Malaria-the disease of fours

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About 3.2 billion people are at high risk of malaria globally, 350 million have the parasite in their body and 198 million were ill with malaria in 2013 with almost 584 000 dying as a result - WHO. (Some new research suggests that 1.24 million died of malaria in 2010 with 85% of the deaths in Sub-Saharan Africa) (the official figures for 2010 were much lower: 216 million ill and 655 000 who died from malaria). This is the most important parasitic disease in the world. Between 2000 and 2012 3.3 million deaths have been averted by new efforts.

The majority of countries in tropical Sub-Saharan Africa (SSA) have a reduction of their potential income by between 1-1.3% per year due malaria and that over a 15 year period this loss of income amounts to almost 20% of their potential earnings. Put in another way probably 20% of their poverty is due to malaria. In the worst affected countries malaria accounts for 40% of public health expenditure, 30-50% of in-patient admissions and up to 60% of out-patient clinic visits. In 1997 it was estimated at the Global Malaria Conference in Hydrabad that annual deaths from malaria were between 2.5 million and 3.5 million.

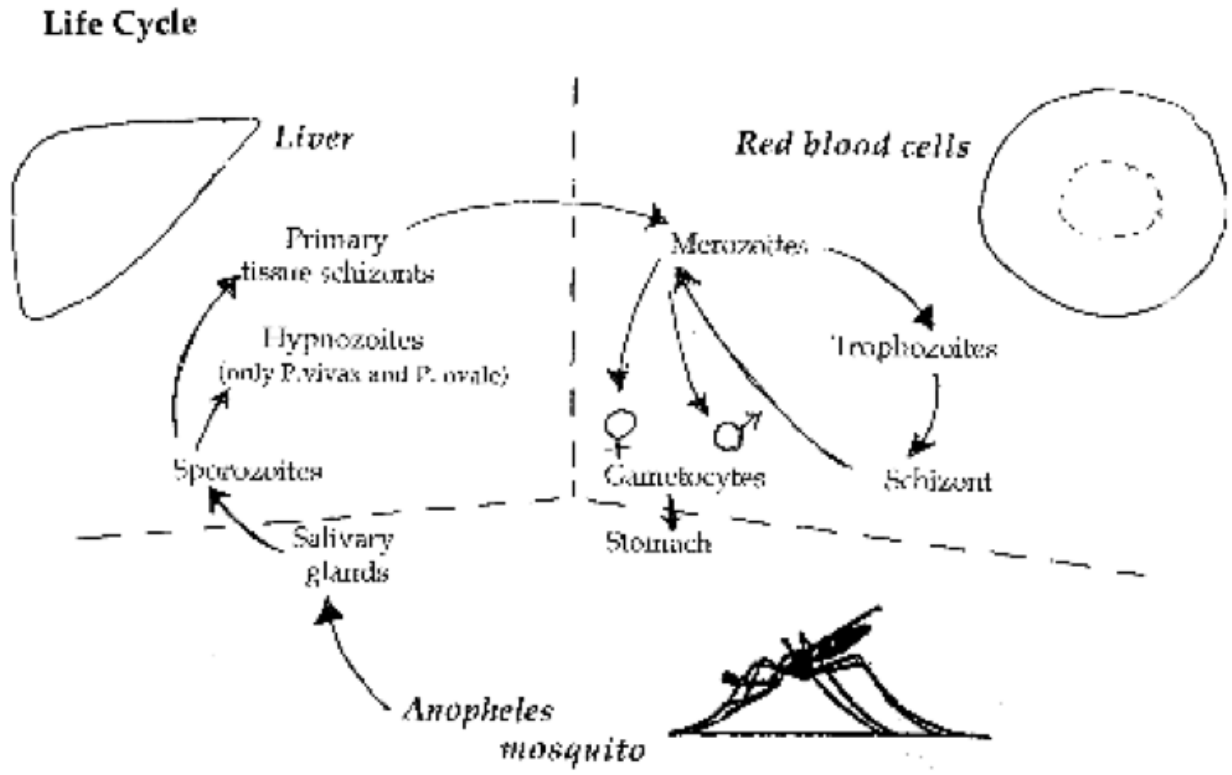
On World Malaria Day: 24 April 2012, WHO hails global progress in combating malaria but highlights the need to further reinforce the fight. The Global Malaria Programme's new initiative, T3: **Test**. **Treat**. **Track**, may need a 4th. **Train** so that these ideas takes root and change practice. This initiative urges malaria-endemic countries and donors to move towards universal access to diagnostic testing and antimalarial treatment, and to build stronger malaria surveillance systems. “In the past ten years, increased investment in malaria prevention and control has saved more than a million lives,” says Dr Margaret Chan, WHO Director-General.

Cause

Malaria is spread by the bite of the female Anopheles mosquito (45 species are important vectors with A. gambiae being the most effective) in which the parasite goes through a complicated life-cycle ending up in the salivary glands. A bite from a mosquito infected with such parasites is accompanied by the injection of saliva to stop the blood from clotting. With the saliva are injected parasites at the **sporozoite** stage where they can spread within 45 minutes through the blood stream of man and reach the hepatocytes of the liver. They bore into these hepatocytes and start asexual reproduction into **schizonts** and finally discharge **merozoites** into the blood stream. In Plasmodium falciparum (the main malaria parasite in Tropical Africa) the liver stage lasts 5.5 days. In P. malariae it lasts 15 days.

