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Educators' guide "Toward a malaria-free world"

(Background information)

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1. Introduction

These teacher guidelines will give you information on the Xplore Health module “Toward a malaria-free world”. It will first introduce the topic to enable you to prepare your lesson using the different multimedia tools that you will find on the website. The guidelines provide information on the state of the art in this research field and on the ethical, legal and social aspects surrounding this topic.

2. State of the art

2.1. Burden of disease

Malaria is considered to be the most important parasitic disease in the world. It is one of the ten leading causes of death in low income countries. In 2010, it was estimated that malaria caused around 225 million clinical episodes worldwide, being responsible for 781,000 deaths. In addition, it also contributes to impoverish local economies and consumes substantial health resources. In Africa it is thought to be responsible for 12 billion US dollars in direct losses every year, yielding a loss of 1.3% of gross domestic product (GDP) per year. Around ninety percent of the cases in Africa occur in children under the age of 5 and pregnant women.

2.2. Causative agents

Human malaria is caused by one of the four species of the parasitic protozoa belonging to the genus *Plasmodium* (*P.*): *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae. P. knowlesi,* traditionally a monkey malaria species, has recently been described to affect humans in certain areas of South East Asia. All species differ in geographical distribution, drug resistance patterns and clinical symptoms. *P. falciparum* and *P. vivax* are the most common species and *P. falciparum* is the most deadly one.

2.3. Geographical distribution

According to the World Health Organization (WHO), malaria is an endemic disease in 106 countries of the world, where around 3000 million people are at risk of being infected. Around 91% of all malaria cases occurred in the African region during 2010, mostly in sub-Saharan Africa. In 2009, not a single case of falciparum malaria was reported in the WHO European region. The following map shows the countries or areas at risk of transmission for 2009.

