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Drug Resistance in Malaria

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ABSTRACT

Drug resistant malaria is primarily caused by Plasmodium falciparum, a species highly prevalent in tropical. It causes severe fever or anaemia that leads to more than a million deaths each year. The emergence of chloroquine resistance has been associated with a dramatic increase in malaria mortality among inhabitants of some endemic regions. The mechanisms of resistance for amino-alcohols (quinine, mefloquine and halofantrine) are still unclear. Epidemiological studies have established that the frequency of chloroquine resistant mutants varies among isolated parasite populations, while resistance to antifolates is highly prevalent in most malarial endemic countries. Established and strong drug pressure combined with low antiparasitic immunity probably explains the multidrug-resistance encountered in the forests of South-east Asia and South America. In Africa, frequent genetic recombination in Plasmodium originate from a high level of malaria transmission, and falciparum chloroquine-resistant prevalence seems to stabilize at the same level as chloroquine-sensitive malaria. Nevertheless, resistance levels may differ according to place and time. In vivo and in vitro tests do not provide an adequate accurate map of resistance. Biochemical tools at a low cost are urgently needed for prospective monitoring of resistance.
Keywords: Drug, Resistance, Malaria.

INTRODUCTION

Malaria is a mosquito-borne infectious disease that affects humans and other animals. Malaria causes symptoms that typically include fever, tiredness, vomiting, and headaches [1]. In severe cases it can cause yellow skin, seizures, coma, or death. Symptoms usually begin ten to fifteen days after being bitten by an infected mosquito. If not properly treated, people may have recurrences of the disease months later. In those who have recently survived an infection, reinfection usually causes milder symptoms. This partial resistance disappears over months to years if the person has no continuing exposure to malaria [2].

It is caused by single-celled microorganisms of the *Plasmodium* group. The disease is most commonly spread by an infected female *Anopheles* mosquito. The mosquito bite introduces the parasites from the mosquito's saliva into a person's blood. The parasites travel to the liver where they mature and reproduce [3]. Five species of *Plasmodium* can infect and be spread by humans. Most deaths are caused by *P. falciparum* because *P. vivax*, *P. ovale*, and *P. malariae* generally cause a milder form of malaria. The species *P. knowlesi* rarely causes disease in humans. Malaria is typically diagnosed by the microscopic examination of blood using blood films, or with antigen-based rapid diagnostic tests [4]. Methods that use the polymerase chain reaction to detect the parasite's DNA have been developed, but are not widely used in areas where malaria is common due to their cost and complexity [5].

The risk of disease can be reduced by preventing mosquito bites through the use of mosquito nets and insect repellents, or with mosquito control measures such as spraying insecticides and draining standing water. Several medications are available to prevent malaria in travellers to areas where the

disease is common. Occasional doses of the combination medication sulfadoxine/pyrimethamine are recommended in infants and after the first trimester of pregnancy in areas with high rates of malaria [6]. Despite a need, no effective vaccine exists, although efforts to develop one are ongoing. The recommended treatment for malaria is a combination of antimalarial medications that includes an artemisinin. The second medication may be either mefloquine, lumefantrine, or sulfadoxine/pyrimethamine. Quinine along with doxycycline may be used if an artemisinin is not available [7]. It is recommended that in areas where the disease is common, malaria is confirmed if possible before treatment is started due to concerns of increasing drug resistance. Resistance among the parasites has developed to several antimalarial medications; for example, chloroquine-resistant *P. falciparum* has spread to most malarial areas, and resistance to artemisinin has become a problem in some parts of Southeast Asia. The disease is widespread in the tropical and subtropical regions that exist in a broad band around the equator. Malaria is commonly associated with poverty and has a major negative effect on economic development [8].

