* are more likely to transmit the malaria parasites from one person to another.
- Most *Anopheles* mosquitoes are not exclusively anthropophilic or zoophilic.
- However, the primary malaria vectors in Africa, *An. gambiae* and *An. funestus*, are strongly anthropophilic and, consequently, are two of the most efficient malaria vectors in the world.

- In many malaria-endemic countries, malaria transmission does not occur in all parts of the country. Even within tropical and subtropical areas, transmission will not occur
 - At very high altitudes
 - During colder seasons in some areas
 - In deserts (excluding the oases)
- Generally, in warmer regions closer to the equator
 - Transmission will be more intense
 - Malaria is transmitted year-round.
- The highest transmission is found in Africa South of the Sahara and in parts of Oceania such as Papua New Guinea.

Epidemiology

- 3.4 billion people live in areas at risk of malaria transmission in 106 countries and territories.
- In 2013 the WHO estimated that 198 million cases of malaria occurred worldwide and 500,000 people died, mostly children in the African Region.
- According to the latest WHO estimates, released in September 2015, there were 214 million cases of malaria in 2015 (range 149–303 million) and 438 000 deaths.
- Some 15 countries – mainly in sub-Saharan Africa – account for 80% of malaria cases and 78% deaths globally. Since 2000, the decline in malaria incidence in these 15 countries (32%) has lagged behind that of other countries globally (54%).

**YOU MEAN TO TELL ME THAT IF I GET
BIT BY A MOSUITO IN YOUR COUNTRY**



I WON'T GET MALARIA?

United States

- Malaria was endemic in the southern United States until the 19th and early 20th centuries, but it has since been eradicated.
- Approximately 1,500–2,000 cases of malaria are reported every year in the United States, almost all in recent travelers.
- Reported malaria cases reached a 40-year high of 1,925 in 2011.
- Almost all US cases of malaria are imported from patients traveling from endemic areas.
- In very rare cases, infections in individuals who have not traveled have occurred near airports (so-called airport malaria).
- Of the species of *Anopheles* mosquitoes found in the United States, the three species that were responsible for malaria transmission prior to elimination (*Anopheles quadrimaculatus* in the east, *An. freeborni* in the west, and *An. pseudopunctipennis* along the U.S./Mexico border) are still prevalent; thus there is a constant risk that malaria could be reintroduced in the United States.

Travelers

- 1500 imported cases of malaria reported annually in the United States
- almost two thirds of malaria infection in travelers are due to *P. falciparum* and almost one third are due to *P. vivax*; cases caused by *P. ovale* and *P. malariae* are uncommon.
- Imported *P. falciparum* malaria occurs almost exclusively in persons receiving no chemoprophylaxis or inadequate chemoprophylaxis.
- Most imported cases of malaria are not in tourists but in immigrants and their children who have returned to the country of their family's origin to visit friends and relatives (so-called VFR travelers) and have forgone chemoprophylaxis;
- Disease caused by *P. falciparum* in travelers most often occurs 9 to 14 days after an infectious bite, but it may occur up to months later, especially in patients who have received suboptimal prophylaxis
- Approximately 95% of cases of malaria occur within 30 days after a return from travel.
- Symptoms caused by the other three species of malaria may appear from 12 days to many months after infection, but these infections are rarely fatal.

Pregnancy

- Maternal complications are thought to be mediated by pregnancy associated decreases in immune function, as well as by placental sequestration of (P falciparum) parasites.
- Anemia from malaria can be more severe in pregnant women.
- Fetal complications include premature birth, anemia, low birth weight, and death.
- Malaria during the first trimester of pregnancy increases the risk for miscarriage. [

Immunity

- Human immunity is another important factor, especially among adults in areas of moderate or intense transmission conditions.
- Partial immunity is developed over years of exposure, and while it never provides complete protection, it does reduce the risk that malaria infection will cause severe disease.
- For this reason, most malaria deaths in Africa occur in young children, whereas in areas with less transmission and low immunity, all age groups are at risk.

Prevention

- Vector control is the main way to prevent and reduce malaria transmission. If coverage of vector control interventions within a specific area is high enough, then a measure of protection will be conferred across the community.



