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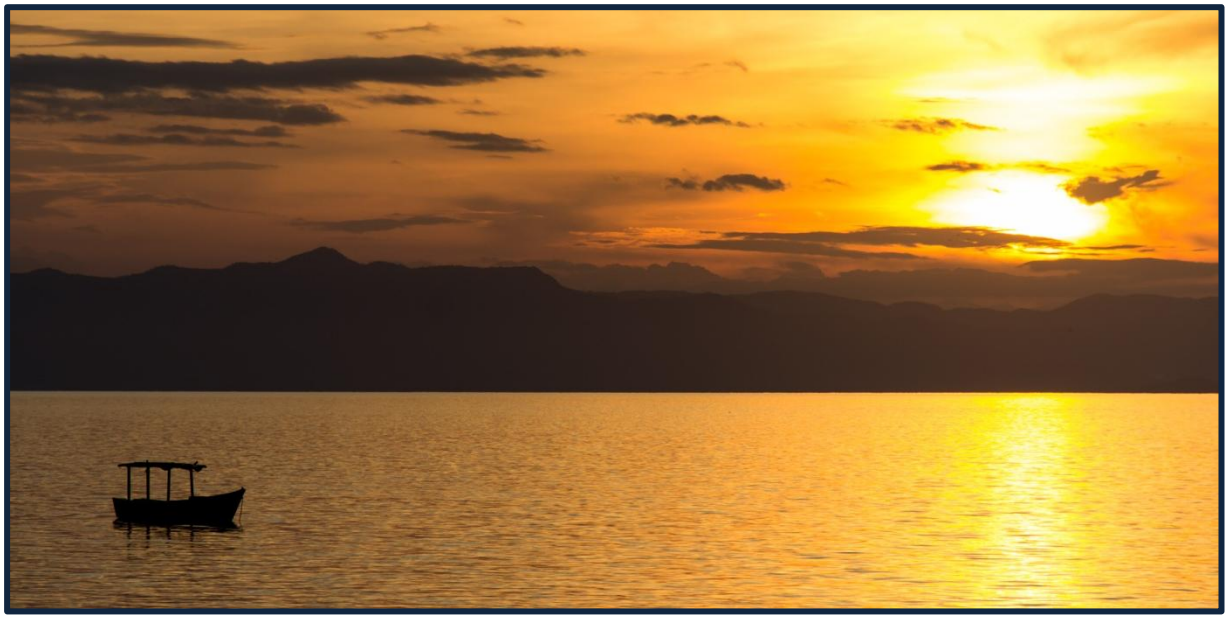
Malaria in Malawi

The current status of diagnosis, prophylaxis and treatment of malaria in Malawi, how international and national guidelines can improve the situation, and how research can change these guidelines for the future



The sun sets over Lake Malawi

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1 Abstract

Background: Malaria is still the number one killer in sub-Saharan Africa, even though it is in principle a preventable and treatable disease. A large amount of progress has been made over the last decades, but there is still a long way to go. We wanted to look at some of the challenges facing one sub-Saharan country, Malawi, with a focus on how international and national guidelines help this country with the burden of this disease. We also wanted to look at how research may change these guidelines in the future, and assess if there is a role for using DDT as a means for controlling malaria.

Method: This study is largely based on literary sources, in addition to a personal excursion to Malawi in order to gain first-hand knowledge and a better understanding of the challenges facing the country.

Discussion and conclusion: We found that the current international guidelines are effective tools in the fight against malaria, and that DDT use is still indicated because of a lack of better alternatives. Through developing these recommendations and helping in their fulfilment, international organizations such as WHO play an important role in the continued fight against malaria. Countries can use the international recommendations to develop their own national guidelines, adapting them to better suit local resources and priorities. On-going research has a lot of potential to help make the guidelines become even more effective in the future. Progress in countries such as Malawi is being made, despite large challenges when it comes to lack of adequate resources.

2 Abbreviations

AA	Artesunate–amodiaquine
ACT	Artemisinin-based combination therapy
AIDS	Acquired immunodeficiency syndrome
AL	Artemether–lumefantrine
AM	Artesunate–mefloquine
ANC	Antenatal care
ASP	Artesunate–sulfadoxine–pyrimethamine
AzCq	Azithromycin–chloroquine
CCS	Country Cooperation Strategy
DP	Dihydroartemisinin–piperaquine
EPA	Environmental Protection Agency
HIV	Human immunodeficiency virus
IPT	Intermittent preventive treatment
IPTc	Intermittent preventive treatment in childhood
IPTi	Intermittent preventive treatment in infancy
IPTp	Intermittent preventive treatment in pregnancy
IRS	Indoor residual spraying
ITN	Insecticide-treated nets
LBW	Low birth weight
LLIN	Long-lasting insecticide-treated net
NMCP	National Malaria Control Programme
NPL	National Priority List
PCR	Polymerase chain reaction
PDS	Panel detection score
RBM	Roll Back Malaria
RDT	Rapid diagnostic test
SP	Sulfadoxine–pyrimethamine
WHO	World Health Organization
WHOPES	World Health Organization Pesticide Evaluation Scheme

3 Introduction

Malaria is still the biggest killer in sub-Saharan Africa, despite continued efforts to contain and counteract the disease. In Malawi, malaria accounts for 40% of hospitalizations of children under five and 40% of overall hospital deaths (1), even though malaria can be prevented and treated effectively given the right resources (2).

The World Health Organization (WHO) has developed international guidelines that hope to help in the fight against malaria, with a focus on preventing, treating and overall reducing the burden of malaria in the world (3). Malawi has implemented most of these guidelines in their own set of national guidelines (1).

In addition, a number of studies and projects are underway, looking at both preventive and therapeutic problems, hoping to find ways to make the fight against malaria more efficient.

Additionally, the use of DDT has been surrounded by controversy over the last decades. It went from being one of the most effective tools in the control of mosquitoes to being effectively banned by the Stockholm convention in 2001, due to environmental considerations and concerns about health and safety (4).

We want to assess what kinds of challenges Malawi is facing concerning malaria, and to look at how the international and national guidelines address these challenges. Further, we want to look at how research can affect these guidelines in the future, and finally evaluate if there still is a role for DDT in the prevention of malaria.

This paper is largely based on literary sources, mainly books, guidelines and scientific studies, in addition to the first-hand knowledge acquired in Malawi. During our trip to Malawi, we visited the Zomba Central Hospital, where we were in contact with several different on-going research projects. We hope to be able to use this experience to gain a better understanding of how the health care system in Malawi works, and how Malawi attempts to solve the challenges they face when it comes to malaria.

We will start by describing the parasite and the disease it causes, looking at how malaria can be diagnosed and treated, followed by a presentation of the different preventive methods and a more in depth review of DDT and its role in fighting malaria.

Thereafter, the aspect of malaria globally will be presented, along with the international guidelines for interventions addressing the problem. Further, an introduction of Malawi and the impact of

malaria there will follow, in addition to a description of the research projects we are connected to locally.

This will be followed by a discussion of the challenges facing Malawi regarding health care system, implementation of guidelines and adherence to them. Finally, we will discuss how research may affect the current situation through changing guidelines, as well as whether there is a role for utilization of DDT.

This paper would not be possible without the helpful assistance of our supervisors, Dr Jon Øyvind Odland from Universitetet i Tromsø and Dr Kamija Phiri from the University of Malawi. We want to thank them for all their support, both in Norway and in Malawi. In addition, we would like to express our sincere gratitude to Dr Andrew Matchado and the rest of the staff at Zomba Central Hospital for making sure our stay there was both productive and memorable.

4 Method

This paper is largely a literary review based on external sources in addition to first-hand experience.

The studies used in this paper were collected through semi-systematic searches on PubMed conducted between November 2012 and May 2013. The studies were selected by title, abstract and contents, with a special focus on studies relevant to sub-Saharan Africa. In addition to the scientific studies, we used additional information on various websites that we deemed trustworthy, as well as in books. The information on the WHO guidelines is mainly based on their publications.

In addition to the literature, we wanted to visit Malawi ourselves to gain first-hand knowledge that we could use to substantiate the information and discussion in this paper. Two of the authors of this paper went to Malawi on the 16th of March, and returned to Norway 20th April. During this trip, we actively reached out to the public health care system in Malawi; we spent a week in Zomba, talking to public health researchers and doctors in Zomba Central Hospital, in addition to coming in contact with other health personnel in Malawi, both local and foreign. The trip to Malawi was entirely self-funded by the authors.

In addition to literary sources we found ourselves, our contact person and supervisor in Malawi, Dr Kamija Phiri, supplied us with additional documents, among them the treatment and prevention guidelines for malaria in Malawi.

5 Theory

We will start by presenting the information we feel is needed to discuss this thesis, divided into nine chapters. First, we will present malaria itself, including how the clinical manifestations are affected by factors such as age, immunity, pregnancy and HIV; afterwards, two chapters will describe how it is diagnosed and treated. The fourth chapter concerns prevention, wherein different measures that can prevent malaria are presented. Because of its importance to the subject of this thesis, DDT is described by itself in the fifth chapter. After this, we will present the global aspects of malaria, followed by a presentation of WHO, and then of the WHO guidelines that apply to malaria endemic countries. Finally, we will present Malawi, with a special focus on the challenges they face when it comes to health care and malaria in particular; in this chapter, we will also give a short summary of the different studies we were connected to during our visit to Malawi.

5.1 Malaria

We will begin by introducing malaria, starting with a short description of the traits of the *Plasmodium* species. This will be followed by the pathophysiology and clinical presentation of the disease, succeeded by how this depends on immunity, age, pregnancy and the presence of HIV-infection.

Malaria is a protozoal infection (5), which can be caused by several *Plasmodium* species: *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi* (6). Malaria is most commonly transmitted through female mosquitoes of the *Anopheles* genus, but can also be transmitted congenitally or through contaminated blood, for example via blood transfusion or used needles (7).

When malaria is transmitted through mosquito bites, *Plasmodium* parasites in the form of sporozoites are transferred from the mosquito's salivary glands into the person's bloodstream. The parasites are incorporated by hepatocytes in the liver, where a maturation process results in schizonts. When the hepatocyte ruptures, the schizont divides into thousands of merozoites (7). These merozoites invade erythrocytes, where they mature into either trophozoites or gametocytes. The trophozoites of the different species can be differentiated using microscopic examination (8). The trophozoites then develop into schizonts, which later rupture and result in more merozoites that can invade new erythrocytes, thus repeating the cycle. Gametocytes stay inside the erythrocytes until they are taken up by a mosquito, which is then re-infected; the life-cycle is complete, with new sporozoites stored inside the mosquito's salivary glands. In addition to the stages described above, *P. vivax* and *P. ovale* have dormant stages, hypnocytes, which remain in the liver (7).

The *Plasmodium* life cycle is reliant on the *Anopheles* mosquito as a vector and an adequate temperature. Therefore, the geographical distribution of malaria is determined by the distribution of

the *Anopheles* mosquitoes, as well as areas having the correct climate. The transmission has traditionally remained at altitudes below 2000 m (5). However, in recent years there has been increased malarial transmission in areas of higher altitudes in Africa, which may be a result of climate change resulting in increased temperatures in high-altitude areas (9).

According to the World Health Organization (WHO), malaria transmission intensity can be divided in four different categories: holoendemic, hyperendemic, mesoendemic and hypoendemic. Holoendemic includes areas with perennial transmission of high intensity, where the prevalence of parasitaemia among infants is above 75%. Hyperendemic includes areas with seasonal transmission of high intensity, defined as prevalence of parasitaemia above 50% in children between 2–9 years of age. Mesoendemic includes areas with intermediate transmission, defined as prevalence of parasitaemia in 11–50% of children between 2–9 years of age. Finally, hypoendemic includes areas where malaria transmission is low, defined as prevalence of parasitaemia below 10% in children between 2–9 years of age (10). The level of transmission intensity can be simplified further into high, moderate and low transmission areas. High transmission areas include holoendemic and hyperendemic areas, while moderate corresponds to mesoendemic area and low to hypoendemic area (11).

5.1.1 Pathophysiology

When malaria infected erythrocytes rupture, merozoites and digestive vacuoles are released. These vacuoles contain haemozoin, a pigment by-product of haemoglobin digestion; this pigment activates both the complement system and the coagulation system, which turns the focus of the immune system away from the merozoites. The immune response induces cytokine release leading to phagocytation of vacuoles (12), and can result in splenomegaly (8). Each erythrocyte cycle lasts about 48 hours in *P. vivax*, *P. ovale* and *P. falciparum,* and 72 hours in *P. malariae* (5). *P. knowlesi* has an erythrocyte cycle of about 24 hours (13).

The malaria-infected erythrocytes by *P. falciparum* have changed cell surfaces, which affects the interaction with endothelial cells by making the infected erythrocytes adhere to the vessel walls (8).

Research has shown that the *Plasmodium* species reduces human immune response towards itself, and through this down-modulation impairs the development of immunity against malaria. The acquired immunity protects only against clinical malaria, allowing asymptomatic parasitaemia. Even this degree of immunity takes years to develop, and requires frequent re-infection over a long time period (14). As the immunity depends on exposure, the degree of protection is affected by the transmission intensity in the area. A correlation between the median parasite density in febrile patients and transmission intensity has been seen. While 95% of febrile patients with *P. falciparum*

had over 200 parasites per microlitre blood in a high transmission setting, the same number for settings with lower transmission was 90–95%. *P. vivax* tends to have higher parasite densities than *P. falciparum* (11). The clinical impact of development of immunity will mentioned later.

5.1.2 Clinical manifestation of malaria

The classic symptom of malaria is high fever spikes every third or fourth day, depending on the *Plasmodium* species (5). This classic fluctuation is caused by the erythrocyte cycle (8), but this pattern is not always distinctive. The fluctuations are less marked with falciparum malaria, and the temperature changes can be more irregular with all species during the first days of illness (5).

Common symptoms in addition to fever include vomiting and headache (5). The clinical manifestation is rarely distinctive (15), and even fever is not always consistent. The lack of fever is not necessarily a sign of mild disease. For instance, in one African trial, children between 8 months and 4 years of age without fever or a history of fever had a higher mortality rate than the febrile children among admitted children with confirmed malaria (16).

Muhe *et al.* observed that splenomegaly, pallor and history of chills were statistically increased in patients with parasitaemia. They further theorized that detection of splenomegaly and pallor could increase the probability of making the correct diagnosis when used by health workers when other diagnostic possibilities are unavailable (17). In Tanzania, a trial based on children admitted with malaria infection found pallor in 59% and splenomegaly in 56% of children between 1 and 7 months of age. The association was weaker in older children, where the signs were present in only 31% and 39%, respectively (16).

In their review over symptoms and signs connected to malaria, Chandramohan *et al.* found that the clinical aspect alone was not sufficient to separate malaria from other febrile illnesses. They also found that predictors associated with malaria differed between locations (18).

5.1.3 Severe malaria and complications after infection

Roca-Feltrer *et al.* estimated the incidence of severe malaria to be 5.7/1000 per year among children below five years of age in malaria endemic areas (19). Patients with severe falciparum infections often have high parasite counts, and may develop severe symptoms from several organ systems (15). The severity of the disease may increase in a short time-span, especially in children where the situation can deteriorate within hours (5). Schellenberg *et al.* found that among malarial admissions, half of the mortality cases died within the first 24 hours (16).

A multicenter study from WHO have measured the prevalence of different clinical features in children with severe falciparum malaria. They found that 54.1% had severe anaemia, 17.7% had

cerebral malaria and 13.2% hypoglycaemia, while jaundice and respiratory distress were present in less than 2% (20). Kidney failure, metabolic acidosis and high lactate levels have also been associated with severe malaria (6).

Cerebral malaria is a clinical syndrome where the patient has reduced consciousness that can develop into coma or death (5). Clinical manifestations connected to impaired consciousness include convulsions, reduced response to painful stimuli, abnormal motor posturing and increased intracranial pressure (13).

Among the children with known outcome 14 days after they were admitted for severe falciparum malaria, almost 10% had died and 1.7% had neurological sequelae. Most of the children made a full recovery. In that study, the case-fatality rate of cerebral malaria was estimated at 17.7% (20). Epilepsy may also be a late sequela to cerebral malaria, which can appear months after the illness itself. It has been estimated that as many as 10% of children with cerebral malaria may go on to develop epilepsy (13).

Severe anaemia has been associated with malaria infection (21). Malaria infection cause anaemia through destruction of infected and uninfected erythrocytes, insufficient erythropoiesis, folate depletion and reduced proportion of red blood cells in the circulation, through sequestration and splenomegaly (5). Perkins *et al.* claims that the most important cause of severe anaemia with *P. falciparum* is suppression of the erythropoiesis (6). The anaemia may develop rapidly or be of a more chronic character (13), the latter caused by persistent infections (22).

Hansbroek *et al.* observed reduced erythrocyte production in almost half of the children with severe anaemia. A fifth of these had another mechanism causing anaemia in addition to the reduced erythrocyte production. For those who tested positive for malaria, the proportion with failure to produce erythrocytes was 42.1%. In this study, they also found that to reverse the production deficit, all the aetiological components should be addressed (23), which may include bacteraemia, hookworm infection, HIV infection or vitamin deficiency (21).

Schellenberg *et al.* found that hypoglycaemia was an independent risk factor for mortality among children admitted to the hospital because of malaria (16). Hypoglycaemia has also been estimated to double the mortality in children when accompanying cerebral malaria or severe anaemia (20).

Even though *P. falciparum* is responsible for most of mortality from severe malaria, other species may progress in severity as well. There are many similarities between severe infections caused by *P. falciparum* and *P. vivax,* though the latter is less common (13). Vivax malaria often includes respiratory symptoms, and patients with severe disease may develop acute respiratory distress

syndrome (ARDS). Increased alveolar permeability through cytokine release is believed to be the mechanism for this. Severe vivax malaria may also progress to coma, though this is rare. As the mechanism for falciparum malaria is connected to its sequestration, the mechanisms for vivax-induced coma are more uncertain. Vivax malaria resulting in renal failure has also been described (24). As *P. vivax* has hypnozoites, relapse of infection is common. These relapses make the chronic complications to malaria infections, such as anaemia, more severe (24). Severe malaria caused by *P. knowlesi* is similar to severe falciparum malaria, but without affecting consciousness (13).

5.1.4 Age and its effect on malaria

Age has an effect on the clinical manifestation of malaria, both directly and through the development of immunity. Immunity will, as described earlier, allow asymptomatic parasitaemia instead of clinical disease. As immunity develops, symptoms of malaria and severity of the disease will thereby subside (25).

There have been several reports on the effect of transmission intensity on the age distribution of clinical disease. Okiro *et al.* found that the proportion of infants among malarial admissions had a strong positive correlation with the transmission intensity in the area (25). Schellenberg *et al.* observed that 54% of the malaria mortality among hospitalized children in a highly endemic area was in children below one year of age (16).

Carneiro *et al.* found that a bisection of the median age for malaria mortality between seasonal moderate endemic areas and perennial highly endemic areas, at 28 and 12 months of age respectively, could be attributed to increased immunity in the high transmission areas. The same tendency is seen in median ages of clinical malaria, at 32 months in areas of perennial high transmission, compared to 72 months in areas with moderate transmission (26).

Even though the reductions described above show a tendency for transmission dependency, the median ages outside high transmission areas were still low. The median age of 28 months for malaria mortality, demonstrates age dependence regardless of transmission intensity (26).

Snow *et al*. found that the relative frequency of cerebral malaria was significantly higher in low-to-moderate transmission areas than in high transmission areas (27). Aponte *et al.* suggest that this difference may be partly caused by the difficulties in evaluate neurological status during infancy (28).

In addition to the difference in mortality rates, the course of the disease may differ according to age. While children often have anaemia and hypoglycaemia as complications to their malaria infection, non-immune adults have higher risk of other complications, including renal failure and pulmonary oedema (6).

Because of the high proportion of malaria illness in childhood, communities with high non-seasonal transmission may consider malaria as a children's disease. The developed immunity against malaria is dependent on constant exposure, as mentioned earlier. Changes in transmission status and increasing prevention may therefore expand the age group at risk for symptomatic infection (15) as their asymptomatic parasite density levels decreases (29).

5.1.5 Malaria in pregnancy

Pregnant women are more susceptible to malaria infections. They have higher parasite counts than other adults, with the highest density between 9 and 16 weeks of gestation (30). They are also more likely to have symptomatic disease (31).

