Malaria – Prevention

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External agents

Anopheles mosquitoes only bite in the evening and at night. It is possible to protect oneself by wearing protective clothing and using an undamaged mosquito net. Effectiveness is increased by treating the net with pyrethroids (insecticides) such as permethrin (Permas®, Peripel®), lambda-cyhalothrin (Danger®, Demand CS®, Matador®) or deltamethrin (K-Otrine®). This will increase further in importance in the future. In most instances, permethrin will be augmented by piperonyl butoxide. Piperonyl butoxide is the most widely used synthetic pyrethrin synergist and there are no reports available on toxic effects on humans resulting from the exposure to it. Piperonyl butoxide is not an insecticide itself but a cytochrome P450 inhibitor which allows pyrethroids such as permetrin to be much more active (10x). Inhibition of the detoxification pathway allows higher unchanged systemic concentrations of the active insecticide to remain within the target animal for a longer period. This is here now.

Long-lasting insecticide treated nets

Mass produced long lasting insecticide treated nets (LLINs) are replacing older style bed nets. Olyset net was the first LLIN which became commercially available. Sumitomo's Olyset® technology incorporates permetrine insecticide directly into polyethylene filaments which can be woven into sturdy bed nets to provide long-lasting protection from night-time biting mosquitoes. Olyset Plus, which received WHO approval in July 2012, retains the controlled-release technology and durability, and contains 2% permethrin and 1% of the synergist piperonyl butoxide (PBO). The fibres have been designed to release the two ingredients at a constant ratio of 2:1. The 'bleed rate' at which permethrin and PBO migrate from the internal reservoir in the fibres to the surface of the net has been adjusted in order to make the net active again within 1-2 days of washing. For this work, Sumitomo Chemical became the co-winner of the 2012 'Application of Core Competence' category – Global Business Coalition Health Award. A major production plant has been set up in Tanzania.

Fine-mesh gauze can be applied to windows and ventilation shafts. One good argument for using a mosquito net is the fact that it also protects from nuisance insects such as *Culex* mosquitoes and bedbugs. In regions where there are few *Culex*, people are not so ready to use a net: after all they

cannot see or hear any mosquitoes (anopheline mosquitoes fly with little noise).

Insecticides based on pyrethrum can be dispersed by means of spraying (spray gun), evaporation (heated electric plate) or burning (mosquito coil, e.g. with esbiotrin). Insecticides can also be applied to the walls or to the curtains by the windows.

There are also various insect repellents. DEET (N,N-diethyl-m-toluamide, now called N,N-diethyl-3-methylbenzamide) is moderately active and can be applied as an alcoholic solution to the skin. This produces a sticky effect when the alcohol evaporates. The effectiveness is only moderate. DEET is absorbed through the skin and is eliminated quickly via the urine. There is no accumulation in the body. The higher the concentration, the longer the duration of action: DEET 20-30% gives 4-6 hours protection, DEET 50% offers 8 hours protection. Concentration higher than 50% don't give significant longer protection.

Alternative repellents are (p)icaridine(Care-Plus®Repel-it; Parazeet®) and IR3535 (Cinq sur Cinq®, Moustidose®).

Intermittent preventive treatment (IPT) and seasonal malaria chemoprophylaxis (SMC)

In highly endemic countries (sub-Saharan Africa), several "preventive" strategies have been promoted and adopted for special risk groups or for some periods of higher transmission. They consist of administering some drugs with antimalarial activity at regular intervals to a group of population with no previous diagnostic testing for malaria. The main aim is to control the malaria morbidity and important reductions of clinical and severe malaria or malaria-related complications (on fetus/newborns for example) have been repeatedly demonstrated.

