Foundational Malaria Knowledge

MACEPA Data Fellowship - Training Materials

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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 and associated short quizzes.

We will meet as a team on **[INSERT DATE]** to discuss module content, check through quizzes, and answer any questions.

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.

Module Topics

- Introduction to Malaria
- Malaria Parasite Biology
- Epidemiology of Malaria
- Malaria Transmission
- Diagnosis and Treatment
- Prevention and Control
- Surveillance and Data Analysis
- Current Challenges and Future Directions

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

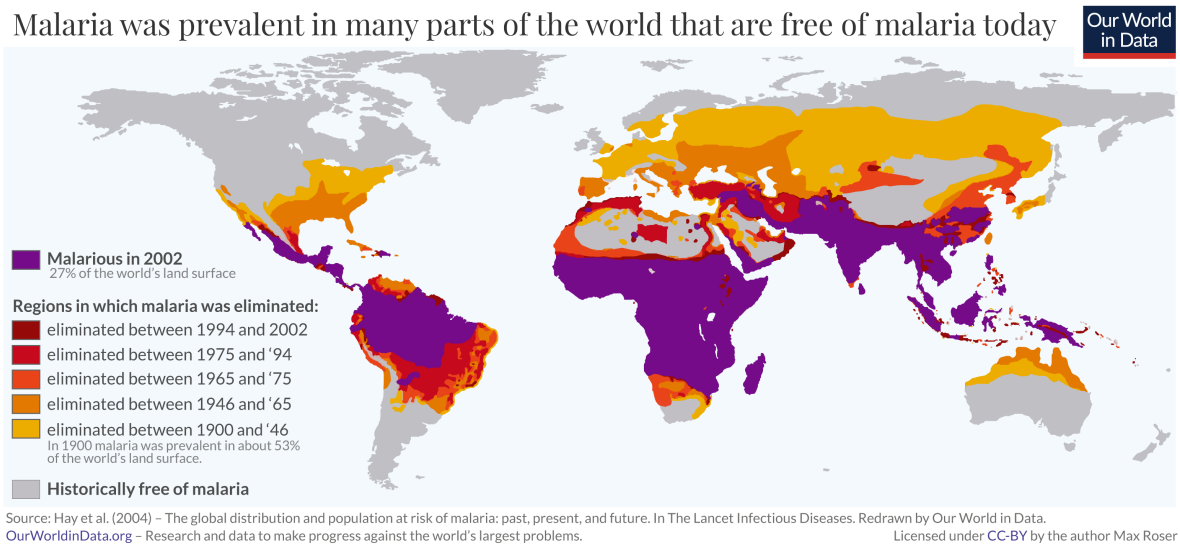

Figure 1.1: Source: Our World in Data https://ourworldindata.org/malaria-past-prevalence

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.

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.