Prevention

- ITN (insecticide treated mosquito)
- Indoor residual spraying
- IPTp (Intermittent Preventive Treatment in pregnancy)
 - sulphadoxine-pyrimethamine (SP)
- Larval Control

RESISTANCE IS MOBILE

The majority of countries with ongoing malaria transmission now report mosquitoes resistant to one or more classes of insecticide.

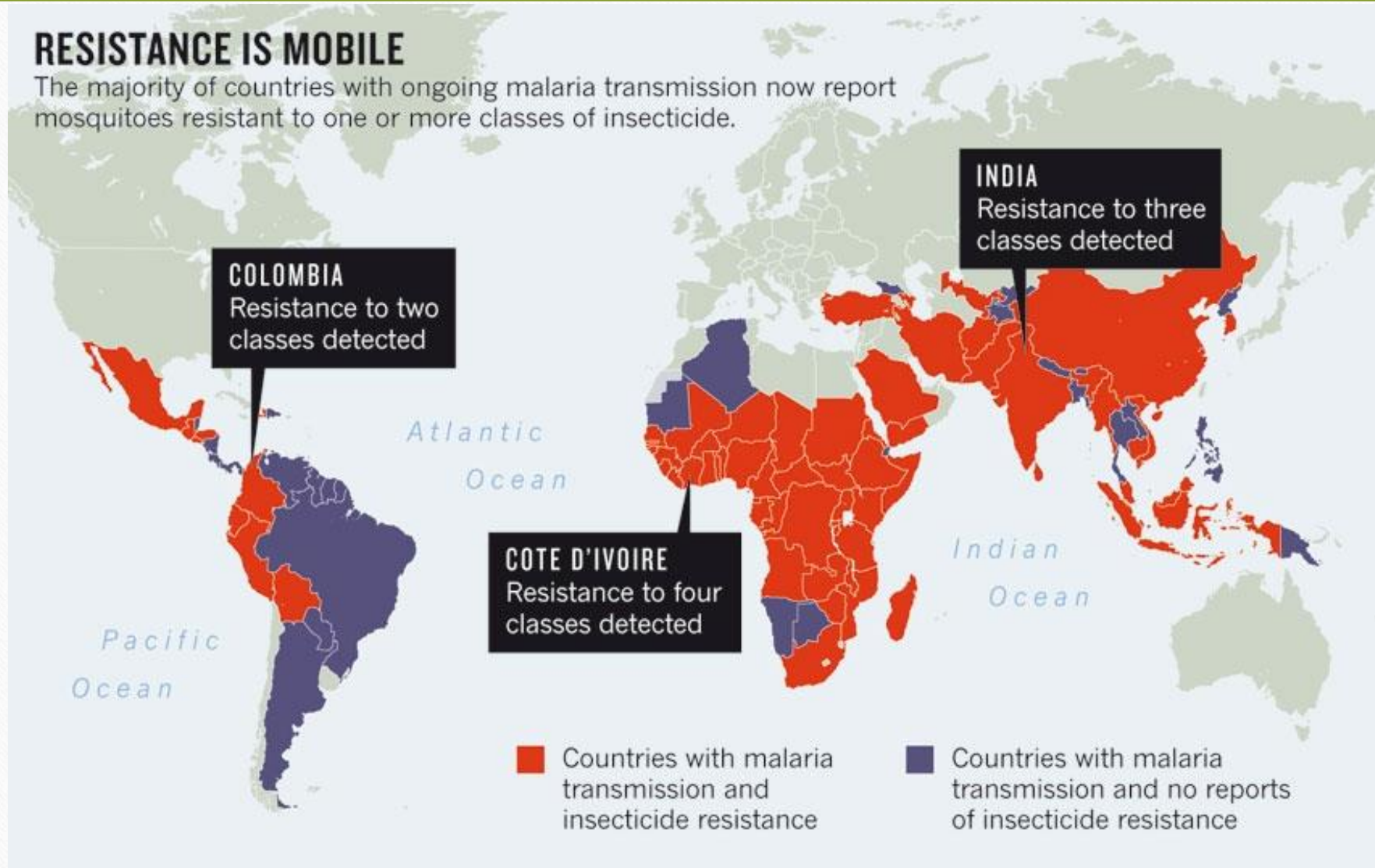
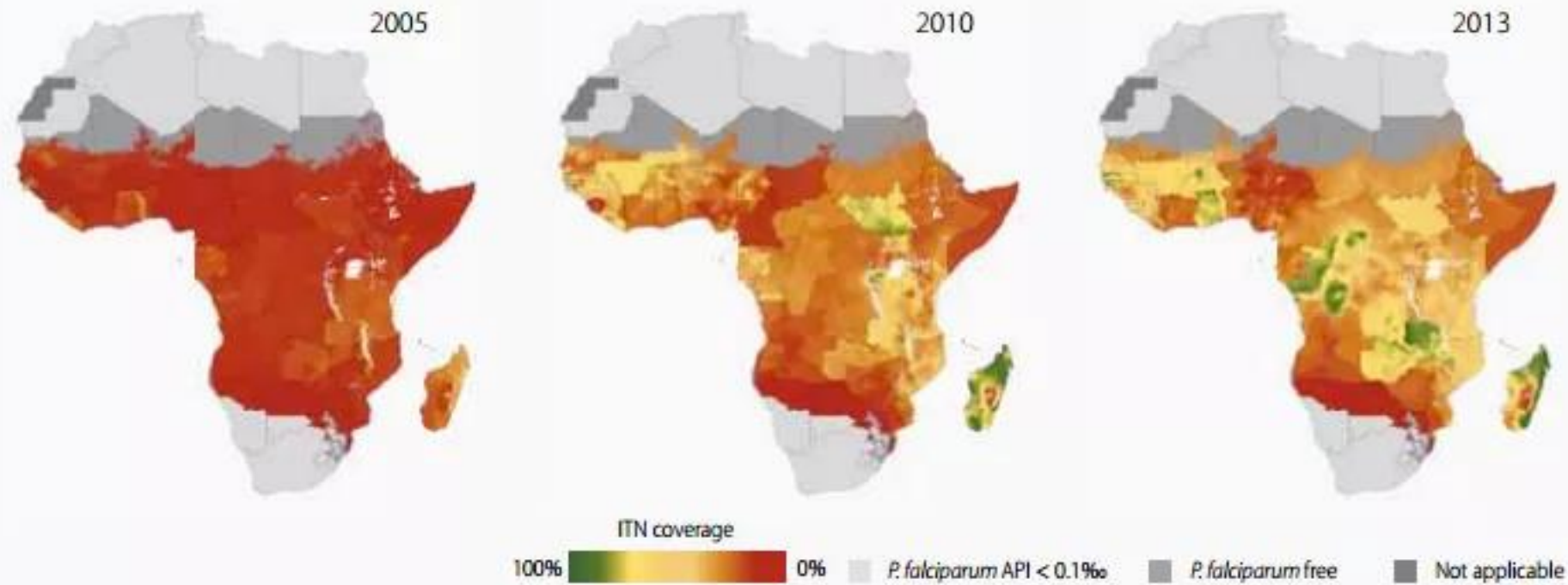