There are three specific changes in the placenta due to *P. falciparum*: first, accumulation of infected erythrocytes in the intervillous spaces; second, fibrin deposit containing malaria pigment, haemozoin; and third, intravillous infiltrates of macrophages and monocytes containing haemozoin. A high density of erythrocytes in the intervillous space is associated with preterm delivery. Intravillous infiltrates of haemozoin-containing leukocytes is associated with low birth weight (LBW) and maternal anaemia, and is more common in primigravidae. These three changes can be found on histopathological examination of placental tissue up to one month after infection. *P. vivax* does not change morphology in the placenta (30), but it is still associated with maternal anaemia and LBW (32).

Pregnant women in non-endemic areas often have severe disease (30), which increase the risk of stillbirths, spontaneous abortions and maternal death (31). In endemic areas, pregnant women may have few symptoms or be asymptomatic due to acquired immunity (31). However, the infection often leads to severe anaemia (33). The severity of maternal malaria infection decreases with parity in endemic areas, but this seems dependent on stable malaria transmission (30).

Guyatt and Snow estimated in 2001 the median proportion of placental infection to be 0.254 in all-parity pregnant women from endemic areas of *P. falciparum* (34). Two other reviews found similar prevalence numbers (32). Using 0.254 as prevalence for malaria in pregnancy, Guyatt and Snow estimated that malaria could be the cause of 11.4% of the neonatal mortality and 5.7% of the infant mortality in endemic areas (34).

Trials have assessed the link between maternal malaria infection during pregnancy and LBW of the new born. Guyatt and Snow found the proportion of LBW to be 0.230 in babies where placental infection was found, compared to a 0.110 where infection were not found. They also found

significant difference in median average birth weight (34). A study in Côte d'Ivoire found similar results, with LBW in 22.2% in cases with placental infection and 10.1% in cases without (35).

In sub-Saharan Africa, babies with LBW have three times higher infant mortality rate than babies with normal birth weight (34, 36). A different study estimated the neonatal mortality at 0.152 among LBW babies, compared to 0.017 among babies with normal birth weight (34).

In addition to the effects described above, maternal malaria infection reduces the transport of antibodies over the placenta. LBW and prematurity is also associated with lower levels of antibodies in cord blood. This may leave the neonate at higher risk for infections and therefore increase neonatal mortality and morbidity further (33).

5.1.6 Malaria and HIV

There is much overlap between the epidemiological areas of malaria and HIV. In sub-Saharan Africa, several countries where a majority of the population is exposed to malaria also have HIV prevalence above 10% in the population between 15–49 years of age (37).

In addition to the ones giving fever in the general population, several other microbes can cause febrile illness in people living with HIV infection. As a result, people with HIV infection have increased probability of a febrile illness with a different aetiology than malaria (37).

In areas where the adult population normally have acquired immunity against malaria, HIV-infected adults have increased risk of clinical malaria. This increase correlates with the degree of immunosuppression (38). In areas where the transmission is insufficient to develop immunity, HIV-infected have an increased risk of developing severe malaria (39). Higher treatment failure rates among HIV-infected adults has also been reported (37).

Malaria transmission rates affect the impact of HIV on malaria in children as well. In stable areas, HIV infection is associated with higher occurrence of clinical malaria. There has been seen a correlation between degree of immunosuppression and parasite densities here as well. In areas with unstable transmission, HIV infection is associated with increased risk of severe malaria (37).

Severe anaemia has been associated with malaria infection (21). HIV can transmit through contaminated blood, and WHO notes that thousands of African children have become HIV positive after receiving blood transfusion for their severe malarial anaemia (37).

As mentioned earlier, malarial infection during pregnancy increases the risk of maternal anaemia, LBW, stillbirth and spontaneous abortion. Both pregnancy and HIV reduce the ability to contain malaria parasitaemia. Pregnant women with HIV infection therefore have increased risk of high levels

of parasitaemia and have increased risk of developing symptomatic disease (40). They also have increased risk of maternal anaemia, prematurity and LBW (37). Normally, the reduction in immunity during pregnancy decreases with increased parity in areas of stable transmission. The largest differences attributed to HIV infection are therefore seen in multigravida women (37).

5.2 Diagnostics

As described above, clinical presentation of malaria may vary, and symptoms are generally unspecific. Additional diagnostic measures are therefore needed to verify the diagnosis. Several different diagnostic techniques are available, of which microscopic diagnosis and rapid diagnostic tests are the most commonly used today. Other possibilities include polymerase chain reaction (PCR), fluorochrome microscopic techniques and serological procedures (41).

A description of the most common techniques, as well as special considerations regarding diagnostics of placental malaria, will follow below.

5.2.1 Peripheral blood film microscopy

A thick and thin blood film is used when using a microscope to diagnosing malaria infection. The thick blood film is more sensitive for parasites, especially at low densities. The samples are stained, often using the Giemsa, Wright's or Field's staining techniques. Parasitaemia at 50 parasites/microlitre blood can be found if someone with experience performs the examination. Differentiating the *Plasmodium* species is easiest in thin blood films (42).

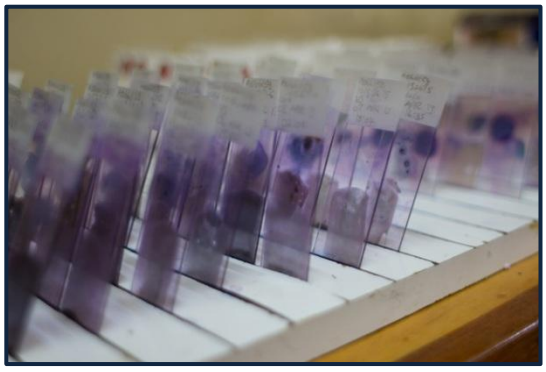

Figure 1: Blood slides used to diagnose malaria using a microscope. Zomba Central Hospital, Malawi; picture taken by authors.

Parasite count (parasites/microlitre) can be found by counting parasites in proportion to either white or red blood cells, depending on the type of blood film used, and estimating the parasite count through the numbers of cells per microlitre (42).

5.2.2 Rapid diagnostic tests

Immunochromatographic tests uses antibodies against malaria antigens, with mechanisms displaying positive test as change of colour. There are several options available as dipstick kits, using different kinds of antigens such as HRP-II, pLDH or aldolase. Some of these, for example HRP-II-based tests, are selective for *P. falciparum*, while others can be used for all species (42).

Several HRP-II-based RDTs have been tested with sensitivities above 75% and specificities above 80%, when parasite density was above a hundred parasites per micro litre. A review by Abba *et al.* found that these RDTs had sensitivity of 95.0% and specificity of 95.2% (43). pLDH-based RDTs have been tested with sensitivity and specificity for *P. falciparum* at 94% and 100%, and for *P. vivax* at 88% and 99%, respectively. This kind contains several antibodies, of which one is falciparum specific. Abba *et al.* found the sensitivity and specificity for pLDH-based test to be 93.2% and 98.5, respectively (43). RDTs based on aldolase have been more dependent on higher parasite densities. These can detect all *Plasmodium* species (42).

Figure 2: An example of an HRP-II RDT used in Malawi. Picture taken by authors.

5.2.3 Other diagnostic methods

PCR-based methods have high sensitivity and specificity, with good ability to make the diagnosis even with low parasite densities (44). This method is demanding in regard of equipment and staff, which limits its use (45). Fluorochrome microscopic techniques may give a sensitive result if the technician has experience; however, it is costly, needs special equipment and is unable to differentiate between the *Plasmodium* species (42). Serology may give useful for information on antibody response for epidemiological purposes (44).

5.2.4 Diagnosing malaria in pregnancy

Diagnosing malaria during pregnancy differs from diagnosing the non-pregnant. The gold standard for diagnosing placental malaria infection is not peripheral blood microscopy, but histological examination of the placenta itself. Another highly specific diagnostic possibility is placental blood microscopy. Neither of these can be done routinely before delivery (45).

Options for detecting placental infecting during pregnancy therefore rely on tests from peripheral blood. Kattenberg *et al.* compared PCR, RDT and peripheral blood microscopy with placental blood microscopy and found that PCR was the most sensitive option, with sensitivity at 94%, while peripheral blood microscopy was the most specific, at 98%. The RDTs was mid-range on both, with sensitivity and specificity at 81% and 94%, respectively. Peripheral microscopy detected only 72% (45).

5.3 Antimalarial medications

In this chapter, we will take a closer look at the different antimalarial treatment options available today, with a special focus on the drugs currently recommended by WHO in their treatment guidelines.

Many different drugs spanning several chemical families are in use today for treatment of malaria (see Table 1 below) (46). The optimal therapeutic choice depends on several factors, including the *Plasmodium* species, the drug resistance in the area, as well as the efficacy, the availability, cost and side effects of the medication, and more (2).

Table 1: Antimalarial drugs currently in use today (46).

Chemical family	Drugs
4-Aminoquinolines	Chloroquine, amodiaquine, piperaquine
Amino-alcohols	Quinine, quinidine, mefloquine, halofantrine, lumefantrine
Sulphonamides/sulphones	Sulfadoxine, sulfalene, dapsone
Biguanides	Proguanil, chlorproguanil
Diaminopyrimidine	Pyrimethamine
8-Aminoquinoline	Primaquine
Sesquiterpene lactones	Artemisinin, arteether, artemether, artesunate, dihydroartemisin
Naphtoquinone	Atovaquone
Antibiotics	Azithromycin, clindamycin, doxycycline, tetracycline

The therapeutic treatment of malaria has a long history spanning several continents. In China, the *qinghao* plant, which we now know contains the antimalarial drug artemisinin, has been used in the treatment of intermittent fevers since at least the 4th Century A.D. In Western medicine, the cinchona tree, native to South America, was the basis for antimalarial treatments; cinchona bark infusions containing quinine has been used against malaria since at least the late 1600s, infamously giving rise to tonic water. Artemisinin and quinine remains cornerstone drugs in the medical treatment of malaria to this day (47).

During the latter half of the 20th Century, the efficacy of the most widely used antimalarial agents, most notably chloroquine and amodiaquine, dropped significantly because of increasing parasite resistance, with devastating public health consequences (47).

Facing the rising drug resistance, the recommended first-line treatment for uncomplicated *P. falciparum* malaria has been artemisinin-based combination therapies (ACTs) since WHO updated its

treatment recommendations in 2001. Today, most malaria-endemic countries use ACTs as their first-line treatment for malaria caused by *P. falciparum*, although other drugs are still used for special patient populations (2).

5.3.1 Quinine and other amino-alcohols

Quinine is an aryl amino-alcohol that has been used to treat malaria in the Western world since the early 1600s. It is a naturally occurring compound found in the bark of the cinchona tree (*Cinchona officinalis*) native to South America (48, 49). Several other closely related compounds exist in the cinchona bark, including quinidine, cinchonine and cinchonidine, all with approximately equally potent antimalarial properties (48).

Even though the drug has been used extensively over the last centuries, it remains a viable treatment option to this day, especially for vulnerable patient groups such as pregnant women or children, and when used in combination with other drugs (48).

Quinine has a small therapeutic window, and the collection of the benign, but unpleasant, side effects often seen at therapeutic concentrations is called cinchonism, and include nausea, headache, tinnitus, hearing impairment and blurred vision. More severe side effects, such as vomiting and vertigo, may also occur. The small therapeutic window is one of the largest challenges when it comes to modern usage of quinine, as the frequent side effects often leads to poor compliance and may contribute to early treatment termination (49).

Despite being one of the oldest drugs used in antimalarial therapy, the antimalarial mechanisms are still not fully understood (48), but it has been theorized that it inhibits the detoxification of haeme, similarly to the 4-aminoquinolones (2).

Other than quinine, which remains as one of the drugs recommended in the treatment of complicated *P. falciparum* malaria, there are also several quinine derivatives in use today (2). The most widely used among these is lumefantrine and mefloquine.

Lumefantrine is currently used as a partner drug in the ACT artemether-lumefantrine. It is a generally well-tolerated drugs with few reported side effects and a relatively short terminal elimination half-life of 3 days. However, bioavailability is highly dependent on administration with fatty foods; the absorption of the drug doubles after a meal (2).

Mefloquine is used in combination with artesunate as an ACT (46); however, it is also among the most widely used antimalarial drugs used for chemoprophylaxis by foreign travellers going to malaria endemic countries. Mefloquine has a half-life of around 21 days. Mefloquine has several side effects,

including rather infamous psychiatric side effects such as sleep disturbances, dysphoria and abnormal dreams. In addition, more serious neuropsychiatric disturbances, such as seizures, encephalopathy and psychosis, have been known to occur. This is especially true when mefloquine is used to treat severe malaria, where the incidence of such disturbances may be as high as 5% (2).

5.3.2 Chloroquine and other 4-aminoquinolines

The 4-aminoquinolines, most notably chloroquine, amodiaquine and piperaquine, have been widely used in the treatment of malaria since after the World War II (47). These drugs work by inhibiting the detoxification of haeme, which is a by-product of haemoglobin digestion; by inhibiting this process, toxic haeme gradually builds up inside the food vacuoles of the parasite, and eventually kills the parasite (50).

The 4-aminoquinolones and their metabolites have very long half-lives; for chloroquine, the estimated terminal elimination half-life is 1–2 months. The half-life of the active metabolite of amodiaquine has been estimated to be between 9 and 30 days (51), while piperaquine has a half-life of approximately 20–22 days (52). These long half-lives are partly beneficial, as they will probably infer an added prophylactic effect post-treatment; however, as will be described later, the longer half-lives of these compounds might also lead to increased resistance (52).

Amodiaquine has a significant risk (between 1 in 1000 and 1 in 5000) of serious and potentially fatal adverse reactions, including neutropenia, agranulocytosis and hepatitis, when used prophylactically. Prophylactic use is therefore no longer recommended. The frequency of serious adverse reactions when used as treatment for malaria is unknown, but studies indicate that the benefits of using amodiaquine in treatment outweigh the risk of serious adverse effects (2, 51).

Extensive resistance over the last decades has rendered chloroquine almost useless for treating *P. falciparum* malaria in most malaria-endemic areas. Recent research has tried to assess if chloroquine has a role in the use for intermittent preventive treatment of malaria in pregnancy in combination with azithromycin, and the results are promising (36). Amodiaquine and piperaquine are still used as partner drugs in ACTs in areas where the efficacy of these drugs remains high (46, 47).

5.3.3 Pyrimethamine and sulfadoxine

Following the emergence of chloroquine resistant malaria, many countries switched to sulfadoxine–pyrimethamine (SP) as their first line treatment for malaria. Even though pyrimethamine and sulfadoxine are two separate drugs, they both target the same biosynthesis pathway and the combination of these drugs is therefore regarded as a monotherapy (46).

SP works by suppressing the folate synthesis pathway in the parasites, thereby inhibiting growth (50); as such, these drugs are relatively slow-acting schizontocides. The half-lives of both drugs are around 4 days. As with other sulphonamide drugs, sulfadoxine may induce severe and potentially fatal allergic reactions, including toxic epidermal necrolysis and Steven–Johnson syndrome. In comparison with other sulphonamide drugs, the relatively long half-life of sulfadoxine may cause the allergic reactions to be more severe (2).

The most common formulations contain 20 parts of sulfadoxine with 1 part pyrimethamine, commonly in 500 mg sulfadoxine and 25 mg pyrimethamine formulation (Fansidar®) (2). Even though widespread resistance has rendered SP almost useless in large parts of the malaria endemic world, it is still frequently used as intermittent preventive treatment for pregnant women, as both drugs are regarded as safe to use in pregnancy. In addition, SP has found use in combination with an artemisinin derivative as an ACT in the parts of the world where resistance to SP has not yet developed extensively (46).

5.3.4 Antibiotics

Several antibiotics also have antimalarial properties, and antibiotics used in malaria treatment include tetracyclines (especially doxycycline) and clindamycin. The use of antibiotics in the treatment of malaria is no longer generally recommended where good alternatives exists (2), but they still have a place in specific patient populations, including pregnant women and use as prophylaxis for travellers, as well as in combination with other drugs (2, 53). Azithromycin is another antibiotic with antimalarial activity, though it is currently mainly used in intermittent preventive treatment in pregnancy (36).

5.3.5 Artemisinin and its derivatives

Artemisinin, also called *qinghaosu*, is another naturally occurring substance used for treating malaria for centuries (47). Artemisinin is a sesquiterpene lactone that was isolated and extracted from the leaves of *Artemesia annua*, or sweet wormwood, in China in the 1970s. It quickly became a focus of attention for its potential use in treating malaria (54).

The parent drug, artemisinin, has now largely been replaced with the more potent synthetic derivatives. The main derivatives in use today are artemether, artesunate and dihydroartemisinin. Dihydroartemisinin is the main active metabolite for the synthetic derivatives of artemisinin, but it can also be given as a drug in its own right (2, 55).

Artemisinin is a very rapidly acting drug with an elimination half-life of approximately 1 hour. The peak plasma concentrations occur 3 hours after administration. Artemisinin and its derivatives work

by inhibiting *Pf*ATPase, which is an essential calcium adesonine triphosphatase. They have a very broad activity against malaria parasites, killing both asexual parasites and gametocytes in *P. falciparum* (2).

In order to prevent the development of resistance, artemisinin and its derivatives should be used in combination with other drugs, so-called ACTs. ACTs now constitute the basis for first-line treatment against malaria in essentially all malaria endemic countries (2, 46). In addition to preventing the development of resistance, ACTs have a far higher treatment efficacy than using artemisinin-based monotherapy (55).

5.3.6 Artemisinin-based combination therapies

The emergence of resistance to commonly used antimalarial drugs, mainly 4-aminoquinolones (e.g. chloroquine) and sulphonamides (sulfadoxine), has been a major obstacle in the fight against malaria for several decades, and has necessitated a change in the recommended treatment guidelines in areas with endemic malaria. Modern malaria treatment guidelines are largely based on ACTs instead of monotherapy (46).

As the name implies, ACTs use artemisinin or one of its derivatives paired with a partner drug with a different pharmacological mode of action. Having two distinct modes of action slows down development of resistance for both the artemisinin derivative, as well as increasing the efficacy of the treatment itself (46).

WHO currently recommends five different ACTs, all of which are in use, either as first-line or second-line treatment, around the world. These five drugs are artemether–lumefantrine, artesunate–amodiaquine, artesunate–mefloquine, artesunate–sulfadoxine–pyrimethamine and dihydroartemisinin–piperaquine (2).

5.3.6.1 Artemether–lumefantrine

The combination artemether–lumefantrine (AL) is currently one of the most widely used ACT, and has seen extensive usage in all parts of Africa, as well as in South America and parts of Southeast Asia (46).

AL is a cheap, effective and well-tolerated ACT, which explains much of its popularity. However, it requires two doses per day, and the absorption of lumefantrine is highly dependent on co-administration with fatty foods, which can be a problem in many malaria-endemic countries (2, 55).

5.3.6.2 Artesunate–amodiaquine

Artesunate–amodiaquine (AA) is another ACT currently in use in western and central parts of Africa as well as China and Southeast Asia, in areas with little malaria parasite resistance to amodiaquine (46, 51).

Severe and potentially fatal adverse reactions such as agranulocytosis and fulminant hepatitis have been described when using amodiaquine as prophylaxis. However, these reactions are rare when amodiaquine is used in malaria treatment (55).

Usage of AA is not recommended in areas where the 28-day cure rates of amodiaquine monotherapy are lower than 80%. Care should also be taken to continuously monitor resistance in areas where not only amodiaquine but also chloroquine is still used as monotherapy, as there is partial cross-resistance between the two drugs (2).

5.3.6.3 Artesunate–mefloquine

The combination artesunate–mefloquine (AM) has been used for several decades along the Thai Burmese border with good effect, and the combination is regarded as safe and effective (56). The principle side effect is vomiting, but mefloquine also has a series of neuropsychiatric reactions, which are more common if mefloquine has been used in the previous two months. As such, AM should not be used to treat reinfections occurring within 2 months of last treatment (55).

Recent studies have revealed high treatment failure rates (>8.8–14%) for AM in Cambodia, Myanmar and Thailand. The high failure rates seem to be at least partially reversible; after implementing RDTs to limit overtreatment and changing to another ACT, the treatment failure rates in one province in Thailand plummeted from 9.9–14.3% in 2002–2004 to 0–5% in 2007–2008 (46).

5.3.6.4 Artesunate–sulfadoxine–pyrimethamine

The combination artesunate–sulfadoxine–pyrimethamine (ASP) should only be used in areas where the malaria parasite sensitivity for SP is sufficiently high. This limits the usage to certain countries in central Asia, the Middle East, and South America. As such, this is among the least used ACTs, though it still has a place in the WHO treatment guidelines (2, 46).

The continued use of SP as monotherapy and as use in intermittent preventive treatment for pregnant women means that SP resistance will likely continue to spread over the following years (55).

