Foundational Malaria Knowledge

MACEPA Data Fellowship - Training Materials

Table of contents

Introduction

Welcome to the "Foundational Malaria Knowledge" module of the PATH Malaria Data Fellowship Program. This module is designed to provide you with a comprehensive understanding of malaria, including its biology, epidemiology, transmission, diagnosis, treatment, and prevention strategies. You will explore the global impact of malaria, learn about the critical role of data in controlling the disease, and discover the latest advancements and challenges in the fight against malaria. By the end of this module, you will have the foundational knowledge necessary to contribute effectively to malaria control and eradication efforts.

These lessons contain materials developed by the MACEPA Data and Analytics teams, as well as external resources (links/citations have been included). Any data used in the tutorial will be public data and may have been adjusted from its source in order to be shared.

Schedule

As a reminder, this module is self-directed learning through a set of chapters in this book.

Module Objectives

- Understand the basic biology of malaria and the malaria parasite.
- Learn about the epidemiology and global impact of malaria.
- Gain insights into malaria transmission, life cycle, and vectors.
- Explore malaria diagnosis, treatment, and prevention strategies.
- Recognize the importance of surveillance, data collection, and analysis in malaria control efforts.

Part I

Introduction to Malaria

This topic serves as an entry point into the module, providing a brief understanding of malaria, its history, and its global impact. Topics brought to light here will be discussed in further detail during this module.

Learning Objectives

- Describe the historical context of malaria.
- Understand the global and regional burden of malaria.
- Identify key populations at risk and the geographical distribution of malaria.
- Appreciate the economic, social, and health impacts of malaria on affected communities.

1 Brief History of Malaria

1.1 Early References and Discoveries

Malaria is an ancient disease, with its presence documented as far back as 2700 BCE in Chinese medical writings. The term "malaria" itself originates from the Italian words "mala" "aria," meaning "bad air," a reflection of the ancient belief that the disease was caused by foul air emanating from marshes and swamps.

Throughout history, malaria has been a significant burden on many civilizations. Ancient Greeks, including Hippocrates, noted the periodic fevers associated with the disease. Roman scholars also wrote extensively about malaria, describing its symptoms and the environmental conditions conducive to its spread.

1.2 Discovery of the parasite

The turning point in understanding malaria came in 1880 when Charles Louis Alphonse Laveran, a French army surgeon, discovered the malaria parasite, Plasmodium, while working in Algeria. This groundbreaking discovery earned Laveran the Nobel Prize in Physiology or Medicine in 1907[1].

Laveran's work laid the foundation for further research, leading to the identification of different Plasmodium species responsible for malaria in humans: *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and later, *P. knowlesi*.

Ronald Ross in 1898 showed that malaria was transmitted from infected mosquitos when they bite humans, this discovery changed the perception of the disease from the previous thinking that it was spread from the foul air of decaying organic matter.

These two findings that describe the biological basis of the disease and its transmission were made just under 150 years ago. And at that time malaria was present in almost every country across the Globe (Figure 6.1). Researchers estimate that up to around 1900 human populations were at risk from malaria across about half of the world's land surface (53%)[2].

[1] Alphonse Laveran – Facts. NobelPrize.org. Nobel Prize Outreach AB 2024. Mon. 5 Aug 2024. https://www.nobelprize.org/prizes/medicine/1907/laveran/facts/

[2] Hay SI, Guerra CA, Tatem AJ, Noor AM, Snow RW. The global distribution and population at risk of malaria: past, present, and future. Lancet Infect Dis. 2004 Jun;4(6):327-36. doi: 10.1016/S1473-3099(04)01043-6

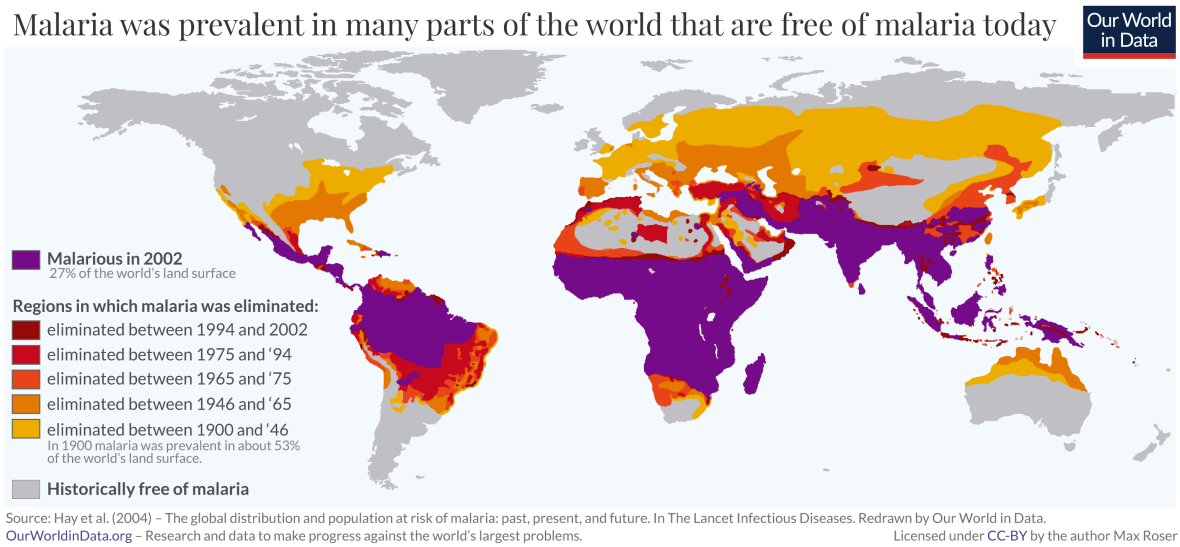

Figure 1.1: Source: Our World in Data https://ourworldindata.org/malaria-past-prevalence

1.3 Malaria and human populations

Since 1900 the malaria map has shrunk, confined to the tropics now, with much of Europe, North America, East Asia, Australia, parts of the Caribbean, South America and Africa having eliminated the disease.

The discovery of quinine in the bark of the cinchona tree in the 17th century became the first treatment against malaria and eventually led to the advent of the anti-malarial drug Chloroquine during World War II. In the 20th century, the advent of DDT spraying and the establishment of the World Health Organization's (WHO) Global Malaria Eradication Program in 1955 marked significant milestones, although the program was discontinued in 1969 due to various challenges and financial and political will for the cause diminishing. The initial aim of eradication was replaced with longer-term control strategies and improvements in disease management.

The late 20th and early 21st centuries have seen significant advances in malaria research and control. The development of artemisinin-based combination therapies (ACTs), the introduction of insecticide-treated nets (ITNs) and indoor residual spraying (IRS) have drastically reduced malaria transmission in many regions. In recent years, the focus has shifted towards innovative strategies, including the development of malaria vaccines. The RTS,S/AS01 vaccine, endorsed by the WHO in 2021, and the R21 vaccine endorsed this past year.

Despite these advances malaria still remains a significant burden on the worlds population and we shall explore this more in the coming topics.

2 Overview of Malaria's Global Impact

2.1 Current Statistics

Malaria remains a major public health challenge, particularly in tropical and subtropical regions. According to the World Health Organization (WHO), there were an estimated 249 million malaria cases worldwide in 2022, with approximately 608,000 deaths. Sub-Saharan Africa bears the brunt of the malaria burden, accounting for about 94% of all malaria cases and 95% of malaria deaths. Children under five years old are the most vulnerable, representing around 80% of all malaria deaths in this region.[1]

2.2 Economic Burden

The economic impact of malaria is thought to be profound, but hard to quantify. Malaria sickness affects both individuals and national economies. Households incur costs related to healthcare, lost workdays, and decreased productivity due to illness or death. At the national level, malaria can hinder economic growth by affecting workforce productivity and increasing healthcare expenditures. In highly endemic areas, malaria can slow economic development and perpetuate cycles of poverty.

For example, it was estimated that malaria costs African countries over $12 billion annually in lost productivity, and slows economic growth in the region by 1.3% a year.[2] The disease affects school attendance and performance, limiting educational opportunities and future economic prospects for children in affected regions.

2.3 Social and Health Impacts

Malaria has far-reaching social and health consequences. It disproportionately affects the most vulnerable populations, including pregnant women and young children. Pregnant women with

[1] WHO World Malaria Report 2023 https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2023

[2] Bartram J, Lewis K, Lenton R, Wright A. Focusing on improved water and sanitation for health. The Lancet. 2005 Feb 26;365(9461):810-2. https://doi.org/10.1016/S0140-6736(05)17991-4

malaria face increased risks of anemia, miscarriage, stillbirth, and low birth weight, which can lead to infant mortality and long-term developmental issues for surviving children.

The disease also strains healthcare systems, leading to overcrowded facilities and limited resources for other health conditions. In regions with high malaria transmission, malaria can have psychological impacts on communities, contributing to anxiety and stress, mild cognitive impairement and other neurological impacts.[3]

[3]Nandish P, BM S, N SN, Shankar G, Tripathi PK, Kashyap H, Jain A, Anvikar A, Chalageri VH. Exploring the hidden mental health consequences of malaria beyond the fever. Frontiers in Human Neuroscience. 2024 Jul 18;18:1432441. https://doi.org/10.3389/fnhum.2024.1432441

3 Malaria Endemic Regions

3.1 Geographical distribution

Malaria remains endemic in over 85 countries and territories, with the highest transmission occurring in Sub-Saharan Africa, Southeast Asia, the Eastern Mediterranean, and parts of the Western Pacific and the Americas. In these regions, climatic conditions such as temperature, humidity, and rainfall create favorable environments for the Anopheles mosquitoes that transmit malaria.

Interactive maps, such as those provided by the Malaria Atlas Project, can visually depict the distribution of malaria cases and highlight regions with the highest burden.

3.2 High-Risk Populations

Certain populations are at higher risk of contracting malaria. These include:

- **Children under five years old**: Due to their developing immune systems, young children are particularly susceptible to severe malaria and death.
- **Pregnant women**: Pregnancy reduces a woman's immunity to malaria, increasing the risk of severe illness, maternal death, and adverse pregnancy outcomes.
- **Travelers and migrants**: Individuals traveling to or migrating from non-endemic to endemic areas may lack immunity, putting them at greater risk of severe malaria.
- **People living in poverty**: Limited access to healthcare, preventive measures, and information increases the vulnerability of impoverished communities to malaria.

3.3 Seasonality and Environmental Factors

Malaria transmission varies seasonally, with peaks often corresponding to rainy seasons when mosquito breeding conditions are optimal. Environmental factors such as standing water, vegetation, and climate changes can influence mosquito populations and malaria transmission dynamics.

For instance, in Sub-Saharan Africa, malaria transmission intensifies during and after the rainy season, while in some parts of Asia and Latin America, transmission can occur year-round but peaks during specific months.

3.4 Global Statistics

Each year the World Malaria Report published by the WHO provides a comprehensive and up-to-date assessment of trends in malaria control and elimination across the globe.

According to the 2023 World Malaria Report Globally in 2022, there were an estimated 249 million malaria cases in 85 malaria endemic countries and areas, an increase of 5 million cases compared with 2021. The main countries contributing to the increase were Pakistan (+2.1 million), Ethiopia (+1.3 million), Nigeria (+1.3 million), Uganda (+597 000) and Papua New Guinea (+423 000). In 2015, the baseline year of the Global technical strategy for malaria 2016–2030 (GTS), there were an estimated 231 million malaria cases.

Malaria case incidence declined from 81 per 1000 population at risk in 2000 to 57 in 2019. Following a small increase of 3% in 2020, incidence rates have remained stable over the past 3 years. In 2022, malaria case incidence was 58 per 1000 population at risk.

Twenty-nine countries accounted for 95% of malaria cases globally. Globally the WHO Africa Region carries a disproportionately high burden of malaria and inndefined and four countries – Nigeria (27%), the Democratic Republic of the Congo (12%), Uganda (5%) and Mozambique (4%) – accounted for almost half of all cases globally and The WHO African Region, with an estimated 233 million cases in 2022, accounted for about 94% of cases globally.

Children under five years of age are particularly vulnerable to malaria and around 77% of global malaria deaths occurred in this age group, predominantly in SSA. About 96% of malaria deaths globally were in 29 countries. Four countries accounted for just over half of all malaria deaths globally in 2022 – Nigeria (31%), the Democratic Republic of the Congo (12%), Niger (6%) and the United Republic of Tanzania (4%).

Part II

The Biology of Malaria

This topic delves into the biology of malaria, providing a detailed understanding of the various Plasmodium species that cause malaria in humans. We will explore the complex life cycle of the parasite, its interaction with human and mosquito hosts, and the biological mechanisms that underlie malaria infection. This foundational knowledge is critical for understanding the disease's transmission, pathology, and the development of effective interventions.