Figure 3.2 Proportion of population sleeping under an ITN, sub-Saharan Africa



Vaccine

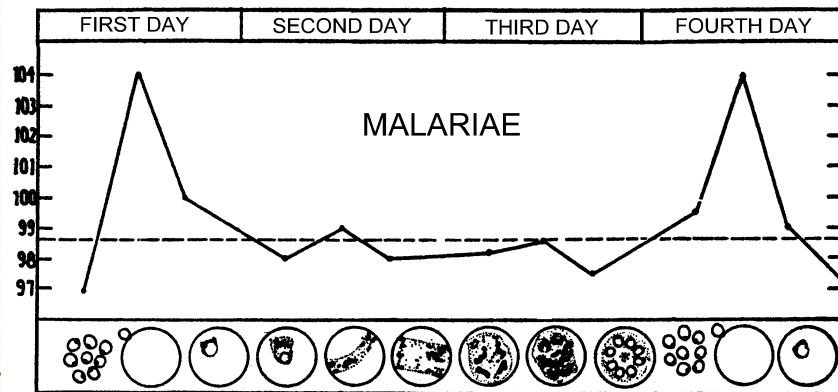
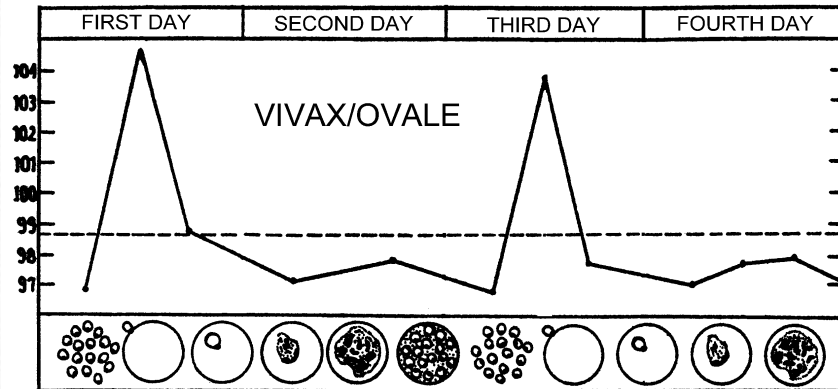
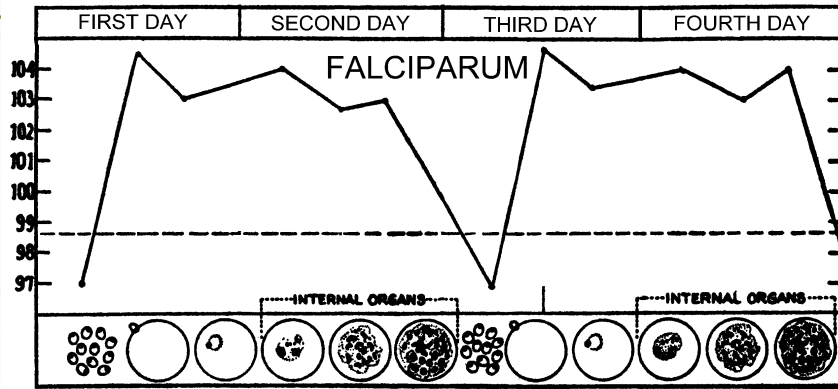
- In 2015, European Union (EU) regulators approved the world's first malaria vaccine for use outside the EU among children aged 6 weeks to 17 months.
- The new vaccine (Mosquirix, GlaxoSmithKline Biologicals), which includes a vaccine for hepatitis B, is awaiting review by the World Health Organization (WHO)
- The earliest any malaria-endemic country could license the product is 2017, according to WHO.

Symptoms

- Headache (noted in virtually all patients with malaria)
- Cough
- Fatigue
- Malaise
- Shaking chills
- Arthralgia
- Myalgia
- Paroxysm of fever, shaking chills, and sweats (every 48 or 72 hours, depending on species)

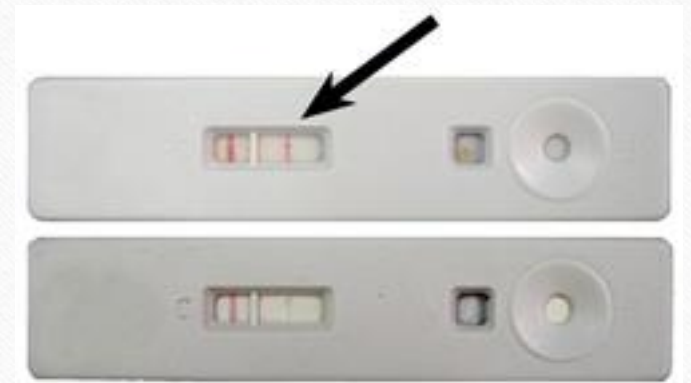
Symptoms

- Less common symptoms include the following:
- Anorexia and lethargy
- Nausea and vomiting
- Diarrhea
- Jaundice