5.3.6.5 Dihydroartemisinin–piperaquine

Dihydroartemisinin–piperaquine (DP) is one of the ACTs recommended as first-line treatment by WHO, and has been used to treat malaria for several decades, especially in South East Asia; it has been used as the recommended first-line treatment in Vietnam for several years (52, 57). Eurartesim® is currently the only formulation that meets international Good Manufacturing Practice standards (52).

Studies on the combination's efficacy have mainly been done in Asia, where they have shown that DP is generally non-inferior when compared to alternatives, and that it has good efficacy and good tolerability (52). Among the strengths that are highlighted are the drug's relatively low price, ease of administration, and its low occurrence of side effects (58). More studies are needed in Africa in order to assess the efficacy there as well, before its use as first-line treatment can be recommended (46).

In addition to this, some studies suggest that DP has the added benefit of yielding increased resistance to reinfection for some time after treatment, with lower gametocyte count and lower risk of recurrent parasitaemia (59). One study in Uganda found a significantly lower risk of recurrent parasitaemia, both newly acquired and due to a possible recrudescence of the original infection, when compared to using artemether–lumefantrine (60).

Like the other 4-aminoquinolones, piperaquine has a long elimination half-life (approximately 20–22 days), and it has been theorized that piperaquine therefore acts as a prophylactic agent as well as being part of the treatment itself, and that this is the reason for the lower recurrence rates using DP (52). If correct, this effect may be beneficial in the short term, but may over time lead to increased resistance to piperaquine as new parasites may be exposed to sub-therapeutic levels of the drug. Piperaquine resistance will in turn lead to lower efficacy of the DP drug combination (60).

5.3.7 Iron supplementation and malaria

The role of iron supplementation in malaria endemic areas has been controversial. Iron-deficiency anaemia is common in these areas, especially among children. This is in part due to repeated malaria infections, so giving iron supplements to children may decrease the anaemia. At the same time, there has been some evidence that suggests that iron supplementation may actually *increase* the risk of malaria by promoting parasite growth. However, a recent Cochrane review has concluded after extensive review that iron supplementation should not be withheld from children living in malaria endemic countries (61). More research is currently underway to assess the possible benefits and risks of using iron supplements in this population.

5.3.8 Resistance to antimalarial drugs

Resistance to antimalarial drugs have been a major obstacle in the fight against malaria for several years. The first documented cases of malaria drug resistance were probably during World War II, where studies on soldiers taking prophylactic mepacrine (Atebrine) revealed reduced prophylactic efficacy of the drug. Since then, drug resistance has continued to define malaria treatment (47).

5.3.8.1 Resistance to chloroquine and other 4–aminoquinolines

The advent of new antimalarial drugs after World War II led to a massive shift in malaria treatment, from quinine and the first generation synthetic antimalarials (including mepacrine) to the more effective, safer and cheaper 4-aminoquinolines chloroquine and amodiaquine. Towards the end of the 1950s, reports of chloroquine and amodiaquine treatment failures began to surface in South America and South-East Asia (47).

Part of the reason why the 4-aminoquinolones are so prone to developing resistance may be their long half-lives, which span from one to several months (2). This means that the parasites are exposed to the drugs for a long time, which in turn gives the parasites ample opportunity to develop resistance (52).

The resistance to chloroquine appears to be mediated by a transport protein, *Pf*CRT (*Plasmodium falciparum* chloroquine resistant transporter), encoded by the *pfcrt* gene. Parasites with mutations in this gene become resistant to chloroquine; the altered transport protein transports chloroquine out of the food vacuoles, and thereby limits the drug's potency for blocking the detoxification of haeme (50).

Genetic sequencing has revealed that there exists several different haplotypes of the mutated *pfcrt* gene, which in turn have characteristic geographic distributions, as well as drug resistance phenotypes (47). Genetic patterns suggest that chloroquine resistance developed at two separate sites; one along the Thailand-Cambodia border, then spreading to other Southeast Asian countries and subsequently to Africa (46, 50), while another resistant lineage developed separately in South America (50).

Research indicates that different mutated haplotypes of the *pfcrt* gene have different fitness costs to the parasite. In certain areas of Africa and South-East Asia where one specific haplotype was abundant, chloroquine-sensitive parasites returned after a few years of discontinued use of chloroquine, while other areas with another haplotype still have a high degree of chloroquine-resistant parasites to this day, even after a longer period of discontinued chloroquine usage (47).

The increasing resistance of *P. falciparum* to chloroquine and similar drugs has led to a massive worldwide shift in drug treatment policies for malaria. Except for a few regions, chloroquine has now been removed from modern malaria treatment guidelines because of the widespread resistance (47).

Amodiaquine remains partly effective against at least some strains of chloroquine-resistant *P. falciparum* malaria; however, there does exists a partial cross-resistance between amodiaquine and chloroquine (2).

Resistance against piperaquine seems to be largely unrelated to chloroquine resistance, at least in most areas of the world. In Africa, studies show good *in vitro* response to piperaquine in chloroquine resistant malaria parasites. However, there are high rates of piperaquine resistance in areas where the drug has been used extensively as monotherapy, mainly in China (52).

The parasite resistance to amodiaquine and piperaquine is still limited enough in most areas to warrant their inclusion as partner drugs in ACTs in the WHO treatment guidelines (2, 46).

5.3.8.2 Resistance to sulfadoxine–pyrimethamine

Resistance to sulfadoxine–pyrimethamine developed soon after the introduction of the drug in Thailand, especially along the Thailand–Cambodia border (46), in the late 1960s; as with chloroquine resistance, this resistance subsequently spread to other parts of Asia and then to Africa, where resistant parasites were detected in Kenya in 1988 (50).

Today, the median treatment failure rates in eastern Africa exceed 50%; in other parts of Africa, that number is around 20%. There are still sensitive parasites in several countries in South America, the Middle East and Central Asia, where the median treatment failure rate is around 5% (46).

Resistance to pyrimethamine and sulfadoxine is mediated by mutations in the genes transcribing the drug target enzymes, *pfdhfr* (transcribing dihydrofolate reductase) and *pfdhps* (transcribing dihydropteroate synthase), respectively. Multiple mutations in these genes lead to increased resistance in the parasites (50).

The tendency of sulfadoxine–pyrimethamine to cause elevated gametocytosis in the patients treated by the drug may lead to increased malaria transmission. This has been proposed as one explanation for the rapid spread of sulfadoxine–pyrimethamine resistant parasites in the world (50).

5.3.8.3 Resistance to artemisinin and ACTs

Parasite resistance to artemisinin represents a potentially huge challenge in the fight against malaria. Artemisinin and its derivatives is the primary drug used in the medical treatment of malaria in most

of the world today, and if extensive resistance develops, the potential ramification for public health is severe (62).

As of 2010, no genetic markers for artemisinin resistance have been found, and measuring artemisinin resistance is therefore difficult. However, patterns of specific parasite strains have been found in patients with treatment failure in several studies, which indicates that there is a genetic basis for artemisinin resistance (46).

As with chloroquine and sulfadoxine–pyrimethamine resistance, artemisinin resistance in *Plasmodium falciparum* parasites first appeared along the Cambodia–Thailand border. Constant monitoring of antimalarial drug efficacy in this area led to early detection of emerging resistance to artemisinin, and subsequently to an early coordinated and international response to contain the spread of resistant parasites (46, 62).

5.4 Preventive measures

In addition to treating the malaria infection adequately, malaria morbidity and mortality can be reduced by preventing the infection in the first place. Preventive methods can be divided into two main groups of intervention strategies: vector control and chemoprevention. Vector control mainly consists of insecticide-treated bed nets (ITNs), indoor residual spraying (IRS) and, in some cases, larval control. Chemoprevention is a term referring to the prophylactic use of antimalarial drugs in high risk groups (IPT), most often pregnant women (IPTp) or infants (IPTi) (63). The different preventive methods, including IRS, ITNs, larviciding and IPT will be described below, while DDT will be discussed on its own in greater detail in the next chapter.

5.4.1 Insecticide-treated bed nets

There are several categories of bed nets used to protect against mosquitoes: untreated nets and nets impregnated with either short-lasting or long-lasting insecticides. The short-lasting insecticide-treated nets need frequent re-impregnation, and only a small portion of nets distributed have been re-treated at all (64). Long-lasting insecticide-treated nets (LLINs) are estimated to retain their insecticide effects for three years or longer, if used as recommended (65). Currently, only insecticides of the pyrethroid class are recommended for treating LLINs (63). Bed nets treated with insecticides works on both an individual and on a community level (63). The individual protection is caused by a direct protection against mosquito bites, while the community protection is a result of reduced mosquito density in the area (66). However, the direct effect of protection against mosquito bites does not solely depend on the insecticide. Guyatt and Snow argue that some of the effect attributed to ITNs is caused by the net themselves, not the insecticide, and present the result from a Gambian study where using untreated nets significantly reduced child mortality (64).

In several of the articles reviewed, both short-lasting and long-lasting insecticide-treated nets were compared together against untreated nets or using no nets at all. When used below, the term ITN will therefore include both kinds of insecticide treatment, both short-lasting and long-lasting ITNs, unless otherwise specified.

Several studies have evaluated the effect of bed nets, and ITNs in particular, in sub-Saharan Africa. In their meta-analysis, Choi *et al.* found that utilization of ITNs gave a significant reduction in malarial incidence, both when compared to untreated nets and no usage of nets (67). A review of studies from areas with endemic *P. falciparum* malaria estimated that ITNs to have a protective efficacy of 17% on malaria prevalence in children. They also found ITNs to reduce the incidence of uncomplicated malaria among children by half (68).

Using ITNs compared to not using nets is also associated with reduced incidence of placental malaria, regardless of parity (69). Among women in their first pregnancies, ITN usage has been shown to have an effect on the incidence of LBW, stillbirths and abortions (69). Eisele *et al.* have estimated that ITN usage alone can help reduce LBW in paucigravidae in endemic *P. falciparum* settings (68).

There are also promising estimations of effect of ITNs on child mortality in sub-Saharan Africa. All-cause mortality for children under five years has an estimated reduction of 18% (68-70). Mortality caused by malaria among children 1–59 months of age is estimated to be reduced by 49–60% when compared to not using nets at all (68).

Noor *et al.* mapped the ITN coverage between 2000 and 2007 in sub-Saharan Africa. They found that in areas of stable transmission, only 1.8% of children slept under an ITN in 2000. By 2007, this had increased tenfold to 18.5% (71). The largest improvement took place in areas where ITNs had been distributed free of charge between 2000 and 2007 (71).

Distribution campaigns in several countries have tried to increase the ITN coverage. In Sierra Leone, the proportion of households with at least one ITN increased from an estimated 37% in 2008 to 87.6% in 2010, after a national campaign distributing ITNs for free (72) , while Tanzania saw an increase from 62.6% to 90.8% of households with at least one ITN after a similar distribution campaign (73).

The use of ITN among those in households with at least one net, were 76.5% (72). In Cameroon, a survey found that 59.7% of households had ITN, but that only 42.6% of the households in the country used ITNs (74). Among households in Ethiopia with at least one ITN, the usage among pregnant women and children under five was 52.1% and 63.0%, respectively (75).

Surveys have found several factors associated with ITN usage. Bennet *et al.* found the use of ITN was associated with knowledge of how malaria is transmitted, whether they were reached by public information about malaria, and the availability of nets (72).

Koenker *et al.* found that the youngest children were generally prioritized for sleeping under ITN. In households with an ITN, 93% of children beneath 23 months of age and 92% of children between 24 and 35 months of age slept under an ITN. The rates for older children were lower, at 55% among children at 5 years of age (76). This correlates to findings in other studies, where increased number of children reduced the probability that a child slept under an ITN (77, 78).

A survey two years after a distribution campaign found that ITN usage was associated with how many ITNs they had in the household, how easy they could use the nets, and the women's knowledge about the nets (75). In Ghana, the use of nets was also associated with knowledge of malaria transmission method, the number and the conditions of nets in the household. It was also associated with the colour of the net and whether the net had been received free of charge, or if it had been bought. The authors suggest that subsidizing nets in the commercial marked may increase the usage among those who can afford to buy them (79).

5.4.2 Indoor residual spraying

Indoor residual spraying (IRS) is a vector control method based on the application of insecticide on all surfaces inside buildings within the target area. Vectors are killed if they come in contact with the insecticide, and in some cases mosquitoes also are repelled from entering the building. These mechanisms reduce human exposure to mosquitoes and thereby reduce malaria transmission. Some *Anopheles* species mainly rest and bite outside, such as *An. arabiensis*, and are therefore less affected by IRS. It is effective against vectors indoors, such as the common *An. gambiae* (80). As IRS mainly reduces the number of mosquitoes leaving the house, the intervention protects the community rather than the individual, in contrast to bed nets (81). In areas where IRS is utilized, spraying coverage above 80% should therefore be attained to reach the intended effect (80). IRS is performed by manually spraying insecticide on walls and ceilings with hand-operated compression air sprayers, preferably ahead of transmission season.

IRS has earlier been used with good results in many parts of the world, especially connected to the Malaria Eradication Programme that was executed in several malaria-endemic parts of the world between 1955 and 1969, where malaria was eliminated from several countries worldwide. This programme was not implemented in most of sub-Saharan Africa, however (80).

After the first decades of insecticide usage in malaria vector control, a period with declining utilization followed, despite the results that were achieved. According to WHO, this reduction may be partly caused by inadequate national prioritization, apprehension of the developing resistance and public approval. The latter especially applies to DDT, which was globally scorned (80). During the last decade however, the insecticide-based vector control has increased dramatically. In 2010, the number of LLINs distributed in Africa was 25 times higher than in 2004, while the number of people protected by IRS was almost eight times higher than in 2005 (81).

There are several insecticides that can be used for IRS, including organochlorines (e.g. DDT), organophosphates, carbamates and pyrethroids. The safety and efficacy of these are constantly being evaluated by WHO (80). Pyrethroids are the most commonly used insecticides today, both for IRS and ITNs (82). The different insecticide classes also have different duration of insecticidal effects. Organophosphates and carbamates have the shortest duration, which in turn means that they require frequent spray cycles in order to achieve optimal coverage. The costs associated with the different insecticides when used in IRS also differ, with DDT and pyrethroids being the cheapest (80).

The efficacy against local vectors is affected by the local insecticide resistance, which reduce the vector's susceptibility toward the insecticide (80), described in detail below. In order to ensure the safety of the population and the environment in target areas, adherence to recommendations on administration and handling of the insecticide is important (80).

5.4.3 Insecticide resistance

As mentioned earlier, pyrethroids are used in both IRS and ITNs, and make pyrethroid resistance a pressing concern when it comes to vector control. Pyrethroid resistance in malaria vectors is widespread (80), and has been confirmed in 27 countries in sub-Saharan Africa as of 2010 (82). Additionally, resistance towards carbamates and organophosphates has been seen in West Africa (80).

Pyrethroid-resistant vectors have two known resistance mechanisms, and it is probable that other mechanisms exist. The first resistance mechanism is often called knockdown resistance (*kdr*); it is a mutation in the target site for the insecticide, which is located on the insect nerve membrane. The other resistance mechanism is a mutation that increases the metabolizing rate of the insecticide (82)

Because insecticides share many of the same modes of action, resistance towards one class of insecticide frequently results in resistance towards other classes as well. For example, the widespread *kdr* mutation gives cross-resistance between pyrethroids and organochlorines. In

addition, cross-resistance between organophosphates and carbamates has been reported in West Africa (82).

Insecticide resistance has developed after exposure to the use of insecticides in either agriculture or in IRS, as the usage of the same insecticide in both agriculture and IRS in the same area may increase the selection pressure. In some cases, agriculture has clearly contributed to resistance development among vectors in an area, while IRS is clearly responsible in others. Agricultural impact on resistance has especially been a problem in areas where cotton and rice are cultivated. Collaboration with the agricultural sector is therefore useful to limit the development of resistance, so that different insecticides should be chosen in agriculture and in vector control, preferably by using an agricultural insecticide that is not recommended for use in IRS (82).

The knowledge about how insecticide resistance affects malaria vector control is scarce, in addition to inconsistency between the few available reports. ITNs have been observed to remain effective, while the efficacy of IRS has been reduced over time (82).

5.4.4 Larviciding

A third option for vector control is anti-larval methods that inhibit mosquito breeding, including the use of larvicides (83). As this method reduces the number of adult mosquitoes, it reduces the risk of bites both indoors and outdoors (83). To be effective, larvicides need to be applied to a high proportion of mosquito breeding sites within flight area of the targeted human dwelling. Typical breeding sites differ between different *Anopheles* species, and range from semi-permanent sites to temporary pools of water, such as flooded foot prints (84). Therefore, this method requires more local knowledge regarding the *Anopheles* species in the area compared to other vector control methods (84).

Larviciding is most useful when the local breeding sites are known and few in number, so as many breeding sites as possible within the estimated flight range should be eliminated. Other local features that may increase the likelihood of success with larviciding include lower temperatures, seasonality and breeding sites that are easy to eliminate. As lower temperatures delay the metamorphosis from larva to adult mosquitoes, colder areas are easier to manage. The maturation period normally takes 7 to 10 days, which demands weekly elimination for optimal effect. Larviciding may be effective when used thoroughly (85), and was the method used for elimination *Anopheles arabiensis* from Brazil and Egypt (86). The utilization of IRS and ITNs may result in a remaining problem of resistant vectors and vectors that mainly bite outdoors. Worrall and Fillinger indicate that the role of larviciding may increase in such settings (83).

5.4.5 Intermittent preventive treatment

Intermittent preventive treatment (IPT) is a preventive strategy focusing on high risk groups, where antimalarial treatment is given regularly, independently of whether a person has malarial infection or not (69). The goal of IPT is to clear the parasitaemia, regardless of whether it gives symptoms or not, and to give some prophylaxis against new malaria infections (36).

Chemoprevention is mainly given during pregnancy (IPTp), but can also be given to infants (IPTi) and children (IPTc). Several qualities are wanted in a drug used for IPT. First, it must be safe to use in the respective patient population, and ideally have few adverse effects. Second, it should be effective with high parasitaemia clearance and preferably some added chemoprotective effect in the period following the treatment. Third, it should be a realistic possibility to offer the drug to the communities, with regard to economic factors as well as drug stability and community acceptance. Finally, an ideal IPT drug should be different from the drug used for first-line treatment, to reduce the selection pressure on the drugs and delay or prevent the emergence of resistance (31, 36, 87).

5.4.5.1 Intermittent preventive treatment in pregnancy

As stated earlier, studies have associated malaria infection during pregnancy with an increase in infant mortality and morbidity through maternal anaemia, infant anaemia, LBW, stillbirth and spontaneous abortion. In areas of stable transmission of *P. falciparum*, 30% of preventable cases of LBW can be attributed to maternal malaria infection (70). Therefore, preventing maternal infection may be one way of increasing infant health. To achieve this, WHO recommends the use of ITNs to pregnant women in areas of malaria transmission, as well as IPTp to pregnant women in *P. falciparum* endemic areas (3).

Vanga-Bosson *et al.* found that using SP as IPT was associated with decreased placental parasitaemia in Côte d'Ivoire. The tendency of reduction in placental parasitaemia was larger if the women received two doses of SP instead of one. They also revealed that children of mothers with placental parasitaemia had significantly higher prevalence of LBW (35). A Cochrane review found significant effect of antimalarial drugs used as IPTp or chemoprophylaxis on placental infection, but not on LBW in all-parity trials (88).

Administration of IPTp to paucigravidae is associated with decreased incidence of LBW, when compared to not using IPTp or other chemoprophylaxis (88). Eisele *et al.* estimated in their review that the protective efficacy on LBW for IPTp and the use of ITN to be 35% among paucigravidae in stable *P. falciparum* transmission areas (68). A different review found a relative risk of 0.71 among paucigravidae in areas of SP resistance and ITN usage (68). Garned and Gülmezoglu estimated that

IPT or prophylaxis might reduce perinatal mortality in paucigravidae, as well as the incidence of anaemia and severe anaemia, compared to no chemoprevention (88).

The timing of IPTp is usually not based on the gestational period, but rather on the safety of the drug that is used. SP is regarded as safe in the second and third trimesters, but is avoided close to term because of concerns that sulpha drugs may give kernicterus in premature new-borns (30). This has not been seen clinically, even though SP has been widely used close to term and in new-borns for symptomatic treatment of malaria and toxoplasmosis. Even though SP is considered safe, it should not be administered together with co-trimoxazole, a prophylactic drug given to HIV-infected, as these two drugs interact and give increased adverse effects (89).

SP has folate antagonistic effect, a drug mechanism that often is associated with an increased risk of neural tube defects if pregnant women are exposed in first trimester. An increase in congenital defects when SP is given after foetal quickening has not been reported. Pregnant women are recommended to take folic acid supplementation (0.4 mg/day), a dosage that will not limit the antimalarial effect of SP, even though high doses of folic acid supplement may reduce this effect (89).