Learning Objectives

- Identify the different Plasmodium species that cause malaria in humans and understand their geographical distribution.
- Explain the life cycle of the malaria parasite, highlighting the stages within the human and mosquito hosts.
- Understand the role of mosquito hosts in malaria transmission.
- Understand the development of naturally acquired immunity to malaria parasites.

4 Plasmodium species

4.1 Species

Malaria is caused by the protozoan parasite Plasmodium of which there are five species that infect humans: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale*, and *Plasmodium knowlesi*. Each species has unique characteristics that influence the course and severity of the disease, as well as its geographical distribution.

- *Plasmodium falciparum* is the most deadly and widespread species, responsible for the majority of malaria-related deaths, particularly in Sub-Saharan Africa. It is known for causing severe malaria, including cerebral malaria, which can be fatal if not promptly treated.
- *Plasmodium vivax* is the most widespread species outside of Sub-Saharan Africa, particularly in Asia and Latin America. While generally less lethal than *P. falciparum*, *P. vivax* can cause severe disease and is notorious for its ability to remain dormant in the liver, leading to relapses.
- *Plasmodium malariae* is less common but can cause chronic infection, sometimes persisting in the blood for years if untreated. It is found in Africa, Asia, and the Americas.
- *Plasmodium ovale* is similar to *P. vivax* in its ability to cause relapses due to dormant liver stages. It is primarily found in West Africa but also occurs in Asia and the Pacific islands.
- *Plasmodium knowlesi* is primarily a parasite of macaque monkeys in Southeast Asia but can infect humans. *P. knowlesi* infections can progress rapidly and be severe[1], making it an emerging concern in the region.

4.2 Geographic distribution

Malaria generally occurs in areas where environmental conditions allow parasite multiplication in the vector. Malaria today is usually restricted to tropical and subtropical areas and altitudes below 1,500 m.,

[1]Singh B, Daneshvar C. Human infections and detection of Plasmodium knowlesi. Clin Microbiol Rev. 2013 Apr;26(2):165-84. doi: 10.1128/CMR.00079-12.

- *P. falciparum* is predominantly found in Sub-Saharan Africa but also exists in Southeast Asia and South America.
- *P. vivax* has a wider global distribution, being prevalent in Asia, Latin America, and parts of Africa.
- *P. malariae* and *P. ovale* have more restricted distributions but are present in parts of Africa, Southeast Asia, and the Western Pacific.
- *P. knowlesi* is mainly found in Southeast Asia, particularly in Malaysia, where it is associated with forested areas inhabited by macaques.

This present distribution could be affected by climatic changes and population movements.

4.3 Pathogenicity and Clinical Manifestations

The symptoms of uncomplicated malaria can be rather non-specific and the diagnosis can be missed if health providers are not alert to the possibility of this disease. Since untreated malaria can progress to severe forms that may be rapidly (<24 hours) fatal rapid diagnosis and treatment is essential.

The first symptoms of disease are usually non-specific and similar to many febrile illnesses. These initial symptoms of malaria occur around 7–14 days following an infectious bite, and patients present with a fever or flu-like illness including shaking, chills, headache, muscle ache and tiredness. Unlike other febrile illness however, malaria fevers are often characterised by their periodic presentation, approximately every two days coinciding with the erythrocyte rupture. At this stage of disease, with prompt treatment with an effective antimalarial, malaria is curable. However, if left untreated or if treatment seeking is delayed, severe malaria complications can occur which often lead to death especially in the case of P. falciparum.

The severity of malaria symptoms varies by species:

- *P. falciparum* is associated with severe symptoms, including high fevers, anemia, and potentially fatal complications such as cerebral malaria acute renal failure, severe anemia, or acute respiratory distress syndrome.
- *P. vivax* often causes milder symptoms but can still lead to severe illness, especially in vulnerable populations. Its ability to relapse makes it a challenging species to control.
- *P. malariae* typically causes a less severe but chronic infection, which can result in nephrotic syndrome and other complications over time.
- *P. ovale* causes similar symptoms to *P. vivax,* with relapses occurring months or even years after the initial infection.

- *P. knowlesi* infections can be severe and rapidly progress, resembling *P. falciparum* in clinical presentation but requiring prompt diagnosis and treatment due to its rapid erythrocytic cycle.

4.4 Lifecycle

The lifecycle of *P. falciparum* is complex and involves many antigenically distinct stages and two hosts: the female Anopheles mosquito and humans (Figure 6.1). Mosquitos can inoculate between 15-200 sporozoites into a human host, and these infective parasites then undergo development inside hepatocytes to form merozoites. After a period of around 7–10 days sporozoites mature into schizonts which then rupture, and merozoites are released into the bloodstream where they invade red blood cells. Within the red blood cells, merozoites replicate, producing around 16–32 daughter merozoites which are then released into the blood stream following red blood cell rupture, where they reinvade new red blood cells. This process of invasion, replication and release occurs with a periodicity of 24–26 hours, and it is these periodic cycles that are associated with clinical disease manifestations. After approximately 10 days, a subset of red blood cell invading merozoites will differentiate into gametocytes, and these gametocytes continue to circulate in hosts until they are ingested by a feeding mosquito. Sexual reproduction then occurs in the mosquito midgut where gametes fuse to produce a zygote that elongates to become a motile ookinete, invades the midgut wall, and forms an oocyst. Following a sporogonic period of approximately 8–10 days, the oocysts burst to release sporozoites that travel to the mosquito's salivary glands, where they are ready for the cycle to repeat when the mosquito host takes a new blood meal.

P. vivax differs from the *P. falciparum* lifecycle in several ways, however, one of the most epidemiologically significant is the ability of *P. vivax* to lie dormant and undetectable in the liver of infected human hosts. This hypnozoite stage can reactivate weeks, months, or even years after the initial infection and re-enters the bloodstream causing relapses in clinical malaria and further onwards transmission. The variation in relapse times results from regional and seasonal variations in mosquito vector populations, with tropical regions tending to experience shorter relapse periods, and longer periods in more temperate areas.

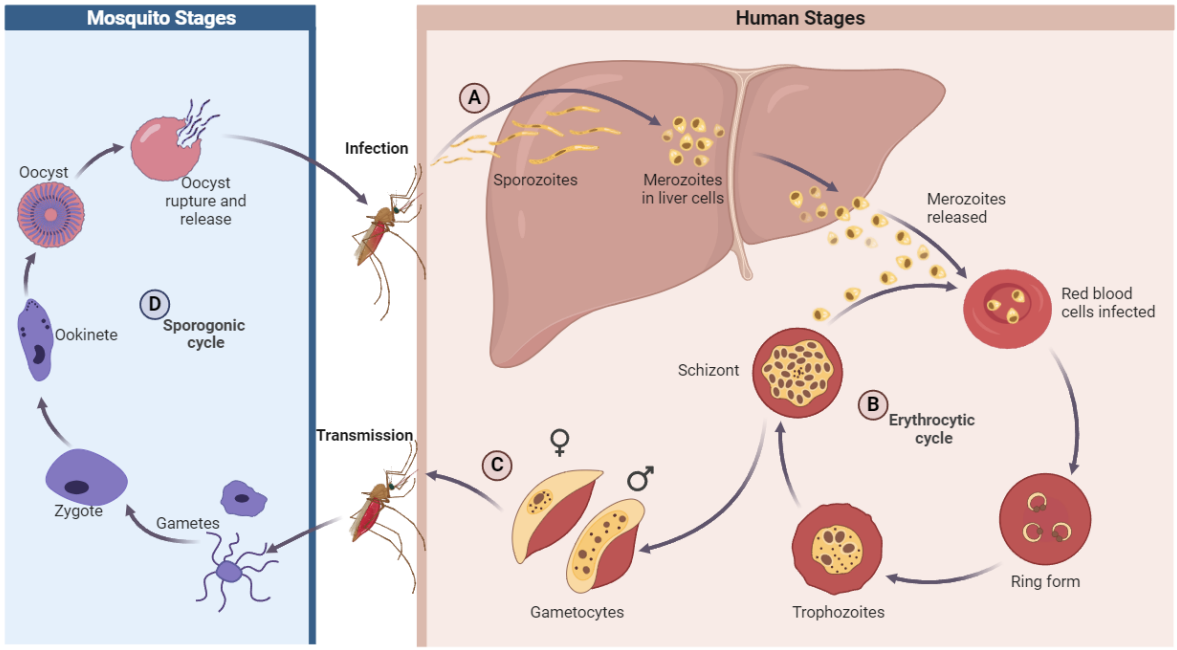

Figure 4.1: **The lifecycle of *P. falciparum* in humans and mosquitos. A)** Inoculation of sporozoites and the pre-erythrocytic infection stages in the liver; **B)** Asexual reproduction and blood stage infection; **C)** Gametocyte production and ingestion during a bloodmeal; and **D)** Sexual reproduction and developmental stages within the mosquito.

5 Anopheles Mosquito Vector

Malaria is a mosquito-borne parasitic disease that infects humans through the bite of an Anopheline mosquito vector. Of the approximately 70 Anopheles species that are able to transmit malaria to humans, an estimated 30–40 are dominant vector species, and are therefore of relevance to public health. Anopheles species are found in varying geographic regions, and within regions distinct environments support different species, which affects malaria epidemiology and transmission (Figure 5.1). The most important species vary by region and include *Anopheles gambiae* and *Anopheles funestus* in Africa, *Anopheles stephensi* in South Asia, and *Anopheles darlingi* in South America (Figure 5.1).

5.1 Key Species

- **Anopheles gambiae Complex**: This group includes several species that are among the most efficient malaria vectors, particularly in Sub-Saharan Africa. *A. gambiae* is known for its strong preference for biting humans (anthropophilic behavior), which makes it an especially effective vector.
- **Anopheles funestus**: Another major vector in Africa, *A. funestus* is highly efficient in transmitting *P. falciparum*, the most deadly malaria parasite. It is often found in more permanent water bodies and is also anthropophilic.
- **Anopheles stephensi**: Found primarily in urban and peri-urban areas of South Asia and parts of the Middle East, *A. stephensi* is a significant vector of urban malaria. Its ability to breed in man-made water containers makes it particularly difficult to control.
- **Anopheles dirus**: This species is a primary vector in Southeast Asia and is known for its adaptation to forested areas, making it a significant concern in rural and forested regions.
- **Anopheles darlingi**: The main malaria vector in the Amazon Basin, *A. darlingi* is highly adaptable, breeding in a variety of natural and man-made water bodies.

[1]Sinka, M.E., Bangs, M.J., Manguin, S. *et al.* A global map of dominant malaria vectors. *Parasites Vectors* **5**, 69 (2012). https://doi.org/10.1186/1756-3305-5-69

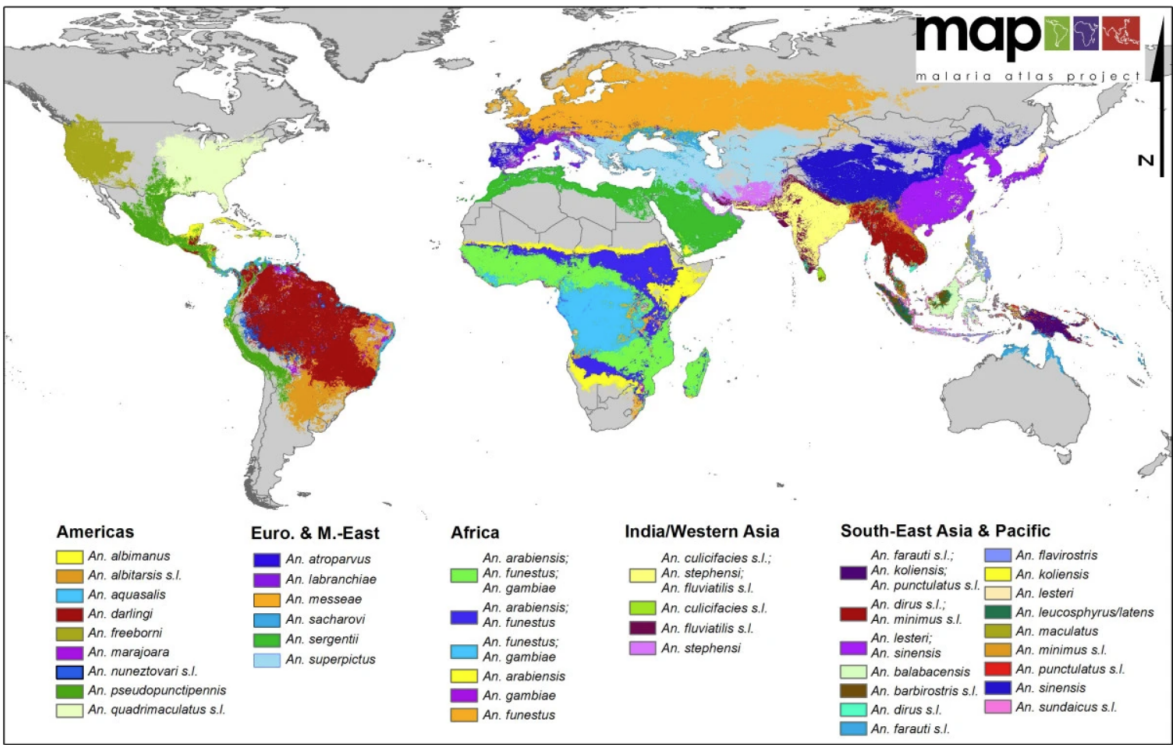

Figure 5.1: A global map of dominant malaria vector species. Reproduced from Sinka et al 2014.[1]

5.2 Anopheles Lifecycle

Malaria parasites are transmitted by the female mosquito of the Anopheles genus. Anopheles species have four distinct life stages: egg, larva and pupa make up the juvenile aquatic stages before the final adult stage. Juvenile stages last for around 5–14 days depending on the species and the ambient temperature. Once at the adult stage mosquitos tend to mate within a few days of emergence and feed on sugar sources for energy. Female mosquitos will also require a blood meal for the development of her eggs. It is this stage that links the female mosquito and the human hosts in the malaria transmission cycle.