At this moment, IPT use is recommended by WHO

- in pregnancy (ITPp) as part of antenatal care: sulfadoxine-pyrimethamine (SP) starting from the second trimester with at least three administrations at one-month intervals minimum
- in infants (< 12 years) during the immunization program: SP (where still effective) at the second and third rounds of vaccination against tetanus/diphtheria/pertussis and at vaccination against measles
- in children (< 6 years) in the sub-Sahel region during the rainy season: SP + amodiaquine once a month during each transmission season (strategy called SMC)

On an important prospective note, ACTs are also increasingly explored as IPT in various populations for preventive purposes. ITP with ACT is currently investigated in pregnant women, infants, children < 6 years, school-age children, whole population where malaria is about to be eliminated. This field and the related WHO recommendations are expected to evolve deeply in the coming years

Chemoprophylaxis for travelers

Chemoprophylaxis is in the first instance intended as prevention of *P. falciparum* malaria. No single drug which is taken preventively is 100% active against sporozoites and no single drug prevents the formation of liver forms (except primaquine). While taking prevention no vivax or ovale malaria will occur but after they have been discontinued an attack with these plasmodia is possible in the following months or years.

In view of the extensive resistance of *P. falciparum*, at present no 100% satisfactory protection against this latter parasite is possible. Advice as to whether or not to take medication and which kind of drug to take, will depend on the region and differ from person to person (short journeys, resident, local population, pregnancy, young children, allergy, chronic diseases, use of other drugs and so on). Recommendations vary from country to country and evolve in time.

- In regions with only *P. vivax* and/or sensitive *P.falciparum* (WHO type A) chloroquine 300 mg/week will suffice.
- In zone C with resistant/multidrug resistant *P. falciparum*, 3 different regimens are currently recommended:
- Atovaquone/proguanil 250/100 mg 1 tablet per day beginning 1 day before departure until 7 days after return
- Doxycycline 100 mg/day during the stay and up to 4 weeks after return
- Mefloquine 250 mg 1 tablet per week, to start two-three weeks before departure, and to continue up to 4 weeks after return

The decision should be individualized, since it depends on several aspects (side effect profile, type of trip, budget). Given the lower cost of generic drugs of atovaquone/proguanil and its good tolerance, atovaquone/proguanil is often chosen as the prophylactic treatment, especially for shorter journeys.

Doxycycline is an alternative in case of atovaquone/proguanil intolerance., Prolonged ingestion of doxycycline can lead to phototoxicity, including photo-onycholysis. Sunscreens do not block ultraviolet A well enough to prevent phototoxic reactions to doxycycline.

Today, the use of mefloquine as preventive treatment has decreased. The plasma half-life of mefloquine is 2 to 3 weeks. Ingestion of 1 tablet per week produces stable blood levels after 7 weeks. Traditionally it is said that mefloquine prophylaxis should be started before departure. This guideline is based on the consideration that intolerance to the drug can be monitored in this way. It is safe to begin the medication 15 days before departure so that 3 tablets are taken before leaving. In this way 75% of the side effects can be detected. At the prophylactic dosage (adults one 250 mg tablet per week) side effects occur in 2 to 3% of people, which require that the prophylaxis be discontinued. Rarely (1 in 12,000 to 15,000) preventive dosages may trigger epilepsy or psychosis may occur. Epilepsy and arrhythmias (including the use of beta-blockers, calcium antagonists and digitalis) are contra-indications for the use of this product. Latest data indicate that it is proven safe during pregnancy. There are sufficient data that it is safe if taken for longer periods. The first case of mefloquine resistance was described in Thailand in 1982. There is already mefloquine resistance on a small scale in many countries, but this can be significant locally: e.g. the cure rate in East Thailand was only 41% in 1993. *P. falciparum* malaria can thus sometimes occur in spite of correct prophylactic use of mefloquine. Mefloquine does not kill sporozoites and liver parasites (therefore *P. vivax* and *P.ovale* malaria are still possible after leaving an endemic zone and after discontinuing mefloquine chemoprophylaxis).

For longer stays we recommend after a period of adequate chemoprophylaxis (a few weeks) at arrival; to travel with stand-by emergency treatment (SBET) of quality, to use in case of malaria, either breakthrough under chemoprophylaxis or attack occurring later. It is of utmost importance to remain alert in case of fever even after several years of tropical stay. Malaria is always possible, even in regions of lower transmission and malaria should be investigated appropriately and treated accordingly. Emergency treatment for travellers in 2016 includes Malarone®, Riamet® or Eurartesim®.