The merozoites bore into red cells and form a vacuole with the invaginated red cell membrane. About 36 hours (54 hrs. in P. malariae) after invasion repeated nuclear division forms a **schizont** or better termed a **meront** and finally the growing parasite fills the red cell and is packed with **merozoites**. It then bursts and 6-36 merozoites are released to invade new red blood cells. The infection expands logarithmically at around 10-fold per cycle. The release of several substances at this bursting stage brings about the symptoms of malaria which include fever, headache, pain in muscles, nausea and vomiting. Finally, if untreated, so many red blood cells are damaged that the person becomes anaemic due to lack of intact blood cells. The spleen which is the dumping ground of broken down red cells may become enlarged and tender. The person may even become jaundiced as the break down products of haemoglobin finally overwhelm the liver's capacity to deal with them, and the inflammatory effect of malaria on the liver cells function. After a series of asexual cycles in P. falciparum a sub-population of the parasite develops into sexual forms (**gametocytes**) with the process taking about 7-10 days. This is the stage that is then taken up by the

female anopheles. The parasite then goes through the complex process within the mosquito which brings us back to our starting point as sporozoites in the salivary glands.



The effect of malaria on nutrition

Many episodes of malaria coming close together will decrease the intake of nutrients since the child that is acutely ill with the disease has nausea and vomiting, and may have a poor appetite even after the acute illness is over. The malaria medicines may also affect the appetite. The high fever increases catabolism and thus increases the need for nutrients.

The effect of nutrition on malaria

Paradoxically severe malnutrition has a relative protective effect against the severe complications of malaria. Children with kwashiorkor virtually never develop cerebral malaria until they have recovered from their malnutrition; they may then suddenly become sick with severe malaria. Maybe the parasite becomes as malnourished as the human host in severe malnutrition. Replication is slower with less severe complications of malaria. Conversely, most children with cerebral malaria are in the well-nourished group.

It may be that iron deficiency anaemia also provides a limited protection against severe malaria, and iron supplements may aggravate the disease.

Parasite types

There are 4 main types of parasites: Plasmodium falciparum, P. malariae, P. ovale, and P. vivax. (P. knowlesi is found on Borneo and parts of peninsular Malaysia)

Plasmodium falciparum is virtually the only life-threatening type and is also the dominant type in most parts of tropical Africa. In Zambia this type accounts for 95% of all malaria. In many parts of Asia the malaria threat is smaller than in Africa and P. vivax is dominant in many countries (India, Pakistan, Sri Lanka etc.)

Only P. vivax and P. ovale can have a long-term liver stage where the parasite can hide for several years and flare-up again. This stage needs special treatment with primaquine to clear the parasite.

Disease situations

There are four situations of malaria threat that are so different from each other that it is as if four different diseases are being described:

1. High transmission with an extremely effective vector (Anopheles gambiae) **of P. falciparum.** Here malaria will almost certainly be the main cause of morbidity and mortality in children under 5 and the main cause of illness amongst adults. Chloroquine treatment is virtually always useless. Impregnated mosquito nets and more effective treatment are the only hope in the community.

2. Low transmission of P. falciparum. Here the disease may occasionally come as epidemics (e.g. during El Nino-associated climate changes) that are a threat to the life and health of both adults and children with massive outbreaks of severe anaemia and cerebral malaria during the outbreaks but little impact otherwise. In an outbreak, there may even be discussion about short-term prophylaxis for children and pregnant women, as well as impregnated mosquito nets and early effective treatment.

3. Moderate transmission of P. vivax and ovale. Here both prophylaxis and treatment with chloroquine are usually effective but follow-up treatment of the liver stage with primaquine is still needed. Environmental changes such as draining marshlands and separating human from animal dwellings often make a big impact.

4. Low transmission of P. vivax, ovale and malariae. Here malaria is an exotic disease without much impact at the community level.

Symptoms

There are 4 main symptoms: headache, muscular pain, fever + rigors (shaking of the body due to the shivering attack), nausea + vomiting. These are usually in the absence of symptoms of respiratory infection such as sore throat, runny nose and coughing. There could be an almost identical presentation with influenza but here there are virtually always respiratory symptoms. Almost always after two days there will be some period completely without fever and the other symptoms.

Signs

There are 4 main signs on examining a person with malaria: raised temperature, anaemia, enlarged spleen, jaundice. However all four may be absent although the absence of fever throughout is rare. Intermittent fever is the usual picture with a normal temperature at times. The latter three signs are less usual in the first attack of malaria.

Diagnosis

Blood films with both thin and thick films are still the main-stay of diagnosis but these need to be accurately made, stained and assessed by an experienced technician to be useful.

There are 4 new methods that are all expensive and mainly useful in looking for falciparum malaria: ParaSight-F, PCR, QBC malaria test, and HRP-2 (Malaquick). The latest Rapid Diagnostic tests, as assessed by malaria experts, have a very high sensitivity and specificity.

Severe complications

There are 4 severe life-threatening complications all with P. falciparum and are due to inflammatory processes resulting from the release of cytokines when the red blood cells burst. Also the parasite causes red blood cells to become more sticky and to form aggregations including rosettes which slow down or stop circulation in the microcirculation to essential organs. This starts in the venules.:

1. cerebral malaria,

2. severe anaemia,
3. renal failure and blackwater fever (passing very dark urine because of a massive break-down of red blood cells with the release of free haemoglobin into the blood at a level that the kidneys cannot control and hence a leak of haemoglobin with its very dark colour in the urine),
4. pulmonary oedema (water in the lungs which become stiff and dangerously ineffective).

Assessment
There are 4 important clinical assessments to follow the course of severe malaria: daily (or twice daily) parasite counts, fluid input/output assessment, daily weighing for assessing fluid balance, measurement of conscious level using e.g. Glasgow or Blantyre coma score. Respiratory rate is also important.