Diagnosis

- Blood smear
 - Thick and Thin smears
- Rapid Diagnostic Test(RDT)
- PCR
- Serology (IFA or ELISA)



Treatment

- Chloroquine is the drug of choice for acute malaria caused by sensitive strains. Chloroquine kills the merozoites, thereby reducing the parasitemia, but does not affect the hypnozoites of *P. vivax* and *P. ovale* in the liver. These are killed by primaquine, which must be used to prevent relapses.
- *P. vivax* and *P. ovale* can relapse due to hypnozoites that remain dormant in the liver. To eradicate the hypnozoites, patients should be treated with a 14-day course of primaquine phosphate.
- Chloroquine (or hydroxychloroquine) remains an effective choice for all *P. vivax* and *P. ovale* infections except for *P. vivax* infections acquired in Papua New Guinea or Indonesia.

Treatment

- For *P. falciparum* infections acquired in areas without chloroquine-resistant strains, which include:
 - Central America west of the Panama Canal,
 - Haiti,
 - the Dominican Republic,
 - and most of the Middle East
- patients in these areas can be treated with oral chloroquine.

Treatment

- For *P. falciparum* infections acquired in areas with chloroquine resistance, four treatment options are available.
 - Atovaquone-proguanil (Malarone)
 - Artemether-lumefantrine (Coartem)
 - Quinine sulfate plus doxycycline, tetracycline, or clindamycin
 - Mefloquine, is associated with rare but potentially severe neuropsychiatric reactions when used at treatment doses.
- Quinine treatment should continue for 7 days for infections acquired in Southeast Asia and for 3 days for infections acquired in Africa or South America.

Complications

- **Cerebral Malaria**-Most common cause of death with malaria (Even with treatment, 15% of children and 20% of adults who develop cerebral malaria die.)
- Seizures - Secondary to either hypoglycemia or cerebral malaria
- Renal failure - As many as 30% of non immune adults infected with *P falciparum* suffer acute renal failure
- Hypoglycemia
- Hemoglobinuria (blackwater fever) - Blackwater fever is the passage of dark urine, described as Madeira wine colored; hemolysis, hemoglobinemia, and the subsequent hemoglobinuria and hemozoinuria cause this condition



URINE
NORMAL PATIENT DILUTED

Complications

- **Non cardiogenic pulmonary edema** - This affliction is most common in pregnant women and results in death in 80% of patients
- Profound hypoglycemia - Hypoglycemia often occurs in young children and pregnant women; it often is difficult to diagnose because adrenergic signs are not always present and because stupor already may have occurred in the patient
- Lactic acidosis - This occurs when the microvasculature becomes clogged with *P falciparum*; if the venous lactate level reaches 45 mg/dL, a poor prognosis is very likely
- Hemolysis resulting in severe anemia and jaundice
- Bleeding (coagulopathy)

Natural Selection

- sickle cell trait (hemoglobin S)
 - sickle cell trait being relatively more protective
- Thalassemias
- Hemoglobin C
- glucose-6-phosphate dehydrogenase (G-6-PD)
- Hemoglobin E may be protective against *P vivax* infection
- Absence of Duffy gene protective against *P vivax*
- Heterozygotic for RBC band 3 ovalocytosis are at reduced risk of infection with *P falciparum*, *P knowlesi*, and, especially, *P vivax* malaria.
- Persons living in areas of malaria endemicity may develop partial immunity to infection with time and repeated exposure.