Prevention of Malaria

Methods used to prevent malaria include medications, mosquito elimination and the prevention of bites. There is no vaccine for malaria. The presence of malaria in an area requires a combination of high human population density, high anopheles mosquito population density and high rates of transmission from humans to mosquitoes and from mosquitoes to humans. If any of these is lowered sufficiently, the parasite eventually disappears from that area, as happened in North America, Europe, and parts of the Middle East [9]. However, unless the parasite is eliminated from the whole world, it could re-establish if conditions revert to a combination that favors the parasite's reproduction. Furthermore, the cost per person of eliminating anopheles mosquitoes rises with decreasing population density, making it economically unfeasible in some areas [10].

Prevention of malaria may be more cost-effective than treatment of the disease in the long run, but the initial costs required are out of reach of many of the world's poorest people. There is a wide difference in the costs of control (i.e. maintenance of low endemicity) and elimination programs between countries. In areas where malaria is common, children under five years old often have anemia, which is sometimes due to malaria. Giving children with anemia in these areas preventive antimalarial medication improves red blood cell levels slightly but does not affect the risk of death or need for hospitalization [11].

Prevention of malaria includes:

- Preventing infection, by avoiding bites by parasite-carrying mosquitoes, or
- Preventing disease, by using antimalarial drugs prophylactically. The drugs do not prevent initial infection through a mosquito bite, but they prevent the development of malaria parasites in the blood, which are the forms that cause disease. This type of prevention is also called “suppression.
- Prevention of disease by administration of antimalarial drugs to particularly vulnerable population groups such as pregnant women and infants.
- Personal protection measures such as insecticide-treated bed nets
- Preventive treatment with antimalarial drugs of vulnerable groups such as pregnant women, who receive intermittent preventive treatment
- Provision of equipment and supplies (e.g., microscopes, drugs, bed nets) to allow the health workers and the communities to carry out the interventions.
- Drug-resistant malaria parasites hinder case management by decreasing the efficacy of antimalarial drugs and by requiring the use of alternate

drugs that are often more costly, less safe and less easy to administer.

- Insecticide resistance decreases the efficacy of interventions that rely on insecticides such as insecticide-treated bed nets and insecticide spraying.
- Inadequate health infrastructures in poor countries are unable to conduct the recommended interventions.
- The people most exposed to malaria are often poor and lack education. They often do not know how to prevent or treat malaria. Even when they do know, they often do not have the financial means to purchase the necessary products, such as drugs or bed nets.

Treatment Of Malaria

Malaria is treated with antimalarial medications; the ones used depends on the type and severity of the disease. While medications against fever are commonly used, their effects on outcomes are not clear. Simple or uncomplicated malaria may be treated with oral medications. The most effective treatment for *P. falciparum* infection is the use of artemisinins in combination with other antimalarials (known as artemisinin-combination therapy, or ACT), which decreases resistance to any single drug component [12]. These additional antimalarials include: amodiaquine, lumefantrine, mefloquine or sulfadoxine/pyrimethamine. Another recommended combination is dihydroartemisinin and piperaquine. ACT is about 90% effective when used to treat uncomplicated malaria. To treat malaria during pregnancy, the WHO recommends the use of quinine plus clindamycin early in the pregnancy (1st trimester), and ACT in later stages (2nd and 3rd trimesters). Malaria with partial resistance to artemisins emerged in Southeast Asia. Infection with *P. vivax*, *P. ovale* or *P. malariae* usually do not require hospitalization. Treatment of *P. vivax* requires both treatment of blood stages (with chloroquine or ACT) and clearance of liver forms with primaquine [13]. Treatment with tafenoquine prevents relapses after confirmed *P. vivax* malaria severe and complicated malaria are almost always caused by infection with *P. falciparum*. The other species usually cause only febrile disease.