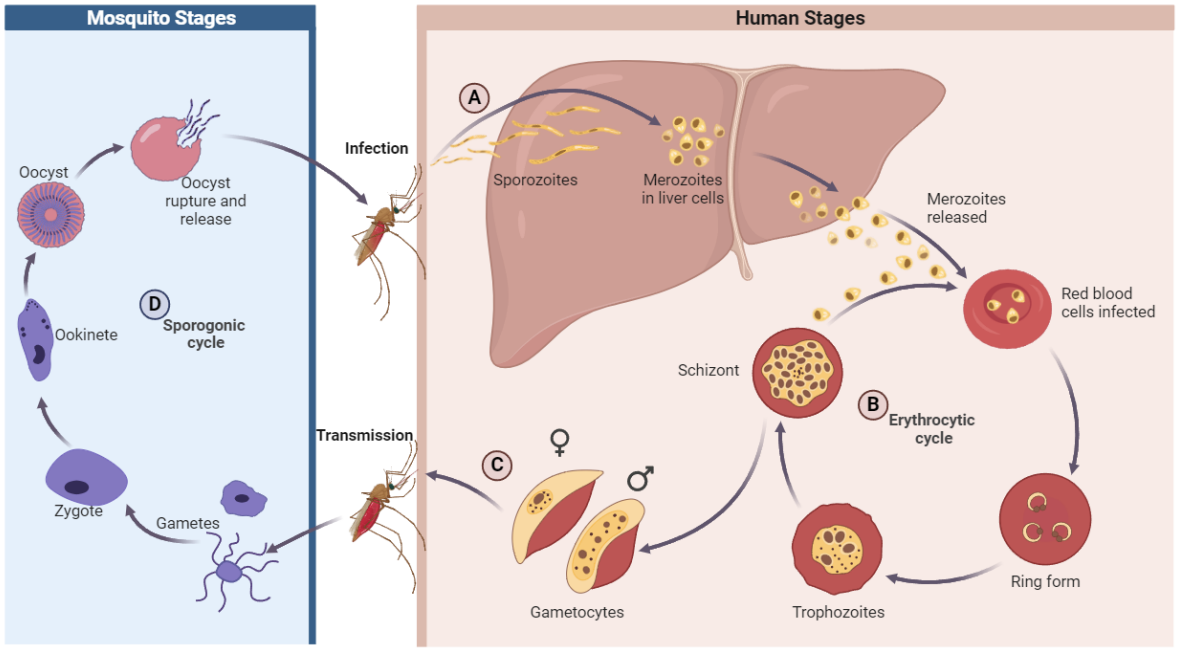

Figure 4.1: **The lifecycle of *P. falciparum* in humans and mosquitos. A)** Inoculation of sporozoites and the pre-erythrocytic infection stages in the liver; **B)** Asexual reproduction and blood stage infection; **C)** Gametocyte production and ingestion during a bloodmeal; and **D)** Sexual reproduction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

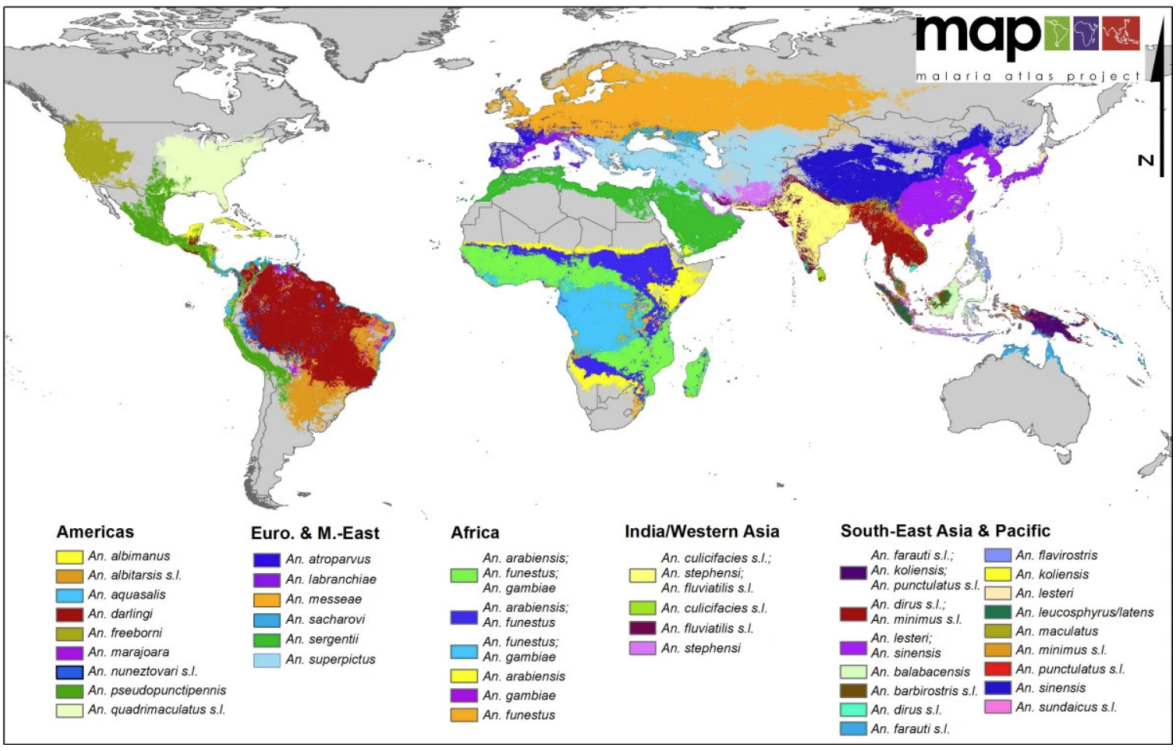

Figure 5.1: A global map of dominant malaria vector species. Reproduced from Sinka et al 2014.[1]