Rapid treatment
There are 4 rapidly-acting groups of drugs for treating acute malaria:
1. chloroquine or amodiaquine for P. vivax, malariae and ovale
2. artemisin-based combination therapy (ACT) for malaria due to P. falciparum
Artemisinine was first discovered in 1972 by Tu YouYou after testing 200 traditional herbs for Malaria treatment and found the substance in Artemesia annua as the best and fastest drug ever tested for malaria treatment. His work was ordered by Chairman Mao Zedong to help treating Chinese soldiers with malaria in the Vietnam war.
3. quinine or quinidine for severe malaria due to P. falciparum,
4. mefloquine for malaria due to P. falciparum (Lariam®).

Halofantrine has been very useful for P. falciparum treatment but now potentially life-threatening cardiac side-effects have been described which limit its value. A closely related drug, lumefantrine, without the cardiac side effects is now the commonest linked drug to artemisinine in ACT

Dual therapy
In an area with chloroquine resistant P. falciparum malaria, which means virtually all of Africa, (resistance to chloroquine with the other 3 types of malaria is still unusual) the strongly recommended treatment is "dual therapy." Here are 4 examples:
*__1. Artemether + lumefantrine (Coartem®).__ Because of the Roll-Back-Malaria programme this is now widely available and is the best. In Europe it is marketed as Riamet®
2. Atovaquone + proguanil (Malarone®) is a rapidly acting anti-malarial which is good for early P. falciparum but very expensive.
3. Amodiaquine (Camoquin®) + Fansidar®. Cheap and well tested in Uganda but is likely to show resistance developing.
4. A new low-cost dual therapy was about to be launched but had to be dropped because of potential problems in those with G6PD deficiency: chloproguanil + dapsone (LapDap®) which was to have been combined with artmether.

If single treatment with amodiaquine is used a follow-up treatment will almost certainly be needed with doxycycline.

For severe malaria choose artemether i.m. or artesunate i.v. or quinine i.v. as these are the three that have been shown to give the quickest response. A short course with one of these until there is good improvement should be followed by oral Coartem® or doxycycline to clear the last parasites (in the

early stages oral Coartem® may be possible). Some countries have suppositories with Artenam available where i.v. treatment is not possible.
In situations that you meet the **extreme anaemia** (seen more in younger children) use an alternative to iv. blood: give the blood that is needed to save their lives intraperitoneally. This is easier to learn and teach others to use. It reduces the risk of overloading the heart causing heart failure when blood is given too quickly without strong diuretics. It has its special use in situations with an epidemic of severe malaria with dozens of children needing blood. Here are the details: Identify a point half way between the Umbilicus and the Xiphisternum. Sterilise the skin with iodine in spirit. After preparing the blood of the right blood group, connect a needle to a giving set with normal saline. Penetrate the skin only, at a right angle to the skin, and then fully open the tap to the giving set. Then advance the needle slowly and as soon as the saline starts to flow (you are now into the peritoneal cavity), shut it down, connect the giving set to the blood and give the quantity of blood needed for the level of anaemia found and then withdraw the needle.
For children under 5 years who come in with coma and who are found to have malaria parasites in their blood, check if possible the retina carefully after dilating the pupil and if "ghost vessels" are seen on the retina this confirms cerebral malaria since it is never seen in any other illness. Start immediately iv. Artesunate, or if it is not available give Artemether. by im. route.
If a child is over 5 years and comes in with coma, first ask the parents where the child has lived over the last 5 years. If the child has lived in an area with Holoendemic or Hyperendemic Malaria then the child will already have semi-immunity to the parasite and therefore, even if malaria parasites are in the blood slide, the coma is not due to malaria. Check immediately for other causes including bacterial meningitis.

Follow-up treatment
There are 4 follow-up slow-acting treatments when there are resistance problems: doxycycline, clindamycin (can be used in pregnancy), Fansidar® or cotrimoxazole.

Chloroquine resistance
There are 4 levels of resistance to chloroquine: **no resistance; R1:** good clinical effect and the blood slide becomes negative but the symptoms come back without new infection within 28 days; **R2:** same as R1 but blood slide never becomes negative; **R3:** no improvement either clinically or on parasite counts.

Prophylaxis
There are 4 ways of avoiding malaria in Africa:
1. Avoid mosquito bites:e.g. use of mosquito nets impregnated with permethrin or deltamethrin over beds (97% effective in semi-immunes). Combine this with local insect repellants e.g. DEET. Put self-closing doors on all outside doors and mosquito nets on all windows.
2. Prophylaxis with an effective drug e.g. in East and Central Africa with mefloquine, or malarone or doxycycline(all 90% effective). Less effective: proguanil + chloroquine (75% effective);
3. Spray all houses within 1 km radius of an institution with insecticide regularly; such programmes of Residual indoor spraying (IRS) are mainly relevant in high density living areas.
4. Drain all puddles, marsh areas, remove tyres, cans and all rain-water accumulating items.
Dosages in P. falciparum malaria treatment in Africa
First choice when available
Artemether-lumefantrine (Coartem®) For adults: 4 tablets as a single initial dose, 4 tablets again

after 8 hours and then 4 tablets twice daily (morning and evening) for the following two days (total course of 24 tablets). For children: 5-15 kg: one tablet as an initial dose, one tablet again after 8 hours and then one tablet twice daily (morning and evening) for the following two days (total course of 6 tablets); 15-25 kg: two tablets as an initial dose, two tablets again after 8 hours and then two tablets twice daily (morning and evening) for the following two days (total course of 12 tablets); 25-35 kg: three tablets as an initial dose, three tablets again after 8 hours and then three tablets twice daily (morning and evening) for the following two days (total course of 18 tablets). Above 35 kg as for adults.

Second choice when available
Atovaquone 1000 mg daily plus proguanil 400mg (Malorone®) daily by mouth after fatty meal for 3 days.
In children 11-20 kg the dosage of atovaquone/proguanil is 250mg/100mg; 21-30 kg 500mg/200mg; 31-40 kg 750mg/300mg and above 40kg adult dose.