Following a blood meal, the female must rest while the eggs are developed, again this process depends on the ambient temperature taking around two to three days in tropical conditions. Females will then lay their eggs in standing water and continue to seek further blood meals to sustain further egg production. This cycle continues until the female dies, around one to two weeks later.

Chances of survival are dependent on temperature and humidity and the ability of the female mosquito to find a blood meal. In order to transmit parasites mosquitos must survive for longer than the extrinsic incubation period of plasmodium which is around 9–18 days depending on species and temperature (higher temperatures accelerate parasite growth). Many Anopheles species are opportunistic in their feeding behaviour and will take a blood meal from whatever host is available either human or animal. The degree to which a species favours humans, known as anthrophily, determines their efficiency as a vector of malaria. *Anopheles gambiae* and *Anopheles funestus* are two highly anthropophilic species that makes them the primary vector in much of sub-Saharan Africa.

5.3 Feeding Behaviors

A summary of some key terms and behviours in mosuqito feeding behaviours:

- **Anthropophily**: Many *Anopheles* species exhibit a strong preference for human blood, a behavior known as anthropophily. This preference significantly enhances their role as malaria vectors. For example, *A. gambiae* is highly anthropophilic, which, coupled with its breeding in proximity to human habitation, makes it one of the most effective malaria vectors globally.
- **Crepuscular and Nocturnal Activity**: Most *Anopheles* mosquitoes are active during twilight hours (dusk and dawn) and at night. This behavior is critical for malaria transmission, as it coincides with human sleeping patterns, making bed nets an effective intervention.
- **Endophagy and Exophagy**:

  - **Endophagic** mosquitoes prefer to feed indoors, making indoor residual spraying (IRS) and insecticide-treated nets (ITNs) effective control measures.
  - **Exophagic** species feed outdoors, requiring different strategies such as outdoor spraying and environmental management.

5.4 Breeding Environments

- **Natural Habitats**: *Anopheles* mosquitoes typically breed in clean, unpolluted water. Natural breeding sites include:
  - **Swamps and Marshes**: Often found in tropical and subtropical regions.
  - **Forest Pools and Streams**: Common in rural and forested areas.
  - **Rice Fields and Irrigation Channels**: These provide extensive breeding habitats in agricultural regions.
- **Man-Made Habitats**: Urbanization and human activities have created additional breeding sites:
  - **Water Containers**: In urban and peri-urban areas, *A. stephensi* and other species can breed in water storage containers, discarded tires, and other small water bodies.
  - **Construction Sites**: Pools of stagnant water at construction sites can serve as breeding grounds, especially in urban areas.

6 Human Immune Response

Morbidity due to *P. falciparum* infections can vary from mild clinical symptoms of febrile illness to severe and life-threatening disease due to vital organ dysfunction. Individuals living in malaria endemic areas, however, do acquire substantial protection against clinical and severe forms of malaria, but rarely, if ever, is sterile immunity achieved.[1] Generally, immunity against severe malaria develops rapidly, followed by immunity against clinical disease and finally, more slowly, the build-up of immune tolerance to blood-stage parasites (Figure 6.1).[2] While immunity to patent parasitaemia can develop by adulthood, subpatent infections that are detectable with advancements in molecular diagnostic techniques still occur. It is this immune tolerance that results in asymptomatic carrier infections among adult populations in malaria-endemic areas.[3][4]

The acquisition of immunity to malaria has been shown to be both age- and exposure-dependent leading to a high degree of variability in patterns of immunity across populations.[5][6][7][8][9] This progressive acquisition of immunity to malaria is why younger children are

[1] Doolan DL, Dobaño C, Baird JK. Acquired immunity to malaria. Clin Microbiol Rev. 2009 Jan;22(1):13-36, https://doi.org/10.1128%2FCMR.00025-08

[2] Griffin Jamie T., Hollingsworth T. Déirdre, Reyburn Hugh, Drakeley Chris J., Riley Eleanor M. and Ghani Azra C. 2015 Gradual acquisition of immunity to severe malaria with increasing exposure. Proc. R. Soc. B.28220142657 http://doi.org/10.1098/rspb.2014.2657

[3] Bousema T, Okell L, Felger I, Drakeley C. Asymptomatic malaria infections: detectability, transmissibility and public health relevance. Nat Rev Microbiol. 2014 Dec;12(12):833-40. doi: 10.1038/nrmicro3364.

[4] Okell LC, Bousema T, Griffin JT, Ouédraogo AL, Ghani AC, Drakeley CJ. Factors determining the occurrence of submicroscopic malaria infections and their relevance for control. Nat Commun. 2012;3:1237. doi: 10.1038/ncomms2241

[5] Griffin Jamie T., Hollingsworth T. Déirdre, Reyburn Hugh, Drakeley Chris J., Riley Eleanor M. and Ghani Azra C. 2015 Gradual acquisition of immunity to severe malaria with increasing exposure. Proc. R. Soc. B.28220142657 http://doi.org/10.1098/rspb.2014.2657

[6] Rodriguez-Barraquer I, Arinaitwe E, Jagannathan P, Kamya MR, Rosenthal PJ, Rek J, Dorsey G, Nankabirwa J, Staedke SG, Kilama M, Drakeley C, Ssewanyana I, Smith DL, Greenhouse B. Quantification of anti-parasite and anti-disease immunity to malaria as a function of age and exposure. Elife. 2018 Jul 25;7:e35832. doi: 10.7554/eLife.35832.

[7] Greenwood B, Marsh K, Snow R. Why do some African children develop severe malaria? Parasitol Today. 1991 Oct;7(10):277-81. doi: 10.1016/0169-4758(91)90096-7

[8] Baird JK. Host age as a determinant of naturally acquired immunity to Plasmodium falciparum. Parasitol Today. 1995 Mar;11(3):105-11. doi: 10.1016/0169-4758(95)80167-7

[9] Reyburn H, Mbatia R, Drakeley C, Bruce J, Carneiro I, Olomi R, Cox J, Nkya WM, Lemnge M, Greenwood BM, Riley EM. Association of transmission intensity and age with clinical manifestations and case fatality of severe Plasmodium falciparum malaria. JAMA. 2005 Mar 23;293(12):1461-70. doi: 10.1001/jama.293.12.1461.

particularly vulnerable to episodes of severe malaria, once a period of protection provided from maternally derived antibodies wanes and before the acquisition of this effective immunity

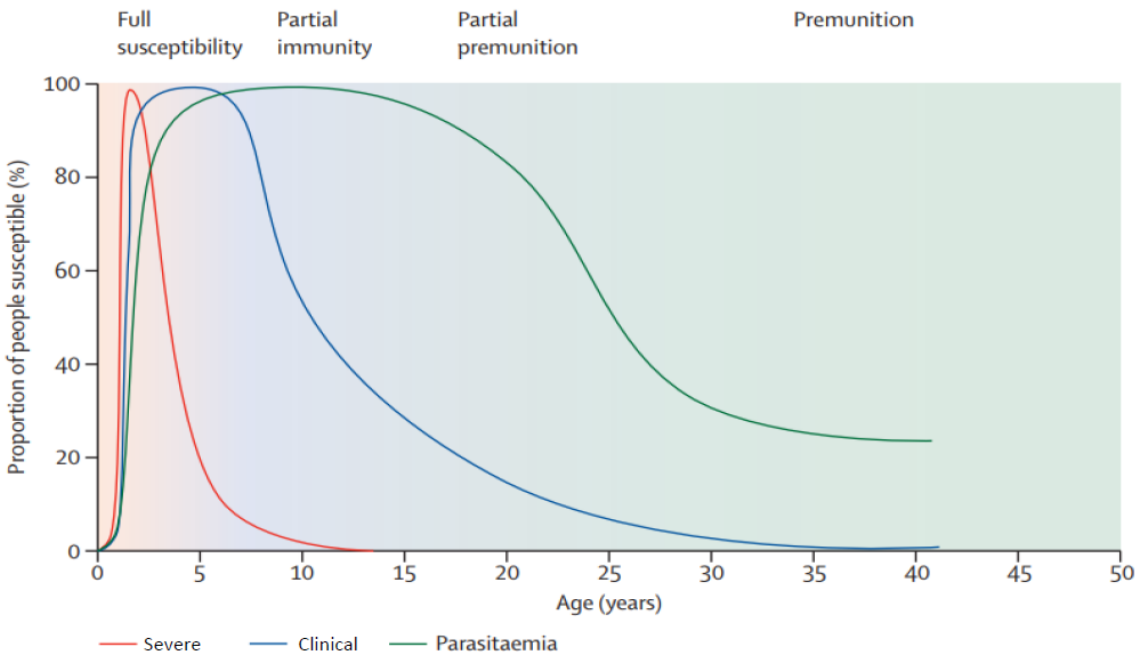

Figure 6.1: Progression of Naturally Acquired Immunity to Malaria. The relationship between age and malaria severity in an area of moderate transmission inte nsity shows how with repeated exposure by early childhood, protection is first acquired against severe disease, then more slowly protection builds up against clinical disease and finally much more slowly develops against parasitaemia. In areas with higher transmission intensity the rate of acquisition of naturally acquired immunity can increase. Reproduced from Griffin et al 2015 doi: https://doi.org/10.1098/rspb.2014.2657.

6.1 Immune response overview

Due to the parasites multistage lifecycle, there are several points at which the immune system could respond to the invading threat. Upon first exposure to blood stage parasites, the innate immune system launches a non-specific immune response triggering a release of pro-inflammatory cytokines which help to limit parasite growth.[10] These cytokine responses also

[10]Stevenson MM, Riley EM. Innate immunity to malaria. Nat Rev Immunol. 2004 Mar;4(3):169-80. doi: 10.1038/nri1311

allow for the effective priming of the humoral and cellular-mediated immune responses which then provide adaptive responses upon re-exposure.

Key to the adaptive immune response is the phenomenon of pattern recognition of parasite antigens by B and T cells, which enables a rapid and more effective parasite specific protective response to each lifecycle stage. However, the exact immune effector mechanisms involved in parasite regulation, control and elimination at each lifecycle stage are not fully characterised. The ability of malaria parasites to evade and interfere with effective immune responses also presents several challenges in mounting and understanding successful immune responses. [11] [12] [13]

The key mechanisms understood to play a significant role at each parasite life-stage are shown in Figure 6.1.