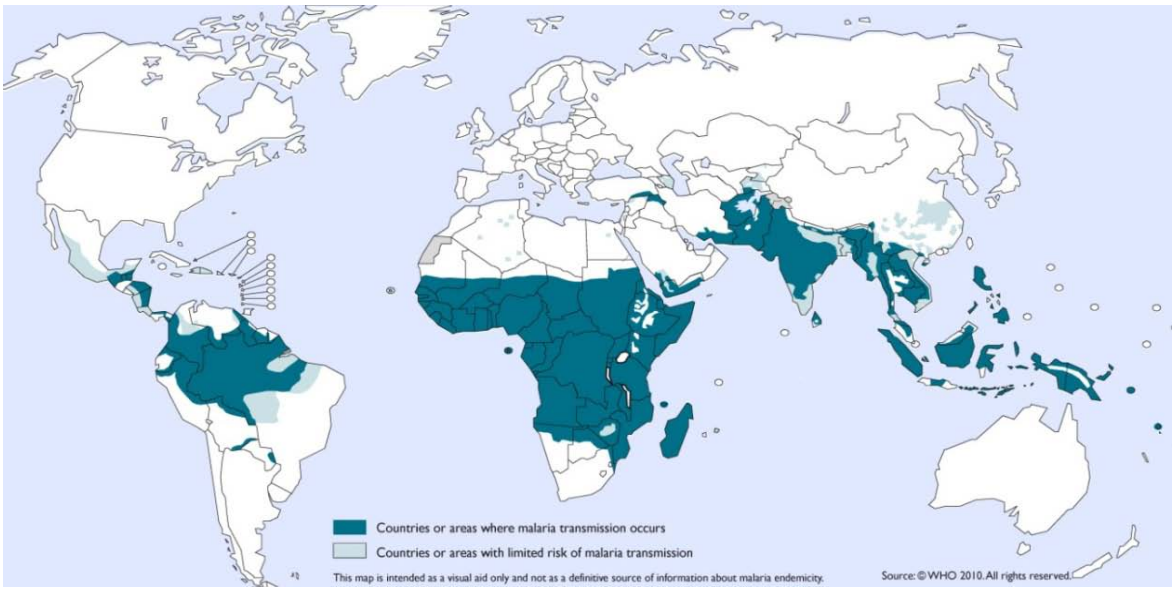

Figure 1. *Countries or areas at risk of transmission for 2009. Source: WHO*

2.4. The infection cycle

The parasite gets into human blood through the bite of a female mosquito called *Anopheles*. The mosquito is also called a vector, since it transmits the parasite from human to human. Inside the human body the parasites can be found at different stages; these stages are steps within the *Plasmodium* life cycle. The first stage that is injected by the mosquito is the sporozoite, which is free-swimming in the blood for some minutes. Then, the parasite infects hepatic cells, where it multiples, grows and transforms into schizonts and merozoites (liver stage) that will be released into the blood stream within vesicles called merosomes. Merozoites then infect red blood cells, grow and multiply within them, transforming into schizonts and new merozoites that perpetuate the blood stage cycle. At some point during this cycle, gametocytes appear in the blood; these are sexually differentiated stages picked up by the mosquito during the blood meal. Inside the mosquito, the parasite also adopts different stages during a cycle of growth: gametes, ookinetes, oocysts and finally sporozoites in the salivary glands that are injected into the human, closing the life cycle (Figure 2).

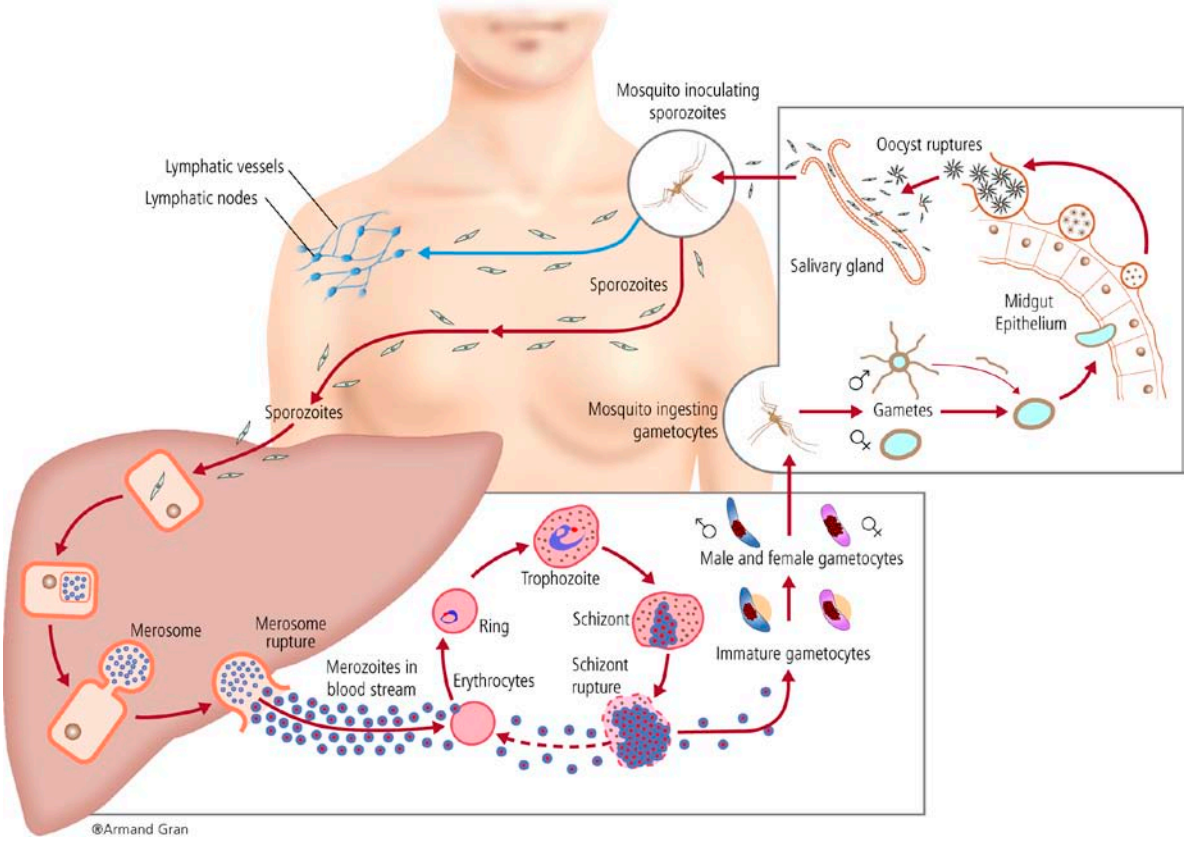

Figure 2. *Plasmodium falciparum Life Cycle.*

2.5. Clinical manifestations

Before the onset of the disease, there is an incubation period following the parasite infection by the mosquito. This period varies depending mainly on the parasite species and the host susceptibility, but it usually lasts around 7-30 days, corresponding to the time it takes from the parasite injection into the human until it gets into the liver and is again released as merozoites into the blood.