Third choice when the above are not available: Amodiaquine 600mg daily by mouth for 2 days then 300 mg on 3rd day (total of 25mg/kg over three days) combined with Fansidar ® 3 tablets single dose.
This is usually adequate treatment but if single treatment with amodiaquine is used and fever or symptoms come back after this add doxycycline 200 mg daily by mouth for 7-10 days

Dosages in P. vivax, P. ovale and P. malariae
First choice when chloroquine resistance is rare or at a low level of resistance. Start with:
Full chloroquine course 10mg base/kg PO stat; then 5mg/kg at 12, 24 and 36 hrs in semi-immunes.
Follow up in P. vivax and P. ovale with primaquine 0.25 - 0.5 mg/kg once daily with food for 14 days (in adults usual dose is 15-30 mg daily).

Dosages in Severe malaria

First choice when available
Artemether (artemisinine derivative) 160 mg (children 1.6 mg/kg) i.m. twice a day for 3-7 days (an i.v. preparation of artenam is available in Sweden but rare in Africa) or if the person is not vomiting an alternative is oral **Artemether + lumefantrine as above or** artesunate 4 mg/kg daily for 3 days then doxycycline 200 mg orally daily for 7 days. Artenam by suppository is an excellent alternative but not yet widely available.
Second choice (more likely to be available)
Quinine dihydrochloride 20 mg salt/kg of body weight (loading dose) by infusion in 5% dextrose saline (5-10 ml/kg related to hydration level) over 4 hours or by i.m. injection. Eight to twelve hours later give a maintenance dose of quinine 10 mg salt/kg in dextrose saline over 4 hours. Repeat this dose every 8-12 hours until oral therapy is possible. If available then go over to **Artemether + lumefantrine as above.** Otherwise Oral therapy: quinine 10mg salt/kg orally thrice daily for 3 days then doxycycline 200 mg daily PO for 7 days,

Alternative: mefloquine 15mg base/kg orally as first dose followed by one further dose of 10mg/kg 8 hrs later but more side-effects than above.

P. vivax follow-up treatment

The *P. vivax* parasite has an uncanny ability to remain dormant in the liver of its host in a form known as the hypnozoite. This liver-stage form can reactivate any time between 3 weeks and several years - leaving its victims vulnerable to relapse into the feverish symptoms of malaria at any time and without warning.
These repeated attacks are rarely fatal; nonetheless, *P. vivax* poses a considerable public health problem - accounting for between 80 to 300 million clinical cases every year. Although *P. vivax* transmission has been reported to occur in Africa, it is widely endemic in South and Southeast Asia, and Central and South America where, in 2009, 2.85 billion people were at risk.
The only approved medicine able to eliminate hypnozoites and thus provide a radical cure for *P. vivax* is **primaquine** . Primaquine, however, has two significant weak points: First, it must be taken daily for 14 days to be effective. Compliance to such a regimen is often unachievable in reality, as patients do not suffer with symptoms for most of this time. Second, in patients who are deficient in the enzyme glucose 6-phospate 1-dehydrogenase (G6PD), primaquine can cause the blood cells to breakdown leading to anaemia. This means that patients already anaemic due to the malaria infection will suffer further - potentially with fatal consequences. Unfortunately, G6PD-deficiency is not a rare occurrence; it can be present in more than 25% of the population in some disease-endemic countries.
A next-generation 8-aminoquinoline, **tafenoquine**, is our lead contender and is currently in clinical development. Studies show tafenoquine could be taken as a 1-day treatment course for liver-stage malaria - a significant improvement on primaquine's 14-day course. However its safety and long-term efficacy is still being tested.

Conclusion
There is undoubtedly an important improvement in malaria research, prevention including indoor residual spraying and impregnated bed-nets, better diagnosis including both microscopy and the rapid tests as well as Dual treatment with Coartem all resulting from the Roll-Back-Malaria interventions and the financing from the Global Fund and many others. In 2010 181 million had access to ACT. 11 African countries had more than 100% of those in need of ACT with access to this treatment. 8 Others had enough to treat 50-100% of cases).
145 million impregnated bed nets were made available (289 million over the last few years) and 88 million sets of rapid diagnostic kits were distributed (35% of all malaria cases had the benefit of rapid diagnosis 2009).

Much discussion has taken place about whether eradication is possible and there is still no consensus about the right strategy in the most affected countries. Some feel that in this setting more lives will be saved if the focus is on **containment** rather than on **eradication**. It seems likely that until a highly effective and affordable vaccine is widely available, the idea of eradication of malaria in these areas is still a dream.

In the field there are some precautions where Roll-Back-Malaria programmes have not yet been introduced and only microscopy is available for diagnosis.

Make sure that the diagnosis is certain. In some laboratories in Africa many blood slides are falsely reported* as positive (especially if it is known by the laboratory assistant that the slide came from an expatriate). In some laboratories even if the slide is found negative, this is inevitably reported as “scanty malaria parasites seen” just so that the lab assistant is covered in case he missed a rare parasite. This can lead to many unnecessary treatments with all their side-effects

* In one study in Tanzania blood slides were first assessed in the local hospital laboratory and then the same slide was taken to a malaria reference laboratory in Sweden and assessed by a very experienced expert. The results were very interesting. When the slide was reported as:
+ for malaria parasites there were 50% false positives.
++ for malaria parasites there were 10% false positives
+++ for malaria parasites there were 3% false positives
Only when the report stated ++++ for malaria parasites were all the slides truly malaria.
Overall there were 3% false negatives.