Severe and complicated malaria are medical emergencies since mortality rates are high (10% to 50%). Cerebral malaria is the form of severe and complicated malaria with the worst neurological symptoms. Recommended treatment for severe malaria is the intravenous use of antimalarial drugs. For severe malaria, parenteral artesunate was superior to quinine in both children and adults. In another systematic review, artemisinin derivatives (artemether and arteether) were as efficacious as quinine in the treatment of cerebral malaria in children [14]. Treatment of severe malaria involves supportive measures that are best done in a critical care unit. This includes the management of high fevers and the seizures that may result from it. It also includes monitoring for poor breathing effort, low blood sugar, and low blood potassium [15].

How is malaria treated?

- Drugs that kill the parasite that causes malaria can be used to treat and prevent the disease. These drugs are called antimalarials.
- However, if you contract malaria while taking one type of antimalarial drug, the same drug cannot be used to treat the infection as the parasite may be resistant to it.
- Different drugs target different features of the parasite's biology and life cycle. For example, chloroquine targets the blood stages of the life cycle whilst primaquine removes the dormant[7] liver stages.
- Because of this, drugs are often used in combination with each other to make sure the malaria parasite is removed from all areas of the body. For example, primaquine can be used along with chloroquine to treat *Plasmodium vivax*.
- Combinations of drugs are also used to try to prevent the parasite from

developing resistance to the individual drugs on their own. This is the strategy used in artemisinin combination therapy (ACT), which uses an artemisinin-based drug plus one partner drug. ACT is currently the front-line treatment for *Plasmodium falciparum* malaria.

- If any parasites are left in the body after treatment, the disease may return. For example, *Plasmodium vivax* and *Plasmodium ovale* are able to lie dormant and hidden in the liver even if the parasite has been cleared from the rest of the body. If the parasite isn't cleared properly from the liver the disease can return months or even years later.
- Partial immunity[7] can be developed over years of exposure to the disease and although it never develops into full immunity it can reduce the severity of disease and risk of death from malaria.
- Most malaria deaths occur in young children under five years whose bodies have not had a chance to develop any immunity to the parasite.

Drugs Use in Treating Malaria

There are only a limited number of drugs which can be used to treat or prevent malaria . The most widely used are quinine and its derivatives and antifolate combination drugs.

Quinine and related compounds

Quinine, along with its dextroisomer quinidine, has been the drug of last resort for the treatment of malaria, especially severe disease. Chloroquine is a 4-aminoquinoline derivative of quinine first synthesized in 1934 and has since been the most widely used antimalarial drug [16]. Historically, it has been the drug of choice for the treatment of non-severe or uncomplicated malaria and for chemoprophylaxis, although drug resistance has dramatically reduced its usefulness. Amodiaquine is a relatively widely available compound closely related to chloroquine. Other quinine-related compounds in common use include primaquine (specifically used for eliminating the exoerythrocytic forms of *P. vivax* and *P. ovale* that cause relapses), and mefloquine (a quinolinemethanol derivative of quinine).

Antifolate combination drugs

These drugs are various combinations of dihydrofolate- reductase inhibitors (proguanil, chlorproguanil, pyrimethamine, and trimethoprim) and sulfa drugs (dapsone, sulfalene, sulfamethoxazole, sulfadoxine, and others). Although these drugs have antimalarial activity when used alone, parasitological resistance can develop rapidly. When used in combination, they produce a synergistic effect on the parasite and can be effective even in the presence of resistance to the individual components. Typical combinations include sulfadoxine/ pyrimethamine, sulfalenepyrimethamine (metakelfin), and sulfamethoxazole- trimethoprim (co-trimoxazole). A new antifolate combination drug is currently being tested in Africa [17]. This drug, a combination of chlorproguanil and dapsone, also known as Lap- Dap, has a much more potent synergistic effect on malaria than existing drugs such as SP. Benefits of this combination include a greater cure rate, even in areas currently experiencing some level of SP resistance, a lower likelihood of resistance developing because of a more advantageous pharmacokinetic and pharmacodynamic profile, and probable low cost [18].