Symptoms only appear during the blood stage of the life cycle. Symptoms can include intermittent fever, headache, sweats, weakness, liver and kidney disorders, vomiting, convulsions and death. However, the infection can also be asymptomatic. What determines whether it causes a mild or a severe case of malaria? There are multiple factors that condition the clinical manifestations of this complex disease: the type of vector (mosquito) and its capacity to transmit disease, the parasite species, innate and acquired susceptibility factors of the host (human), the quality and accessibility of health systems, political and social factors, poverty levels and environmental factors.

2.6. Naturally acquired immunity to malaria

People living in malaria endemic areas exposed from birth to repeated infections by *P. falciparum* either die or acquire a natural immunity against malaria. In areas of stable transmission, severe malaria or malaria-related deaths are rare after 5 years of age, except during pregnancy, when women become more susceptible. This type of clinical immunity develops with age as a result of continuous exposure to the infection, and can result in long periods without malaria symptoms in older children and adults. This immunity is usually accompanied by an important decrease in parasite densities, the so-called anti-parasite immunity, which also increases with age but is never complete. Although researchers have been able to describe that malaria affects primarily the young age groups, and that the burden of disease is affected by the intensity of exposure to *Plasmodium*, it is still unclear how our immune system responds to these parasites in an effective manner, and this is an important research area.

2.7. Malaria control measures

Currently, the main malaria control measures are: vector control measures, measures to reduce human-vector contact and use of drugs for treatment and prevention (prophylaxis).

- **Vector control strategies**, including the use of insecticide-treated nets (ITN) and the use of insecticides to spray on the walls of the houses (Indoor Residual Spraying, IRS)
- **Reduction of human-vector contact**: insecticide-treated nets (ITNs)
- **Use of drugs for treatment and prevention**, including early diagnosis (with blood slides or rapid diagnostic tests [RDTs]) treatment with effective antimalarial drugs (artemisinin-based combination therapies [ACTs]) and Intermittent Preventive Treatment in Pregnant Woman and Infants (IPTp and IPTi, respectively) for prevention.

The use of insecticide treated nets has been promoted by the World Health Organization as one of the key strategies for malaria control. In fact, the WHO recommends universal coverage with ITNs for all people at risk of malaria. ITNs have been widely shown to be effective in reducing childhood morbidity and mortality through reducing mosquito bites while sleeping. In other words, ITNs decrease the interaction of the host with the mosquitoes during the period when the latter are most infective (at night). In different economic analyses, ITNs were shown to be one of the most cost-effective measures to reduce transmission of malaria. The current WHO recommendation is to use long lasting insecticide treated nets

(LLINs), which last at least three years without the need for periodic re-treatment. It has been estimated that from 2008-2010, around 289 million ITNs were distributed in the world, covering around 76% of people at risk. This is still below the 80% target set by the Roll Back Malaria (RBM) Partnership, a malaria initiative launched by the WHO, UNICEF, UNDP, and the World Bank.

Indoor residual spraying has been widely used in recent years. In Africa, 75 million people (which represents 10% of the population at risk) were protected with indoor residual spraying with insecticide in 2009. This strategy acts by reducing the number of mosquitoes present in the households. Pyrethroids are the most important type of insecticide used for spraying, even though DDT, a widespread insecticide in the past, is still currently used in some African and South-East Asian countries despite its potential toxicity and mosquito resistance.

Prompt diagnosis and treatment of malaria cases avert millions of deaths annually. Until a few years ago, malaria was only diagnosed by direct microscopic examination of intracellular parasites in a stained blood film. This method enables the identification of the *Plasmodium* species, quantification of the number of parasites in blood (related to severity) and the evaluation of response to treatment. However, this technique requires electricity and specific training, which are not always available in many settings where malaria is endemic, and malaria is treated empirically, without laboratory confirmation. Currently, the WHO recommends, in all endemic areas, the use of rapid diagnostic tests (RDT), a new device that detects antigens of the parasite in the blood without the need for microscopy. This technique is ideal for remote areas and can also distinguish between *P. vivax* and *P. falciparum*. According to the WHO, about 30 million RDTs were delivered by ministries of health in 2009 with a clear increasing trend for the near future.