Of course such mistakes are understandable when the microscope is old, the stain reagents are old, the light source is poor and the laboratory assistant is poorly motivated (his salary may not have been paid for 6 months) or inadequately trained.

Breaking News 2013

Malaria successes

Since 2000 3.3 million lives have been saved through the Roll-Back-Malaria campaign supported by the Global Fund.

Macha Philip Thuma: A whole district in Southern Zambia, Macha District, has shown that a combination of **widespread good diagnostics** for malaria with **ACT** for those shown to have malaria plus widespread use of **Impregnated Bed Nets** and **mass screening programmes** to find **parasite carriers** without symptoms and treating these has reduced the number of clinical cases of malaria coming to the district hospital by 98% over the last 10 years. This **level has been sustained over the last 3 years.** This gives hope for similar results if the same improvements are introduced and maintained in other areas.
New research areas are opening up:
1. A sugar has been identified, chondroitin sulphate, which is essential to the parasite attaching to the cells of the midgut in the mosquito. If this sugar can be eliminated or reduced the parasite cycle can be interrupted.
2. It is possible to genetically modify a bacterium commonly found in the mosquito's midgut. The bacterium, *Pantoea agglomerans*, was modified to secrete proteins toxic to the malaria parasite, but the toxins do not harm the mosquito or humans. This also interrupted the parasite cycle.
3. An APN1, a mosquito antigen appears to play a major role in parasite establishment within the mosquito. Preliminary field research has shown that antibodies induced by this antigen are capable of blocking transmission of the two deadliest malaria parasites, *Plasmodium falciparum* and *P. vivax*. When a mosquito takes blood from a vaccinated person, these antibodies prevent the parasite from attaching to and invading the mosquito's gut.

Malaria eradication: is it possible? Is it worth it? Should we do it?

July 2013 – The malaria map is rapidly shrinking. In 1900, endemic malaria was present in almost every country. Nowadays, the disease has been eliminated in 111 countries and 34 countries are advancing towards elimination. Elimination is defined as the absence of transmission in a defined geography—typically a country. Successful malaria control programmes in the remaining 64 countries with ongoing transmission have helped to reduce global incidence by 17% and mortality by 26% since 2000. For the 34 eliminating countries, the reductions were 85% in incidence and 87%

in mortality. This progress is encouraging, but is worldwide eradication of human malaria possible? If so, is it a worthwhile goal and should we commit to it?

Hope for wiping out malaria vested in vaccines

April 25, 2013 – The last 10 years have seen significant gains in the fight against malaria. Around the world, cases of the disease have dropped—so too the number of deaths. But malaria still kills an estimated 660,000 people every year, most of them African children. The gains are fragile and could easily be reversed. On World Malaria Day, international Geneva correspondent, Vincent Landon, takes a look at where we are in the war on malaria and why new hope is vested in vaccines.

Malaria outbreak in Chad 6th Sept.

Chad's malaria surge has been blamed on a lack of protective bed nets and unusual rain patterns. A tenfold spike in malaria infections in south-east Chad, with many of the severest cases in young children, has triggered an emergency operation by Médecins Sans Frontières (MSF).

The number of reported new cases rose from 1,228 in the first week of August to 14,021 by the end of the month at the charity's project in Am Timan, Salamat region. The estimated death toll is more than 50; the town has a population of 213,000.

At its outreach sites, the charity's teams said 73% of patients they have been treating were suffering from the mosquito-borne disease.

One in four deaths in Chad is attributed to malaria and it is the most common cause of death in children. MSF said it was not unusual for cases to peak during the rainy season, from July to November, but the increase was alarming.

Jason Mills, the charity's head of mission in the country, said the most likely explanation was a lack of protective bed nets combined with unusual rain patterns. Heavy rain left pools of stagnant water, which was exacerbated by further rain and a large number of mosquitoes, he added.

The rest of the country has also been inundated, particularly the south. The government plans to treat 800,000 cases this year, an increase of 25% on 2012, and has so far treated 450,000, disrupting medical supplies. Rain patterns were probably the cause, Mills said.

MSF said it sent an emergency team to support local health centres with malaria diagnostic tests and treatment supplies, as well as training health ministry staff and improving epidemiological surveillance.

It erected a malaria treatment tent within the Am Timan hospital compound where uncomplicated cases could receive attention. More than 1,400 patients have been treated in the tent over two weeks.

MSF plans to distribute mosquito nets to households in affected areas and launch a public-education campaign. Mills added: "The goal of our emergency response is to improve the early diagnosis and treatment of non-severe malaria and to improve the management of severe and complicated forms of the disease. Many people who live outside the town of Am Timan have limited access to healthcare. The majority of those who are dying of malaria right now are dying in their homes."

MSF said it would continue its emergency response to the malaria outbreak in Am Timan and surrounding areas until late November.

Cristina Mach, the MSF medical co-ordinator in Chad, said: "While malaria is endemic here, the rate of infections this year is beyond all forecasts. Existing diagnosis and treatment supplies in the country are severely strained."

The organisation quoted one resident, Halima Ibrahim, as saying: "Several weeks ago, my eight-

year old daughter Salimata Ali started to shiver and complained of a headache. We took her to a local healer who gave her tablets, but she continued to shiver and couldn't speak properly.
"The next day the head of my village came to our compound with doctors from MSF. They tested her and then gave her medication. Three days later she was a lot better."
Latest available statistics from the World Health Organisation show more than 650,000 people around the world died from malaria in 2010, mainly children in Africa.

Interview with Sir Richard Feacham Global Health Group UCSF

Exciting progress has been made in the global fight against malaria. The malaria map continues to shrink each year; in the last ten years four countries have been certified malaria-free, and thirty-four additional countries are now working towards malaria elimination targets.