[11] Langhorne J, Ndungu FM, Sponaas AM, Marsh K. Immunity to malaria: more questions than answers. Nat Immunol. 2008 Jul;9(7):725-32. doi: 10.1038/ni.f.205

[12] Ramasamy R. Molecular basis for evasion of host immunity and pathogenesis in malaria. Biochim Biophys Acta. 1998 Feb 27;1406(1):10-27. doi: 10.1016/s0925-4439(97)00078-1

[13] Gomes PS, Bhardwaj J, Rivera-Correa J, Freire-De-Lima CG, Morrot A. Immune Escape Strategies of Malaria Parasites. Front Microbiol. 2016 Oct 17;7:1617. doi: 10.3389/fmicb.2016.01617

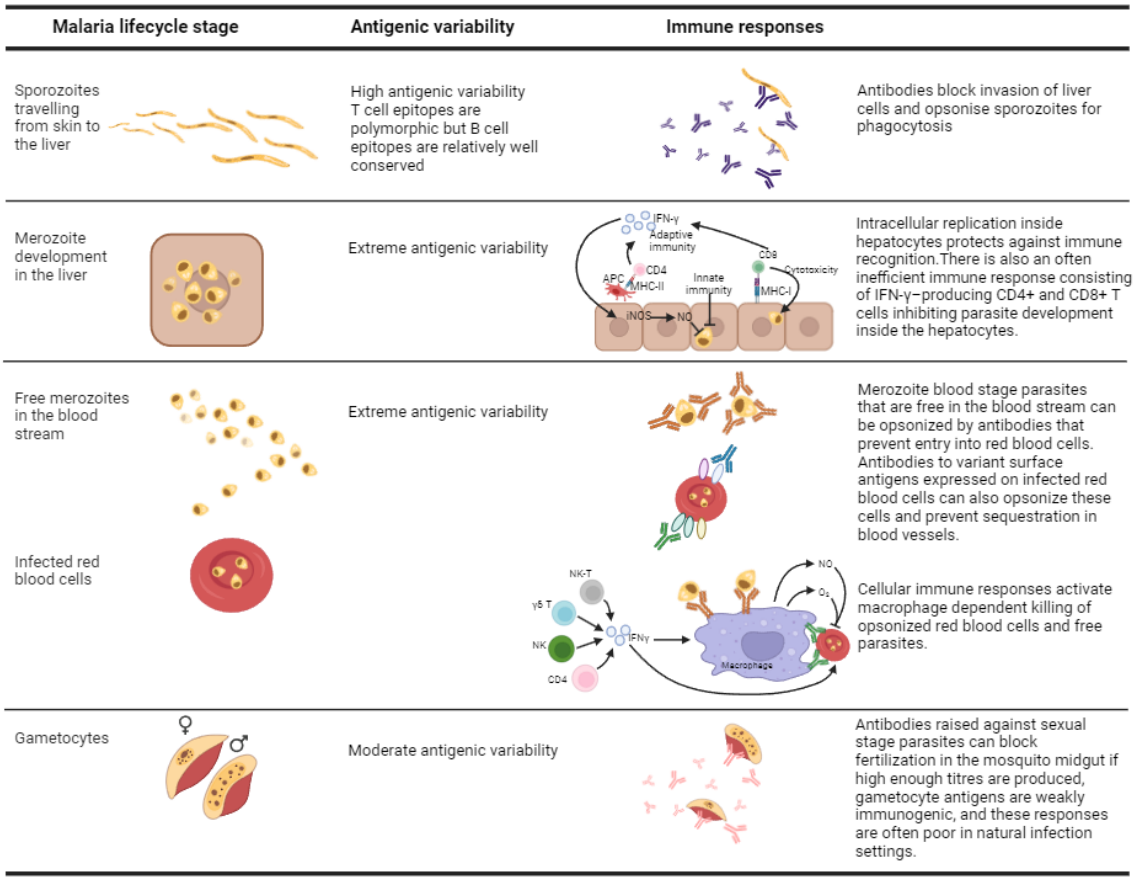

Figure 6.2: Overview of the immune responses directed against each malaria parasite life stage.

Key Take-aways

Naturally occurring immune responses to sporozoite life-stages are poor and frequently inefficient at eliminating parasites and are generally considered inadequate to confer protection against clinical malaria.

The majority of naturally acquired immunity is directed against blood stage parasites – both freely circulating merozoites and infected red blood cells. However inflammatory responses associated with immune response to this stage can result in significant immunopathology.

Gametocyte specific antibodies are often poorly induced and not widely circulating in populations

6.2 Prof. Kevin Marsh - "Immunity to Malaria in Humans"

Below is a great lecture by Professor Kevin Marsh that describes how knowledge of immunity to malaria in humans has developed over the past thirty years and what impact this has for future research. This seminar was delivered at the University of Oxfords Centre for Tropical Medicine, Oxford, UK, 29th October 2013.

Watch this for a great overview to a very complex topic!

https://www.youtube.com/embed/bJ6nS-I-HiM

Part III

Malaria Transmission

Malaria transmission is a complex process that involves multiple factors, including the biology of the *Plasmodium* parasite, the behavior of *Anopheles* mosquitoes, and various environmental, climatic, and human factors. Understanding how malaria is transmitted is crucial for developing effective prevention and control strategies. This chapter explores the key components of malaria transmission, focusing on the role of the mosquito vector, environmental influences, and human behaviors that contribute to the spread of the disease and how malaria transmission can be measured and described in the literature.

Learning objectives

- Identify the key *Anopheles* mosquito species responsible for malaria transmission and understand their role in the transmission process.
- Describe how environmental factors like temperature, rainfall, and humidity influence malaria transmission.
- Recognize the impact of human behaviors, including agriculture, migration, and urbanization, on malaria transmission.
- Explain the malaria transmission cycle and the concept of the basic reproduction number (R0).
- Understand the concept of heterogeneity in malaria transmission and its implications for control efforts.
- Apply knowledge of malaria transmission to propose effective malaria control strategies.

7 Role of Anopheles Mosquitoes in Malaria Transmission

We will recap and delve into more details introduced in the previous topic and discuss the relevance to malaria transmission.

As a reminder, there are about 500 Anopheles species in the world. However, only 30 to 40 are considered important vectors of human malaria. These species are spread throughout the globe, as seen here in Figure 7.1, and they have very different behaviors during larval and adult stages. During larval development, which lasts about 7 to 10 days, mosquito are adapted to very different ecological habitats. Some mosquito species for instance, prefer breeding in temporary breeding sites, such as those provided by rain puddles. While others would prefer breeding in permanent breeding sites, such as rice fields. Some mosquitoes are highly adapted to salt water, and so live in coastal areas. While other mosquitoes can only survive in fresh water. These different ecological habitats expose mosquitoes to different environments. For instance, different temperature conditions and temperature shifts between day and night, also different microorganisms, predators, and nutritional reserves. In turn, the ecological habitats to which these mosquitoes are exposed as larvae will impact the physiology of adults emerging from those breeding sites, with possible consequences for malaria transmission. For instance, larvae that are adapted to temporary breeding sites, might have reduced availability of nutrients and might have a shorter developmental time. So the adults emerging from those breeding sites will generally be smaller in size and might need to feed more often as adults, on blood, in order to meet the energetic demands of flying, mating, reproducing, and so on. This in turn, might create more opportunities for Plasmodium parasites for their own transmissions, because a mosquito that bites more often obviously will be more capable of transmitting malaria.

7.1 Vectors of Asia, Africa & the Americas

A great talk from the Ifakara Health Institute on Malaria Vectors

https://www.youtube.com/watch?v=_XuBruejjIY&ab_channel=IfakaraHealthInstitute%28IFAKARA%29

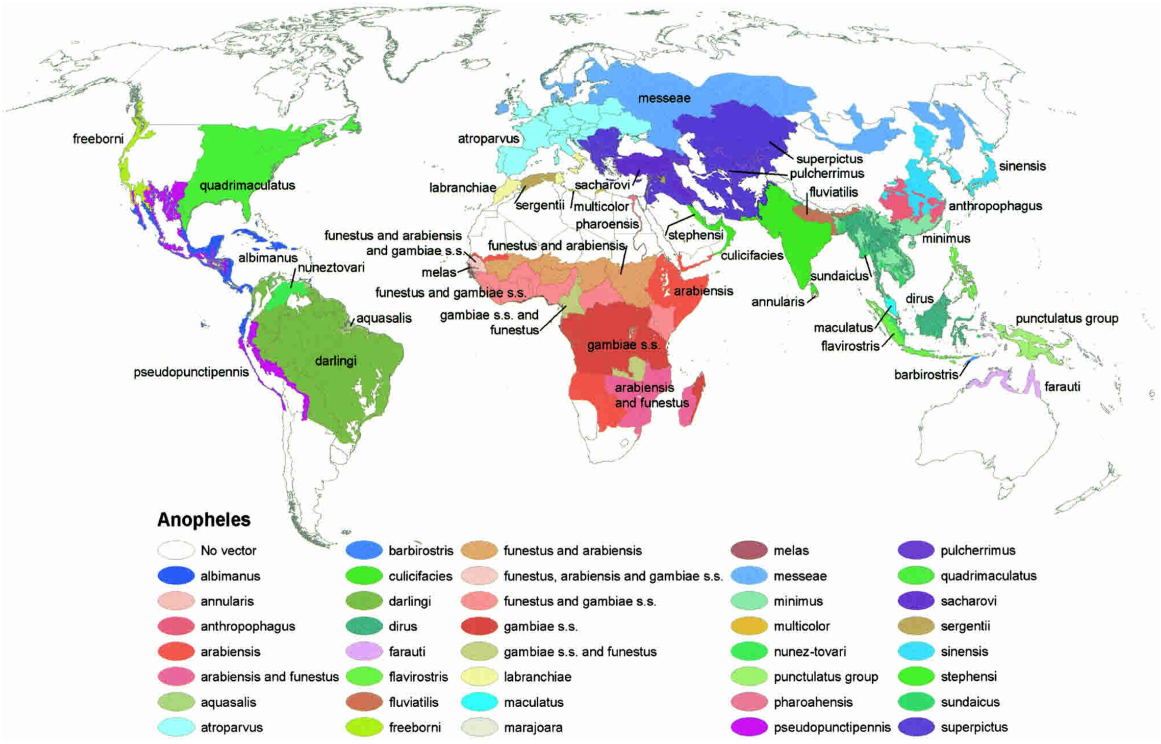

Figure 7.1: Global distribution (Robinson projection) of dominant or potentially important malaria vectors. Sourced from

7.2 Biology and Behavior of Anopheles Mosquitoes

As described in the previous chapter, malaria transmission is primarily driven by the Anopheles mosquito, which acts as the vector for the Plasmodium parasite. The biology and behavior of Anopheles mosquitoes are critical to their efficiency as vectors.

- **Feeding Behavior**: Female *Anopheles* mosquitoes are hematophagous, meaning they feed on blood to obtain the nutrients required for egg development. Their preference for human blood (anthropophily) makes them particularly effective vectors of malaria. Mosquitoes that feed primarily at night are most dangerous because they coincide with human sleep patterns, increasing the likelihood of undisturbed feeding. Blood feeding is really an essential component in the mosquito life cycle. And this is a step in which mosquitoes from different species exhibit quite a variety of behaviors.

  - Some mosquito species are highly adapted to feeding on humans. So they are highly anthropophilic. While other mosquito species predominantly feed on animals, such as birds, or cows, or rats. The propensity of a mosquito to feed on humans, rather than animals, can actually be measured. And this is the **human blood index**. The human blood index can be measured by collecting mosquitoes in the field and looking at the content of their blood to see whether it's from animal or from human origin. This value goes from 0 to 1. With 0, being mosquitoes that feed exclusively on animals, so highly zoophilic. And 1, with mosquitoes that feed only on humans, so highly anthropophilic. Many mosquito species with a high level of anthropophilia actually cluster in Africa. And these mosquitoes belong to mosquitoes of the *Anopheles gambiae complex*, such as *Anopheles gambiae*, *Anopheles coluzzii*. But also, *Anopheles funestus*, which is another very important vector of human malaria in Africa.

- **Resting Behavior**: After feeding, *Anopheles* mosquitoes typically rest indoors (endophily) or outdoors (exophily). Indoor resting mosquitoes are targeted by indoor residual spraying (IRS) and insecticide-treated nets (ITNs), which are effective control strategies.

- **Flight Range**: *Anopheles* mosquitoes generally have a limited flight range, typically staying within a few kilometers of their breeding sites. However, their ability to locate humans through carbon dioxide and body odor means that even small numbers of mosquitoes can sustain transmission if they are close to human habitation.

7.3 Vector Competence and Efficiency

Not all *Anopheles* species are equally competent malaria vectors. Vector competence refers to the mosquito's ability to acquire, maintain, and transmit the malaria parasite. This compe-

tence is influenced by factors such as:

- **Susceptibility to Infection**: Some *Anopheles* species are more susceptible to *Plasmodium* infection, meaning they are more likely to become infected after feeding on an infected person.
- **Parasite Development**: The development of the malaria parasite within the mosquito, known as the extrinsic incubation period, must be completed before the mosquito can transmit the parasite to another human. This period is temperature-dependent, with warmer temperatures accelerating parasite development.
- **Feeding Frequency and Longevity**: Mosquitoes that feed more frequently and live longer are more likely to transmit malaria because they have more opportunities to pick up and pass on the parasite.