Antibiotics

Tetracycline and derivatives such as doxycycline are very potent antimalarials and are used for both treatment and prophylaxis. In areas where response to quinine has deteriorated, tetracyclines are often used in combination with quinine to improve cure rates. Clindamycin has been used but offers only limited advantage when compared to other available antimalarial drugs. Parasitological response is slow to clindamycin and recrudescence rates are high. Its efficacy among non-immune individuals has not been fully established [19].

Artemisinin compounds

A number of sesquiterpine lactone compounds have been synthesized from the plant *Artemisia annua* (artesunate, artemether, arteether). These compounds

are used for treatment of severe malaria and have shown very rapid parasite clearance times and faster fever resolution than occurs with quinine [20]. In some areas of South-East Asia, combinations of artemisinins and mefloquine offer the only reliable treatment for even uncomplicated malaria, due to the development and prevalence of multidrug resistant falciparum malaria. Combination therapy (an artemisinin compound given in combination with another antimalarial, typically a long half-life drug like mefloquine) has reportedly been responsible for inhibiting intensification of drug resistance and for decreased malaria transmission levels [21].

Miscellaneous compounds

Halofantrine is a phenanthrene-methanol compound with activity against the erythrocytic stages of the malaria parasite. Its use has been especially recommended in areas with multiple drug-resistant falciparum. Recent studies have indicated, however, that the drug can produce potentially fatal cardiac conduction abnormalities, limiting its usefulness. Atovaquone is a hydroxynapthoquinonethat is currently being used most widely for the treatment of opportunistic infections in immunosuppressed patients [22]. It is effective against chloroquine-resistant *P. falciparum*, but because, when used alone, resistance develops rapidly, atovaquone is usually given in combination with proguanil. A new fixed dose antimalarial combination of 250 mg atovaquone and 100 mg proguanil (MalaroneTM) is being brought to market worldwide and is additionally being distributed through a donation programme, the drugs originally synthesized in China are currently undergoing field trials [23].

Combination therapy with antimalarials

The use of two antimalarials simultaneously, especially when the antimalarials have different mechanisms of action, has the potential for inhibiting the development of resistance to either of the components. The efficacy of a combination of a 4-aminoquinoline drug (either chloroquine or amodiaquine) with sulfadoxine/pyrimethamine. The studies reviewed were mostly done in areas and at times when both SP and chloroquine/amodiaquine retained a fair amount of efficacy, and it is not clear from these studies how well such a combination would act in areas where one of the components was significantly compromised [24]. Additionally, to date, there are no data to suggest whether this slightly improved clearance would translate into prolonged useful life span for either drug. Another combination therapy approach, combining an artemisinin derivative with other, longer half-life antimalarials [25].

Drug Resistance

Drug resistance is the reduction in effectiveness of a medication such as an antimicrobial or an antineoplastic in treating a disease or condition. The term is used in the context of resistance that pathogens or cancers have "acquired", that is, resistance has evolved. Antimicrobial resistance and antineoplastic resistance challenge clinical care and drive research. When an organism is resistant to more than one drug, it is said to be multidrug-resistant [4]. The development of antibiotic resistance in particular stems from the drugs targeting only specific bacterial molecules (almost always proteins). Because the drug is *so* specific, any mutation in these molecules will interfere with or negate its destructive effect, resulting in antibiotic resistance. Furthermore there is mounting concern over the abuse of antibiotics in the farming of livestock, which in the European Union alone accounts for three times the volume dispensed to humans – leading to development of super-resistant bacteria [7].

Drug resistance has also played a significant role in the occurrence and severity of epidemics in some parts of the world. Population movement has introduced resistant parasites to areas previously free of drug resistance [12]. The economics of developing new pharmaceuticals for tropical diseases, including malaria, are such that there is a great disparity between the public health importance of the disease and the amount

of resources invested in developing new cures. This disparity comes at a time when malaria parasites have demonstrated some level of resistance to almost every antimalarial drug currently available, significantly increasing the cost and complexity of achieving parasitological cure [8].