The global malaria eradication strategy, as outlined in 2008 by the Roll Back Malaria Global Malaria Action Plan, calls for a three part strategy:

1. Aggressive malaria control in the areas that are hardest hit with malaria, using the best tools available, such as **indoor residual spraying,** long-lasting **insecticide treated nets**, and prompt **diagnosis** and **treatment** of malaria with artemisinin-based combination therapies (ACT).
2. Progressive elimination of malaria in countries where possible, to shrink the malaria map.
3. Research and development to bring forward new tools, such as new drugs, diagnostics, and a vaccine.

All three parts of this strategy must continue to be pursued simultaneously. All are important, and all contribute to the overarching goal of a world free from malaria.

How successful have these malaria control strategies been?

The World Health Organization estimates that due to aggressive malaria control using the best interventions available, over one million lives have been saved since 2000, and in the last 5 years alone, deaths from malaria in Africa have decreased by 33%.
These dramatic reductions in malaria burden around the world, including in sub-Saharan Africa, illustrate the success of global commitments to malaria control in recent years.

Your recent research suggested that malaria control strategies must evolve to keep up with the changing patterns of malaria infection. Please can you explain how malaria infection patterns are changing?

Malaria transmission is a fast moving and changing target, and we must be prepared to shift our strategy and adapt interventions to continue shrinking the malaria map.
In eliminating countries, malaria is becoming clustered into small geographical areas (we call these hotspots) or clustered demographically into subpopulations with shared social and behavioral risk factors for malaria (we call these hot-pops).
We also know that malaria is increasingly imported into low transmission settings from high endemic areas, and that a higher proportion of cases are caused by Plasmodium vivax in settings outside of sub-Saharan Africa.
The challenge is to track these changes in epidemiology and to target and adapt interventions more effectively.

How do you think malaria control strategies should be altered to keep up with the changing malaria infection patterns?

There is a need to re-strategize around how to best detect and target cases and infections, in low transmission settings, and particularly within hotspots and hot-pops.

Building robust surveillance and response systems can help national malaria control programs do this, allowing them to monitor and respond to the epidemiologic situation on the ground.
Additionally, it is critical that we develop novel tools that can address these changing trends. For example, occupation-based infection control methods that protect people that are often outside their home – such as insecticide-treated clothing or hammocks – are being developed to help protect migrants or labourers working in high-risk settings.
It is also likely that we will see much greater use of targeted mass drug administration to clear the residual parasite pool in asymptomatic individuals, especially in elimination settings.
Why when malaria is reduced to low levels does it become increasingly concentrated in particular places or communities?
As malaria decreases, cases become clustered into geographical hotspots where groups of people, or individual households, have higher malaria transmission compared to others.
The same can happen within the larger population. For example, groups with specific occupations (hot-pops), such as rubber tappers or soldiers living and working in the forest, are at higher risk for malaria.
These hotspots and hot-pops are more at risk for a variety of reasons, including marginalization for geographic, economic and political reasons, or due to poverty, lack of access to health care and/or high mobility.
They may lack of access to malaria control interventions, live or work close to mosquito breeding sites, or have poor housing, putting them at greater risk for malaria than others.
Why do some groups of people avoid accessing health systems for malaria treatment? What can be done to help provide malaria treatments to these hard-to-reach populations?
At-risk populations are vulnerable in many ways, and might avoid accessing the health system for several reasons, including the high cost of treatment, fear of unwanted attention from government authorities that may be alerted by health workers, geographic lack of access, or low knowledge or perceived risk of malaria.
While ensuring universal access to a robust health system is ideal, national malaria control programs can also develop targeted systems to detect and treat cases in these populations.
Do you think vaccines will be important in the eradication of malaria?
We know that disease eradication is incredibly challenging, with or without a vaccine. **Would an effective malaria vaccine help us reach eventual eradication?** Without a doubt, yes. However, advances in malaria drugs will also play a critical role in elimination and eventual eradication.
It is essential that we use today's tools effectively while investing in the research and development needed to build new tools to support malaria control and elimination in the future.
How can you predict malaria infection patterns going forward?
We will continue to see large numbers of malaria cases in children under five and pregnant women in the malaria heartland, particularly in sub-Saharan Africa.
However, as countries reduce their malaria burden, we anticipate that they will follow similar epidemiologic trends to those described above: malaria will become increasingly male, adult, imported and, outside sub-Saharan Africa, caused by P.vivax.
As readers will know, P.vivax is harder to detect and treat than P. falciparum and typically proves to be the more stubborn parasite in elimination settings.
Are you concerned about the allocation of funding for malaria control?
Absolutely. We have seen a flat-lining of malaria funding in recent years. The World Health Organization estimates that there is an annual shortfall of around USD $3 billion for malaria control. Filling this gap is critical.
Malaria-eliminating countries are particularly susceptible to funding changes. When countries

reach a low malaria burden, their governments may reallocate funding and resources to other pressing priorities.
A recent review of historical malaria resurgences noted that, of the 75 resurgence events documented since 1930, almost all were attributed at least in part to the weakening of malaria control programs. When cases are low, it is exactly the time when funding must be maintained to make the final push to elimination.
For all these reasons the full replenishment of the Global Fund in 2013 is critical. Without this, our goals for malaria control, elimination and eventual eradication will be put in jeopardy.

Ivermectin to reduce malaria transmission: a research agenda for a promising new tool for elimination

A recent study published in the *Malaria Journal* highlights the potential use of ivermectin as a new antimalarial drug. With the looming threat of global insecticide and drug resistance, the development of news tools, and the adaptation of current ones, is critical to malaria elimination efforts. Ivermectin has worked safely and effectively in onchocerciasis and lymphatic filariasis control programs globally and can be an alternative to current antimalarial drugs.