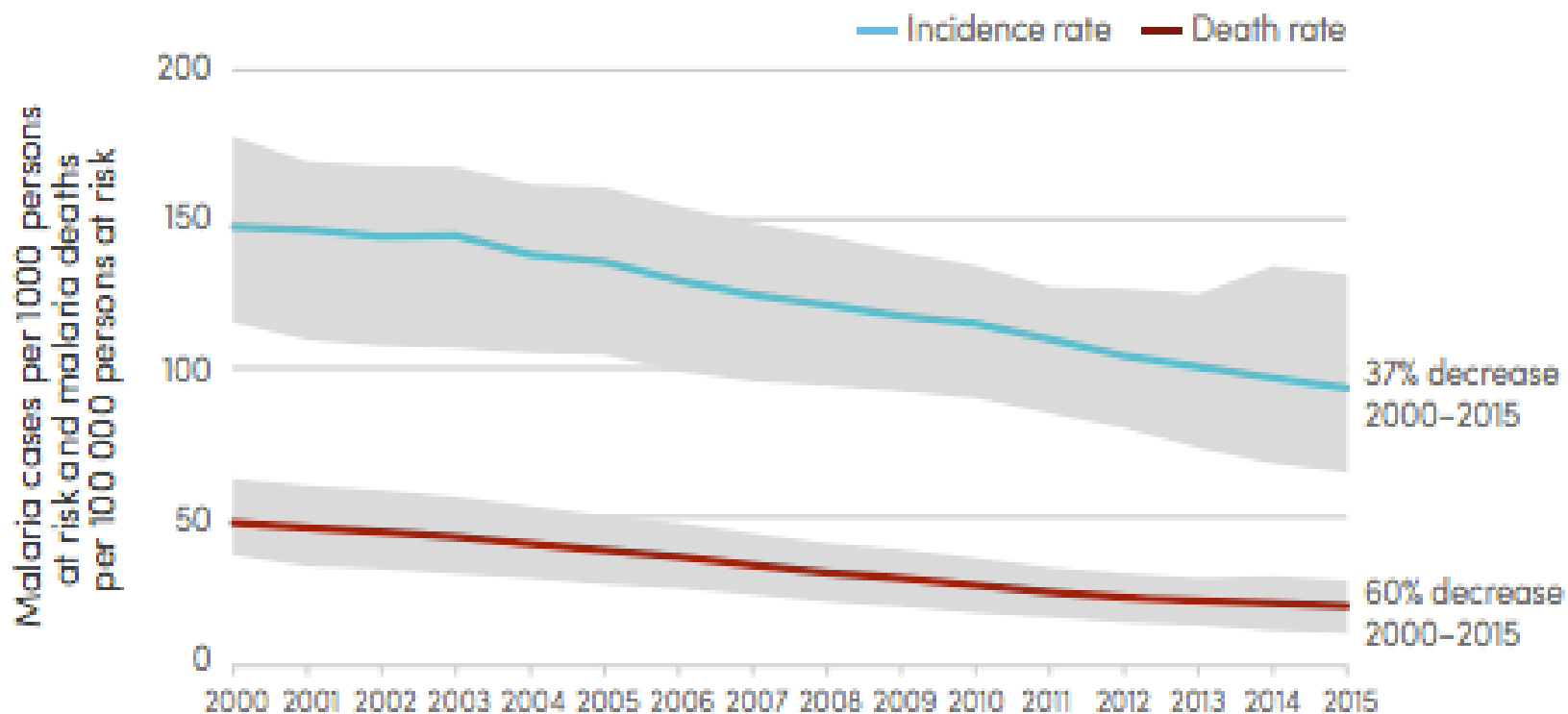
Some Good News

- The malaria-specific target of the Millennium Development Goals (target C) called for “halting and beginning to reverse the global incidence of malaria by 2015.” This target has been achieved, with a 37% global decline in malaria incidence since 2000.
- In 2005, the World Health Assembly called for a 75% reduction in the global burden of malaria by 2015. Fifty-seven countries with malaria transmission in 2000 reduced their malaria cases by 75% by 2015, in line with this target.