Bacteria are capable of not only altering the enzyme targeted by antibiotics, but also by the use of enzymes to modify the antibiotic itself and thus neutralize it. Examples of target-altering pathogens are *Staphylococcus aureus*, vancomycin-resistant enterococci and macrolide-resistant *Streptococcus*, while examples of antibiotic-modifying microbes are *Pseudomonas aeruginosa* and aminoglycoside-resistant *Acinetobacter baumannii*. Resistance to chemicals is only one aspect of the problem, another being resistance to physical factors such as temperature, pressure, sound, radiation and magnetism, and not discussed in this article, but found at Physical factors affecting microbial life [2].

Drug, toxin, or chemical resistance is a consequence of evolution and is a response to pressures imposed on any living organism. Individual organisms vary in their sensitivity to the drug used and some with greater fitness may be capable of surviving drug treatment [7]. Drug-resistant traits are accordingly inherited by subsequent offspring, resulting in a population that is more drug-resistant. Unless the drug used makes sexual reproduction or cell-division or horizontal gene transfer impossible in the entire target population, resistance to the drug will inevitably follow. This can be seen in cancerous tumors where some cells may develop resistance to the drugs used in chemotherapy. Chemotherapy causes fibroblasts near tumors to produce large amounts of the protein. This protein stimulates the growth of cancer cells which are drug-resistant. MicroRNAs have also been shown to affect acquired drug resistance in cancer cells and this can be used for therapeutic purposes. Malaria in 2012 has become a resurgent threat in South East Asia and sub-Saharan Africa, and drug-resistant strains of *Plasmodium falciparum* are posing massive problems for health authorities. Leprosy has shown an increasing resistance to dapsone [17].

A rapid process of sharing resistance exists among single-celled organisms, and is termed horizontal gene transfer in which there is a direct exchange of genes, particularly in the biofilm state. A similar asexual method is used by fungi and is called "parasexuality". Examples of drug-resistant strains are to be found in microorganisms such as bacteria and viruses, parasites both endo- and ecto-, plants, fungi, arthropods, mammals, birds, reptiles, fish, and amphibians [2]. In the domestic environment, drug-resistant strains of organism may arise from seemingly safe activities such as the use of bleach, tooth-brushing and mouth washing, the use of antibiotics, disinfectants and detergents, shampoos, and soaps, particularly antibacterial soaps, hand-washing, surface sprays, application of deodorants, sunblocks and any cosmetic or health-care product, insecticides, and dips, The chemicals contained in these preparations, besides harming beneficial organisms, may intentionally or inadvertently target organisms that have the potential to develop resistance [17].

Cause of Drug Resistance

Antimalarial drug resistance has been defined as the “ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject”. This definition was later modified to specify that the drug in question must “gain access to the parasite or the infected red blood cell for the duration of the time necessary for its normal action” Most researchers interpret this as referring only to persistence of parasites after treatment doses of an antimalarial rather than prophylaxis failure, although the latter is a useful tool for early warning of the presence of drug resistance [5].

This definition of resistance requires demonstration of malaria parasitaemia in a patient who has received an observed treatment dose of an antimalarial drug

and simultaneous demonstration of adequate blood drug and metabolite concentrations using established laboratory methods (such as high performance liquid chromatography) or *in vitro* test. In practice, this is rarely done with *in vivo* studies. *In vivo* studies of drugs for which true resistance is well known (such as chloroquine) infrequently include confirmation of drug absorption and metabolism; demonstration of persistence of parasites in a patient receiving directly observed therapy is usually considered sufficient. Some drugs, such as mefloquine, are known to produce widely varying blood levels after appropriate dosing and apparent resistance can often be explained by inadequate blood levels [11].