There are concerns regarding the effect of using SP for IPTp because of the increasing resistance towards SP. During the last decade, several trials have evaluated alternatives to SP as IPTp. A trial in Ghana in 2008 compared amodiaquine, SP plus amodiaquine, and SP given as IPTp. They found similar rates of anaemia and LBW between the three alternatives, with a significant reduction of prevalence from enrolment to delivery for both parameters. However, the women who received amodiaquine alone or SP plus amodiaquine had higher incidence of adverse effects, reaching statistical significance (90).

In their review, Garner and Gülmezoglu found one trial from 1991 where proguanil gave fewer episodes of fever and less parasitaemia among all-parities compared to chloroquine. SP reduced the incidence of LBW and maternal parasitaemia compared to chloroquine in low-parity women, estimated from two trials from 1994 and 2005 (88).

Azithromycin is a macrolide that has been used to treat bacterial infections in pregnancy, and thus has been considered safe to use during pregnancy. Azithromycin–chloroquine and mefloquine seem to have similar effect on clearance of *P. falciparum*. Both can be given earlier in pregnancy than SP, which may increase their effect during pregnancy (36).

Since azithromycin is an antibiotic drug, it has an effect on other infections than malaria, such as sexually transmitted diseases and pneumococcal infections. The former is known to increase the risk of several parameters for reproductive health, such as prematurity, birth weight and perinatal

mortality. This effect may therefore add to the health benefit from malaria reduction. The effect on *S. pneumoniae* may become a problem because of the risk of increased resistance towards azithromycin or even development of cross-resistance with erythromycin. Chico *et al.* therefore conclude that trials regarding prevention with azithromycin should keep pneumococcal resistance under surveillance (36).

Mefloquine has maintained efficacy for treatment and prevention, with effect on parasitaemia and LBW among pregnant women (31). McClure *et al.* found chloroquine and mefloquine to affect placental infection in a similar degree as SP used as IPT (91). Several studies on the safety of mefloquine during pregnancy have not found any serious adverse effects, but a few small trials have shown a tendency of increased rate of stillbirths (31). The overall evidence still suggests that mefloquine is safe during pregnancy (92).

5.4.5.2 Intermittent preventive treatment in infancy

A meta-analysis of the effect of SP as intermittent preventive treatment in infancy (IPTi) showed promising results, with an effect on clinical malaria at 30.3%. They also estimated a protective efficacy of 21.3% against anaemia (93), even though only three of the seven trials included had a significant effect on anaemia alone (94).

In Tanzania, one study found reduced incidence of malaria infection by 60% and anaemia by 50% for infants given SP as IPTi (95). Another study from a different area of Tanzania found that amodiaquine used as IPTi gave similar effects on clinical malaria and anaemia (96). However, Gosling *et al.* found a significant effect on clinical malaria only for mefloquine in their trial, not for SP or chlorproguanil–dapsone. The lack of effect for SP may illustrate the effect of high SP resistance, since the latter trial was carried out in an area where SP efficacy was estimated at 18% (97).

Menéndez *et al.* found that IPTi with Deltaprim (pyrimethamine and dapsone) had a protective efficacy of 57.3% against severe anaemia and 60.5% against all malaria during the intervention period (98). Chandramohan *et al.* also found a significant reduction of malaria episodes and anaemia in their IPTi trial in Ghana, as well as a reduced number of hospital admissions caused by malaria. The intervention group in this trial was given SP at vaccination visits and at 12 months of age, but the effects above maintained significance the first 15 months of age (99). A trial on weekly prophylaxis with Deltaprim during infancy also found a reduced risk of clinical malaria, anaemia and severe malaria among the intervention group during the time of prophylaxis (28).

5.4.5.3 Chemoprevention for older children

In areas of seasonal transmission, several trials have been done regarding chemoprevention to children after infancy. A review by Wilson found that IPT given monthly to children during transmission season had a significant effect on reducing episodes of clinical malaria, when estimated from the results of several trials from Sahel and sub-Sahelian areas. IPT also reduced the all-cause mortality in the intervention groups in the period of peak malaria transmission (100).

A trial in Senegal, where children under ten years of age received the combination of SP and amodiaquine each month during the peak transmission period, found reduced prevalence of parasitaemia and anaemia in the intervention group compared to the control group (101).

The tendency of reduced anaemia risk among the interventions groups in areas of seasonal transmission was also found in a review by Meremikwu *et al*. In this review, they also estimated IPTc to reduce the risk of clinical malaria and severe malaria. These results are also maintained in two studies with high ITN coverage (102).

Kweku *et al.* compared the effects of different IPT combinations to placebo in children 3–59 months of age in Ghana. They found that both monthly or bimonthly artesunate–amodiaquine and bimonthly SP gave significant results in reducing clinical malaria and anaemia (103).

A trial from Uganda, however, found that IPT with SP gave the same risk of parasitaemia as placebo while amodiaquine plus SP and dihydroartemisinin–piperaquine both reduced the risk of parasitaemia in children between 8 and 14 years of age. The prevalence of five molecular markers for SP resistance, including *pfdhfr* and *pfdhps*, was over 80% in the area of this trial (104).

In the twelve trials reviewed by Wilson, no serious adverse events were reported (100). There were not seen any serious adverse effects in neither of the trials review by Meremikwo *et al.* either; however, the combination of SP and amodiaquine has been seen to increase vomiting in children (102).

5.4.5.4 Rebound effect

Studies on immune response among pregnant women have shown reduced levels of malaria specific antibodies in women using preventive measures, both with ITN and IPTp. The severity of malaria infection during pregnancy shows parity dependence in endemic areas, with more severe disease in primigravidae. Whether this effect will be maintained in settings with high levels of prevention during pregnancy is uncertain (30).

The positive effect of IPT seems to be limited to the period of receiving the antimalarial drug. Several studies have shown an increase in incidence of malaria episodes after completion of IPTi, called a rebound effect (98, 105, 106).

Dicko *et al.* however, concluded that children receiving IPT did not have increased risk of malarial parasitaemia or malarial complications the following season, even though an increase in the incidence of clinical episodes of malaria may be seen (106).

A trial on IPTi in Tanzania found that the intervention group had significantly higher incidence rates for malaria episodes and severe anaemia in the year after discontinuing IPT. They did not find any difference in the severity of malaria episodes when comparing parameters on severity from the episodes in the intervention and control groups (98).

One trial where weekly chemoprophylaxis was given during infancy found that the incidence rate remained significantly higher in the intervention group the first 18 months after discontinuing prophylaxis. They did not find significant differences three years after discontinuing the prophylaxis. There was a tendency of higher cumulative incidence for clinical malaria in the intervention group, while there was a lower tendency for severe malaria in this group (28).

An immunological trial on antibody response to malaria in preschool children receiving IPT found that the IgG levels towards schizonts of *P. falciparum* was reduced by 33% in the intervention group 8 months after the last IPT dose. The antibody level was strongly associated with prevalence of present parasitaemia or history of clinical malaria previously, regardless of treatment received. They suggest that the effect of IPT on immunological response may be caused by a reduction in exposure, rather than through a direct effect on the immune system. This hypothesis is supported by research findings where IPTi shows no impact on the vaccine response among infants (107).

Dicko *et al.* found similar incidence rates in those who had received IPT with SP and those receiving placebo the year after intervention (108). Two review articles from areas of seasonal malaria transmission did not find significant increase in incidence rates the year after IPTc (100, 102). Wilson remarked that three studies in her review had a tendency to an increased incidence rate among intervention groups the year after IPT, but that none of the studies had significant results (100).

In a Gambian study, they followed children who had received IPT with dapsone plus pyrimethamine until they turned five years of age. The incidence rate for clinical malaria was higher in the intervention group the first years after chemoprophylaxis was discontinued, but the two groups had the same prevalence at age 10 and the mortality rate in this follow-up period was the same for both groups (109).

5.5 DDT

In this chapter, we will take a closer look at DDT, how it is used, as well as how it affects insects, the environment and at its potential ramifications for human health. After this, we will look at what kind of effect DDT had 50 years ago, and the road from being a celebrated pesticide to facing increasing scrutiny, leading to its eventual ban. The first part is mainly based on the "Toxicological Profile for DDT, DDE and DDD" from 2002, made by the Agency for Toxic Substances and Disease Registry, a subset of the United States Department of Health and Human Services. The historical perspectives are mainly based on the book *DDT, Silent Spring, and the Rise of Environmentalism* by Thomas R. Dunlap.

DDT stands for 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane, a synthetic chemical that was first synthesized in a German laboratory in 1874 (4). It is a white crystalline chemical without taste or odour. DDT biodegrades slowly into DDE (1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene) and DDD (1,1-dichloro-2,2-bis(p-chlorophenyl)ethane) (110).

5.5.1 How DDT enters the environment

DDT enters the environment during both production and use. In the past, vast amounts of DDT have been sprayed on crops and in forests in order to control insects, releasing large amounts of DDT into the air, soil and water. Therefore, most of the DDT in the environment is a result of past use, though DDT continues to enter the environment in areas where it still is manufactured and applied (111).

In addition to the direct dispersion into the air when sprayed, DDT may also enter the air through evaporation from contaminated water and soil, which can then be deposited on new land or water surfaces. In this way, DDT can be widely spread throughout the atmosphere, resulting in contamination far from the places it originally was applied; even though DDT has mostly been used in warm or temperate climates, traces of DDT has been found in Arctic and Antarctic regions (111).

Because of the slow biodegradability of DDT, any DDT that enters the environment lasts for a long time, potentially for several hundred years. In the USA, the Environmental Protection Agency (EPA) has put together the National Priorities List (NPL), which is a list of what is considered to be the most serious hazardous waste sites in the nation. People living or working in near vicinity with the sites identified in the NPL are at high risk of being exposed to DDT, either through soil, dust or vapours containing the chemical (111).

5.5.2 How DDT enters the body

The main way DDT enters the body is through contaminated food, but small amounts of DDT may be breathed in as well. Because DDT is frequently attached to large particles in the air, DDT does not

usually enter the alveoli in the lungs, but rather becomes stuck in the mucous and swallowed. DDT does not pass through skin easily. Therefore, the majority of the DDT that enters the human body enters through the gastrointestinal tract (110).

5.5.3 The effect of DDT on insects

DDT is an insecticide, which means that it is toxic to insects. It primarily acts on the nervous system of the insect, with a slightly delayed action; after contact with an oily DDT solution, it takes about twenty minutes before an observable effect on the insect. By inhibiting the nervous system of the insect, it induces spasms and paralysation, which eventually kills the insect (4).

5.5.4 How DDT, DDE and DDD can affect human health

DDT and its metabolites, DDE and DDD, have been measured in human fat tissue, as well as many bodily fluids, including blood, urine, semen and breast milk. However, most of the data on the human toxicity of DDT comes from animal studies (111).

Acute toxicity has been seen in people exposed to large amounts of DDT, with excitability, tremors and seizures, in addition to more benign symptoms such as sweating, headache, nausea, vomiting and dizziness. These effects were reversible, and went away after exposure was stopped. These effects are explained by experiments on laboratory animals, which have shown that DDT has a toxic effect on the nervous system in animals as well as insects (111).

There is little information on the long-term effects of chronic DDT exposure in humans. One study where low-dose DDT (35 mg) was given to adults daily for 18 months showed no significant effects. However, long-term exposure of less than 20 mg DDT daily, for example in DDT factory workers, has been correlated with minor changes in liver enzymes, but not with an increase in mortality or cancer (111).

Current knowledge about the long-term effects of chronic DDT exposure is therefore mainly based on animal studies in addition to a few human studies. Several studies have shown that chronic exposure to moderate levels of DDT is potentially hepatotoxic in animals, as well as having detrimental effects on reproductive health and negatively affecting the adrenal gland. DDT has been classified as a possible human carcinogen based on animal studies (111).

5.5.4.1 The effect of DDT on reproductive health and in infants

As mentioned above, studies have shown that DDT negatively affects reproductive health in animals. This may be partially explained by the fact that DDT and its metabolites display weak oestrogenic and anti-androgenic effects (111). Studies have shown that DDT slows the growth of the reproductive and nervous systems in the foetus, and exposure during pregnancy is associated with pre-term labour;

this has been substantiated in one human trial as well, where an elevated level of DDE in pregnant women was correlated with prematurity. Another human trial found an association with DDE concentrations in breast milk with decreased duration of lactation period (111).

In addition, several studies have shown detrimental long-term effects when animals have been exposed to DDT or its metabolites early in life. One study observed the delayed puberty in male rats exposed to DDE during adolescence; other studies have shown changes nervous system development, with decreased neurological performance later in life. These findings have raised concerns that DDT exposure during early life may have detrimental effects on development in humans as well (111).

As previously noted, DDT has been found in most bodily fluids, including breast milk, and this represents another way children can be exposed to DDT. However, EPA concludes that the potential risks of DDT exposure are offset by the benefits of breastfeeding (111).

Ultimately, there is little solid information about the effects of DDT on human pregnancy and childhood, though animal studies indicate that there are some potentially serious harmful effects when exposed to moderate or high doses of DDT. One complicating factor is that DDT concentrations tend to be higher in children compared to adults because of the size; one study from 1985–1991 in the USA observed that 8.5 month-old infants had 4 times higher concentrations compared to adults (111).

5.5.5 The history of DDT

The book *DDT, Silent Spring, and the Rise of Environmentalism* by Thomas R. Dunlap is a collection of excerpts from a variety of sources. Texts from scientific studies, government reports, advertisements from industry journals, articles from popular magazines, and an excerpt from the book *Silent Spring* by the American environmentalist Rachel Carson, gives an impression about the early success of DDT, the discovery of its environmental effects and the shifting attitudes toward DDT as well as pesticides in general. In addition, the book also contains some information about the recent debates about using DDT as a potential measure to fight malaria in Africa.

5.5.5.1 The DDT revolution

Even though DDT was originally synthesized in Germany in 1874, its insecticide properties were unknown until the late 1930s when chemists in Switzerland began testing synthetic organic compounds in the search for new pesticides. It was quickly discovered that it was very effective in killing insects, and it seemed reasonably safe to humans as well. The compound was named DDT, and became widely used in World War II to combat insect-borne diseases in the Pacific Ocean theatre

and typhus-carrying lice in the European theatre. In addition to dusting soldiers with DDT, the chemical was used extensively in civilian life; housewives sprayed their houses to make them insect free, and farmers sprayed DDT on their fields and on animal houses (4, pp. 4-5).

During and after World War II, the benefits of DDT were well known. Besides its applications in agriculture and in civilian life, it was also a great tool for limiting the spread of disease-carrying insects, such as mosquitoes carrying malaria and lice carrying typhus. In the text "How Magic is DDT?" from early 1945, Brigadier General Simmons writes that DDT played an important role in the war by controlling malaria among allied troops. Malaria had been a major burden during earlier war efforts, and any means that could help control the disease and reduce the prevalence were very valuable. He further states that the strategic value of controlling malaria and typhus was only scratching the surface of the true potential of DDT (4, pp. 36-38).

Following the extensive use in the 1940s, the Surgeon General's Office of the United States Army requested that the potential toxicity of DDT should be assessed; however, the study found that, with the exception of massive exposure leading to acute toxicity, no definite evidence of adverse effects following normal use were found (4, pp. 26-28).

Even though DDT was widely celebrated, some began to investigate the potential ramifications of its use more closely. The rapid implementation and massive production of DDT without first assessing the potential long-term effects of its use, gradually led to increasing doubt about its safety (4).

5.5.5.2 Discovering and publicizing the harmful effects of DDT

Studies from the late 1940s showed that essentially all Americans had been exposed to DDT in some form. DDT had been used extensively without knowing how it entered and affected the environment, and without knowing how it could be handled and potentially cleaned up. Experiments started to show that DDT was stored in the fat of animals, and that long-term exposure to relatively small amounts of DDT eventually led to liver failure. These studies, indicating potential toxicity in animals, raised the possibility of toxicity in humans as well. Despite the results of these preliminary studies, the Food and Drug Administration in the USA concluded that the potential benefits of DDT outweighed the risks involved (4, pp. 52-55).

By the late 1950s, the amount of DDT in the soil, water and atmosphere reached critical levels, and its effect on the environment became more and more clear. Robins were dying in large numbers, and the forests became noticeably quieter as songbirds died off; despite increasing public attention, massive spraying campaigns continued. The dead robins were studied, showing the cumulative effect of DDT on the food chain, raising further concerns for human health (4, pp. 4-5). By the early 1960s,

the same effects were seen in peregrine falcons throughout North America and Europe, with a sharp decrease in the population. Research showed that peregrine falcon eggshells contained DDT (4, pp. 68-74) and were thinner than normal, and it was theorized that this was due to a change in calcium metabolism of the birds (4, p. 84). Additionally, in the late 1950s, signs of DDT resistance in mosquitoes started to appear. In addition to the possible detrimental health effects of DDT, this signified the need for basic research (4, pp. 89-90).

Rachel Carson released *Silent Spring* in 1962, a book that quickly became a best-seller and that would permanently change the public attitude towards DDT. In addition to some research showing the potential toxicity of DDT, it also contained a lot of anecdotal and circumstantial evidence, including examples such as disappearance of birds and bees, as well as the reported frequency of illnesses among farmers, their families and their animals (4, pp. 102-103).

Even though public opinion had already shifted, the scientific view was more cautious; even though the available evidence gave cause for concern, most scientists were not ready to come out against DDT, because too little was known about the potential harmful effects of DDT (4, pp. 82-83).

Following the massive shift in public opinion after the publication of *Silent Spring*, President Kennedy asked for a report from his Science Advisory Committee. This report, finished in 1963, verified the claims that DDT persisted for a long time in the environment, and that it could spread from one ecosystem to another. It also stated that there was too little information to make any definite conclusions when it came to the potentially harmful health effects of DDT, and recommended that further studies should be performed in order to assess the levels of exposure in the population, as well as the long-term effects of DDT exposure (4, pp. 104-108).

The Environmental Protection Agency (EPA) was founded in 1970; in 1972, this organization banned all domestic use of DDT in the USA with the exception of public health emergencies. Because of environmentalist pressures from the USA as well as increasing insecticide resistance, the use of DDT declined worldwide throughout the 1970s. By the 1990s, the use of DDT reached an all-time low; at the same time, malaria rates in tropical countries were on the rise. This led to a debate whether or not Africa could benefit from using DDT as well (4, p. 9).

5.5.5.3 Is there still a role for DDT?

Despite the mainstream popularity of *Silent Spring*, the book also met widespread criticism from several sources. Some have criticized the book for using a simple and elegant language to convince people of the dangers of DDT (4, p. 113), while at the same time ignoring the benefits that DDT has achieved. In addition to leaving out many of the positive effects DDT has had since it was first used,

Carson also establishes a link between DDT and cancer, hepatitis and mental disorders, without having the scientific evidence to back these claims up. Some have criticized the book for taking a one-sided stance in the cases it focuses on. For instance, the book brings up the increase in cat deaths following an antimalarial programme carried out by WHO in Indonesia, but fails to look at how many lives were potentially saved by this programme. DDT was used because earlier eradication programmes had dubious effects at best; in addition, it was easy to use, effective and inexpensive (4, p. 125).

There are several different views on DDT today, but most seem to agree that DDT can be used in certain circumstances. While some lay the blame for the increase in malaria increase in developing countries on the international ban on DDT (4, pp. 127-128), others feel that DDT is a tool and not a solution. Large organizations such as WHO conclude that DDT can be considered a temporary tool, to be used with caution in the fight against malaria, and only when the benefits clearly outweigh the risks (4, pp. 136-139).

5.6 Malaria in the world

According to the Global Health Observatory, malaria occurs in 99 countries (112). In 2011, there were a total of 26 million reported malaria cases and 106,820 reported deaths worldwide caused by malaria. However, the real burden of the disease is probably much larger than the reported numbers indicate (113).

There has been an estimated global reduction of 25% in the malaria mortality rate over the last decade. Some of the most important reasons for this are the large interventions when it comes to vector control, diagnostics and treatment (114). In sub-Saharan Africa, ITN coverage has increased rapidly over the last decade, and was over 50% in 2011. Nevertheless, the ITN distribution is still insufficient to provide universal coverage in the population (115). The number of diagnostic tests has also increased greatly over the last years, and in 2011, statistics showed that diagnostic tests were used in three out of four suspected malaria cases worldwide; however, WHO implies that this number may be too high, because it depends on countries reporting their usage (116).