7.4 Mosquito Lifespan and the Extrinsic Incubation Period

The lifespan of the mosquito is a critical factor in malaria transmission. The extrinsic incubation period, which is the time required for the malaria parasite to develop within the mosquito, typically lasts 10-21 days, depending on the temperature. If a mosquito survives this period, it becomes infectious and can transmit malaria to humans. Therefore, the longer the mosquito lives, the greater the likelihood that it will contribute to malaria transmission.

7.5 Local vector species composition

In any given area, there might be multiple Anopheles species that live in sympatry and this might complicate control measures. For instance, let's have a look at Africa, and the Anopheles gambiae complex. This complex comprises eight mosquito species that are morphologically identical and can only be distinguished on the molecular level. These species include some of the most important malaria vectors, such as *Anopheles gambiae*, *Anopheles arabiensis*, and *Anopheles coluzzii*. *Anopheles gambiae* and *Anopheles coluzzii* have very similar biting behavior, because they both tend to feed on humans and late at night and indoors. However, they show quite different ecological habitats due to larval developments. *Anopheles gambiae* tend to prefer living in temporary breeding sites, such as rain puddles. While *Anopheles coluzzii* prefer living in permanent breeding sites, such as rice fields. *Anopheles arabiensis* is a third important malaria vector that shares habitats with *Anopheles gambiae* and *Anopheles coluzzii.* Historically, this mosquito species was not considered to be a very important vector for human malaria, because these mosquitoes also feed on animals, apart from humans, and so they dilute potential infectious bites. However, because of their plastic behavior, and the fact that these mosquitoes can feed outdoors and rest outdoors, apart from feeding and resting indoors, these

mosquitoes become more difficult to be controlled with current vector control strategies. And so in recent years, they've become more and more relevant for malaria transmission.

When multiple mosquito species live in sympatry, it becomes difficult to understand the relative contribution to malaria transmission. The species composition of *Anopheles* mosquitoes is critically important to malaria transmission because different species vary in their behavior, habitat preferences, and susceptibility to control measures. Changes in the dominant vector species can affect the overall transmission dynamics, influencing where, when, and how intensely malaria is transmitted. For example, species that are more resistant to insecticides or have different feeding patterns may sustain transmission even in areas with strong control measures. Therefore, understanding and monitoring species composition is essential for designing effective and targeted malaria interventions.

The recent study by Msugupakulya et al. (2023) highlights a notable shift in the primary malaria vectors in East and Southern Africa over the past two decades.[1] Historically, the *Anopheles gambiae* complex, particularly *An. gambiae* and *An. arabiensis*, were the dominant contributor to malaria transmission. However, from 2011 onwards, *Anopheles funestus* has emerged as the primary vector, especially in regions where insecticide-treated nets (ITNs) and indoor residual spraying (IRS) have been widely implemented. The changing vector composition suggests that control strategies need to adapt to the evolving landscape and monitor for changes in the species compostion of mosquitos across the continent.

[1] Msugupakulya, B.J., Urio, N.H., Jumanne, M. *et al.* Changes in contributions of different *Anopheles* vector species to malaria transmission in east and southern Africa from 2000 to 2022. *Parasites Vectors* **16**, 408 (2023). https://doi.org/10.1186/s13071-023-06019-1

8 Environmental and Climatic Factors and Their Role in Transmission

Climate is one of the most important determinants of malaria transmission. Temperature, rainfall, and humidity all influence mosquito survival, breeding, and the development of the malaria parasite within the mosquito.

- **Temperature**: Optimal temperatures for malaria transmission range between 20°C and 30°C (68°F to 86°F). Higher temperatures shorten the extrinsic incubation period, allowing mosquitoes to become infectious more quickly. However, extremely high temperatures (above 40°C) can reduce mosquito survival, limiting transmission.
- **Rainfall**: Rainfall creates breeding sites for *Anopheles* mosquitoes by forming pools of stagnant water, which are ideal for laying eggs. However, excessive rainfall can wash away breeding sites, reducing mosquito populations.
- **Humidity**: High humidity levels extend mosquito lifespan by reducing the rate of desiccation. Mosquitoes are more active and feed more frequently in humid conditions, increasing the risk of malaria transmission.

8.1 Breeding Habitats and Environmental Conditions

Anopheles mosquitoes breed in a variety of aquatic environments, and the availability and quality of these breeding sites play a crucial role in malaria transmission.

- **Natural Breeding Sites**: These include swamps, marshes, ponds, and slow-moving streams. These sites are abundant in rural and forested areas, making such regions more prone to malaria.
- **Man-Made Breeding Sites**: Urbanization and human activities have led to the creation of artificial breeding sites, such as irrigation channels, rice fields, and water storage containers. These sites can support large mosquito populations even in densely populated areas.

8.2 Seasonality of Malaria Transmission

Malaria transmission is often seasonal, particularly in regions with distinct wet and dry seasons. The transmission typically peaks during or after the rainy season when breeding sites are most abundant, and mosquito populations are at their highest.

- **Endemic Regions**: In stable endemic regions, malaria transmission occurs year-round, but there are still seasonal peaks.
- **Epidemic-Prone Regions**: In areas where malaria is not endemic or is close to elimination, transmission can occur in short, intense outbreaks during favorable climatic conditions, leading to outbreaks.

9 Human Behavioral Factors in Malaria Transmission

Human behavior plays a crucial role in determining the risk of malaria transmission. Certain activities, social practices, and economic conditions can either increase or reduce exposure to *Anopheles* mosquitoes, directly influencing the spread of malaria. Understanding these behaviors is essential for developing effective prevention strategies that fit within the local context.

9.1 Exposured to Mosquito Bites

Human activities that increase exposure to mosquitoes, especially during peak biting times, significantly heighten the risk of malaria transmission. *Anopheles* mosquitoes are most active during dusk and dawn, and individuals who are outdoors during these times, whether for work, leisure, or travel, are at greater risk.

- **Agricultural Work**: In rural areas, late-night or early-morning agricultural activities increase exposure to mosquitoes. Farmers who work in fields near mosquito breeding sites, such as rice paddies, are particularly vulnerable. Fishing communities who work at night on open water also face higher risk of malaria due to increased mosquito exposure.
- **Household Practices**: The use of open windows or poorly constructed housing without screens allows mosquitoes easy entry into homes. Sleeping without the protection of insecticide-treated bed nets (ITNs) also greatly increases the risk of malaria, particularly for children and pregnant women.

> Tip
>
> Some good articles on Human Behaviours and High Risk Populations for malaria transmission are noted below - take a read through!
>
> - Identifying and characterizing high-risk populations in pilot malaria elimination districts in Madagascar: a mixed-methods study
> - Tailoring malaria interventions to high–risk groups in Senegal

- Malaria prevention and treatment in migrant agricultural workers in Dangur district, Benishangul-Gumuz, Ethiopia: social and behavioural aspects
- Protecting Cambodia's Migrant Workers Against Malaria through an Innovative Net-Lending Scheme

9.2 Socioeconomic Status

Communities with limited resources may lack access to essential malaria prevention tools such as bed nets, insecticides, or medical treatment.

- **Healthcare Access**: Poorer households may not have timely access to health services, leading to delayed diagnosis and treatment. This increases the duration of infection and, consequently, the risk of further transmission within the community.
- **Living Conditions**: Overcrowded living conditions and inadequate housing infrastructure, often seen in impoverished areas, create environments conducive to malaria transmission. Houses with open eaves, unsealed walls, or a lack of windows and screens offer easy entry for mosquitoes.

9.3 Cultural Practices

Cultural and social practices significantly influence exposure to mosquito bites and the resulting risk of malaria transmission. In many communities, outdoor gatherings, celebrations, and rituals play a central role in social life, but they also increase the risk of malaria transmission due to prolonged outdoor exposure during peak mosquito activity.

A qualitative study conducted in South-Eastern Tanzania by Moshi et al. (2018) explored how cultural practices and social gatherings contribute to malaria transmission. The study found that outdoor events, including religious, cultural, and social celebrations, often expose people to mosquito bites during evening and nighttime hours when *Anopheles* mosquitoes are most active. Events like weddings, funerals, male circumcision ceremonies, and religious festivals, where participants stay outdoors overnight, create environments where mosquito bites are common. Despite the known risks, protective measures such as bed nets or repellents are rarely used during these events due to cultural norms or perceived inappropriateness.

9.4 Urbanization

Urbanization presents a complex scenario for malaria transmission. While urban areas typically have lower transmission rates due to better infrastructure and healthcare, unplanned urbanization can create conditions favorable for mosquitoes.

- **Urban Slums**: In rapidly growing cities, informal settlements or slums often lack adequate sanitation and drainage systems, leading to the accumulation of stagnant water, which serves as breeding sites for mosquitoes. Poor housing quality and limited access to preventive measures increase the risk of transmission in these areas.
- **Shifts in Vector Behavior**: In urban areas, mosquitoes may adapt their feeding patterns or find alternative breeding sites, such as containers of standing water in construction sites, broken pipes, or discarded tires. These environmental changes, combined with high population density, can sustain malaria transmission in urban settings.

! Responding to malaria in urban areas: a new framework from WHO and UN-Habitat

In 2022 the WHO released a Global Framework for the response to malaria in urban areas.
Given the rapidly urbanizing world, most people in malaria-affected countries will soon be living in urban areas. If you take the example of Nigeria, which accounts for about a quarter of the global burden of malaria, nearly half of the population is already living in urban areas.
There are many challenges to Urban Malaria - including new and highly adaptive vectors, the challenges of social inequity – an issue found in both rural and urban settings and the rapid and often unplanned urbanization in malaria endemic countries. And then, of course, we are dealing with a lack of financial and other resources.
The framework is avaliable here: https://www.who.int/publications/i/item/9789240061781

10 Measuring Malaria Transmission Dynamics

Understanding the relationship between the prevalence of malaria infection, clinical incidence and transmission intensity is key to understanding the epidemiology and the impact of control interventions on malaria. Malaria transmission intensity varies greatly between populations, agegroups and over space and time and can be quantified using measurements from epidemiological studies. A wide variety of methods and metrics have been developed to quantify malaria transmission intensity.

10.1 Entomological Inoculation Rate (EIR)

The Entomological Inoculation Rate (EIR) is one of the most widely used metrics to measure malaria transmission. EIR represents the number of infective mosquito bites a person receives over a specific time period, usually expressed as bites per person per year.

- **Calculation of EIR**: EIR is calculated as the product of the human biting rate (the number of bites per person per year) and the sporozoite rate (the proportion of mosquitos with sporozoites in their salivary glands)
  - Human biting rates are estimated by catching and counting the number of mosquitos that attempt to feed on a human, and the sporozite rate it found by examining those mosquitos for the presence of sporozoites.
  - **Example**: If a person receives 10 mosquito bites per night, and 1% of mosquitoes are infected with *Plasmodium* sporozoites, the EIR would be 36.5 infective bites per year.
- **Importance of EIR**: EIR provides a direct measure of the intensity of malaria transmission in a given area. Higher EIRs indicate more intense transmission, often seen in areas with dense mosquito populations and favorable environmental conditions for breeding. While considered one of the mainstays in quantifying malaria transmission, measuring the EIR is time consuming and costly, requiring intensive and repeated measures throughout the year and large sample sizes.

Examples in the literature

- An estimation of the entomological inoculation rate for Ifakara: a semi-urban area in a region of intense malaria transmission in Tanzania
- Identifying Plasmodium falciparum transmission patterns through parasite prevalence and entomological inoculation rate

10.2 Force of Infection

While the EIR measures the average number of infectious bites per year, not every infectious bite results in clinical malaria, the force of infection (FOI) is defined as the number of infections per person per unit time and counts all new human malaria infections in some time interval with or without clinical symptoms, and whether or not a person is already infected. It provides a measure of the likelihood of someone becoming infected over a specific time period.

- The number of infectious bites that actually progress to malaria per unit of time describes the efficiency of transmission and can be estimated as FOI/EIR.
- The FOI is often quantified using transmission models of malaria but can also be estimated from cohort studies.
- Another method of measuring the FOI is using serological markers of malaria infection. Antibody measurements in exposed populations can be used to estimate the seroconversion rate which is defined as the rate at which individuals become seropositive.

Examples in the Literature

- A quantitative analysis of transmission efficiency versus intensity for malaria
- The Garki project: research on the epidemiology and control of malaria in the Sudan savanna of West Africa by L. Molineaux and G. Gramiccia
- Estimating age-time-dependent malaria force of infection accounting for unobserved heterogeneity
- Force of infection is key to understanding the epidemiology of Plasmodium falciparum malaria in Papua New Guinean children
- The Dynamics of Natural Plasmodium falciparum Infections

10.3 Serological Markers

Serological markers measure antibodies in blood samples to detect past exposure to malaria parasites. Serological surveys can provide insights into cumulative exposure and historical transmission patterns in a population.