The most widely used antimalarial drug in the 20th century was chloroquine, which was, together with DDT, the most effective measure for malaria control. However, the parasite (especially *P. falciparum*) developed resistance to chloroquine (resistance is the capacity to withstand exposure to drugs previously toxic to them), mainly acquired by spontaneous mutations of certain parasite variants after continuous drug exposure. The mechanisms of resistance to antimalarial drugs vary depending on the drug, and parasite resistance patterns are different depending on the geographical area. Parasites have developed resistance to most of the antimalarial drugs developed in the past, such as atovaquone or antifolate therapies. In 2004, a new generation of drugs derived from the Chinese plant *Artemisia annua*, artemisinins, have been recommended by the WHO as the drugs of choice for uncomplicated malaria, as a combination therapy (ACT). By the end of 2009, 90% of

endemic countries with *P. falciparum* had adopted ACTs as national policy for first-line treatment. However, the use of ACTs is far from meeting the WHO recommendations in settings like Africa, due to lack of accessibility to the drugs. Most worryingly, there is already evidence of resistance to these combination therapies in some countries in South East Asia, probably related to their use as single therapy, applied before the combination was seen as the best approach and recommended.

Chloroquine, however, is still effective against *P. vivax* in most countries, but it has to be accompanied by a drug called primaquine, which acts against a form of liver parasite called hypnozoite that can remain dormant in the liver for some time. Primaquine has side effects in patients lacking the G6PD enzyme, for example, it can destroy red blood cells. There is ongoing research of new alternatives, such as tafenoquine, which could soon replace primaquine due to faster action against the parasites and a probable better safety profile.
One new potential treatment is the use of a drug called artesunate, which is given intravenously for severe malaria. The classic treatment for severe malaria was quinine, which has some inconveniences: secondary adverse events, a narrow therapeutic range and a relatively complex administration scheme.

Antimalarial drugs are also used as preventive strategies. They would not be suitable for continuous use in endemic areas due to the rapid appearance of resistance and potential interference with acquired natural immunity. However, intermittent administration of antimalarial drugs in the most vulnerable groups (pregnant women and infants) has shown to be an effective strategy to reduce morbidity of both neonates and mothers. In fact, 33 out of 43 endemic countries in Africa had adopted intermittent preventive treatment for pregnant women (IPTp) as national policy by the end of 2009. Intermittent preventive treatment for infants (IPTi) has not yet been implemented despite the efficacy shown in multiple clinical trials. Other uses of antimalarial drugs as prophylaxis include mass drug administration to populations in order to eliminate malaria foci, where there is high transmission in a localised geographical area.

2.8. Malaria vaccines

One of the desirable new strategies for malaria control and eradication would be the existence of an effective antimalarial vaccine. The experimental malaria vaccine RTS,S/AS0, produced by GlaxoSmithKline, is the only candidate that has shown a moderate and maintained efficacy against *P. falciparum* infection and clinical disease, both in young infants and in children up to 5 years of age. A phase III clinical trial is ongoing with thousands of children in Africa, the last step before international regulatory authorities licenses its use in humans. This will probably be the first vaccine to be registered. However, as the efficacy of RTS,S is partial (about 50% of individuals), it would be added to the available malaria control measures, not substituting them. In addition, the immunological mechanism of action of the vaccine is not known. In order to rationally develop a new generation of improved vaccines with higher efficacy we would need to understand which immune responses this vaccine induces and which ones are important for protection against the disease. We also need to develop vaccines directed at other species of *Plasmodium* that cause significant disease burden but are not targeted by RTS,S, such as *P. vivax.*

2.9. Malaria eradication

Recent years have witnessed renewed stimuli for malaria control and the long term goal of malaria eradication has been re-established. This has been possible due to the recent advances in malaria control in many countries, the commitment of political and public health leaders and the rise of international funding for malaria in recent years (around $1.8 billion USD in 2010). However, there is general consensus that with currently available tools malaria can be better controlled and eliminated in some areas, but that worldwide eradication will not be achievable.

This is not the first time the international community has aimed to eradicate malaria (eradicate meaning 0 malaria cases in the world). In the 1950s and 1960s, an eradication campaign was lead by the WHO; its main tool being the use of DDT for mosquito control and chloroquine used for treatment. This initiative persisted for several years, but ultimately failed to obtain the objective of eradication.