However, the progress in the fight against malaria the recent years has now slowed down as a result of the development of resistance against antimalarial drugs and insecticides, as well as the stagnation of funding. Addressing these problems is important to keep reducing the burden of the disease globally (114).

5.7 The World Health Organization

To get a better understanding of how the World Health Organization (WHO) is organized and how it can help countries in the fight against malaria, we first want to present the organization itself, and describe some of their more relevant programmes.

WHO is a part of the United Nations (117), and was established in 1948 (118). The organization works globally to improve health worldwide through technical support and guidance to nations, as well as monitoring global health and promoting research on health issues (117).

WHO strives to make essential health care available to all, especially targeting vulnerable population groups in the world, and use impact on women's health and African health as parameters of their influence (119).

To achieve this, several aspects affecting health are targeted, including access to health services and ensuring its quality, as well as presenting health information and recommendations. Factors like having adequate human resources and solid access to drugs and equipment are important to improve the quality of the health care systems. Vulnerable groups are especially targeted, and interventions are prioritized to areas where they might give the most benefit (119).

WHO publishes the World Health Report, where statistics on specific subjects regarding global health are presented (120).

5.7.1 The WHO Global Malaria Programme

The WHO Global Malaria Programme administrates WHO's efforts against malaria. They present recommendations and monitor malaria statistics globally, as well as publishing the annual "World Malaria Report". The programme addresses different aspects of fighting malaria, and give guidance that can be used in national malaria programmes (121).

5.7.2 Roll Back Malaria partnership

The main goal of the Roll Back Malaria (RBM) partnership is enhancing the fight against malaria through coordinating different interventions. It was established in 1998, and has over 500 partners worldwide, including the main actors WHO, United Nations Children's Fund (UNICEF), United Nations Development Programme (UNDP), and the World Bank. RBM attempts to coordinate the utilization of resources to increase their worth, and thereby reduce the malaria burden globally (122).

5.8 The WHO malaria guidelines

WHO has given out guidance to assist countries in their fight against malaria, including diagnosis and treatment, chemoprevention during pregnancy, infancy and childhood, vector control with focus on

ITNs and IRS, as well as managing resistance towards antimalarials and insecticides. In addition, guidelines for surveillance and persistent evaluation is important to sustain the effectiveness of the guidelines, and make new guidelines where it is needed (3).

5.8.1 Recommendations in diagnosing malaria

Diagnostic tools like microscopy and RDTs, when used in combination with efficacious treatment, allow for effective case management. WHO states that parasitological diagnosis should be sought before starting the treatment (3). Nevertheless, treatment should not be postponed more than two hours while waiting for the confirmation of the diagnosis (123). The parasitological diagnosis should preferably be performed using microscopy, but RDTs can be used when this is not available (3). As described earlier, clinical manifestation is rarely distinctive and parasitological verification is therefore needed. In settings where microscopy or RDTs are unavailable, treatment can be started on clinical suspicion. This may lead to excess use of antimalarial drugs and postponed treatment of other febrile illnesses (3).

5.8.1.1 Guidelines for microscopy

Microscopic diagnosis is recommended if adequate quality of microscopy services is available. Even though parasitological diagnosis using confirmation is used at some larger health care institutions, the quality is not always adequate. To improve the standards, WHO has given guidelines regarding microscopy, as well as for the monitoring of this diagnostic method in order to ensure that it is utilized correctly. For a microscopy service to be regarded as adequate, a good quality diagnosis should be given within an acceptable timeframe, which in turn require having all necessary resources available. In order to ensure optimal quality of diagnosis, the operating technicians should be trained and educated. WHO proposes that a mandate should be established to ensure the implementation of these requirements (3).

5.8.1.2 Guidelines for rapid diagnostic tests

As mentioned above, WHO states that parasitological diagnosis should be sought before starting the treatment, and RDTs are an option in settings without access to adequate microscopic diagnosis (3). These tests have become more frequently available and utilized over the last years (124).

Limited knowledge regarding the test qualities made implementing their utilization in guidelines more difficult, especially since results from field trials depended on local settings. To overcome this, an evaluation programme on RDTs was established in 2006, called the WHO Malaria RDT Product Testing Programme. The results were presented in a report, helping to guide countries when selecting RDTs and thereby improving quality of the RDTs (124).

During RDT testing, this programme evaluates how often the tests show correct results, either positive or negative, as well as how often the tests were regarded as invalid (124). The usability and robustness of the tests were also assessed, including how stable their performance was under different temperatures. The tests are evaluated by using a panel detection score (PDS), which is the percentage of tests that are positive when blood with parasite density of 200 or 2000 parasites/µl are tested in laboratory settings. WHO uses PDS because the results only depend on the intrinsic test traits, while sensitivity and specificity are tested in clinical settings with errors connected to this (125).

In areas with high transmission intensity, the threshold for clinical disease is normally above 200 parasites per microlitre, which is the lower density limit tested in this programme. The test sensitivity depends on parasite density (124). The symptomatic threshold of parasite density depends on acquired immunity, and will therefore for most part correlate with transmission intensity as well (11). As described earlier, vulnerable individuals, such as pregnant women and HIV infected, have lower threshold density even in high endemic areas.

Several criteria should be met before the RDT can be recommended by the WHO: the PDS should be above 75% in samples with 200 parasites/µl, with less than 10% false positives and less than 5% invalid results (123). In addition, the usefulness of RDTs does not solely depend on their intrinsic qualities that are revealed in a laboratory setting, but also on several external factors, such as their stability during transport and storage, their usability and cost (123).

5.8.2 Recommendations in treatment

The increasing antimalarial drug resistance over the last decades has prompted sweeping changes in the malaria treatment guidelines stipulated by the WHO. Modern malaria treatment is largely based on the use of ACTs instead of monotherapies. As previously stated, the reason for this is twofold. First, ACTs are generally more effective than the available monotherapies; second, using two drugs with different modes of action slows development of resistance. Five ACTs are currently recommended by the WHO (2, 46):

- Artemether–lumefantrine
- Artesunate–amodiaquine
- Artesunate–mefloquine
- Artesunate–sulfadoxine–pyrimethamine
- Dihydroartemisinin–piperaquine

5.8.2.1 Guidelines for treating uncomplicated malaria

Current malaria treatment guidelines recommend using ACTs for the treatment of uncomplicated malaria; the five recommended ACTs are regarded as equally valid, though local resistance tolerability patterns have to be assessed in order to select the right ACT for the region. Other considerations include the availability and cost of fixed-dose combinations, which simplifies treatment and increases compliance (2).

The guidelines further stipulate that treatment should be given for at least three consecutive days, in order to ensure that artemisinin kills off over 90% of the parasites. Research shows a clear increase in 28-day treatment failure rates for shorter durations. By having the artemisinin take care of the majority of the parasites, the partner drugs will be exposed to fewer parasites, thus reducing the risk of developing resistance even further (2).

In the case of treatment failures, emphasis is placed on having a second-line treatment available. Ideally, the second-line treatment should be an alternative ACT known to be effective in the area; if this is not possible, a longer 7-day treatment course of either artesunate or quinine should be given in combination with either tetracycline, doxycycline or clindamycin (2).

5.8.2.2 Guidelines for treating complicated malaria

When it comes to treating complicated malaria, the guidelines recommend prompt intravenous treatment with artesunate for both children and adults. This is preferred over quinine for several reasons, but mainly because of studies showing artesunate significantly reducing risk of death compared to quinine. Other factors such as not requiring rate-controlled infusions and better tolerability also contribute to the recommendation of artesunate over quinine. If parenteral artesunate is unavailable, either artemether or quinine is regarded as acceptable alternatives (2).

In addition to the prompt treatment with artesunate or suitable alternatives, the treatment guidelines recommend various adjunctive treatments for certain complications of malaria, attempting to reduce the high mortality of severe malaria (2).

5.8.2.3 Guidelines for treating special patient populations

Pregnant women are a high-risk group for developing severe malaria, and emphasis is placed on giving these patients prompt treatment if they develop symptoms of acute malaria. However, there is still a lack of information on the safety and efficacy of many antimalarial drugs when used in pregnancy, including ACTs (2).

In the first trimester, pregnant women with symptoms of uncomplicated malaria should ideally be treated with quinine plus clindamycin for seven days; if clindamycin is unavailable, quinine

monotherapy is recommended. Second-line treatment for pregnant women is artesunate plus clindamycin (2).

As some women in the first trimester may not be aware that they are pregnant, asking about the possibility should always be done before starting treatment. Small-scale studies indicate that artemisinin derivatives are adequately safe for use in the first trimester, but more research is needed before this can be incorporated into treatment guidelines (2).

For the second and third trimesters, use of artemisinin derivatives has been shown to be reasonably safe, and uncomplicated malaria in these women can be treated with ACTs. DP is the only exception, as there is still insufficient information to use as first-line treatment for pregnant women. If ACTs are unavailable, a seven-day course of artesunate plus clindamycin is indicated (2).

Pregnant women with complicated malaria have a significantly higher mortality, approximately 50%, compared to non-pregnant women. Prompt treatment is therefore the highest priority. In the first trimester, both parenteral quinine and parenteral artesunate are valid options for treatment, even though there are uncertainties over the safety of the artemisinin derivatives. In the second and third trimesters, parenteral artesunate is preferred over quinine, as quinine has been shown to increase risk of hypoglycaemia in pregnant women (2).

Lactating women should follow the general guidelines. None of the drugs currently recommended as first-line treatment appear to be present in the breast milk in large amounts, and it is unlikely that using the current first-line drugs is harmful for infants. Breastfeeding women should however avoid tetracycline and primaquine (2).

For infants and young children, the general guidelines should also be followed, as artemisinin derivatives have been shown to be safe and well tolerated by children. However, special care has to be taken in order to administer accurate dosing, which may be difficult, especially if paediatric formulations are unavailable (2).

5.8.2.4 Guidelines for limiting antimalarial resistance

In order to monitor the resistance to antimalarial drugs worldwide effectively, malaria-endemic countries are encouraged by WHO to assess the malarial resistance for the first-line treatment and second-line treatments, as well as other applicable drugs, at regular intervals, ideally at least once every two years (46).

To ensure adequate treatment efficacy and to limit developing further development of resistance, WHO recommends that treatment policy changes should be initiated when any of the currently used treatment options have treatment failure rates exceeding 10% (46).

5.8.3 Recommendations for malaria prevention

Malaria prevention is mainly based on malaria vector control and chemoprevention (3). The former consists of ITN utilization, IRS and larval control (3), of which the first two is more common because of their efficacy under several different circumstances and imperfect coverage (82). Chemoprevention is recommended to pregnant women and infants in high transmission areas, as well as to children in seasonal transmission areas (126).

5.8.3.1 Guidelines for using insecticide treated nets

WHO state that the long lasting option is preferable, which means that the nets distributed by campaigns following the WHO guidelines are LLINs (3). Large campaigns are also recommended to survey the net duration at selected sites, to assess the need for new distribution as the duration may vary. This may also enable campaigns to choose the products best suited for local settings (65). There is also a kit for re-treating other nets with long-lasting insecticide. WHO's goal is to have full coverage of long-lasting ITNs, with one net for every second person. When this is not achieved, pregnant women and children below five years of age should be prioritized (3).

5.8.3.2 Guidelines for using indoor residual spraying

The guidelines regarding IRS are detailed, both when it comes to requirements and recommendations. WHO recommends utilization of IRS as a vector control method in countries where knowledge of local vector traits indicates that this intervention is cost-effective. Vector traits include local resistance towards insecticides, which should be evaluated and monitored before and during implementation of IRS. In addition to thoroughly selecting areas for intervention, the insecticide should be carefully selected and the execution should be well planned (80).

Transmission intensity and the other implemented intervention methods in the area should also be considered. The guidelines do not give any strict rules regarding which settings IRS can be implemented in, but state that spraying in densely populated areas and as well as in areas where malaria has a seasonal pattern may give higher efficacy. The latter may also result in the need of fewer rounds of IRS, as one round should ideally last six months (81). The degree of coverage of LLINs should affect the choice of insecticide, as described in more detail below (82).

Combining IRS with ITNs should currently only be done in specific settings. Using non-pyrethroid-based IRS in areas with pyrethroid resistance and high LLIN coverage may help reducing the selection

pressure and slow resistance development. Combining the two measures can also be done in transitional periods when changing intervention methods, in addition to increasing the effect of existing interventions (81).

The insecticide indicated in an area also depends on the housing material (81), an important aspect since the overall efficacy depends on the ability to spray at least 80% of the buildings in the area. It also is important to maintain insecticide susceptibility, and therefore avoid inadequate or inaccurate usage (80). Methods to maintain susceptibility will be further discussed below.

The WHO guidelines state that all peripheral aspects regarding IRS should be established before implementing the measure. This includes the training of staff, solving logistical challenges, and having the resources and equipment for insecticide handling ready. WHO has also developed recommendations for the spraying equipment and its maintenance. Strides should be taken to avoid excess contamination of the surrounding areas to minimize environmental and human exposure, which include managing waste (81).

The insecticides recommended by the WHO Pesticide Evaluation Scheme (WHOPES) are considered to be safe to humans and to the environment when used as recommended (81). Adherence to the IRS guidelines is therefore important to minimize potential hazards. Following safety measures during spraying, such as removing food and covering furniture may reduce unnecessary exposure in the population. For the spray operators, safety equipment should be used and routine health controls may be indicated depending on the insecticide used. WHO also emphasize the importance of trained staff, including spray operators and technicians (81).

Malaria vector control through IRS depends on collaboration from the population at risk. To ensure their informed consent, WHO recommends strategies for public information, including developing so-called information, education and communication (IEC) strategies and to conduct IEC campaigns before the start of each spray round. Addressing local leaders may help in the community acceptance to the intervention as well (81).

As many countries may have difficulties with adherence of these recommendations because of limited resources, WHO states that they will help countries in challenges related to local research and administration of this intervention. In addition, WHO aims to increase research and progress on IRS related topics (80). In return, WHO requires reports on usage details, as well as effect and resistance when available (81).

5.8.3.3 Guidelines for managing insecticide resistance

The keyword in this topic is prevention. WHO recommends six tactics in total to reduce development

of resistance, as this is more effective beforehand. First, in areas intending to use insecticides for vector control, there should be a focus on resistance from the beginning, and the methods that have the least impact on resistance should be chosen. Secondly, the planning should aim for the most effective usage of the measure itself, both to reduce the costs and to avoid vector exposure in suboptimal dosages, which might cause selective pressure. Thirdly, methods combining exposure of different insecticides should be considered, such as changing the insecticide used in IRS between different years, avoiding IRS with pyrethroids in areas with LLINs, and preferably, using products combining different insecticides (82).

The fourth tactic focuses on monitoring, emphasizing the need for continuously observing and evaluating the resistance in areas of insecticide use. Fifth, WHO also stress the need for progress in vector control, both in finding alternative methods and new insecticides. As pyrethroids are still the only insecticides used to treat LLINs, finding new options is especially pressing. The sixth and final tactic is prioritizing short-term investments in order to make the measure viable in the long-term. An example on such short-term cost would be choosing a different insecticide for IRS than pyrethroid when used in combination with LLINs, and in that way avoiding increased selection pressure (82).

The distribution of LLINs has increased rapidly over the last decade, but the increasing pyrethroid resistance may jeopardize their efficacy. Pyrethroids are currently the only insecticide group recommended for treating the bed nets. Nevertheless, even if extensive pyrethroid resistance develops, the bed nets will still be able to give some protection against malaria infection, in much the same way as untreated nets. With a reduced effect of the insecticide, there is an increased importance of having an undamaged net, however (81).

The six tactics to reduce evolution of resistance mentioned above should be followed in areas that are implementing IRS, especially when using pyrethroids. This insecticide can still be used in some areas, but should be avoided in areas of extensive ITN usage, since the recommended nets are impregnated with the same insecticides (81).

There should be a thorough surveillance of resistance, and actions should be taken as a result of the current resistance situation. One method for monitoring resistance is by using bioassays, through which the susceptibility to the insecticide can be estimated. If less than 80% of the mosquitoes die, WHO recommends changing insecticide; if more than 80% die, the situation should continue to be monitored and assessed, but usage of the current insecticide can continue (81).

The WHOPES focuses on the pesticide use and safety, including research of new options and monitoring the global use (127). As resistance limits the number of efficient alternatives, WHOPES promotes development of new insecticides for public health use (128).

5.8.3.4 Guidelines for larviciding

The WHO guidelines regarding larviciding in sub-Saharan Africa specify that the use should be thorough and according to local knowledge and features, and preferably only in areas with a few, known and semi-permanent breeding sites. This intervention is described to chiefly be an addition to other vector control methods, such as ITNs or IRS. This recommendation is based on the estimation of IRS and/or ITNs as more cost-effective in most settings. Urban areas with seasonal transmission are the most likely to benefit from larviciding (85).

5.8.3.5 Guidelines for intermittent preventive treatment in pregnancy

WHO have recommended IPTp consisting of two courses of SP to pregnant women in malaria endemic areas since 2004. The courses should have at least one month between them, with the first in the second trimester and the following course within the last month of pregnancy. To HIV-positive women, three courses are recommended (34). In this group of women, it is also important that co-trimoxazole and SP should not be administered simultaneously (89).

The WHO recommendation for using SP in IPTp has been adopted as national policy in 31 of 37 endemic countries in Africa, with the remaining countries using more frequent IPTp (129). Several trials have focused on effect of increased frequency, especially in areas with extensive resistance. However, the results are inconsistent. McClure *et al.* found a decreased risk of LBW among women receiving more than two doses of SP in several of the studies they reviewed (91). Diakite *et al.* found lower LBW rates among those who received three doses compared to those receiving two doses of SP (130).

A recent review of seven trials found lower risk for LBW if the women received more than two doses of SP as IPTp, even in areas with high resistance. They also found a significant decrease in preterm births among the women receiving more frequent administration of SP. In these seven trials, there were no signs of association between increased frequency of SP and the risk of neonatal kernicterus (129).

Kuile *et al.* did not find significant difference between two doses and monthly SP in HIV-negative women, even in areas of resistance up to 24%. In Malawi, however, where the resistance was 39%, the monthly regime showed significant reduction in peripheral parasitaemia. In their analysis on the effect of IPT on paucigravidae given two doses of SP, Kuile *et al.* found significant protection against

maternal anaemia, LBW, and placental malaria, compared to controls in an area of resistance between 19 and 26% (131). Paucigravidae with HIV infection, however, were found to have a statistically significant lower risk of placental malaria when receiving monthly SP instead of two doses of SP as IPTp (131). This suggests that even with inconclusive results, implementing IPTp with increased frequency in national guidelines may be justified.

5.8.3.6 Guidelines for intermittent preventive treatments for infants

WHO recommends to give IPT with SP to infants in areas where malaria transmission is moderate or high and where the prevalence of the *pfdhps* mutation is below 50%. They suggest the treatment to be coordinated with the vaccine program (3). This recommendation from March 2010 has as of 2012 yet to be implemented in any national guidelines (92). The requirement of measuring resistance prevalence using molecular markers may be one reason for this lack of response, as this information is not available at regional level in several endemic countries. Increased levels of molecular markers are associated with increased treatment failure. However, this association is weaker for prophylaxis and trials have shown significant efficacy of IPTi in areas of moderate treatment failure (92).

5.8.3.7 Guidelines for seasonal malaria chemoprevention

In 2012, WHO implemented seasonal malarial chemoprevention into their recommendations. This may be given to children between 3 and 59 months of age in highly seasonal areas in the sub-Sahel region, and is based on monthly administration of the combination of amodiaquine plus sulfadoxine–pyrimethamine during transmission season. As with other chemopreventive methods, this should not be given to children receiving co-trimoxazole. An additional requirement is that the efficacy of the drug combination should be above 90% (126).

5.8.4 Recommendations in the use of DDT

During the latter half of the 20th century, the potential effects of DDT on human health as well as on the environment led to increasing scrutiny and scepticism, and the chemical became banned in the USA in 1972. The Stockholm Convention on Persistent Organic Pollutants classified DDT as a persistent organic pollutant, in addition to 11 other chemicals, severely restricting their production and use. When it comes to DDT, all use is banned, with the exception of indoor application as a measure against vector-borne diseases; this exemption is in effect until better insecticide alternatives are developed. WHO has evaluated the findings of the Stockholm Convention, and applied their recommendations in their own guidelines. DDT has the longest insecticidal duration when used in IRS, resulting in fewer required spray cycles in order to achieve optimal effect, making it a more realistic alternative for IRS than most other insecticides. Because of this, DDT is still recommended by the WHO as a measure to control malaria in certain circumstances (132).