Malaria Treatment Failure

A distinction must be made between a failure to clear malarial parasitaemia or resolve clinical disease following a treatment with an antimalarial druand true antimalarial drug resistance. While drug resistance can cause treatment failure, not all treatment failure is due to drug resistance. Many factors can contribute to treatment failure including incorrect dosing, non-compliance with duration of dosing regimen, poor drug quality, drug interactions, poor or erratic absorption, and misdiagnosis. Probably all of these factors, while causing treatment failure (or apparent treatment failure) in the individual, may also contribute to the development and intensification of true drug resistance through increasing the likelihood of exposure of parasites to suboptimal drug levels [14].

Drug-Resistant *P. Falciparum*

Chloroquine-resistant *P. falciparum* first developed independently in three to four areas in Southeast Asia, Oceania, and South America in the late 1950s and early 1960s. Since then, chloroquine resistance has spread to nearly all areas of the world where falciparum malaria is transmitted levels [16]. *P. falciparum* has also developed resistance to nearly all of the other currently available antimalarial drugs, such as sulfadoxine/pyrimethamine, mefloquine, halofantrine, and quinine. Although resistance to these drugs tends to be much less widespread geographically, in some areas of the world, the impact of multi-drug resistant malaria can be extensive. Most recently, resistance to the artemisinin and non-artemisinin components of artemisinin-based combination therapy has emerged in parts of Southeast Asia, impacting the efficacy of this vital antimalarial class [12].

Drug-Resistant *P. Vivax*

Chloroquine-resistant *P. vivax* malaria was first identified in 1989 among Australians living in or traveling to Papua New Guinea. *P. vivax* resistance to chloroquine has also now been identified in Southeast Asia, Ethiopia, and Madagascar. Isolated reports have suggested chloroquine-resistance *P. vivax* in other countries and regions, but further evaluation is needed. Vivax malaria parasites, particularly from Oceania, show greater resistance to chloroquine than *P. vivax* isolates from other regions of the world.

Biochemical Mechanisms of Malaria Drug Resistance

In general, resistance appears to occur through spontaneous mutations that confer reduced sensitivity to a given drug or class of drugs. For some drugs, only a single point mutation is required to confer resistance, while for other drugs, multiple mutations appear to be required. Provided the mutations are not deleterious to the survival or reproduction of the parasite, drug pressure will remove susceptible parasites while resistant parasites survive. Single malaria isolates have been found to be made up of heterogeneous populations of parasites that can have widely varying drug response characteristics, from highly resistant to completely sensitive. Similarly, within a geographical area, malaria infections demonstrate a range of drug susceptibility World Health Organization (2010). Over time, resistance becomes established in the population and can be very stable, persisting long after specific drug pressure is removed. The biochemical mechanism of resistance has been well described for chloroquine, the antifolate combination drugs, and atovaquone.

Chloroquine Resistance

As the malaria parasite digests haemoglobin, large amounts of a toxic by-product are formed. The parasite polymerizes this by-product in its food vacuole, producing non-toxic haemozoin (malaria pigment). It is believed that resistance of *P. falciparum* to chloroquine is related to an increased capacity for the parasite to expel chloroquine at a rate that does not allow chloroquine to reach levels required for inhibition of haempolymerization. This chloroquine efflux occurs at a rate of 40 to 50 times faster among resistant parasites than sensitive ones [4]. Further evidence supporting this mechanism is provided by the fact that chloroquine resistance can be reversed by drugs which interfere with this efflux system. It is unclear whether parasite resistance to other quinoline antimalarials (amodiaquine, mefloquine, halofantrine, and quinine) occurs via similar mechanisms [17].

Antifolate combination drugs

Antifolate combination drugs, such as sulfadoxine + pyrimethamine, act through sequential andsynergistic blockade of 2 key enzymes involved withfolate synthesis. Pyrimethamine and related compounds inhibit the step mediated by dihydrofolatereductase (DHFR) while sulfones and sulfonamides inhibit the step mediated by dihydropteroate synthase (DHPS). Specific gene mutations encoding for resistance to both DHPS and DHFR have been identified. Specific combinations of these mutations have been associated with varying degrees of resistance to antifolate combination drugs [10].