In 2008, after a call from the Bill and Melinda Gates Foundation, the Roll Back Malaria initiative declared that eradication was a moral obligation for the international community and suggested that it should be the final goal. The Global Malaria Action Plan (GMAP) was launched in order to guide and unify the malaria community in its efforts to move from control to elimination stages.

Moreover a new research and development (R&D) initiative was created in parallel to the GMAP. The Malaria Eradication Research Agenda (MalERA) initiative has been a rigorous scientific consultation process to identify knowledge gaps and new tools that will be needed to eradicate malaria globally, based on the understanding that the academic and research community will necessarily play a crucial role in the fight against malaria and its eradication worldwide. Such a goal would be unachievable without the development of a new generation of tools focused on interrupting transmission.

To date, the goal of eradication has already been incorporated into the agenda of many research organisations and has been embraced by the major malaria product development partnerships. There is common agreement that although MalERA focuses on an R&D agenda for the long-term goal of malaria eradication, it remains crucial to maintain focus on control efforts and continue to develop and improve tools by addressing fundamental research questions.

3. Ethical, Legal and Social Aspects (ELSA)

In this section you will find a number of opinions and incentives for discussion in class on ethical, legal and social aspects (ELSA) related to malaria:

3.1. Introduction

Malaria is a common parasitic disease causing about 800,000 deaths per year worldwide, and an even greater burden of illness with significant personal, social and economic consequences. The disease was at one time endemic to Mediterranean Europe, and as far north as the English Midlands, but malaria control measures have effectively eradicated malaria in the developed world and, as a result, it is now popularly considered a “tropical disease”. However, climate change and globalisation of disease transmission patterns mean that in the future malaria may prove to be a genuinely global health problem once again. Moreover designating it a “tropical disease” obscures the fact that according to the World Health Organisation the disease is endemic to 106 countries, and potentially affects about 3 billion people.

The ethical issues presented by malaria can be conveniently considered as those concerning *prevention*, *treatment*, *eradication* and *research*.

3.2. Prevention

Malaria is caused by parasitic infection, by a parasite of the genus *Plasmodium*. The parasite is transmitted from human to human (and occasionally from other species to humans) via the *Anopheles* mosquito (the "vector" of infection). Prevention of malaria may focus on:

- human immunity
- control of the vector species
- prevention of human exposure to the vector
- preventive treatment

Human immunity

Immunity may arise in one of three main ways. Some people possess a form of *genetic* immunity. As many people know, people who possess *one* copy of the gene for Sickle Cell Anaemia or Thalassaemia have a form of natural immunity against malaria infection. This is thought to explain the prevalence of this gene in some parts of Africa (and African diaspora), where immunity to malaria provides a biological advantage to possessors of this gene over those who do not have the gene. But possession of two copies of the gene causes serious illness in its own right. There are ethical difficulties involved in screening and reproductive health advice programmes which seek to identify individual carriers of the Sickle Cell or Thalassaemia gene: counselling and advice for people who are carriers of the gene and who wish to have children with another person with the gene can be complex, and there is a significant risk of stigma and social exclusion where a person is considered to be at genetic risk of having a child with Sickle Cell Anaemia or Thalassaemia even where there is an advantage to having one copy (but not two) of the gene. The social context of genetic testing in communities where malaria and Sickle Cell are both common is complex, and can interact in important ways with social arrangements around marriage and relationships, and child-bearing. Many people are aware of the risk of having a child with sickle cell anaemia on the basis of family history; but the number of people who know and understand the genetics is a question open for discussion. And where genetic testing services are available, there may be some uncertainty about what information is disclosed, to whom, and with what confidentiality safeguards.

In addition, in communities where malaria is endemic, many people develop a natural *acquired* immunity to malaria – if they survive long enough. Surviving through childhood to

the age of 5 after repeated exposure to the malaria parasite is a good indication of the development of acquired immunity, but obviously the other side to this is that without adequate malaria prevention high childhood mortality from malaria is expected. In addition, during pregnancy women become more susceptible to malaria, and transmission from mother to the foetus is also possible. Hence, even in a context of common acquired immunity, malaria poses a very significant problem to maternal and child health. This can have a significant impact not only on family welfare, but on economic development (where resources are diverted from productive economic activity to nursing sick children, older children are diverted from school or work to childcare following the death of a mother, and an increase in birth-rates where child mortality is high). From an ethical point of view, a disease which is especially selective toward the most vulnerable in a population raises significant questions of justice.