World Malaria report 2014

The World malaria report 2014 summarizes information received from 97 malaria-endemic countries and other sources, and updates the analyses presented in 2013. It assesses global and regional malaria trends, highlights progress made towards global targets, and describes opportunities and challenges presented in this report are for 2013.
The public health challenge posed by malaria
Malaria transmission occurs in all six WHO regions. Globally, an estimated **3.2 billion people are at risk of being infected with malaria and developing disease,** and **1.2 billion are at high risk** (>1 in 1000 chance of getting malaria in a year). According to the latest estimates, **198 million cases of malaria occurred globally in 2013** (uncertainty range 124–283 million) and the disease led to 584 000 deaths (uncertainty range 367 000–755 000).
The burden is heaviest in the WHO African Region, where an estimated 90% of all malaria deaths occur, and in children aged under 5 years, who account for 78% of all deaths.
Expansion of malaria funding International and domestic funding for malaria control and elimination totalled US$ 2.7 billion in 2013. Although this represented a threefold increase since 2005, it is still significantly below the estimated US$ 5.1 billion that is required to achieve global targets for malaria control and elimination. Total malaria funding will only match resource needs if international and domestic funders prioritize further investments for malaria control. Overall, funding for countries in the WHO African Region accounted for 72% of the global total. Between 2005 and 2013, international disbursements for malaria for this region increased at an annual rate of 22%. During the same period, the average annual rate of increase for domestic funding in the region was 4%.
Globally, domestic funding for malaria was estimated to be US$ 527 million in 2013. This represents 18% of the total malaria funding in 2013. In regions outside Africa, the annual rate of domestic funding has not increased in recent years.
Progress in vector control During the past 10 years, coverage with vector control interventions increased substantially in sub-Saharan Africa. In 2013, almost half of the population at risk (49%, range 44–54%) had access to an insecticide-treated mosquito net (ITN) in their household, compared to 3% in 2004. An estimated 44% (range 39–48%) of the population at risk were sleeping

under an ITN in 2013, compared to 2% in 2004. Pregnant women and children were more likely than the general population to sleep under an
ITN. In terms of long-lasting insecticidal net (LLIN) delivery, 2014 has been the strongest year so far. A total of 214 million nets are projected to be delivered to countries in sub-Saharan Africa by the end of 2014, bringing the total number of LLINs delivered to
that region since 2012 to 427 million.
Globally, 123 million people were protected from malaria through the use of **indoor residual spraying.** This represents 3.5% of the global population at risk. In the WHO African Region, 55 million people, or 7% of the population at risk, were protected. This has decreased from 11% in 2010; the decline is due to a withdrawal or downsizing of spraying programmes in some countries. In sub-Saharan Africa, the proportion of the population protected by at least one vector control method has increased in recent years, and it reached 48% in 2013 (range 44–51%).
Globally, 38 countries reported the use of larval control to complement core vector control methods. **Insecticide resistance in malaria vectors** has been reported in 49 of 63 reporting countries around the world since 2010. Of these, 39 have reported resistance to two or more insecticide classes. The most commonly reported resistance is to pyrethroids, the most frequently used insecticide in malaria vector control. WHO has established a system to track insecticide resistance monitoring. In 2013, some 82 countries report undertaking insecticide resistance monitoring. However, only 42 of these countries provided WHO with resistance data for 2013, suggesting that many countries do not monitor insecticide resistance annually.
Trends in the administration of preventive therapies The proportion of women who receive **intermittent preventive treatment in pregnancy** (IPTp) for malaria has been increasing over time, although the levels remain below programme targets. IPTp has been adopted in 37 countries and 57% of pregnant women in those countries received at least one dose of IPTp in 2013. However, only nine of those countries have reported to WHO on the recommended number of three or more doses of IPTp, and within those countries, only 17% of pregnant women received three or more doses. In most countries, attendance rates at antenatal care services are much higher than current levels of IPTp administration. This
suggests that there are missed opportunities to expand access to this life-saving intervention.
The adoption and implementation of **preventive therapies for children aged under 5 years** and for infants has been slower than expected. As of 2013, six of the 16 countries recommended by WHO to adopt seasonal malaria chemoprevention for children aged under 5 years have done so. Only one country has adopted intermittent preventive treatment for infants, but has not yet implemented the treatment.
Scaling up diagnostic testing The proportion of patients suspected of having malaria who receive a malaria diagnostic test has increased substantially since 2010, when WHO recommended testing of all suspected malaria cases. **In 2013, 62% of patients with suspected malaria** in public health facilities in the WHO African Region received a diagnostic test, compared to 40% in 2010**.**
The total number of **rapid diagnostic tests** (RDTs) distributed by national malaria control programmes increased from fewer than 200 000 in 2005 to more than **160 million in 2013.** Of these, 83% were delivered to countries in the WHO African Region. The quality of RDTs has improved substantially since the start of the RDT product testing programme in 2008. In the latest round of product testing, nearly all tested products met WHO standard of detection at parasite levels commonly seen in endemic areas.
In 2013, the number of patients **tested by microscopic examination** remained unchanged from the previous year, at **197 million**. The global total of microscopic examinations is dominated by India, which accounted for over 120 million slide examinations in 2013.