WHO monitors any new information regarding the safety of DDT continuously. In 2000, an assessment into the current information on the safety of DDT was performed; it was found that, though extensive research had shown toxic effects in laboratory animals, the current levels of exposure in humans were generally within safe limits. DDT was therefore regarded as safe in its use as a vector control measure, as long as the guidelines for its safe application and use were strictly followed.

DDT is currently only recommended for use in IRS in areas where there are susceptible vectors. Therefore, before DDT can be introduced as a measure to control malaria in an area, local insecticide resistance has to be assessed. Because of widespread resistance towards organochlorines such as DDT, many countries started using pyrethroids instead; this may lead to pyrethroid resistance, which not only affects the efficacy of IRS, but also the LLINs, which are pyrethroid treated as well (132). An example of this was seen in South Africa, where DDT had to be reintroduced shortly after discontinuation because of the appearance of pyrethroid-resistant *An. funestus* vectors (133).

In order to avoid unnecessary exposure in workers and in the population, DDT application and storage should follow national guidelines as well as recommendations outlined in the WHO technical guidance documents and in the Stockholm Convention (132).

In order to monitor the current usage of DDT in IRS, any use of DDT must be reported to both WHO and the Secretariat of the Stockholm Convention. These institutions will evaluate the current use in terms of benefits and safety, and take into account information about local resistance patterns, as well as alternative measures that can be utilized to control malaria in the area; the effect of these evaluations is to limit the unnecessary use of DDT (132).

Progress in developing alternative insecticides and vector control strategies in the last decades has been insufficient; until suitable alternatives are found, WHO concludes that there still is indication for using DDT in some areas (132).

5.9 Malawi

In order to gain better understanding of what kinds of challenges Malawi faces when it comes to malaria, we will first introduce some facts about the country and its health care system. In addition, we will examine the role of WHO in the context of improving the health in Malawi. After this, we will give an outline on the current malaria situation in Malawi, including Malawi's national guidelines for diagnosing, treating and preventing malaria. Finally, we will give a quick overview of some of the studies that are currently on going, and that we were able to be involved with under our visit to Malawi.

5.9.1 About Malawi

Malawi is a completely landlocked country in sub-Saharan Africa, with borders to Mozambique, Tanzania and Zambia. Malawi's eastern border is dominated by the 475 kilometre long Lake Malawi (134), which accounts for about one fifth of the total area of the country (135). The Rift Valley runs through the country (134), creating a diverse geographical landscape with high plateaus in the north and central areas, and fertile lands surrounded by large mountain peaks west and south in the country (134, 135). The country has two seasons, a cold-dry season from April to November, and a hot-wet season from November to April (135).

Figure 3: Lake Malawi is a defining feature in Malawi's geography and culture. Cape Maclear, Malawi; picture taken by authors.

Malawi is an agricultural country; comprising nearly one-third of the gross domestic product, agriculture also accounts for the vast majority of the domestic exports (134). Tobacco is Malawi's most important export, but significant amounts of tea and sugar are also exported (135).

In the 2008 census, Malawi had a population of 13,077,160 people, with an average growth rate of 2.8% per year between 1998 and 2008. Almost 85% of the population was classified as rural, and 67% were under age 25 (134).

5.9.2 Health and development challenges in Malawi

The health care system in Malawi is divided into three levels: primary, secondary and tertiary care. Primary care is provided on the community level, mainly through health centres or small community hospitals. Secondary care is provided by larger district hospitals, of which there are 56 in total in

Malawi. Finally, tertiary care is provided through five central hospitals throughout the country. In addition to this, there is a wide network of charity-driven or privately-owned health care facilities throughout Malawi, mainly providing primary and secondary care (136).

Figure 4: Zomba Central Hospital, one of Malawi's five central hospitals. Picture taken by authors.

Malawi is facing a big challenge dealing with a growing burden of communicable diseases like HIV/AIDS, malaria and tuberculosis. Malaria is responsible for about 40% of hospitalizations of children under five, as well as 40% of total hospital deaths. The national prevalence of HIV was estimated at 12% in adults in 2007 (136). In addition to these well-known diseases, several neglected tropical diseases are probably on the return, even though the true extent of this is still unknown. Malawi also have a significant burden of non-communicable diseases like cancer, and these diseases contribute significantly to both the overall mortality in Malawi, as well as the public health expenditure (136).

The human resources situation in Malawi is also a challenge; a survey from 2006 revealed that Malawi had the lowest ratio of health care workers in the region, with 2 physicians and 59 nurses per 100,000 people. This problem appears to be twofold. The output of training institutions is not only too low to satisfy the demand for health care workers, those that are trained often go on to work in the private sector or outside of the country. Efforts have been made to increase the training output, in the hopes that this may alleviate the human resource shortages over time (136).

Additionally, there are several other factors that may affect public health. In 2010, over 90% of households lacked electricity or access to improved sanitation, and about 20% did not have access to

an improved water source (134). These factors represent other significant public health challenges in Malawi.

5.9.2.1 Maternal health

The fertility rate in Malawi is strongly correlated with the women's education level; in 2010, it ranged from 6.9 in women with no education, to 2.1 in women with more than secondary education (134). Malawi has a high maternal mortality ratio, which in 2008 was at 807 per 100,000 live births; there may be several reasons for this, including for instance that only half of the pregnant women receive the recommended IPTp regimen, and that only half of the deliveries are performed by trained health care workers (136).

5.9.2.2 Child health

While neonatal mortality has remained mostly the same since 1985, the mortality rates for infants and children under-five have fallen. Part of this may be because of an increased focus on immunization during childhood, which has effectively eliminated measles and neonatal tetanus, as well as significantly reducing polio (136).

Malaria, pneumonia, diarrhoea and HIV/AIDS were the main contributors to childhood morbidity and mortality in 2005. Malnutrition in children is still a significant problem in Malawi (136), and there is still a large potential for reducing the burden of malaria by focusing on preventive methods in children; in 2010, only 40% of children under five were sleeping under ITNs, even though over 55% of households had at least one ITN available (134).

5.9.3 WHO in Malawi

As stated earlier, WHO is working closely with governments around the world to improve global health. This includes cooperation with Malawi. The WHO Malawi Country Office works with the Malawian government and other relevant partners in order to promote public health in Malawi (137).

5.9.3.1 Country Cooperation Strategy

The Country Cooperation Strategy (CCS) is a document provided by the WHO Regional Office. It identifies challenges and needs in the health care system, and gives support in developing the national health plan (136). The CCS focuses on increasing the national health security, strengthening the health care system, and reducing poverty and inequality while at the same time investing in health (136).

The first generation CCS was in effect in 2005–2007 and focused on supplying strategies for cooperation between the national government and relevant partners in an effort to strengthen the

health care. The second generation CCS came into effect in 2008, and is valid through 2013, and focuses on weaknesses in the public health system that were uncovered during the first CCS (136).

In 2007, Malawi changed the first-line treatment in their national treatment guidelines from SP monotherapy to ACTs. WHO gave the government strategic and financial support during this change. In addition, several measures were taken in order to strengthen reproductive health, mainly by strengthening the maternal health care service and developing national guidelines for maternal care during the time the first generation CCS was in effect (136).

The second generation CCS has three priority areas. The first is enhancing the health security, both on an individual and national level. Second is an overall strengthening of the health system in Malawi. The third area is to reduce the health burden of poverty by investing in health and counteracting causes of poverty.

When it comes to the first priority area, enhancing the health security, several approaches are taken. The first CCS revealed that the handling of epidemics and natural disasters was a significant weakness in Malawi, and measures are taken to increase readiness for such events. In addition to this, work continues with reducing the burden of both communicable and non-communicable diseases, as well as reducing the maternal and childhood mortality rate further. This is done by supporting various preventive measures in the population as well as strengthening the systems for monitoring, preventing and handling disease in vulnerable patient populations (136).

Strengthening of the health system is another challenge, as resources are limited and priorities have to be made in order to utilize them to the fullest. The central aspect to this is to increase the overall capacity in the health care system, as well as promoting evidence-based medicine (136).

The third priority is investing in health and reducing the health burden of poverty. This is approached by, amongst other things, involving the communities in the planning and implementing health improvement measures; by getting the civil populations directly involved in health care matters, it is hoped that some of the inequity in the current system will be counteracted (136).

5.9.4 Malaria in Malawi and the national guidelines

P. falciparum is the major *Plasmodium* species, and the most common *Anopheles* species are *An. gambiae, An. funestus* and *An. arabiensis* (138). Vector resistance against the pyrethroids and DDT was demonstrated in 2009. Malawi has high transmission of malaria, and 95% of the country is endemic. The transmission is perennial in most areas, but with seasonal variation (1). Transmission intensity varies with the topography, with the lowest rates in the high altitude areas in the north and south. (139).

6.7 million malaria cases were reported in 2010 (1), but the real incidence is uncertain as few cases are reported (139). Reported cases of malaria, regardless of diagnostic method, increased from 2005 to 2010; this increase is possibly due to improved reporting, and does not necessarily represent a real increase in malaria cases in this period (1). Malaria is an important cause of morbidity and mortality in Malawi; 40% of hospitalizations in under-fives and 40% of the overall mortality in hospitals is caused by malaria. The disease also causes morbidity indirectly through the economical strain it places on the population. In very poor households, 30% of the budget is spent on malaria (1).

There are several challenges when it comes to diagnosis and treatment. The guidelines in Malawi recommend parasitological diagnosis, but this may be difficult to carry out consistently. Microscopic diagnosis is only available to all patients at 25% of the health facilities due to a shortage of trained technicians and laboratory supplies, as well as unstable electrical supply. Scaling up RDTs for use in confirming malaria diagnosis has been on-going since 2011, but there have been problems with shortages here as well (1).

Malawi has been a pioneer in changing the drug for first-line treatment of malaria according to increase in resistance. They were first in sub-Saharan Africa to change from chloroquine in 1993, and again to change from SP in 2007. The national guidelines now stipulate that artemether–lumefantrine should be used as the first line treatment for malaria infection. The drug for second line treatment is artesunate–amodiaquine, while quinine intravenously is still recommended for severe malaria. First line treatment is free of charge when indicated (1). In addition, the national guidelines stipulate rapid treatment for suspected malaria illness, preferable less than 24 hours after symptoms start (140).

The proportion of children under five years of age receiving the recommended treatment for their febrile illness within this time frame is still just 25%. In areas that are hard to reach, antimalarial treatment may be given by local health surveillance assistants to increase availability of treatment within the recommended time (1). The ratio of children with fever in the previous two weeks who received an appropriate antimalarial drug has increased slightly, from 24% in 2004 to 28% in 2010 (139).

In public health care facilities, children are treated according to the new guidelines from 2007. However, full adherence is not achieved at community level or in the private health facilities. Second line treatment is rarely administered in situations where parasitological diagnosis can be attained (139). Challenges facing malaria treatment include reported stock-outs of drugs and higher utilization of ACTs compared to confirmed reported malaria cases, indicating possible overtreatment. Training health personnel in the new guidelines and improving the diagnostic services may improve

adherence to treatment guidelines (139).

Malawi's first national ITN programme was established in 2003, and distribution is now divided between giving out free LLINs at antenatal care (ANC) and immunization clinics (see Figure 5), large distribution campaigns, as well as private purchase through commercial outlets (1). However, stock-outs of ITNs have been reported in some facilities, and some reports suggest that there is misuse of ITNs in the population as well (139). Today, all Malawians are recommended to sleep under a bed net, preferably a LLIN, in contrast to the earlier recommendation of use only among children under five years of age and pregnant women (1).

Figure 5: Bed nets ready for distribution to pregnant women. Zomba Central Hospital, Malawi; picture taken by authors.

A report from 2010 found that ownership of ITNs and utilization among pregnant women had risen from under 10% in 2002 to 60% in 2010, and that utilization among children under five had increased from 8% to 54% over the same time period (139).

The majority of children under five years of age in households with an ITN slept under the bed net (80.7%), with an even higher percentage among children under three years of age (140).In addition, IRS has been recommended since 2007, though without including utilization of DDT in the guidelines (138). IRS has already been applied in one district for some time, and has recently been rolled out to include another six districts (1, 139).

Malawi has implemented IPTp and bed net distribution in their antenatal care programme. Prompt treatment for clinical episodes of malaria is also given in ANC. There have been reports that quinine and SP has been administrated to uncomplicated cases in pregnant women (139). In 1993, Malawi implemented IPT with two doses of SP during pregnancy in their national guidelines, as the first country in Africa and nine years before WHO recommended it in their guidelines. The IPTp guidelines were modified in 2002 to include recommendations from WHO regarding HIV-infected pregnant women, and now stipulates that women should be given at least two doses of SP during pregnancy. This preventive treatment should be given under observation and free of charge at ANC clinics (1).

In Malawi, 90% of women visit antenatal care clinics at least once during their pregnancy. The

coverage of IPTp is lower; while 76% received SP at least once during pregnancy, only one in two pregnant women received the recommended IPTp regimen of at least two doses. Nevertheless, this is almost two times as many as in 2000. The country report from RBM indicates that this gap between attendance at ANC and coverage of IPTp may result from imprecise guidelines on when IPT should be given, shortages of equipment or shortage of the drug itself, in addition to personal concerns about the safety and efficacy of the drug (1).

The National Malaria Control Programme (NMCP) develops a National Malaria Strategic Plan that emphasises on important challenges within the recommended interventions, in addition to asserting goals for a five year period (140). A programme review from 2010 noted the impact of the interventions, and addressed the challenges limiting improvement (139). As the goals for 2010 were not achieved, they were asserted into the aim for 2015.

The National Malaria Strategic Plan states that interventions should strive to increase ITN utilization among pregnant women and children under 5 to 80% within 2015. They also hope to achieve at least one ITN in 9 out of 10 households. In addition to this personal vector control, they hope to implement IRS in 12 districts with high malaria burden. The goal for coverage of the recommended regimen of IPTp is 80%. When it comes to diagnostics, they hope to have confirmed diagnosis in 80% with RDTs and in 50% by microscopy in the future. For treatment, the target is to treat malaria cases with the recommended drug within 24 hours in half the cases (1).

In addition to scarcity of resources, community attitudes can be a challenge in reaching the intervention goals. For example, treatment within 24 hours after onset of symptoms may be difficult if the parents postpone seeking treatment. Education and health information may diminish misconceptions regarding the interventions, and in this way improve attendance. NMCP therefore proposes further expansion of public information strategies, preferably in collaboration with the local malaria coordinator (139).

The NMCP also encourages surveillance of malaria statistics, which can be used for decision-making later. This surveillance has demonstrated that few malaria cases were confirmed before treatment in general; for the central hospitals, only 25% were confirmed before 2010. NMCP urge for increased collaboration between research community and surveillance teams, so the research can be better adapted to the current needs. To maintain the improvements achieved over the last decade, the NMCP addresses the need for increasing human resources, in addition to continued efforts to scale up the existing interventions. Changes in the malaria strategic plan should be based on evidence, and continued monitoring is therefore also important (139).

5.9.5 On-going malaria research in Malawi

There is a lot of on-going current malaria research in Malawi. An outline of some of the projects is given here; the challenges related to later in this paper. These projects are based either partly or fully in Zomba in Malawi, and are supervised by Dr Kamija Phiri of Malawi's College of Medicine.

Figure 6: A nurse working in research at Zomba Central Hospital, Malawi. Picture taken by authors.

5.9.5.1 Pfizer study: Finding new alternatives for IPTp

The Pfizer study is an open-label study, comparing different IPTp regimes. The study looks at the efficacy of the combination azithromycin plus chloroquine (AzCq), compared to sulfadoxine–pyrimethamine (SP), which is the current first-line drug for use as IPTp.

The study is an international collaboration, with fieldwork in Malawi, Tanzania, Kenya, Uganda and Benin. Pregnant women between 14 and 26 weeks of gestation are randomized to receive either SP or AzCq as IPTp. Exclusion criteria include symptoms of active malaria disease and taking IPTp or other antimalarials in the last four weeks.

The women were given three courses, with 4–8 weeks between each course (depending on gestational age in enrolment). They were followed with routine screening for sexually transmitted diseases, urine dipsticks, and haemoglobin during pregnancy, tested for placental malaria at delivery

and were followed up 28 days after birth. In addition, several of the participants were tested with nasopharyngeal swabs for monitoring any resistance of *S. pneumoniae.*

5.9.5.2 Pfizer sub study: Testing efficacy of novel drug combination for use as IPTp

The second trial also concerned the use of a drug combination of azithromycin and chloroquine during pregnancy. Asymptomatic paucigravidae with parasitaemia at enrolment were given treatment with AzCq and followed weekly with estimating haemoglobin level and malaria parasite count for the next 42 days. The tablets were given with food, and administration was observed.

5.9.5.3 MALARID: The role of iron supplementation after malaria

The MALARID study is trying to assess whether iron supplement should be given to children treated for malaria, and if so, what the ideal time of the prospective iron supplementation is. Children between 4 and 30 months that tested positive for malaria on a rapid diagnostic test were treated according to national guidelines. Participants were asked to come back three days after starting the treatment to confirm that they are malaria free. They were then randomized into three groups: one group receiving iron supplement immediately (that is, right after ending the malaria treatment); the second group received iron supplements two weeks later, and the third group received a placebo.

Children with treatment failure or severe anaemia were evaluated further for proper treatment; they were therefore not included in the study. Enrolled children were followed up every two weeks the next three months. In these follow up sessions, their guardians were asked about several factors, including any adverse health symptoms, sickness in the family, usage of bed nets, and more. In addition, the weight, height, mid upper arm circumference and full blood count of the children were assessed.

Figure 7: Measuring Hb in children as part of the MALARID study. Zomba Central Hospital, Malawi; picture taken by the authors.

5.9.5.4 MaRCH: Malaria rebound following co-trimoxazole prophylaxis in children

In the MaRCH study, malaria prevalence was assessed in three groups of children: children with HIV negative mothers (controls), children with HIV positive mothers with a negative PCR test for HIV at 6 weeks of age (unexposed cases), and children with HIV positive mothers who have a positive PCR test for HIV at 6 weeks of age (exposed cases). The overarching goal of the study is to assess whether there is a rebound effect, i.e. an increased malaria incidence, following the discontinuation of prophylactic use of co-trimoxazole in children.

The exposed children were followed up every two months with measurement of weight, height, mid-upper arm circumference, vital signs (if needed), and lab tests every second month. Two independent technicians estimated the parasite density, both unaware about the children's exposure status. In addition to the measurements, the mothers were asked questions about the use of bet nets, compliance of medicine for the exposed, health of child since last visit, and so on. On these visits, the medication for the next two months is given. In addition to the planned visits, they were asked to come in if the child got ill during this trial. The unexposed children were followed up in the field, with the same measurements and questions.

5.9.5.5 MIH: The effect of co-trimoxazole on immunity against malaria

The last study we were in contact with hopes to assess the effect of co-trimoxazole on developing immunity against malaria. This study uses the same case and control groups as the MaRCH study detailed above. The children from HIV infected mothers are tested for HIV at six weeks and then again at twelve months of age. All of the children are given co-trimoxazole the first twelve months. If they test positive at 12 months, they are started on antiviral medications. If they test negative, the mothers are encouraged to stop breastfeeding, and the test is retaken after six weeks. If this test is negative as well, the co-trimoxazole is discontinued. Follow ups were conducted regularly, and malaria incidence was recorded.

6 Discussion

There are still substantial challenges facing sub-Saharan Africa in regards to malaria. While many countries outside of sub-Saharan Africa have achieved a partial or complete eradication of malaria, the disease continues to be a heavy burden for sub-Saharan countries (63).

It is telling that the mortality of malaria is so low in the Western world when the burden of the disease is so vast in most malaria endemic countries; with the right resources, almost all malaria deaths are preventable deaths (63). What can be done to improve the situation in sub-Saharan Africa and particularly in Malawi?

In this chapter, we are going to discuss the different challenges that Malawi are facing when it comes to fighting malaria, and why it can be difficult for Malawi to implement some of the international guidelines described earlier. In addition, we will discuss the relevance of the guidelines themselves, and how both local and international research can contribute to changing the guidelines and make better guidelines for the future. Finally, we will discuss the role of DDT today, and some of the challenges regarding its use in the future.

6.1 Health care challenges in Malawi

Malawi has come a long way in the fight against malaria. However, to combat this disease effectively, several problem areas have yet to be covered sufficiently. Malawi faces several challenges that make an optimal approach to these problem areas difficult (140). In this chapter, we will take a closer look at what makes fighting malaria in Malawi difficult.

6.1.1 The lack of human resources

Strengthening the health care system has long been a prioritized area in Malawi, as seen by the focus in both past and current Country Cooperation Strategies; the training of qualified and skilled workers is central to this effort. In addition, there is a need to improve and strengthen the structure of the health care system in the districts, and to improve the coordination and communication of all the different partners involved in the malaria control in Malawi (136). We feel that this is one of the most important areas to focus on for the future, if the fight against malaria should continue to gain momentum.