Some Good News

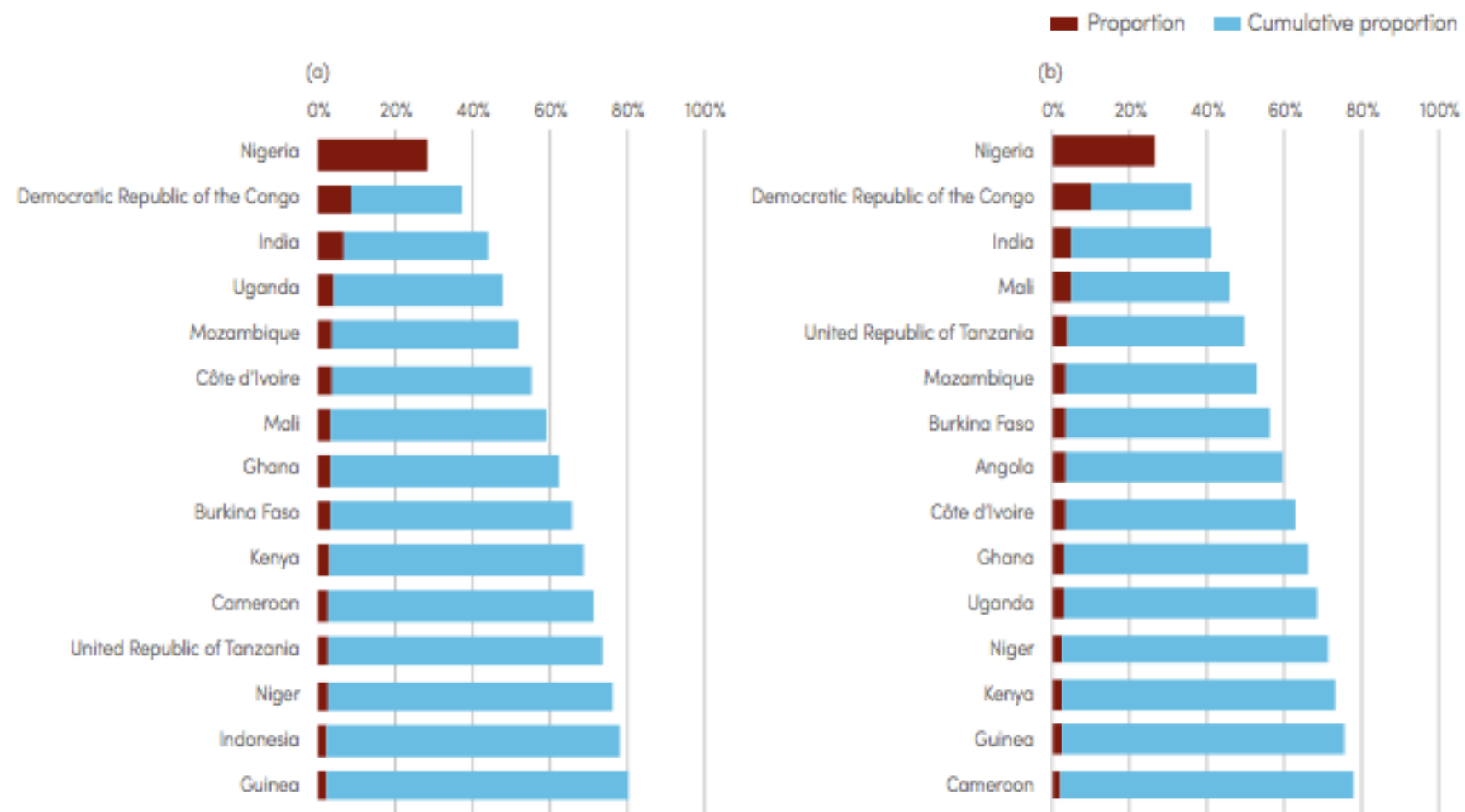
- Between 2000 and 2015, malaria incidence (the rate of new cases) fell by 37% globally. In that same period, malaria death rates fell by 60% globally among all age groups, and by 65% among children under 5.
- Since 2000, the malaria mortality rate declined by 85% in the South-East Asia Region, by 72% in the Region of the Americas, by 65% in the Western Pacific Region, and by 64% in the Eastern Mediterranean Region.
- For the first time, the European Region reported zero indigenous cases of malaria in 2015.
- Between 2000 and 2015, the mortality rate among children under five fell by 65% worldwide and by 71% in Africa.

Figure 2.1 Estimated malaria case incidence and death rate globally, 2000–2015



Source: WHO estimates

Figure 5.1 Estimated proportion, and cumulative proportion, of the global number of (a) malaria cases and (b) malaria deaths in 2015 for countries accounting for the highest share of the malaria disease burden



Source: WHO estimates