- **Use in Low-Transmission Settings**: In areas where clinical cases are rare, serological surveys can help detect transmission trends that may not be visible through case incidence alone. These markers are particularly useful for identifying areas of low but persistent transmission.
- **Monitoring Transmission**: Serological data can be used to track reductions in exposure over time, serving as an indicator of the long-term success of malaria control efforts.

Examples in the literature

- Estimating medium- and long-term trends in malaria transmission by using serological markers of malaria exposure
- Estimating malaria transmission intensity from Plasmodium falciparum serological data using antibody density models
- Sero-epidemiological evaluation of malaria transmission in The Gambia before and after mass drug administration

10.4 Parasite Prevalence Rate

A further mainstay of malaria transmission metrics is the parasite prevalence rate (*PfPR)* defined as the proportion of a population infected with malaria. This is measured through cross-sectional surveys and is widely collected (e.g. in DHS and MIS surveys). It is important to note that the method of parasite detection (microscopy or polymerase chain reaction (PCR) testing) will influence the estimate the parasite prevalence.

Parasite prevalence rates measure the burden of both asymptomatic and symptomatic malaria infections at a specific period in time. Parasite prevalence rates have been crucial for mapping global malaria burden reductions and tracking declines in malaria over time.

- **Use of PR**: PR is crucial for detecting asymptomatic carriers who can continue to transmit malaria. It also provides a snapshot of the overall burden of malaria in a population, allowing for the identification of transmission hotspots.

- **Application in Control Programs**: PR is used to track trends in infection rates over time, assess the success of interventions, and monitor areas at risk of resurgence.

Examples from the literature

- Submicroscopic Infection in Plasmodium falciparum-Endemic Populations: A Systematic Review and Meta-Analysis
- Estimating malaria parasite prevalence from community surveys in Uganda: a comparison of microscopy, rapid diagnostic tests and polymerase chain reaction

10.5 Clinical Malaria Incidence

Measurements of clinical malaria incidence, defined as the number of clinical malaria episodes (usually defined as fever plus parasite density above a given threshold) per population over a given time period instead captures a direct measure of disease burden. Clinical malaria incidence can be measured by active or passive case detection or indirectly estimated using other routine health information data.

In addition to clinical malaria incidence, measurements of severe malaria at the population level can be determined as the number of severe cases per person year at risk, but is often measured via the number of cases presenting to the hospital. This can be biased by differential levels of access to care and differences in diagnosis of severe malaria.

- **Importance of Incidence**: Monitoring the incidence of clinical malaria provides direct information on the burden of symptomatic disease. This metric is particularly important for understanding the impact of malaria on public health and healthcare systems.
- **Application in Elimination Programs**: In areas aiming for malaria elimination, reductions in clinical malaria incidence are a critical indicator of progress. A low incidence rate suggests that transmission is being controlled effectively.

Examples from the literature

- Defining clinical malaria: the specificity and incidence of endpoints from active and passive surveillance of children in rural Kenya
- The global distribution of clinical episodes of Plasmodium falciparum malaria
- Estimating malaria incidence from routine health facility-based surveillance data in Uganda
- Using ante-natal clinic prevalence data to monitor temporal changes in malaria incidence in a humanitarian setting in the Democratic Republic of Congo

- Observational study: 27 years of severe malaria surveillance in Kilifi, Kenya

10.6 Entomological measures

A number of metrics derived from entomological data on vector behaviour are also of importance for measuring malaria transmission.

- **Vectoral capacity:** Vectoral capacity describes the potential intensity of transmission by malaria vectors and is defined as the expected number of infectious bites that could eventually arise assuming perfect efficiency of transmission from all mosquito bites on a single human on a single day
  - **Importance of Vectorial Capacity**: This metric helps estimate the transmission potential of a mosquito population. It can be used to predict how environmental or behavioral changes (such as increased mosquito populations or changes in feeding behavior) might impact malaria transmission.
  - **Use in Planning Interventions**: Vectorial capacity helps in designing effective control strategies, such as vector control programs, by identifying areas where mosquito populations are most likely to sustain transmission.
- **Stability index:** The stability index provides a measure of the capacity of the environment to sustain malaria transmission and is defined as the number of human bites taken over the course of a vector's lifetime

Examples from the Literature

- Vectorial capacity and vector control: reconsidering sensitivity to parameters for malaria elimination
- A global index representing the stability of malaria transmission
- Statics and dynamics of malaria infection in Anopheles mosquitoes

10.7 Basic Reporoduction Number (R_0) and Real-Time Reproduction Number (R_t)

The basic reproduction number (R_0) is a theoretical metric used to estimate how many secondary cases are generated by a single malaria infection in a fully susceptible population. The real-time reproduction number (R_t) measures the effective transmission in a population at a given moment, accounting for interventions and immunity.

- **Use of R_0 and R_t**: R_0 provides an understanding of transmission potential in a new or susceptible population, while Rt reflects current transmission dynamics.
  - $\mathbf{R_0 > 1}$: Transmission will continue to increase.
  - $\mathbf{R_0 < 1}$: Transmission will eventually die out, as there are not enough new cases being generated to sustain transmission.
- **Target for Control Programs**: The goal of malaria elimination programs is to reduce R_0 to below 1, which indicates that transmission is no longer self-sustaining.

Examples from the literature

- Revisiting the Basic Reproductive Number for Malaria and Its Implications for Malaria Control
- Is a reproduction number of one a threshold for Plasmodium falciparum malaria elimination?
- Estimating spatiotemporally varying malaria reproduction numbers in a near elimination setting
- Understanding the effective reproduction number of Plasmodium falciparum malaria with seasonal variation at sub-national level in Nigeria

10.8 Heterogeneity in Transmission

When thinking about malaria transmission intensity, it is important to consider the variation in transmission. Heterogeneity in malaria transmission exists across all spatial scales, from differences within households to continental geographic variation. Large-scale geographic variation in transmission is primarily driven by climatic and environmental factors including temperature, altitude, land-use and urbanicity and the impact that these have on vector and parasite survival and breeding site availability, for example.

On a smaller scale, heterogeneity within communities can be driven by proximity to breeding sites, housing quality and host availability through the ownership and use of bed-nets, and attractiveness to mosquitos. In addition, we also observe substantial temporal variation in malaria transmission which results from seasonal climate patterns, particularly rainfall, with transmission peaking during the rainy season and lowest during the dry season.

Additionally, as mentioned above not all infectious mosquito bites result in blood-stage infection, and factors that impact the efficiency of a mosquito bite including immunity and heterogeneity in mosquito biting are also important determinants in the heterogeneity of malaria transmission.

Examples from the literature

- Urban malaria in sub-Saharan Africa: dynamic of the vectorial system and the entomological inoculation rate
- Modelling the global constraints of temperature on transmission of Plasmodium falciparum and P. vivax
- Estimating Air Temperature and Its Influence on Malaria Transmission across Africa
- Exploring agricultural land-use and childhood malaria associations in sub-Saharan Africa
- Relationship Between Altitude and Intensity of Malaria Transmission in the Usambara Mountains, Tanzania
- The Risk of a Mosquito-Borne Infection in a Heterogeneous Environment
- Factors Determining the Heterogeneity of Malaria Incidence in Children in Kampala, Uganda.
- Housing Improvements and Malaria Risk in Sub-Saharan Africa: A Multi-Country Analysis of Survey Data
- Insecticidetreated net (ITN) ownership, usage, and malaria transmission in the highlands of western Kenya.
- Nonrandom Selection and Multiple Blood Feeding of Human Hosts by *Anopheles* Vectors: Implications for Malaria Transmission in Papua New Guinea

Part IV

Malaria Diagnosis and Treatment

Effective **diagnosis** and **treatment** are essential aspects of malaria control programs. Accurate diagnosis ensures that patients receive appropriate care, preventing the overuse of antimalarial drugs and improving treatment outcomes. Timely and correct treatment not only saves lives but also reduces the spread of drug resistance.

This chapter will explore the key **diagnostic methods**—microscopy, rapid diagnostic tests (RDTs), and molecular techniques—and the situations in which they are most effective. We will also review the **treatment protocols** for both uncomplicated and severe malaria, focusing on first-line therapies and considerations for special populations, such as children and pregnant women.

Finally, the chapter addresses the growing challenge of **drug resistance** and the strategies required to mitigate its impact. By understanding the latest diagnostic tools, treatment protocols, and resistance management approaches, participants will gain practical insights essential for improving malaria case management in diverse settings.

Learning Objectives

- Compare microscopy, rapid diagnostic tests (RDTs), and molecular techniques for malaria detection.
- Identify when and where to use each diagnostic tool based on context and resources.
- Describe the recommended first-line treatments for uncomplicated and severe malaria.
- Identify common antimalarial drugs and their mechanisms of action.
- Explain treatment considerations for special populations (e.g., pregnant women, infants).
- Recognize the emergence and impact of drug resistance on malaria control.
- Explore strategies to manage and prevent resistance.
- Understand challenges in ensuring equitable access to diagnostics and treatment.

11 Diagnostic Methods

Accurate and timely diagnosis is essential in malaria case management to ensure that patients receive the correct treatment, improve health outcomes, and reduce unnecessary antimalarial use. When a patient with fever presents to a health facility, a health worker may suspect malaria based on the patient's symptoms. However, these symptoms are similar to those seen with many other diseases, making accurate clinical diagnosis difficult. For many years, national malaria programs recommended treating patients for malaria based on symptoms alone, because most health facilities did not have the equipment and trained staff to perform laboratory tests. Malaria was extremely common and potentially fatal, and providing treatment based on clinical diagnosis alone could save lives.

In 2010, the World Health Organization recommended confirming all suspected cases of malaria with a diagnostic test prior to treatment. In the subsequent years, national malaria programs in endemic areas have continued to expand access to Rapid Diagnostic Tests (RDTs) and high-quality microscopy services for malaria in health facilities. In addition, community health workers (CHWs) in many countries have received training on integrated community case management of common childhood illnesses, including malaria, pneumonia, and diarrhea. Many CHWs are now able to use RDTs for febrile patients and to treat them with recommended antimalarials if they are positive.

11.1 Microscopy

- **Process:**
  - Thin and thick blood smears are prepared and stained with Giemsa or Field's stain.
  - A trained microscopist examines the slides under a microscope to identify parasites and count parasite density.
- **Advantages:**
  - **High sensitivity and specificity** in experienced hands.
  - Allows for identification of **all Plasmodium species** and quantification of parasite load, crucial for monitoring severe malaria.
- **Limitations:**

- Requires **skilled personnel** and a well-maintained laboratory.
- Can be **time-consuming**

11.2 Rapid Diagnostic Tests (RDTs)

- **Process:**
  - A small drop of blood is placed on an RDT strip, which reacts with malaria antigens. A color change indicates a positive or negative result.
  - Common targets include **Histidine-Rich Protein 2 (HRP2)** for *Plasmodium falciparum* and **Plasmodium-specific lactate dehydrogenase (pLDH)** for other species.
- **Advantages:**
  - **Fast** results (15-20 minutes) without the need for advanced laboratory infrastructure.
  - Easy to use, making it ideal for **community health workers** and remote clinics.
- **Limitations:**
  - Sensitivity may decline with **low parasite densities** or **HRP2 gene deletions** in *P. falciparum*.
  - Cannot provide **parasite counts** or differentiate between some malaria species effectively.

11.3 Molecular Techniques (e.g., PCR)

- **Process:**
  - Polymerase Chain Reaction (PCR) amplifies the DNA of malaria parasites to confirm the presence of the infection. Other molecular methods include **Loop-Mediated Isothermal Amplification (LAMP)**.
- **Advantages:**
  - **Highly sensitive and specific**, able to detect mixed infections and low-level parasitemia.
  - Useful for **surveillance**, especially in elimination settings where infections are rare but need to be identified precisely.

- **Limitations:**
  - Requires **specialized equipment** and trained personnel, making it unsuitable for most routine clinical settings.
  - Higher **cost** compared to microscopy and RDTs.

12 Treatment Protocols

The World Health Organization recommends treating patients with malaria within 24 – 48 hours after their first symptoms appear. Treatment of a patient with malaria should follow the country's national guidelines, which typically take the following into consideration:

- Type (species) of the infecting parasite
- Clinical status of the patient
- Accompanying illness(es) or condition(s)
- Pregnancy status
- Drug allergies, and other medications taken by the patient
- Where the infection was acquired and the presence of antimalarial drug resistance.

12.1 Uncomplicated malaria

Patients who have uncomplicated malaria can usually be treated on an outpatient basis; however, patients with severe malaria should be hospitalized.