The local population should not take chronic chemoprophylaxis and most people develop semi-immunity. There are however some high-risk groups: e.g. pregnancy, children less than 5 years and HIV patients. During pregnancy particularly in the second and third trimesters and also immediately post-partum, the immunological resistance to malaria falls. Intermittent preventive therapy in pregnancy (“IPTp”) protects against maternal anaemia and low birth weight, and its use in areas in medium to high transmission is recommended by WHO (in most African programs Fansidar is used). The efficacy of IPTp is reduced in HIV-positive women.

Vaccination

Research into a malaria vaccine is based on a number of possibilities. An immune response can be

triggered against sporozoites and liver forms (pre-erythrocytic vaccines), erythrocytic forms (blood-stage vaccines) and/or gametocytes (transmission blocking vaccines). However the immune response does not necessarily have a protective effect. A 100% effective malaria vaccine is not likely to be developed in the foreseeable future but a vaccine which leads to partial protection is being evaluated in different fields.

RTS,S/AS01

In the early 1980s antibodies against sporozoites were used to identify the main antigen, circumsporozoite protein (CSP). The CSP is expressed on the surface of the parasite during the infective sporozoite stage.

In 1996 the first favourable results became known. A randomized and controlled study in the Gambia on 306 volunteers showed RTS,S/AS01 to provide significant protection against natural *P. falciparum* infection. The RTS,S/AS01 is a recombinant vaccine against the pre-erythrocytic stage of the parasite in which regions of *P falciparum* CSP are fused to hepatitis B surface antigen. It was developed by a public-private partnership with support from the Bill and Melinda Gates Foundation. The results of the large phase III trial that enrolled 15,459 infants was carried out at 11 clinical trial centers in seven countries (Burkina Faso, Gabon, Malawi, Mozambique, Ghana, Tanzania, Kenya) were published in 2012. In this trial 3 vaccines were given with a 1-month interval and some received a booster 20 months after the first vaccine to assess if higher immunity is maintained with a booster vaccine. Initial results demonstrated a vaccine efficacy of about 31% for both clinical and severe malaria in African children and a 26% vaccine efficacy against severe malaria However, a follow-up study over 7 years showed that these results were offset by rebound in later years in areas with high exposure to malaria parasites. In year five to seven after vaccination, the vaccinated group even had a higher risk of febrile convulsions than the control group with a possible higher risk for cerebral malaria and meningitis in areas with high exposure. Nevertheless, pilot implementation studies are currently being initiated in Kenya, Malawi and Ghana and will learn whether large-scale use of the RTS,S/AS01 vaccine may enter future malaria preventive programs.

PfSPZ

PfSPZ is a newly developed vaccine, eliciting an immune response against *Plasmodium falciparum*. It is made of non-replicating irradiated whole sporozoites (SPZ), the parasite stage that infected mosquitoes inject during a bite. The vaccine is unique in using whole parasites as its ingredient. In healthy volunteers a strong protection was noted in lab studies with development of CD8+ T-cells

producing IFNy. These T cells play a key role in the immune response to fight malaria in the liver. The difficulty with this vaccine however is that PfSPZ must be injected intravenously, that poses challenges for mass vaccination campaigns. On top of this, it must be stored in liquid nitrogen at –195 °C or colder. Sanaria, the developing company, is developing a robot that can dissect salivary glands of mosquitos. This step should make preparation and further development of the vaccine faster and easier.

A pilot trial that will enrol 2.100 people aged 2-50 years on the west African island of Bioko is being planned. If the first results are promising, the plan is to vaccinate another 10.000 people and ultimately all 280.000 habitants of the island. PfSPZ's efficacy in the field will inevitable be lower than in lab studies because people might have weaker responses to the vaccine due to pre-existing exposure to malaria or local strains of the malaria parasite might differ from the one used in the vaccine. But combined with conventional measures such as indoor insecticide spraying and insecticide treated bed nets, there is the hope to be able to completely eradicate malaria on the island.

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