One of the major challenges in the continued fight against malaria in Malawi is the human resources situation. More personnel are needed on a national, regional, district and community level in order to further roll back malaria, and to provide satisfactory care for the affected patients. The reason for this is twofold: first, there are too few people educated each year to meet the demand, and second,

the skilled workers who get educated often tend to seek more lucrative jobs, either in the private market or out of the country (136).

This corresponds with what we experienced ourselves during our visit to Malawi. The Zomba Central Hospital always seemed to operate at above maximum capacity, and there was a significant proportion of foreign health care personnel working throughout Malawi, especially at the bigger hospitals at the regional level.

The presence of foreign health care professionals may also raises issues on its own. We got the impression that many of the foreign doctors who travel to Malawi to work were young and inexperienced, and had little to no experience with the tropical diseases, the chronic illnesses and lack of resources that characterize the clinical landscape in Malawi. We talked to a few foreign doctors working at the Queen Elizabeth's Central Hospital in Blantyre, who felt that their knowledge was inadequate for the amount of responsibility they had been given, and that they themselves did not get as much out of it as they had hoped.

Additionally, most of the foreign health care personnel we talked with described short temporary employment periods, typically from three to six months at a time, as common among foreign health care personnel in Malawi. If this correlates to reality, the expertise the foreign doctors bring with them may lack continuity and feel fragmented and disorganized. The constant need for training the newly arrived foreign doctors may put an additional strain on the available resources, and only has a temporary benefit. These factors may in turn affect the general quality of health care, as well as the management of various diseases in Malawi, including malaria.

If the foreign health care personnel worked for a longer time in Malawi, the country would probably need to use fewer resources on the training of these temporary workers. In this way, the country may see financial benefits, while at the same time freeing up human resources in the health care system so that other workers can focus on patients, not on the training of new, foreign and temporary doctors. Additionally, the quality of the health care expertise the foreign workers provide would probably be greater because they would gain additional knowledge through experience with the clinical landscape in Malawi. At the same time, this will probably impede the recruitment of foreign workers to Malawi.

6.1.2 The quality of the health care workers

Another challenge facing Malawi is the quality of the health care workers themselves. For instance, WHO recommends that microscopy should be used in the diagnosis of malaria. However, in order to

utilize diagnostic microscopy, several costly requirements have to be fulfilled in order to avoid a potential increase in error, which may lead to misdiagnosis and mistreatment (3).

During our stay in Malawi, we got the impression that almost all of the health care professionals were very diligent and hard working. At the same time, we observed one instance where equipment was used incorrectly during our visit to the health care institutions; this did not seem to be a result of negligence, but rather a failure in proper training of the health care professional using the equipment. It is worth noting that this probably was an isolated incident; however, the potential ramifications of systematic errors in the handling of equipment may be severe, and this incident serves to emphasize the importance of proper training.

6.1.3 The challenges in diagnosing malaria

According to WHO, potential malaria patients of all ages should receive diagnostic tests in Malawi; however, if diagnostic equipment is lacking, treatment on basis of clinical suspicion is indicated. Not confirming the diagnosis will probably lead to overtreatment (3), but at the same time patients with malaria will get the treatment they need before it is too late (123). Another concern is that overtreatment will increase antimalarial resistance development (41). The question quickly becomes whether it is cheaper to implement parasitological confirmation rather than over-treating the population and in the process risk development of antimalarial resistance.

The WHO guidelines stipulate that the malaria diagnosis should be confirmed through microscopy; failing that, RDTs should be utilized (3). As mentioned above, using diagnostic microscopy requires implementing several costly measures (3), making it unrealistic to implement in anything but the larger health care institutions in Malawi (1).

Using RDTs also requires additional elements before they can be implemented. This includes knowledge of the epidemiology in the relevant areas, as parasite densities and therefore the optimal type of RDT will vary with this parameter (3). Selecting an RDT with low sensitivity may work well in an area with high disease transmission, while the same RDT in an area with low disease transmission will probably underdiagnose the disease. In addition to the considerable epidemiological groundwork needed before starting using RDTs (3), the epidemiology of malaria will likely vary over time, requiring repeated assessments at regular intervals. This is another considerable challenge in a country such as Malawi, where resources are already spread thin.

However, the potential benefits of confirming the malaria diagnosis are significant and probably cost-effective; the reduction of unnecessary treatments will have significant economic benefits, as well as

lowering the risk of developing resistance and missing other diseases causing fever (2). Malawi started using RDTs in 2011 (1).

6.1.4 Selecting the right treatment

Malawi follows the WHO guidelines when it comes to malaria treatment. For uncomplicated malaria, the first-line treatment in Malawi is artemether–lumefantrine, and the second-line treatment is artesunate–amodiaquine; both drugs are ACTs and recommended by the WHO. For complicated malaria, Malawi still uses quinine (1). However, as discussed earlier, recent research indicates that using artesunate monotherapy may be a better choice for treating complicated malaria, and Malawi and many other countries may benefit from changing the first-line treatment for complicated malaria to artesunate; this is reflected in the latest malaria treatment guidelines from WHO (2).

There are several challenges involved in treating malaria in Malawi, one of the biggest being drug shortages (139). In order to treat malaria effectively, it is vital that health care personnel have access to the first- or second-line drugs. Recent efforts in Malawi have focused on strengthening the drug supply chain and frequently assessing the current drug stockpiles (1).

In addition, the national treatment guidelines stipulate that malaria should ideally be treated within 24 hours of symptom debut (140); this proves to be an additional challenge for several reasons. First, while much of the population recognize that fever can be caused by malaria, far from everyone will visit a doctor for help (139). Secondly, even if they do want to visit a doctor, a significant proportion of Malawi's population lives in rural areas with limited transport capabilities (134), discussed later, making it almost impossible to reach treatment before 24 hours has elapsed.

Chloroquine was readily available for purchase over-the-counter at all the major pharmacies we visited in Malawi. A treatment course of chloroquine was significantly cheaper than a treatment course with the current first-line treatment in Malawi. This represents a possible issue in the future. If the general population prefer using the cheaper chloroquine to the more expensive first-line treatment for self-treating malaria, ignoring the government's recommendations in the process, part of the rationale for using ACTs is lost. Malaria parasites in Malawi are among the most chloroquine sensitive in the world, but if a selective evolutionary pressure is applied to the parasites, it is likely that chloroquine resistance will develop rapidly, considering the extent of chloroquine resistance in the neighbouring areas (46). An important way of counteracting this is the recommendation that first-line treatment should be given free of charge at health care institutions (140).

At the same time, as discussed earlier, because only about 10% of the suspected malaria cases are confirmed through parasitological diagnosis, there is probably a significant overtreatment with ACTs

in Malawi (139). Because of the limited diagnostic capacity, clinicians and health care personnel are often left to make a diagnosis based on clinical symptoms alone; some febrile patients without malaria will probably receive antimalarial treatment because of this. In addition to the fact that the real cause of the fever goes untreated, overtreatment increases the risk of resistance development. This is perhaps especially true for the non-artemisinin partner drugs in the ACTs, which have a long half-life, meaning that malaria parasites may be exposed to sub-therapeutic drug levels in the time after the treatment (46).

Even patients where parasitological confirmation has been performed may end up treated for malaria when they are not malaria sick. Part of this comes from the method, which may be too sensitive for the area and therefore pick up false positives, but this may also be due to health care professionals distrusting the diagnostic test results, especially if they are negative (139).

These problems underscore the importance of integrating sensitive and selective parasitological confirmation with coordinated drug use. A coordinated effort to educate the health care professionals responsible for treatment may help alleviate some of the potential problems down the line.

6.1.5 Preventing malaria in Malawi

There has been a big focus on distributing ITNs throughout Malawi, and 60% of households now have at least one ITN. Even if the goal of 80% has not been achieved, the improvement from the 6% ownership in 2002 is substantial (139). As the current national guidelines recommend that everyone in malaria endemic areas use bed nets, the remaining distance to full coverage is still considerable (1). In the households with bed nets, the youngest children should be prioritized (3, 140).

ITNs were provided free of charge for pregnant women who made a visit to an ANC clinic and to children at their first visit to a vaccination clinic. The nets distributed through health clinics and campaigns are LLINs, which last longer than regular insecticide-treated nets (1). The effect of the insecticide decreases with time, and the deterioration rates varies between different areas. WHO therefore recommends evaluating the net efficacy in areas of large campaigns to estimate how soon a new campaign should be executed (65). This will give useful information for planning campaigns, but the research demands resources. If the duration of nets seems to be short, information of net maintenance may be useful (3). In addition, distribution to children after infancy may be implemented as a way to increase utilization among the older preschool children (140).

The LLINs are given freely through health clinics to high-risk groups, while others purchase their nets in commercial outlets (1). The ownership of nets among the rest of the population therefore relies on

them prioritizing this purchase. According to locals we talked to during our visit in Malawi, a big ITN (covering a bed for two people) cost around 2000 kwacha, which at the time was equivalent to about US $5. He described this as an investment he saved up money for, implying the need of prioritizing this in his personal budget. The commercial distribution may result in increased socio-economic association regarding ITN ownership, increasing the burden among the poor. However, there are also positive sides to this distribution method. The commercial nets need less subsidization and the method is therefore more sustainable. The money that would have been used on subsidizing nets to non-pregnant adults may therefore be used on nets for the high risk groups instead.

The efficacy of bed nets also depends on the correct utilization of the available nets. As mentioned earlier, several surveys from different sub-Saharan countries have seen that utilization of bed nets is not carried out in all households with an available net (72, 74, 75). Several factors were correlated with the use, including education of the parents and their knowledge about malaria transmission. Educating the public in using the nets correctly, how malaria is transmitted, and the possible benefits from protecting oneself from mosquito bites, could help improve the utilization of nets (72, 75, 79). As the risk of transmission is highest after dark, methods for protecting oneself outside of the bed net might also be beneficial.

IRS is another potentially effective method of controlling malaria in Malawi; it was very recently was expanded from one to seven districts in Malawi (1). The recommendations from WHO when it comes to using IRS are clear. IRS is usually the first-line intervention in areas with a high rate of seasonal transmission, and it is a good tool to rapidly decrease the amount of transmission. However, if the results are to be maintained, several years of continuous spraying have to be done (81).

While bed nets are a largely one-time expense with infrequent additional costs, given that they are reusable and long lasting, usage of IRS requires a long time commitment and follow-up (80). This makes it a more extensive form of intervention, and also affects its cost effectiveness. Introducing and continuously using IRS requires frequent monitoring of the situation at hand (80), which makes it a potentially very costly public policy to implement. On the other hand, bed nets require a personal commitment from the person at risk (74, 75), while IRS should be done by independent professionals (80). This means that IRS may be less dependent on many of the external factors that affect the usage of bed nets, including information and education of the public. It is possible that educating a skilled spray team capable of covering large parts of the population is more cost effective and easier than educating an entire community in the usage of bed nets.

One additional complicating factor is the requirement of a multi-disciplinary team when it comes to using IRS, because of the extensive pre-emptive research needed before the implementation of this

method. In addition to the qualified medical personnel required to assess the malaria situation, many other factors are also relevant to the usage of IRS, including entomological and societal factors, and should be assessed by respective qualified personnel (81).

Additionally, one of the big challenges in relation to preventive measures is the general lack of information, especially on the cost effectiveness of both ITNs and IRS, the effectiveness of combining the two, and which of the two selects most strongly for insecticide resistance. Even though there is little solid information on the present alternatives for preventive treatments, the need for developing novel and effective insecticides is pressing (82).

There is a lot of uncertainty about the long-term effects of both utilizing current preventive measures as well as researching future options. The potential reward, with reduced or even eliminated malaria transmission, is huge, but the associated costs are high as well, and with no guarantees of any pay off. This short term vs. long-term dilemma permeates the entire malaria discussion, but especially when it comes to preventive measures; using IRS for a long time will probably reduce transmission, but at high cost (81). With today's knowledge, this makes it very difficult to know what priority preventive measures should have, but with more research, these questions may be easier to answer.

Another important discussion is the usage of pyrethroid-based IRS in areas with pyrethroid based ITNs. It is highly probable that the short-term effects of using a pyrethroid-based IRS in an area with a high malaria transmission rate will have a favourable effect on the prevalence of the disease; however, long term effects include a high possibility of the vector developing insecticide resistance. This would mean a reduced efficacy of both the pyrethroid IRS and ITNs, which would potentially be much more costly in the end (82).

IPTp was first implemented in Malawi's national guidelines for managing malaria in 1993. In a survey from Malawi from 2012, 54% said they had taken the recommended course of IPTp during their last pregnancy, while 76% had taken at least one dose of IPTp. This means that a significant proportion of pregnant women only receive one round of IPTp, or even no IPTp at all (1), raising concerns about the efficacy of the measure. Several trials have compared the efficacy of IPTp given with different frequencies, but these show inconsistent results. The general tendency implies that pregnant women receiving two or more doses of SP show better effect (91, 130, 131).

The importance of increased frequency of IPTp is highest in HIV-infected pregnant women (131). After trials demonstrated a significant increase in effectiveness of IPTp in HIV-infected pregnant women when the frequency of administration increased, WHO started recommending three doses to HIV-infected pregnant women (34). In Malawi, over 10% of adults are HIV positive (134). In view of

their benefit from more frequent IPTp, this high prevalence shows the importance of following the recommended regimen of at least two doses of SP.

IPTp is given routinely at ANC visits, which 90% of women in Malawi attend at least once during their pregnancy. As theorized earlier, the low coverage of IPT compared to attendance at ANC clinics may be a result of several factors, among them imprecise guidelines on when the IPT doses should be given, shortages of equipment or the drug itself, as well as concerns about the safety and efficacy of the drug (1).

The confidence in SP's efficacy may be declining as a result of the increased resistance towards SP and the consequent replacement of SP as the first-line drug in Malawi. However, high treatment failure rates in children does not necessarily imply a similar failure rate of IPTp. The effect of two doses of SP to HIV-negative pregnant women was still significant compared to those not receiving IPTp in settings with relatively widespread SP resistance (131). This implies that there still is a use for IPTp with SP when used according to guidelines in Malawi, where resistance to SP is widespread.

6.1.6 Resistance development in Malawi

Another challenge facing Malawi and other malaria endemic countries is the development of resistance, both to antimalarial drugs and insecticides (63).

Performing research to assess resistance is one of the central elements in the WHO guidelines. As said earlier, WHO requires that resistance assessed regularly when using methods that may induce resistance. The reason for this is clear: The cost, both economic and for the public health, is unacceptable if resistant disease vectors or parasites should develop (46, 82).

This quickly becomes apparent when looking back at the history of malaria treatment, which has largely been shaped by continuously developing resistance. Following the increased parasite resistance to chloroquine in the late 20th Century, the world saw an increase in malaria cases despite increased funding on malaria control, with devastating consequences. Great strides have to be taken in order to contain and prevent the development of new resistance, so that a similar situation may be avoided in the future (46).

Malawi follows the WHO recommended guidelines when it comes to monitoring antimalarial resistance. These state that resistance towards first- and second-line treatments should be assessed every other year (46). During our stay in Malawi, the Ministry of Health were in the process of assessing the efficacy of the first-line drug (AL) in addition to the second-line drug (AA), as well as a third ACT, DP.

6.1.7 Inequality of wealth and the burden of disease in Malawi

The enormous inequality of wealth and access to health care is another problem in Malawi. As mentioned earlier, Malawi is a poor country with limited available resources, and the resources should be utilized where they will benefit the largest amount of people. This means that larger settlements, mainly the larger cities, have traditionally been prioritized with access to adequate care through diagnosing and treating of malaria (1).

Malaria is by its nature a disease that mainly burdens the poor. As we have seen throughout this paper, malaria is a disease that is preventable, and it is readily treatable, given the access to certain resources. Poverty increases the risk of both getting malaria and dying of malaria (63).

In addition, transportation costs are also very high in Malawi, with gasoline prices at 710 kwacha, which at the time of the visit equalled US $1.8, per litre; this price was expected to rise in the near future. This severely limits the poor population's ability to travel, since both cost of private and public transportation is dependent on the gasoline price. Thus, getting to a health care institution capable of treating malaria may represent a major financial challenge for a large proportion of the poor population.

Closely related to poverty is the lack of knowledge about malaria in Malawi's general population. Malaria treatment and prevention services are challenged by community attitudes such as late treatment seeking behaviour, as well as misconceptions about IPT, ITNs and treatment. This is particularly a problem among the poor. Even though the guidelines themselves are clear about what needs to be done, fully implementing them requires cooperation from the population at risk. The population needs to be educated on protecting themselves against mosquitoes, recognizing malaria symptoms, as well as seeking treatment. As such, educating the people in correct adherence to the guidelines is necessary (1).

Additionally, Malawi is a country with a lot of co-morbidity, especially with HIV. As noted earlier, the HIV prevalence in Malawi is high, over 10% nationwide (134). In areas where the malaria transmission is insufficient to develop immunity, HIV-infected have an increased risk of developing severe malaria (39). Preventing malaria in HIV-infected is a challenge in itself, especially among pregnant women. The current prevention guidelines in Malawi stipulate that SP should be used as IPTp (1). However, many HIV-positive pregnant women already take prophylactic co-trimoxazole against opportunistic infections. Co-trimoxazole contains sulfamethoxazole, a sulphonamide, and these patients should not use other drugs containing sulphonamides, for example SP (89). In practice, this problem can be solved by switching to another drug for IPTp; this will be discussed in detail later.

Another worrying aspect of the high HIV prevalence is the increased risk of being infected with HIV after receiving blood transfusions (37). Malaria is an important cause of anaemia in Malawi, and blood transfusions following severe anaemia may have devastating consequences if the patient becomes infected with HIV (37).

There is a general lack of information and specific guidelines when it comes to co-morbidity of malaria and other diseases. It is unclear how much of a problem this is in practice, but given the large proportion of co-morbidity in several African countries due to the geographical overlap of several different diseases, this can be a valuable area to focus on in the future.

Another potential obstacle is the rapidly growing population in Malawi. In addition to increasing the strain on an already strained public health care system, the population growth itself is disproportionate, with the poorest parts of the population increasing the most (134). This means that the population that is most at risk and the weakest equipped to fight the disease continues to grow, placing an additional burden on the health care system.

Finally, external factors such as climate also affect the malaria situation in Malawi. Even though there is transmission throughout the year in most parts of Malawi, the incidence varies largely depending on the season, with transmission peaking in the wet seasons (1). This may complicate selecting the optimal prevention strategies and diagnostic capabilities, as well as making drug stockpiles difficult to plan.

6.2 The implementation of the WHO guidelines in Malawi

In this part, we will discuss the international and national guidelines as they relate to Malawi. We will look at how these guidelines form the basis of malaria prevention, diagnosis and treatment in Malawi, as well as the challenges that Malawi is facing when it comes to implementing these measures. Finally, we want to discuss what the consequences of the degree of adherence to the different guidelines have, and if any of these ramifications are more serious than others are.

6.2.1 The relevance of guidelines

We feel that both the international and the national guidelines are reasonably clear and specific, and that they can lay the groundwork for effective measures against malaria. Developing these guidelines has been a long and costly process because of the research behind them, and the efforts continue to this day.

At the same time, some of the recommendations outlined in the guidelines are more difficult to implement for several reasons. Still, having specific guidelines will help immensely in figuring out how to systematically and consistently prevent and treat malaria. One of the best examples of how

guidelines can make the fight against malaria more effective comes from standardized treatment guidelines. Instead of having a myriad of different options to choose from, having a standardized treatment helps physicians and pharmacists to make good therapeutic decisions quickly.

6.2.2 The applicability of international guidelines in Malawi

Malawi has implemented most of the intervention methods recommended by WHO against malaria in holoendemic areas, with the significant exception of IPTi (1). International research on IPTi has demonstrated good effect during administration (93-95), and the rebound effect seems to be transient (28, 106). The recommended regimen is attached to the recommended vaccination programme, and would therefore utilize an already existing programme (3). Despite all these positive aspects of IPTi, the recommendation is still not implemented in the national guidelines (92).

The main reason for this is probably the requirement of using molecular resistance markers. Before the recommendation can be implemented, the prevalence of a mutation for resistance in the parasite has to be assessed and confirmed to be under a certain threshold (3). This demands research on a molecular level, a very costly demand that may be difficult to fulfil. Resistance is often measured in treatment failure rates in the population, a parameter that seems more practical to evaluate and to interpret, instead of using molecular markers. If the guidelines where based on the treatment failure rate in children instead of the prevalence of a specific genetic marker, IPTi may be easier to implement for countries with limited resources (92). However, the high rates of treatment failure in Malawi mean that IPTi would probably not be implemented under the current circumstances.