A promising approach to malaria prevention would be the development of a cheap and easily administered and transported malaria vaccine. There are encouraging signs of the development of vaccines for malaria. However, these in turn pose ethical challenges. The affordability of such a vaccine, and the availability of the vaccine in a safe, robust and transportable form, useable in settings remote from hospitals and clinics, will be crucial if a vaccine is to be more than a “luxury” for the relatively wealthy. Even if there are benefits to a vaccine available only on a limited basis, complete population coverage will be greatly preferable as a public health intervention. And in the medium or long term, if human immunity via vaccination is to be an effective contribution to malaria *eradication*, the vaccine will need to be used rapidly and extensively enough to eradicate malaria before the parasite can evolve around the vaccine and develop resistance.

Control of the vector species

An enormously successful approach to malaria control has been the use of insecticidal sprays and insecticide treated nets (ITNs). ITNs protect people while they sleep, which is the time of day when mosquitoes are most active and the risk of infection is greatest. Nets can be short or long-lasting, and are found to be very cost effective, being cheap and relatively easily distributed. They have a benefit to individuals, and also a public health benefit in that reducing the number of people infected at any given time reduces the “power” of malaria transmission. Even people without nets may be less likely to become infected. However, this strategy rarely eliminates the possibility of infection altogether, and there is also the problem of the vector’s acquired resistance to the insecticide.

An advantage of nets is that they are relatively safe to the user. Another popular approach, spraying whole rooms or buildings, may be more effective than the use of nets in limiting the spread of malaria in a population, but carries some risk of toxicity and resistance due to the greater quantity of insecticide used in room spraying than is needed in a net and the potential for environmental seepage and inhalation or ingestion.

Historically, an important method of vector control was wide area spraying with insecticides. This was particularly well known in the era when DDT was in widespread use. There is ongoing controversy about the safety, effectiveness and cost-effectiveness of the use of DDT and other insecticides. The World Health Organization keeps the safety of DDT under review, both for wide area use and for indoor spraying.

Prevention of human exposure to the vector

The methods used for vector control can be considered both as methods for reducing or eliminating the vector population in an area of human habitation *and* as a means for protecting human individuals from being exposed to the vector. But the ITN is most obviously a method for stopping mosquitoes from biting humans as much as it is a means for killing mosquitoes.

Preventive treatment

Medication (of which there is a variety of types) can be effective both prophylactically and as therapy. As is well known, travellers to areas where malaria is endemic are advised to take antimalarial medication as a prophylaxis, so that even if they are bitten, the medication can block the lifecycle of the malaria parasite. Less effective, but still efficient, is taking antimalarials post-exposure. Either strategy can significantly reduce one's chance of developing clinical malaria, but problems of cost, availability, drug resistance, and timely intervention make the use of preventative medications impossible for most people who live in malaria endemic areas. A strategy called Intermittent Preventive Treatment for pregnant women (IPTp) is now recommended in areas where acquired immunity is common, since this selective treatment is for a group at heightened risk of infection and illness, and is time-limited in that it is only given during pregnancy and shortly after. However this strategy leaves other vulnerable groups unable to access treatment, and although the benefits to pregnant women and their newborn infants are important, there is a difficult moral question about fair resource allocation here. In addition, some people are unable to take some classes of antimalarials because genetically they lack an enzyme necessary to break down the drug safely. Testing for this genetic deficiency is currently out of the reach of all but the wealthiest

city dwellers, and the ethical dilemma of offering treatment which may in itself be inherently dangerous for some people who take it is troubling.

3.3. Treatment

As noted above, there are effective treatments which can limit the development of malaria post-infection, and which are beneficial in the acute phase of malaria infection. However, all antimalarials have side-effects, some of which are serious in their own right, and not all antimalarials are safe or effective for all patients. Moreover, effective antimalarials may be relatively expensive, such that use in clinically optimal ways may be out of the reach of most patients. Older types of antimalarials are proving ineffective in many parts of the world due to evolved parasite resistance, and newer treatments can be expensive due to higher manufacturing costs, patent protection, and other factors. Access to essential medicines is a key issue here; but so is tailoring treatment strategies so they are used in a cost-effective way to deliver optimal health benefits to an entire population.