The medications recommended for treatment of uncomplicated malaria cases are active against the parasite forms in the blood (the forms that cause disease). The World Health Organization (WHO) recommends the use of artemisinin-based combination therapies (e.g., artemether-lumefantrine or dihydroartemisinin-piperaquine) for the treatment of uncomplicated malaria to prevent or delay the development of antimalarial resistance. WHO recently expanded the recommendation for Artemisinin-based combination therapy, or ACT, use to include infants less than five kilograms bodyweight and all pregnant women, even those in the first trimester. Artemether-lumefantrine is the preferred option for use in the first trimester of pregnancy.

WHO's Consolidated guidelines for malaria

12.2 Severe malaria

Severe malaria occurs when an infection is complicated by serious organ failure or abnormalities in the patient's blood or metabolism.

Patients who have severe P. falciparum malaria or who cannot take oral medications should be treated with parenteral medications in a hospital. The World Health Organization recommends parenteral artesunate for treatment of severe P. falciparum malaria in both adults and children, including pregnant women in all trimesters and lactating women. If artesunate is not available, parenteral artemether should be used in preference to quinine for the treatment of severe malaria. Intravenous treatment for severe malaria should be followed by a complete course of an oral ACT.

Some malaria-endemic countries recommend pre-referral treatment with artesunate be given by suppository or injection before a severely ill patient is referred to a hospital for definitive care.

WHO case management information pages

13 Drug Resistance and Challenges

The emergence and spread of **drug-resistant malaria parasites** represents a signigicant challenge to effective malaria control and elimination. To date, parasite resistance to antimalarial medicines has been documented in 3 of the 5 malaria species known to affect humans: *P. falciparum*, *P. vivax* and *P. malariae*. Parasite resistance results in a delayed or incomplete clearance of parasites from the patient's blood when the person is being treated with an antimalarial.

https://www.youtube.com/watch?v=zwz4R_TcNPo&ab_channel=MalariaConsortium

13.1 Overview

Drug resistance occurs when malaria parasites evolve to survive treatment with antimalarial medications, reducing the drug's effectiveness. Resistance typically arises due to **genetic mutations** in the parasite, which can accumulate and spread under drug pressure.

13.1.1 History of Drug Resistance:

Chloroquine-resistant *P. falciparum* first developed independently in three to four areas in Southeast Asia, Oceania, and South America in the late 1950s and early 1960s. Since then, chloroquine resistance has spread to nearly all areas of the world where falciparum malaria is transmitted, with the exception of Central America west of Panama Canal, Haiti, and the Dominican Republic.

P. falciparum has also developed resistance to nearly all of the other currently available antimalarial drugs, such as sulfadoxine/pyrimethamine, mefloquine, and quinine. Although resistance to these drugs tends to be less widespread geographically, in some areas of the world, the impact of multi-drug resistant malaria can be substantial. Most recently, partial artemisinin resistance has independently emerged in parts of Southeast Asia, South America, and East Africa, impacting the efficacy of artemisinin-based combination therapy, the main class of antimalarials used worldwide.

Chloroquine-resistant *P. vivax* malaria was first identified in 1989 among Australians living in or traveling to Papua New Guinea. *P. vivax* resistance to chloroquine is a major challenge in

Oceania and some countries in Southeast Asia. Emerging evidence has suggested chloroquine-resistant *P. vivax* in other countries and regions but has not impacted treatment policies and further evaluation is needed.

13.1.2 Mechanisms of Resistance

- **Single or Multiple Gene Mutations:**
  - Mutations in specific genes, such as the *pfkelch13*gene, have been associated with artemisinin resistance.
  - Mutations in *pfdhfr*and *pfdhps* genes are linked to sulfadoxine-pyrimethamine resistance.
  - *Pfplasmepsin 2-3* copy number linked to piperaquine resistance.
  - *Pfmdr1* copy number linked to mefloquine resistance.
- **Partner Drug Failure:**
  - In ACTs, the artemisinin component clears most parasites quickly, while the partner drug (e.g., lumefantrine) eliminates the remaining parasites.
  - Resistance to partner drugs such as **piperaquine** has also emerged, further complicating treatment efforts.

13.1.3 Current Impact of Drug Resistance

- **Geographical Spread:**
  - Artemisinin resistance was initially confined to the **Greater Mekong Subregion**, but recent evidence suggests **delayed clearance times** and drug failure are appearing in **Africa**.
  - The spread of resistance increases the risk of **treatment failure** and **malaria resurgence**.
- **Consequences of Drug Resistance:**
  - **Higher treatment failure rates** lead to prolonged illness and increased mortality.
  - Resistance forces health programs to switch to **more expensive treatment regimens**.
  - Drug resistance can compromise **Seasonal Malaria Chemoprevention (SMC)** programs by reducing the efficacy of SP, a key preventive drug in many regions.

13.1.4 Strategies to Address Drug Resistance

1. **Surveillance and Monitoring:**
    - **Therapeutic Efficacy Studies (TES):** Regular monitoring of drug effectiveness through TES helps detect early signs of resistance.
    - **Molecular Surveillance:** Tracking mutations (e.g., kelch13) allows programs to monitor the spread of artemisinin resistance.
2. **Rotational Use of Antimalarial Drugs:**
    - Cycling different ACTs reduces the selection pressure on any one drug, slowing resistance development.
3. **New Drug Development:**
    - Investment in **next-generation antimalarials** is essential. Drugs in the pipeline include **triple ACTs (TACTs)**, which combine artemisinin and two partner drugs to outmaneuver resistance.
4. **Combination Prevention Strategies:**
    - Integrating **preventive interventions** such as **insecticide-treated nets (ITNs)**, **indoor residual spraying (IRS)**, and **SMC** helps reduce malaria transmission, decreasing reliance on antimalarial drugs.

13.1.5 Challenges in Ensuring Access to Diagnostics and Treatment

1. **Equitable Access to Quality Care:**
    - Many communities in malaria-endemic areas lack access to **diagnostic tools** and **antimalarial drugs**, leading to **delayed treatment** or reliance on unregulated drug markets.
    - Ensuring **supply chain stability** and preventing stockouts is a major challenge, especially in remote areas.
2. **Training and Capacity Building:**
    - Effective malaria management requires **trained healthcare workers** capable of diagnosing malaria accurately and following treatment protocols. Inadequate training can lead to misdiagnosis and inappropriate treatment.
3. **Patient Adherence and Treatment Completion:**

- Non-adherence to treatment regimens increases the likelihood of resistance developing. Programs must promote **treatment completion** and address barriers such as **drug side effects** and **distance to health facilities**.

4. **Funding and Resource Allocation:**

   - Combating resistance and ensuring equitable access to treatment require **sustained financial investment**. However, malaria control programs often face funding shortages and competing health priorities.

13.1.6 Future Directions and Global Cooperation

1. **Global Initiatives to Combat Resistance:**

   - The **Global Plan for Artemisinin Resistance Containment (GPARC)** and the **WHO Global Technical Strategy for Malaria** provide frameworks for managing resistance.
   - Regional networks, such as the **Greater Mekong Subregion Partnership**, coordinate efforts to monitor and contain resistance.

2. **Role of Research and Innovation:**

   - Ongoing research into new drugs and diagnostics is essential to stay ahead of evolving resistance.
   - **Genomic studies** are helping to better understand resistance mechanisms and guide drug development.

3. **Community Engagement and Awareness:**

   - Educating communities about **malaria prevention** and the importance of completing treatment can enhance program success. Community health workers play a crucial role in improving **awareness and adherence** at the grassroots level.

14 Malaria Meds: a MasterClass with Profs. Timothy Wells, Pierre Hugo, George Jagoe & Abdoulaye Djimde

A great talk on Malaria Treatment and Diagnosis from the Ifakara Heallth Institue on all of the topics covered in this chapter.

https://www.youtube.com/watch?v=YJQee6MSPTQ&ab_channel=IfakaraHealthInstitute%28IFAKARA%29

Part V

Prevention and Control

Prevention and control strategies are essential to reducing malaria transmission and achieving elimination goals. These efforts involve a combination of **vector control**, **chemoprevention**, **vaccines**, and **community-based approaches** to interrupt the life cycle of malaria parasites and protect at-risk populations. This chapter explores key interventions and their role in global malaria control efforts.

Throughout this Chapter we will link to some great talks by leading malaria scientists and public health specialists that were hosted by the Ifakara Health Instiitute.

Learning Objectives

- **Understand Vector Control:**
  - Explain the role of **ITNs** and **IRS** in reducing malaria transmission.
- **Apply Chemoprevention and Vaccination:**
  - Identify target groups for **SMC** and **IPT**.
  - Describe the benefits and limitations of malaria vaccines like **RTS,S**.
- **Explore Community-Based Interventions:**
  - Recognize the role of **CHWs** and **iCCM** in malaria management.
- **Analyze Challenges:**
  - Understand the impact of **insecticide and drug resistance** on control efforts.
- **Evaluate Integrated Approaches:**
  - Appreciate the value of combining multiple interventions for effective malaria control.

15 Insecticide Treated Nets

Insecticide-Treated Nets (ITNs) are one of the most effective and widely used tools in malaria prevention. By protecting individuals from mosquito bites at night—the peak biting time for Anopheles mosquitoes—ITNs reduce both infections and overall transmission.

Types of ITNs:

- **Conventional ITNs:** Treated with insecticides that remain effective for several washes.
- **Long-Lasting Insecticidal Nets (LLINs):** These retain their effectiveness for at several years and multiple washes without re-treatment.

How ITNs Work:

- ITNs act as both a **physical barrier** and a **chemical deterrent**.
- When mosquitoes come into contact with the net, they are either **repelled** or **killed** by the insecticide.

Impact of ITNs on Malaria Transmission:

- Studies show that widespread ITN use can reduce child mortality by **20%** and malaria incidence by **50%**.
- ITNs are most effective when **at least 80% of the population** in a given area uses them regularly.

> Stop and Read
>
> A 2015 paper estimated that almost 68% of the reduction in malaria burden between 2000-2015 can be attributed to the widespread adoption of ITNs.

Challenges and Limitations:

- **Insecticide resistance**: Some mosquito populations have become resistant to pyrethroids, the main insecticide used in ITNs.
- **Net distribution and usage gaps**: Not all households receive enough nets, people don't always use when in bed, and some may use them for purposes other than malaria prevention.

Solutions and Innovations:

- Newer **PBO (Piperonyl Butoxide) nets** and **Dual Active Ingredient (Dual-AI) nets** have been developed to counter pyrethroid resistance.
- **Mass net distribution campaigns** and regular **monitoring** are essential to maintaining coverage.

See the video below for an indepth look at ITNs and their use in malaria control.

https://www.youtube.com/watch?v=Y6fA8ViX8c8&ab_channel=IfakaraHealthInstitute%28IFAKARA%29

16 Indoor Residual Spraying

Indoor Residual Spraying (IRS) is a malaria prevention method that targets indoor resting mosquitoes. IRS involves coating interior walls and other sprayable surfaces in a house with a residual (long-lasting) insecticide. IRS takes advantage of the indoor resting behavior of many malaria mosquitoes that rest on these surfaces inside houses after taking a blood meal. The insecticide will kill mosquitoes and other insects that come in contact with these treated surfaces for several months. IRS does not directly prevent people from being bitten by mosquitoes. However, IRS usually kills adult mosquitoes after they have fed on blood and rest on a treated surface, which shortens the mosquito's lifespan and prevents the development and subsequent transmission of malaria parasites to other people. A very high proportion of households in an area, ideally over 80%, must be treated to protect a community.

How IRS Works:

- IRS works by coating walls with **long-lasting insecticides**. Mosquitoes that come into contact with the sprayed surfaces are killed.
- IRS is particularly effective against **endophilic mosquitoes** (species that rest indoors).

When and Where to Use IRS:

- IRS is deployed in **high-transmission areas** and during malaria outbreaks.
- It is often used **seasonally**, just before the rainy season when mosquito populations increase.

Impact on Malaria Control:

- IRS has been instrumental in **eliminating malaria** in several regions, including parts of **Southern Africa**.
- It works best when **at least 85% of homes** in a targeted area are sprayed.

Challenges and Innovations:

- **Insecticide resistance** limits the effectiveness of IRS.
- Programs are exploring **non-pyrethroid insecticides** such as **organophosphates** and **neonicotinoids**.

- **Community acceptance** can be a barrier, as people may be reluctant to allow spraying in their homes.
- **Changing of the built home environment**, behaviours such as building work on residences can also impact the effectiveness of IRS.

See the video below for an informative explanation of IRS from the WHO

https://www.youtube.com/watch?v=uTNoT2gSLz0&ab_channel=WorldHealthOrganization%28WHO%29

17 Chemoprevention

Chemoprevention involves the use of antimalarial drugs to prevent infection in high-risk groups, particularly **young children** and **pregnant women**.