Other WHO guidelines not implemented in Malawi's national guidelines are seasonal malarial chemoprevention and larviciding. Seasonal malarial chemoprevention is recommended in sub-Sahelan areas with seasonal transmission (126). As most of Malawi has perennial transmission (139), interventions directed at reducing transmission all year are prioritized instead.

Larviciding is recommended in urban areas with fixed breeding sites as an addition to the ideal use of IRS and/or ITNs. Malawi has recently started implementing IRS in the areas with the highest burdens of disease, and focusing on fully implementing this method should be prioritized first (85). As Malawi has transmission with *An. gambiae* (138), a vector without fixed breeding sites, mapping the breeding sites would be difficult (85). In addition, most of the population in Malawi lives in rural areas (134). In the current situation, larviciding is therefore not recommended in Malawi.

All of the factors mentioned so far in the discussion, make fulfilling the WHO guidelines for malaria a difficult task in Malawi. The resources needed for adhering to some of the recommendations may be

utilized more effectively other places in the health care system, or for making sure that the recommendations that are utilized are followed more closely. In the end, as it usually is when it comes to public health care policies, it ends up being a question about prioritizing.

6.2.3 Prioritizing the guidelines

The WHO guidelines recommend detailed evaluation and research of the different interventions on a national or local level before, during and after implementation. They also specify which areas that will benefit most from the different interventions when it comes to transmission intensity, vector species and local resistance. As the resources needed to adhere fully to the guidelines may exceed the available resources, achieving certain guidelines may seem unachievable in many situations.

Perhaps one solution is to try to assess which measures are the most cost-effective in particular conditions. Making recommendations for focus areas for specific countries or areas may be more effective and lead to a more coordinated effort, compared to leaving each country to decide for themselves what they want to focus on. In this way, it would become easier to implement the most important aspects of the guidelines even though the nation is unable to abide completely to all of the recommendations at the same time.

This highlights one of the central challenges when it comes to guidelines: making guidelines that are specific enough to be useful, while at the same time being general enough to make room for the national differences between malaria endemic countries.

6.2.4 Developing national guidelines

With basis in the international guidelines from WHO, Malawi has formed their own national guidelines (1). Developing national guidelines is costly and requires a lot of effort, but we feel that having a set of national guidelines is an invaluable in the fight against malaria in a malaria endemic country.

Part of the problem of international guidelines is that they often may be too generalized. Having own national guidelines with only a subset of the different alternatives given in the international guidelines may make it possible for health care professionals to work more efficiently, and it makes it easier to adjust for the specific challenges in one particular nation. National guidelines should ideally be a selection of the most relevant recommendations made in the international guidelines, made understandable by the health care professionals that use them.

However, Malawi is still a country with a lot of diversity, both geographically and socially; perhaps Malawi could benefit from using even more specific regional guidelines in order to further intensify the fight against malaria. The current national guidelines do open for regional differences in the

implementation of different preventive treatments (e.g. IRS, which previously only was used in the Nkhotakota district (1)), but having specific guidelines tailored to the local conditions may serve to further increase the effectiveness of different measures.

It quickly becomes a question of diminishing returns. Having international guidelines is an essential tool in the fight against malaria; national guidelines may aid this even further by making it easier to make decisions correct for that particular country. Regional guidelines will probably not hurt the cause, but the cost-benefit of such regional guidelines is probably dubious at best, when so much of the same effect can be achieved by slightly more general national guidelines.

Another benefit of having national guidelines instead of following international guidelines is that the national guidelines can have a faster turnaround than the international ones. The international guidelines is a comprehensive work, and changing them is not done overnight. As such, national guidelines give the health care system in a country a better response time to new information. As will be discussed later, parts of the national guidelines in Malawi have frequently been ahead of the curve when it comes to preventing and treating malaria.

6.2.5 Partial implementations of guidelines

Another question worth discussing is whether implementing the guidelines optimally is a requirement for implementing them at all. WHO stipulate several requirements that have to be fulfilled in order to use specific measures. However, with the limited resources several of these countries have at hand, many countries will inevitably fail to fulfil these conditions.

The informal 80–20 rule states that 20% effort gives 80% of the results. While this is not exactly a scientifically rigorous principle, we still feel that it rings true when it comes to this situation. It illustrates that doing a little goes a long way, but achieving optimal results require a whole lot more effort; it is another way of stating the law of diminishing returns. Based on this principle, and in light of the lack of alternatives, we feel that using the methods and measures described in the guidelines can be justified in some areas, even if the requirements stipulated by WHO are not fulfilled, when considering the alternatives.

One good example to illustrate this point is the requirements placed on confirming the malaria diagnosis. In order to utilize microscopy or RDTs, as previously discussed, several requirements must be fulfilled. At the same time, even failing at fulfilling these criteria, the margins of error will probably be magnitudes less than making a clinical diagnosis.

Another example is treatment. We observed over-the-counter sale of chloroquine. Using chloroquine against malaria is not compatible with the current treatment guidelines, even though the malaria

parasites in Malawi are reasonably sensitive to chloroquine. However, the free sale of chloroquine, which is significantly cheaper than the current first-line treatment in Malawi, may result in better treatment coverage for people that for some reason cannot utilize the first-line treatment provided for free by the government.

The same applies to preventive measures, which will have at least some effect even if the corresponding requirements are not fully met. For example, as mentioned earlier, non-insecticide-treated nets will still give some protection, even if this effect is low compared to ITNs; if the alternative to using non-insecticide-treated nets is using no nets at all, using the nets will end up saving lives, even if they are not used to their full potential (64). The same principle goes for other measures as well. Even if IRS is performed incorrectly and for instance does not cover 100% of the surfaces, the effect will most likely be higher than without the intervention.

6.2.6 Guidelines requiring strict adherence

Even if some of the requirements surrounding the malaria guidelines can probably be eased without major consequence, there are some guidelines that probably call for stricter adherence to the requirements.

One example of this is the problem concerning resistance. Resistance to both antimalarials and insecticides have shaped the fight against malaria for several decades, and has led to vast financial and human costs. In order to contain and even counteract the development and spread of resistance, it is important that the guidelines are followed as strictly as possible (46).

To use one of the previous examples, the sale of over-the-counter chloroquine in pharmacies in Malawi can represent a potential problem. Even though chloroquine is not used in the treatment of malaria, there is currently a lot of on-going research on the use of azithromycin–chloroquine in intermittent preventive treatment, especially in pregnant women (36). If chloroquine becomes widely used in the population, both because of its availability and cost, and resistance develops as a result, the consequences may be an increased burden of disease among pregnant women.

Ethically, the correct usage of IRS should be prioritized as well; in particular, avoiding unnecessary exposure to dangerous substances should be kept to a minimum. Training staff in correct and safe insecticide spraying is essential in order to keep the workers safe (81).

Overall, we feel that most of the guidelines are strict for a reason, and that even though many of the requirements stipulated by WHO may seem costly, they may end up with a lower economic and health cost in the future. For instance, researching the efficacy of the treatments regularly will make sure that treatment failures are kept to a minimum; assessing the malaria prevalence in an area may

lead to choosing the correct diagnostic tool, preventing overtreatment and potentially development of resistance.

6.3 Malaria research in Malawi

In this chapter, we will take a look at the specific challenges regarding the current research projects we were in contact with in Malawi, in addition to how these research projects may impact Malawi's public health policies in the future. Finally, we will assess the importance of local research, and how local research may end up influencing international guidelines.

6.3.1 Research challenges

Research is both costly and time consuming. One of the big problems of research is staying relevant; when research projects span years, by the time they are finished and the results are published, they may lack much of their original relevance. In addition to this, we saw several challenges surrounding the research projects described earlier in this document.

One of the central challenges when it comes to researching in Malawi is the literacy level. A significant portion of the population in Malawi cannot read which leads to several problems when it comes to research. The most significant of these problems is giving consent. In Malawi, consent forms are given in both English and the local language, Chichewa, but if a participant is illiterate, an impartial witness has to validate that the verbal explanation is the same as the written. In order to ensure that the participants have a good understanding when it comes to the study, they are asked questions about the study; failing to answer these questions restarts this process, and the information has to be repeated in order to guarantee informed consent.

If the participant is a minor, their legal guardian is informed for them and has to make a decision; the same rules apply to legal guardians as with the other participants.

An additional challenge when it comes to recruitment is the superstitious beliefs in the population, especially among the poor and in the more isolated villages. In order to overcome this challenge, strategic cooperation with the community leaders was sometimes necessary.

Related to this, the general lack of knowledge about health and health care is also an obstacle. The Pfizer sub study assessing the effect of IPTp in asymptomatic pregnant women with parasitaemia has some trouble with recruiting women to the project, simply because the women feel fine and do not feel the need to take medication. Some of the projects may also go against common sense, e.g. drawing blood from anaemic children in the MALARID study; however, this is necessary in order to do the research needed to change public policies down the line. This further illustrates the need for public awareness campaigns.

Finally, the logistics presented another problem in itself. The participants had difficulties getting to the research centres in question. Many of the study participants came from rural areas with poor road conditions and a general lack of transportation facilities; in addition, they were often very poor, and could not afford the bus ticket to get to the research site. This problem was solved partly by reimbursing the travelling costs, which were given on either arrival, or, more rarely, up-front. Up-front payments were problematic as, as one researcher explained, they ran the risk of losing both the transportation money and the follow up for that participant. Another solution was to do home visits to the participants instead of requiring them to show up to the research site itself. This was a good method for ensuring a better follow-up rate, however it also presented with some problems on its own; participants were frequently not at home, prompting the researchers to have to go back on the following day.

6.3.2 The role of research on changing public health care policies

As we have seen, research is expensive, time consuming and technically challenging, but at the same time, research provides invaluable information that can be used to change public health care policies in meaningful ways.

6.3.2.1 Resistance surveillance

As mentioned earlier, resistance against antimalarial drugs and pesticides is an important challenge in the fight against malaria. Research on drug resistance has changed Malawi's national guidelines for malaria treatment twice: first in 1993 because of the increasing chloroquine resistance, and second in 2007 because of SP resistance (1). Continued monitoring of resistance towards the new first line drug, ACT, may help implement a rapid policy change if resistance develops.

6.3.2.2 Alternatives for IPTp

As a further increase in SP resistance may jeopardize the efficacy of SP as IPTp, drugs for replacing SP are being sought. The coverage of IPTp may also be reduced by the use of co-tromoxazole in HIV-infected pregnant women, as this combination increase the risk of adverse effects (89). As the prevalence of HIV is high in Malawi (138), this may add to the need of finding an alternative drug for IPTp. Two of the on-going studies we observed in Zomba assessed azithromycin–chloroquine as an alternative for IPTp, in hope that this drug combination will demonstrate a higher efficacy than SP. If the usefulness exceeds the increased side effects at administration, this could give more effective malaria prophylaxis (36).

Azithromycin is an antibiotic drug and thereby also reduces the prevalence of sexually transmitted diseases and pneumonia. Again, the importance of monitoring the possible development of resistance is important, in both parasites and bacteria (36). If the trials show promising results, this

may help control and even revert the increasing SP resistance in Malawi, as IPTp is the last indication for SP administration in Malawi. Research on an alternative for IPTi would also be useful, as resistance towards SP may be the main reason for not implementing this preventive method into national guidelines (92).

6.3.2.3 Iron supplementation

The MALARID study is another example on how ingoing research may affect the national guidelines. Malaria is associated with anaemia, and moderate and severe anaemia is common on presentation among symptomatic malaria infection in children. One of the mechanisms by which malaria can induce anaemia is erythropoiesis. As mentioned earlier needs all aetiological components to be addressed to reverse this suppression, including iron deficiency. Iron supplementation may therefore increase erythropoiesis in children with malarial anaemia (61).

The MALARID study hopes to assess whether iron supplementation should be given routinely to anaemic children and when this supplementation would be of best use. Their result may thereafter be incorporated into national policy on how to address this problem. At the moment, insecurity regarding both the safety and effectiveness of iron supplementation may reduce administration of iron to moderate anaemic children, though there appears to be little evidence to substantiate this view (61). As anaemia is common in Malawi (134), standardized guidelines for iron supplementation may increase utilization of this measure, and perhaps reduce the prevalence of chronic anaemia in the population.

6.3.2.4 The role of local research

National research assessing the insecticide resistance may inform the authorities to change their recommendations regarding IRS and bed nets. Implementing several of the preventive measures described in the guidelines requires assessment in order to select the correct course of action. Thus, local research has real significance when it comes to making sure that the selected measures are effective.

One area of special attention when it comes to research in Malawi was the role of iron in malaria. At the time of our visit, the guidelines made no mention of post-treatment iron replacement therapy, but it was known that a substantial subset of patients had malaria-induced anaemia after treatment. Because of the lack of clear guidelines, iron treatment was given sporadically and inconsistently, without really knowing if it helped or harmed the patient. The research being done at the time of our visit may help in developing evidence-based guidelines for this aspect in the future.

6.3.2.5 The importance of local research and its relevance for international guidelines

Local research showing reduced treatment efficacy or widespread side effects may lead to a rapid international response to change current guidelines. Since resistance develops locally, it is important that all malaria endemic countries perform research and regularly assesses the resistance situation, not only for their own sake, but also for the international antimalarial movement (46).

The WHO guidelines are based on research done in malaria endemic countries, often performed by local authorities and health care professionals. The continued focus on local research makes sure that the guidelines are up-to-date and equipped to handle the ever-changing clinical landscape.

6.4 The future role of DDT

DDT made a huge revolution in the fight against malaria during and after World War II. Many countries in the western part of the world used DDT before a thorough investigation about the consequences of such use was assessed, and an uncritical attitude towards the pesticide caused an extensive and massive use of DDT in many different applications. After a while, however, the use of DDT was followed by an increasing scepticism, and research was performed to evaluate what potential hazards were involved with the use of DDT. This led to developing the current restrictions that limit the use of DDT today (4).

In this part, we will discuss the consequences of the sceptical attitude towards DDT, and what the following ban for most uses of DDT means for the world. We will look at why it can be difficult for some countries to use DDT today, in part because of international attitudes and pressures. In addition, we have discussed what kinds of restrictions we think are necessary when it comes to the use of DDT, and what may perhaps be done in the future to change the current worldwide attitudes towards DDT.

During the past years, there has been an extensive debate about how the positive effects of DDT have largely been neglected. The big focus on the uncontrolled and ignorant application of DDT may have drawn the attention from the fact that the use of DDT has achieved many goals that would otherwise not be achieved. It is easy to look back and decide the best course of action in hindsight, but it is important to ask whether DDT would have been used less if the potential harm was known beforehand. Many of the results in the fight against disease-bearing insects were achieved before an assessment of the potential human health risks was even possible; in the beginning, there was no real dilemma in the use of DDT, because the cons were simply not known (4).

In addition, it is possible that it became easier for the West to ban DDT because of potentially negative health effects, considering that they had already achieved many goals through its use.

Without taking into account the current situation in malaria endemic countries, a ban on DDT might make sense; however, considering the heavy burden of malaria in large parts of the world, it is entirely possible that the potential benefits greatly outweigh the risks. However, the West shares its knowledge about the risks involved with the use of DDT in good faith, without, perhaps, fully realizing the pressing need for solutions that many malaria endemic countries so desperately need. For industrialized countries, the potential harm involved in the use of DDT may seem so severe that its use should be banned outright, even though its benefits may counterbalance the risks in other areas.

Another challenge is that researching increasingly demands thorough precursory investigation, and extensive evaluations of the results before a conclusion can be reached. Criticism is an important part of research, and meeting new methods and products with scepticism is natural in today's scientific landscape, for better or for worse. In order to approve of a new product, vast resources have to be used first to assess and reassess all aspects. For the developing world, particularly in comparison with the industrial world, there is a pressing need for solutions, and the need to evaluate all aspects of a new product or measure constantly, may compromise the economy of the country, as well as the quality of life and the ability to fight the disease effectively in a reasonably timely matter. In the end, it is not likely that this problem will be solved, as it is intrinsic to the ethical values of our society today; in order to do no harm, one first has to assess the benefits and risks involved, and that can be a costly and time-consuming affair.

In the WHO guidelines for DDT, statistically significant investigations that confirm the harm DDT has on human health are rejected. Instead, the aspect of DDT that causes most concern is the increasing resistance, which is currently the limiting factor of its use. In addition, WHO mentions that there is a need for further investigation on potential harmful effects of DDT on humans, as there is no clear answer to this question today (132).

WHO concludes that there still is a role for DDT in the fight against malaria, but that there is a need for developing new and effective insecticides (132). The scepticism and following ban of DDT in the industrialized nations has probably affected Africa's opportunity to be able to make use of DDT.

Because many countries in Africa, including Malawi, depend on the support and contributions from industrialized countries in the fight against malaria, the industrialized countries also have a lot of impact on decision-making. This may lead to several challenges. It may be difficult for industrialized countries to understand the plight of developing countries when it comes to malaria, and perhaps especially when it comes to time as a critical factor. Malaria is a preventable, treatable disease, and not being able to come to a consensus about which measures that can be used is probably one of the

reasons why malaria is still a problem in large parts of the world.

Since DDT was banned in the USA in 1972, there has been little development of new and effective insecticides (82), especially when compared to the pharmaceutical industry, which has made huge progress in developing new medicines over the last decades (2). Is this a question about priorities, or is it a result of other factors? For a profit-driven industry, the priority is to develop novel solutions that are economically sound. Uncertainty about the long-term profitability of developing new insecticides may be one of the reasons why this development has been slow (4).

DDT has achieved wonders when it comes to fighting insect-borne diseases in large parts of the world, but concerns about the potential harmful effects has led to limitations in today's use. As a result, countries in Africa have not had the full opportunity to exploit the potential of DDT in the fight against malaria, for better or for worse.

7 Conclusion

Throughout this paper, we have described the status regarding malaria in Malawi and which interventions are used to combat this problem, as well as how research may affect national and international guidelines. We have seen that Malawi has taken great strides in the fight against malaria over the last years; Malawi has achieved a lot with limited resources, and the general situation is improving.

Malawi faces several difficult challenges when it comes to malaria. Malawi lacks the monetary and human resources to achieve satisfactory coverage of health care for the whole population. In addition, many challenges are related to the inequality of wealth in Malawi. Some of these challenges are difficult to overcome in the current situation in Malawi without significant socioeconomic progress and social restructuring.

The current guidelines in use, both internationally and nationally, give Malawi a good set of tools in order to fight malaria. Even though Malawi has not been able to fully implement all aspects of the international guidelines, the measures they have implemented have had positive effects on the public health in Malawi, and have proven to be vital tools in reducing the burden of disease. Continued adherence to the guidelines is vital to achieving future success in the fight against malaria.

Of all the challenges that are mentioned, we feel that spreading information and knowledge about malaria is among the most important. Making the population at risk more aware of the risks, preventive measures and treatment is probably a cost-effective way to promote increased adherence to the current guidelines.

Nevertheless, the current lack of information makes it difficult to point the finger at any one thing that can be done better. We feel that the general lack of resources, both economic and human, in the Malawian health care system is the limiting factor in this situation. With resources spread so thin already, it is not easy to say where the priority in the future should be. Continuing to research and assess the current situation may reveal areas worth focusing on in the future, and that this may help Malawi in achieving a sustainable and effective long-term plan in fighting malaria. Over time, this may be more effective than focusing more effort on the performance of current guidelines.

Furthermore, research is needed in order to ensure that the current measures are as effective as possible, and that novel ways of combating malaria may be developed. Solid research forms the backbone of public health policies, both on a national and international level; in order to change them in meaningful ways, sufficient research has to be performed first.

DDT has earlier had good results in the fight against malaria, but the potential hazards have given rise to scepticism. WHO has not been able to come to any conclusions about the health hazards associated with its use, but focuses on resistance as the main problem when it comes to DDT. This is a result of lack of knowledge, since the long-term effects of DDT exposure are uncertain. The implementation of DDT in recommendations may be justified, although it demands thorough evaluating beforehand and surveillance of any possible hazards, as well as monitoring resistance, during and after implementation. DDT should not be seen as a permanent solution, and ideally, research would find a new insecticide to replace DDT, but progress over the last few decades has been slow.

Additionally, the fight against malaria in Malawi is largely dependent on several external factors. These factors include monetary support from other countries, as well as continued research by the pharmaceutical and chemical industry to find new and effective ways of treating and preventing malaria. Despite the challenges involved, the fight against malaria seems to be going reasonably well when we consider the limited resources available.

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The authors took all pictures used within this document during their five-week trip to Malawi.