There may be tension between different strategies for distributing treatment which may aim to select beneficiaries according to *need*, *social justice* considerations, balancing the use of treatment to prevent transmission with the use of treatment to treat acute illness, the ability to maintain pharmaceutical quality and safety in remote settings, and *ability to pay*. There are serious concerns that malaria is more likely to affect you if you are poor (your living conditions and ability to access preventative measures will be worse, and your general state of health may also be worse so that you are more susceptible to infection) *and* your ability to access treatment is worse *and* your economic circumstances are worsened by your malaria making your ability to work and trade worse than otherwise. Hence, poverty and malaria infection together create and exacerbate significant health and economic inequalities. So there are both economic and human rights/social justice arguments for public intervention to improve malaria treatment and prevention programmes for people with fewer resources.

3.4. Eradication

Malaria has been successfully eradicated in several parts of the world, through a combination of medical and environmental strategies. Drainage of habitats which support mosquito breeding and the use of insecticides have been highly successful in some regions. However, eradication requires significant investment and systematic, coordinated efforts. The widespread use of insecticides has significant actual or potential ecological impact on other species and human health. And developing resistance on the part of the vector or parasite can undermine eradication efforts if these are not carried out vigorously and systematically.

There are important ethical and social questions about: resource allocation between malaria eradication and other public health and development activities; actual or perceived risks of large scale insecticide use; the social impact of drainage schemes in terms of loss of work or residence for those who live in or are from wetlands.

An emerging issue is that even where malaria eradication has been successful, it may be reversed or reversible due to the environmental or human consequences of climate change. Areas which had been rendered inhospitable to the vector may become, once again, suitable habitats due to rising temperatures or changes in water distribution. Movement of human populations may mean that populations in which the parasite is endemic may come into contact with mosquito populations which were not previously vectors of malarial infection. Hence, although many people will not have considered this in detail, there is a close connection between the ethical issues relating to climate change, and those relating to infectious disease, especially malaria which may be considered *both* an infectious/parasitic disease *and* an environmental disease.

3.5. Research

Conducting clinical trials in settings in the developing world poses well-known problems. Some of these are process-related: it may be difficult to obtain informed consent to participate in such trials (or to donate blood samples for genetic research or parasitological studies, or other types of research) for reasons to do with language, cultural diversity, or relative lack of knowledge of urban/developed world medical practice and scientific research. As in other fields of medical research, considerable efforts have been made in recent years to develop consent processes which are suitable and respectful of these difficulties and differences. However, this can obscure the extent to which difficulties in obtaining valid consent reflect deeper ethical concerns. Actual or potential participants and host communities may have valid concerns about the extent to which they are a “resource” for researchers, but may not see the financial or medical benefits of such research in due course. Participants in research may either not fully grasp the extent to which the treatment they receive may not be effective, or even unsafe, if they are receiving experimental treatment, or placebo control (of course, this is equally true in developed world settings, but in developing world settings participants may feel they have less choice in whether or not to participate).

There may be significant difficulties concerning the extent to which participants in research take part, mainly or partly to get the benefit of ancillary medical care which may otherwise be

unaffordable to them. Where they are able to benefit from such care, they may be in a moral quandary because while they can get this care, other members of their family, being non-participants, may not. On the other side of the research-participant relationship, where overseas researchers use local fieldworkers for recruitment and sample collection, local fieldworkers may feel a divided loyalty to their employer and to the communities they are members of or are invited into in course of their research.

A different kind of ethical dilemma in malaria research concerns priority setting in research. There is the question of how much of the resources, globally, are devoted to malaria research vis-à-vis other types of medical research, in light of the global burden of disease. Relative to the scale of the world malaria problem, arguably too little money is spent on malaria research. Within the field of malaria research, there is a similar priority problem: how much of the resources should be devoted to different aspects of malaria control: prevention vs. treatment; environmental interventions vs. individual interventions; drugs vs. vaccines; and so on. One concern is that of the malaria research budget, in global terms. Much greater resources go into (relatively) high unit cost interventions which may not be affordable or even that useful in global public health terms. Counter to this argument is the idea that all interventions start expensive, but become cheaper as competition increases and patent protection elapses. Incentives may be necessary to encourage Research and Development, but in the medium term there is a global health benefit even where the short term benefit is narrowly available to the well-off. This is an empirical argument as much as an argument about a principle.

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