17.1 Intermittent preventive treatment of malaria in pregnant women (IPTp)

Adults who have survived repeated malaria infections throughout their lifetimes usually become partially immune to severe or fatal malaria, though immunity wanes if there is not ongoing exposure to the parasite. However, because of the changes in women's immune systems during pregnancy and the presence of a new organ (the placenta) with new places for parasites to bind, pregnant women are more susceptible to malaria infection than non-pregnant women.

Malaria infection during pregnancy can have adverse effects on both mother and fetus, including maternal anemia, fetal loss, premature delivery, intrauterine growth retardation, and delivery of low birth-weight infants (<2500 g or <5.5 pounds), a risk factor for fetal death.

The problems that malaria infection causes differ somewhat by the type of malaria transmission area: stable (high) or unstable (low) transmission.

In high transmission areas, women have developed immunity that generally prevents severe disease; however, the parasite specifically targets the placenta, leading to an increased risk during pregnancy. In these settings, maternal anemia and delivery of low birth-weight infants (<2500 g or <5.5 pounds) are frequent complications of malaria. It is a particular problem for women in their first and second pregnancies, for younger women, and for women who are HIV-positive.

In low transmission areas, women generally have developed no immunity to malaria. Malaria infection is more likely to result in severe malaria disease, maternal anemia, premature delivery, or fetal loss.

IPTp entails administration of a curative dose of an effective antimalarial drug (currently sulfadoxine-pyrimethamine) to all HIV-negative pregnant women in areas of moderate to high malaria transmission, without testing whether or not they are infected with the malaria parasite. IPTp should be given at each routine antenatal care visit, starting as early as possible in the second trimester.

An exmaple of IPT-p programs in Kenya is descirbed in this video:

https://www.youtube.com/watch?v=JaS7h-Q0wGw&ab_channel=PopulationCouncil

17.2 Seasonal Malaria Chemoprevention

Seasonal malaria chemoprevention (SMC) is the administration of treatment doses of longer-acting antimalarial medications to children at monthly intervals (cycles) in areas of highly seasonal transmission (~60% of annual cases occurring in four consecutive months) with the aim of maintaining protective drug concentrations in the blood throughout a complete season of peak transmission. WHO first recommended SMC in 2012 based on a pooled analysis of clinical trials that demonstrated up to 70% reduction of uncomplicated malaria among young children during the high-transmission season. The recommendation included monthly treatment with sulfadoxine-pyrimethamine (SP) plus amodiaquine (AQ) to children 3—59 months of age during the period of peak malaria transmission (typically 3—4 monthly cycles) in the Sahel region of Africa where minimal SP and AQ resistance had been found.

In 2022, WHO SMC guidelines were updated to include more flexibility in implementation of SMC in moderate to high malaria burden areas with seasonal transmission, based on local epidemiology, transmission patterns or evidence of effectiveness. In addition, WHO updated a field guide for SMC implementation in 2023.

Children less than five years of age are typically targeted for SMC as they are the most vulnerable to serious disease; however, SMC can include older children. Most countries administer SMC via door-to-door campaigns in which a community distributor gives the first day's dose of SP and AQ and the second and third doses of AQ are given by the child's caregiver. Other medications can be considered; however, SMC medications should not include compounds that are used to treat clinical disease in SMC distribution regions. In addition, SMC should not be used in areas where other chemoprevention interventions are being used in the same population (e.g., perennial malaria chemoprevention or mass drug administration).

Since WHO first recommended SMC in 2012, the intervention has scaled up from protecting 0.2 million children per cycle living in two Sahel countries to 49 million children living in 17 countries in sub-Saharan Africa by 2022 (WMR 2023). Post-distribution coverage surveys suggest that this intervention is widely accepted by caregivers. Drug resistance monitoring and systems to evaluate the protective effect of SMC under programmatic conditions at the population level should be supported.

Video from the WHO on SMC delivery and the updated guidelines

https://www.youtube.com/watch?v=nFF40Tbpjn4&ab_channel=WorldHealthOrganization%28WHO%29

Video from Malaria Consortium on the future of SMC and it's delivery in new geographies following the WHO updated guidelines

https://www.youtube.com/watch?v=44M4uJhwxuM&ab_channel=MalariaConsortium

17.3 Perennial Malaria Chemoprevention

In settings of moderate to high malaria transmission, countries may consider giving full treatment courses of antimalarials to children at highest risk of severe malaria at selected intervals, a strategy known as perennial malaria chemoprevention (PMC), and formerly known as intermittent preventive treatment of malaria in infants (IPTi). The drug sulfadoxine-pyrimethamine (SP) has been widely used for chemoprevention, including for PMC, although other drugs may be used. PMC is typically delivered during the first one to two years of life primarily during routine vaccination visits delivered through the Expanded Program on Immunization (EPI) platform. Several countries are implementing pilots of PMC to test additional delivery mechanisms outside the EPI platform, such as community delivery, and to understand the effectiveness of SP for PMC in settings with high SP resistance.

Video from the WHO on PMC guidelines

https://www.youtube.com/watch?v=Lqi4D-RKjhQ&ab_channel=WorldHealthOrganization%28WHO%29

18 Vaccines

Malaria vaccines have been in development since the 1960's, with substantial progress in the last decade. October 6, 2021, marked a historic day in the development of malaria vaccines, with release of the World Health Organization (WHO) recommendation for widespread use of the RTS,S/AS01 (RTS,S) malaria vaccine among children living in sub-Saharan Africa and other regions with moderate to high *P. falciparum* malaria transmission. Two years later, the WHO approved a second malaria vaccine (R21/Matrix-M) for use in malaria endemic countries.

18.1 Barriers to developing a malaria vaccine

The development of a malaria vaccine has faced several obstacles: the lack of a traditional market, few developers, and the technical complexity of developing any vaccine against a parasite.

Malaria parasites have a complex life cycle, and there is poor understanding of the complex immune response to malaria infection. Malaria parasites are also genetically complex, producing thousands of potential antigens. Unlike the diseases for which we currently have effective vaccines, exposure to malaria parasites does not confer lifelong protection. Acquired immunity only partially protects against future disease, and in many cases, people still become infected with the parasite; malaria infection can persist for months without symptoms of disease.

18.2 RTS,S/AS01 vaccine

More than a dozen vaccine candidates are now in clinical development, with two approved for use in children under five years of age living in areas of e moderate to high malaria transmission. GlaxoSmithKline Biologicals' RTS,S/AS01 became the first malaria vaccine to receive a WHO recommendation for widespread use on October 6, 2021.

The vaccine has been in development since the mid-1980s and has advanced thanks to a unique public-private partnership of GSKBio, the PATH Malaria Vaccine Initiative, and African and other research organizations, with funding support from the Bill and Melinda Gates Foundation. Following the pivotal Phase 3 trial in 11 sites from 7 countries showing that the vaccine was efficacious, in 2015 a large-scale pilot implementation accompanied by rigorous evaluation

provided the conclusive evidence on feasibility, safety, and population impact that led to the WHO recommendation. Key findings from the malaria vaccine pilots include:

- **Feasible to deliver:** Vaccine introduction is feasible, with good and equitable coverage of RTS,S seen through routine immunization systems, even in the context of the COVID-19 pandemic.
- **Reaching the unreached:** RTS,S increased equity in access to malaria prevention.
  - More than two-thirds of children in the three pilot countries who were not sleeping under an ITN benefitted from the RTS,S vaccine.
  - Layering the tools results in over 90% of children benefitting from at least one preventive intervention (ITN or the malaria vaccine).
- **Strong safety profile:** RTS,S vaccine has a favorable safety profile. By the time of pilot completion in 2023, >6 million doses of the vaccine have been administered with >2.5 million children receiving at least one dose of the vaccine in three African countries, with no new safety signals identified.
- **No negative impact on uptake of bed nets, other childhood vaccinations, or health seeking behavior for febrile illness.** In areas where the vaccine has been introduced, there has been no decrease in the use of insecticide-treated nets, uptake of other childhood vaccinations or health seeking behavior for febrile illness.
- **High impact in real-life childhood vaccination settings:** In addition to the 39% reduction in clinical malaria seen in the Phase 3 trial, the pilot found significant reduction (30%) in severe malaria and 13% reduction in all-cause mortality in children, even when introduced in areas where insecticide-treated nets are widely used and there is good access to diagnosis and treatment.
- **Highly cost-effective:** Modelling estimates that the vaccine is cost effective in areas of moderate to high malaria transmission.

Following the WHO recommendation of RTS,S for widespread use in moderate to high transmission settings, next steps included funding decisions from the global health community for broader rollout, and country decision-making on whether to adopt the vaccine as part of national malaria control strategies. Shortly after WHO recommendation, GAVI committed funding to support vaccine introduction and established the application process. The immediate unprecedented demand for the vaccine exceeded the available limited RTS,S supply, leading to development of the transparent, fair, and equitable vaccine allocation framework by WHO and GAVI.

WHO's timely recommendation of the second-in-class RTS,S-like vaccine (R21/Matrix-M) in 2023 is expected to result in sufficient vaccine supply to benefit all children living in malaria-endemic areas.

18.3 R21/Matrix-M Vaccine

The R21/Matrix-M malaria vaccine, developed by the University of Oxford and manufactured and scaled up by the Serum Institute of India (SII), is only the second vaccine the world has seen against malaria. The vaccine also contains Novavax's Matrix-M, an "adjuvant" which boosts the immune system response to make it more powerful and long-lasting. This technology – that was used in Novavax's COVID-19 vaccine – induces the influx of antigen-presenting cells at the injection site and enhances antigen presentation in local lymph nodes, which means that the immune system is triggered as strongly as possible. In a phase 3 trial, the vaccine was 75% effective when given before the high transmission season, and 68% effective when given on an age-based schedule in areas with year-round malaria

However, the idea is not to replace RTS,S but to be complementary – Gndefinedavi has already approved funding for a malaria vaccine programme and is ready to support rollout of R21 alongside RTS,S.

https://www.youtube.com/watch?v=L4JU3mH_a0M&t=5929s&ab_channel=IfakaraHealthInstitute%28IFAKARA%29

18.4 Malaria vaccines: the way forward

A number of other malaria vaccine candidates are in development or trial phases, including transmission-blocking vaccines that target the sexual stage of parasite development in the mosquito and mRNA vaccines against malaria. The world's leading global health organizations have developed the Malaria Vaccine Technology Roadmap for accelerating development of a highly effective malaria vaccine.

The roadmap includes the following strategic goals for malaria vaccines by 2030:

- Develop and license malaria vaccines with protective efficacy of at least 75% against clinical malaria for areas with ongoing malaria transmission.
- Develop malaria vaccines that reduce transmission and human malaria infection, enabling elimination in multiple settings through mass vaccination campaigns.

https://www.youtube.com/watch?v=Nntfiz3Grv4&ab_channel=IfakaraHealthInstitute%28IFAKARA%29

19 Community Based Interventions

Community engagement is essential to malaria prevention and treatment efforts. **Community health workers (CHWs)** play a vital role in delivering interventions, particularly in remote and underserved areas.

- **Integrated Community Case Management (iCCM):**
  - CHWs are trained to **diagnose and treat malaria, pneumonia, and diarrhea** at the community level.
  - iCCM ensures that children receive **timely treatment** without needing to visit health facilities.
- **Health Education and Behavior Change Communication (SBCC):**
  - **Awareness campaigns** promote the use of ITNs and adherence to treatment.
  - Communities are educated on **environmental management**, such as eliminating mosquito breeding sites.
- **Community Involvement in Vector Control:**
  - CHWs help distribute ITNs and participate in **household IRS campaigns**.
  - Community participation ensures greater acceptance and coverage of interventions.
- **Challenges:**
  - CHWs often face **training and resource gaps**, which limit their ability to provide consistent care.
  - **Sustained funding** is necessary to maintain community-based programs.

20 Useful Resources on Malaria Control Interventions and New Approaches

Gene Drive for Malaria Elimination

https://www.youtube.com/watch?v=_5qkftXuuUE&ab_channel=IfakaraHealthInstitute%28IFAKARA%29

https://www.youtube.com/watch?v=l-NxPPZICss&ab_channel=IfakaraHealthInstitute%28IFAKARA%29

Vector Control

https://www.youtube.com/watch?v=N9YaKbgEfBk&t=284s&ab_channel=IfakaraHealthInstitute%28IFAKARA%29

https://www.youtube.com/watch?v=WnX7R5NlUR0&ab_channel=IfakaraHealthInstitute%28IFAKARA%29

Sustaining Gains in Malaria Reductions with Interventions

https://www.youtube.com/watch?v=aI9pixtvFvw&t=252s&ab_channel=IfakaraHealthInstitute%28IFAKARA%29