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

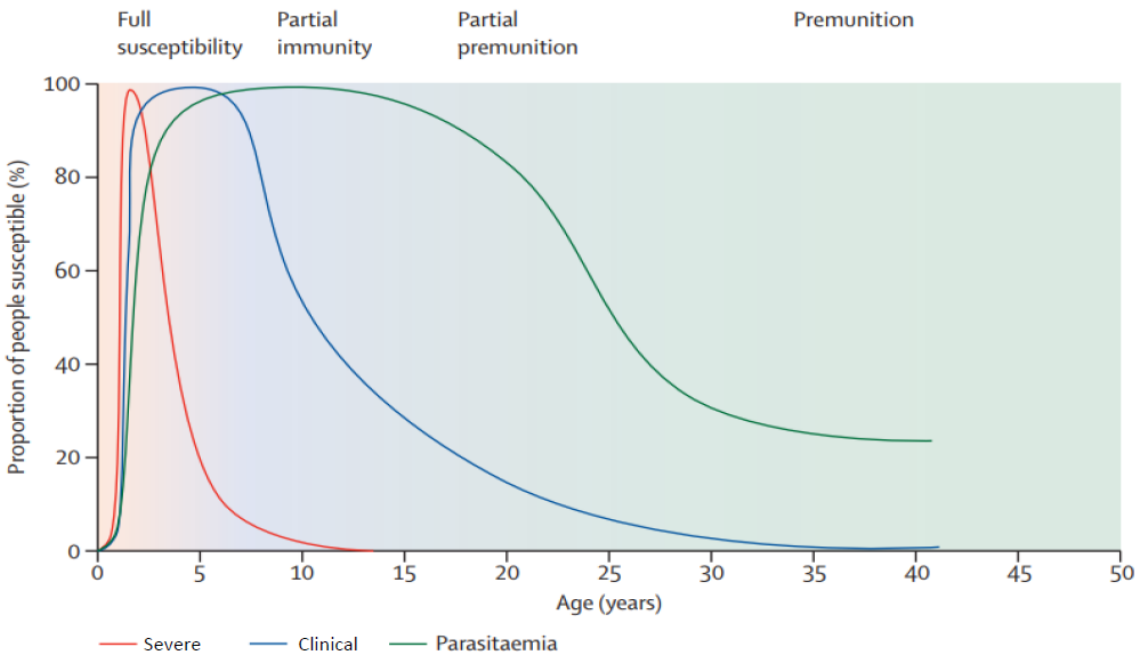

Figure 6.1: Progression of Naturally Acquired Immunity to Malaria. The relationship between age and malaria severity in an area of moderate transmission inte nsity shows how with repeated exposure by early childhood, protection is first acquired against severe disease, then more slowly protection builds 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

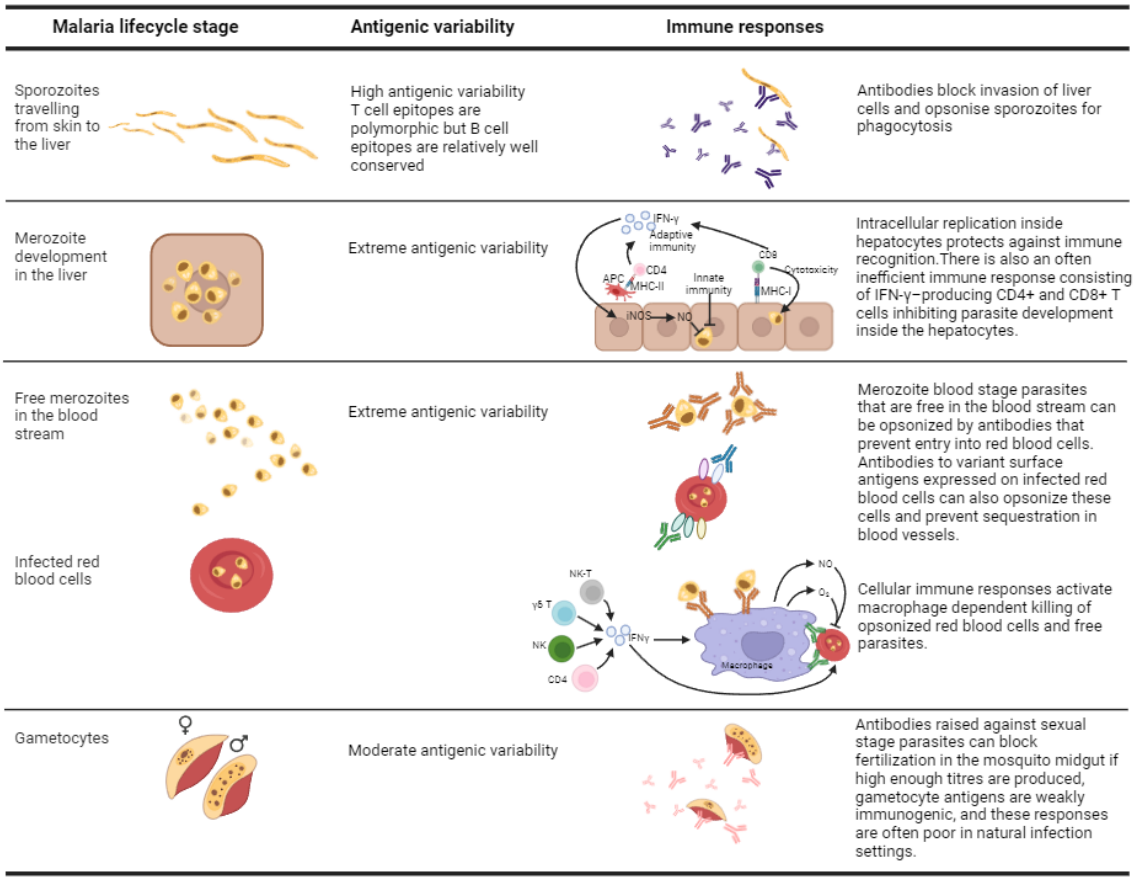

Figure 6.2: Overview of the immune responses directed against each malaria parasite life stage.

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