4Atovaquone

Atovaquone acts through inhibition of electron transport at the cytochrome *bc1* complex. Although resistance to atovaquone develops very rapidly when used alone, when combined with a second drug, such as proguanil (the combination used in MalaroneTM) or tetracycline, resistance develops more slowly. Resistance is conferred by single-point mutations in the cytochrome-b gene.

Factors Contributing to the Spread of Resistance

Numerous factors contributing to the advent, spread, and intensification of drug resistance exist, although their relative contribution to resistance is unknown. Factors that have been associated with antimalarial drug resistance include such disparate issues as human behaviour (dealt with in detail elsewhere), vector and parasite biology, pharmacokinetics, and economics. As mentioned previously, conditions leading to malaria treatment failure may also contribute to the development of resistance.

Biological influences on resistance

Based on data on the response of sensitive parasites to antimalarial drugs *in vitro* and the pharmacokinetic profiles of common antimalarial drugs, there is thought to always be a residuum of parasites that are able to survive treatment. Under normal circumstances, these parasites are removed by the immune system (non-specifically in the case of non-immune individuals). Factors that decrease the effectiveness of the immune system in clearing parasite residuum after treatment also appear to increase survivorship of parasites and facilitate development and intensification of resistance [21]. This mechanism has been suggested as a significant contributor to resistance in South-East Asia, where parasites are repeatedly cycled through populations of non-immune individuals, the nonspecific immune response of non-immune individuals is less effective at clearing parasite residuum than the specific immune response of semi-immune individuals. The same mechanism may also explain poorer treatment response among young children and pregnant women [8]. The contribution to development and intensification of resistance of other prevalent immunosuppressive states has not been evaluated. Among refugee children in the former Zaire, those who were malnourished (low weight for height) had significantly poorer parasitological response to both chloroquine and SP treatment. Similarly, evidence from prevention of malaria during pregnancy suggests that parasitological response to

treatment among individuals infected with the human immunodeficiency virus (HIV) may also be poor. HIV-seropositive women require more frequent treatment with SP during pregnancy in order to have the same risk of placental malaria as is seen among HIV-seronegative women. Parasitological response to treatment of acute malaria among HIV-seropositive individuals has not been evaluated [13].

The current prevalence of malnutrition among African children under 5 years has been estimated to be 30% and an estimated 4 to 5 million children are expected to be infected with HIV at the beginning of this new century. If it is proven that malnutrition or HIV infection plays a significant role in facilitating the development or intensification of antimalarial drug resistance, the prevalence of these illnesses could pose a tremendous threat to existing and future antimalarial drugs [23].

Some characteristics of recrudescent or drug resistant infections appear to provide a survival advantage or to facilitate the spread of resistance conferring genes in a population. In one study, patients experiencing chloroquine treatment failure had recrudescent infections that tended to be less severe or even asymptomatic. Schizont maturation may also be more efficient among resistant parasites [9]. There is some evidence that certain combinations of drug-resistant parasites and vector species enhance transmission of drug resistance, while other combinations inhibit transmission of resistant parasites. Many antimalarial drugs in current usage are closely related chemically and development of resistance to one can facilitate development of resistance to others. Chloroquine and amodiaquine are both 4-aminoquinolines and cross-resistance between these two drugs is well known. Development of resistance to mefloquine may also lead to resistance to halofantrine and quinine [14].

Antifolate combination drugs have similar action and widespread use of sulfadoxine/ pyrimethamine for the treatment of malaria may lead to increased parasitological resistance to other antifolate combination drugs. Development of high levels of resistance through continued accumulation of DHFR mutations may compromise the useful life span of newer antifolate combination drugs such as chlorproguanil/dapsone (LapDap) even before they are brought into use [5]. This increased risk of resistance due to SP use may even affect nonmalarial pathogens; use of SP for treatment of malaria increased resistance to trimethoprim/sufamethoxazole among respiratory pathogens. There is an interesting theory that development of resistance to a number of antimalarial drugs among some falciparum parasites produces a level of genetic plasticity that allows the parasite to rapidly adapt to a new drug, even when the new drug is not chemically related to drugs previously experienced. The underlying mechanism of this plasticity is currently unknown, but this capacity may help explain the rapidity with which South-East Asian strains of falciparum develop resistance to new antimalarial drugs [20].

Programmatic influences on resistance

Programmatic influences on development of antimalarial drug resistance include overall drug pressure, inadequate drug intake (poor compliance or inappropriate dosing regimens), pharmacokinetic and pharmacodynamic properties of the drug or drug combination, and drug interactions. Additionally, reliance on presumptive treatment can facilitate the development of antimalarial drug resistance. Overall drug pressure especially that exerted by programmes utilizing mass drug administration, probably has the greatest impact on development of resistance. Studies have suggested that resistance rates are higher in urban and periurban areas than rural communities, where access to and use of drug is greater [2].

The use of presumptive treatment for malaria has the potential for facilitating resistance by greatly increasing the number of people who are treated unnecessarily but will still be exerting selective pressure on the circulating parasite population. In some areas and at some times of the year, the number of patients being treated unnecessarily for

malaria can be very large [10]. Concurrent treatment with other drugs can increase the likelihood of treatment failure and may contribute to development of drug resistance. Folate administration for treatment of anaemia and possibly when used as a routine supplement during pregnancy can increase treatment failure rates. Similarly, concurrent illness may have an influence, as was mentioned previously with regard to malnourishment [9].

Drug quality has also been implicated in ineffective treatment and possibly drug resistance. Either through poor manufacturing practices, intentional counterfeiting, or deterioration due to inadequate handling and storage, drugs may not contain sufficient quantities of the active ingredients. In an analysis of chloroquine and antibiotics available in Nigeria and Thailand, between 37% and 40% of samples assayed had substandard content of active ingredients, mostly from poor manufacturing practices. Another study in Africa found chloroquine stored under realistic tropical conditions lost at least 10% of its activity in a little over a year [16].

CONCLUSION

Resistance to the antimalarial drugs has increased the mortality and morbidity rate that is achieved so far through the malaria control program. Monitoring the drug resistance to the available antimalarial drugs helps to implement effective drug policy, through the *in vivo* efficacy studies, *in vitro* drug susceptibility tests and detection of molecular markers. It is important to understand the mechanism of the antimalarial drugs, as it is one of the key factors in the emergence and spread of drug resistance.

Emergence and spread of antimalarial drug resistance constitute a major threat toward the treatment of malaria and if not handled properly, could reverse the malaria control program and containment achieved so far worldwide. The drug resistance has been reported mainly for *P. falciparum* and *P. vivax*. Antimalarial combination therapy targeting different mechanism of action could prolong the emergence and spread of drug-resistant parasites. Understanding the site of action and mechanism of the antimalarials is an important tool to identify drug-resistant marker, to prevent the development of drug resistance further and in the development of new antimalarial drugs/vaccines. The molecular markers of drug resistance play a vital role in the detection of resistance in clinical and field isolates when compared to the *in vivo* efficacy studies and *in vitro* tests. Thus, earlier detection of drug-resistant parasites in clinical isolates will aid in employing immediate and appropriate treatment that in turn reduces treatment failure and thereby mortality, and also prevents the spread of resistance.

Hence, continuous monitoring and surveillance of drug-resistant molecular markers in malaria endemic regions is important in determining and assisting an effective national drug policy for malaria treatment. Therefore, more research is necessary to find new antimalarial drugs/vaccines for multidrug resistance parasites and in identification and validation of genetic markers for multidrug resistance, thereby containment and treatment of malaria can be achieved hand in hand.

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