In 2013, for the first time, the total number of diagnostic tests provided in the WHO African Region in the public health sector exceeded the number of artemisinin-based combination therapies (ACTs) distributed. This is an encouraging sign and, given that fewer than half of patients tested will require treatment, **the ratio of diagnostic tests to ACTs should eventually reach two to one.** Expanding access to treatment. However, the estimated proportion of all children with malaria who received ACTs was estimated at between 9–26% This is because a substantial proportion of these patients do not seek care, and not all those who seek care receive antimalarial treatment.
Antimalarial drug resistance P. falciparum resistance to artemisinin has been detected in five countries of the Greater Mekong subregion: **Cambodia, the Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam.** In many areas along the Cambodia–Thailand border, P. falciparum has become resistant to most available antimalarial medicines.
The number of countries that allow marketing of oral artemisinin-based monotherapies has declined rapidly. As of **November 2014**, only **eight countries allow the marketing of oral monotherapies.** However, 24 pharmaceutical companies, mostly in India, continue to market oral monotherapies.
Therapeutic efficacy studies remain the gold standard for guiding drug policy, and should be undertaken every 2 years. Studies of first- or second-line antimalarial treatments were completed in 72% of countries where P. falciparum efficacy studies were feasible.
Gaps in intervention coverage Despite impressive increases in malaria intervention coverage, it is estimated that, in 2013, 278 million of the 840 million people at risk of malaria in sub-Saharan Africa lived in households without even a single ITN, 15 million of the 35 million pregnant women did not receive even a single dose of IPTp, and between 56 and 69 million children with malaria did not receive an ACT. Poverty and low levels of education are significant determinants of lack of access to these essential services. More can be done to ensure all those at risk receive appropriate preventive measures, diagnostic testing and treatment.
Changes in malaria incidence and mortality
Reported malaria cases Of the 106 countries that had ongoing malaria transmission in 2000, reported data in 66 were found to be sufficiently complete and consistent to reliably assess trends between 2000 and 2013.
Based on an assessment of trends in reported malaria cases, a **total of 64 countries** are on track to meet the Millennium Development Goal target of reversing the incidence of malaria. Of these, 55 are on track to meet Roll Back Malaria and World Health Assembly targets of **reducing malaria case incidence rates by 75% by 2015**.
In 2013, two countries reported zero indigenous cases for the first time (Azerbaijan and Sri Lanka), and eleven countries succeeded in maintaining zero cases (Argentina, Armenia, Egypt, Georgia, Iraq, Kyrgyzstan, Morocco, Oman, Paraguay, Turkmenistan and Uzbekistan). Another four countries reported fewer than 10 local cases annually (Algeria, Cabo Verde, Costa Rica and El Salvador).
The 55 countries that recorded decreases of >75% in case incidence accounted for only 13 million (6%) of the total estimated cases of 227 million in 2000. Only five countries with more than 1 million estimated cases in 2000 (Afghanistan, Bangladesh, Brazil, Cambodia, and Papua New Guinea) are projected to achieve a reduction of 75% or more in malaria case incidence. This is partly because progress has been faster in countries with lower numbers of cases, but also because of poorer quality surveillance data being submitted by countries with larger estimated numbers of cases, particularly in sub-Saharan Africa.
Malaria infections

A new analysis of data reveals that the prevalence of malaria parasite infection, including both symptomatic and asymptomatic infections, has decreased significantly across sub-Saharan Africa since 2000. In sub-Saharan Africa, average infection prevalence in children aged 2–10 years fell from 26% in 2000 to 14% in 2013 – a relative decline of 48%.
Although declines in malaria parasite infection were seen across the African continent, they were particularly pronounced in Central Africa. Even with a large growth of populations in stable transmission areas, the number of infections at any one time across Africa fell from 173 million in 2000 to 128 million in 2013 – a reduction of 26% in the number of people infected.
Estimated malaria cases and deaths Between 2000 and 2013, estimated malaria mortality rates decreased by 47% worldwide and by 54% in the WHO African Region. They are estimated to have decreased by 53% in children aged under 5 years globally, and by 58% in the WHO African Region. If the annual rate of decrease that has occurred over the past 13 years is maintained, then by 2015 malaria mortality rates are projected to decrease by 55% globally, and by 62% in the WHO African Region. In children aged under 5 years, by 2015 they are projected to decrease by 61% globally and by 67% in the WHO African Region.
Estimated malaria cases and deaths averted
It is estimated that, globally, 670 million fewer cases and 4.3 million fewer malaria deaths occurred between 2001 and 2013 than would have occurred had incidence and mortality rates remained unchanged since 2000. Of the estimated 4.3 million deaths averted between 2001 and 2013, 3.9 million (92%) were in children aged under 5 years in sub-Saharan Africa. These 3.9 million averted deaths accounted for 20% of the 20 million fewer under 5 deaths that would have occurred between 2001 and 2013 had under-5 mortality rates for 2000 applied for each year between 2001 and 2013. Thus, reductions in malaria deaths have contributed substantially to progress towards achieving the target for MDG 4, which is to reduce, by two thirds, the under-5 mortality rate between 1990 and 2015.

Since the year 2000
Average malaria infection prevalence declined 48% in children aged 2–10, from 26% to 14% in 2013. The number of malaria infections at any one time dropped 26%, from 173 million to 128 million in 2013.
Malaria mortality rates have decreased by 47% worldwide and by 54% in the WHO Africa Region.
In 2013 Only US$ 2.7 billion of the US$ 5.1 billion required to achieve global malaria control and elimination targets were available through international and domestic funds.
49% of the at-risk population in sub-Saharan Africa had access to an ITN in their household.
44% of the population at risk in sub-Saharan Africa were sleeping under an ITN, indicating that 90% of people used the nets available to them.
278 million of the 840 million people at risk of malaria in sub-Saharan Africa lived in households without even a single ITN.
15 million of the 35 million pregnant women did not receive a single dose of IPTp.
62% of patients with suspected malaria cases in the WHO African Region received a diagnostic test in public health facilities.
57% of pregnant women received at least one dose of IPTp, and 17% received three or more doses in the nine reporting countries.
197 million patients worldwide were tested for malaria by microscopic examination.
70% of malaria patients could be treated with ACTs distributed to public facilities in Africa; however, because not all children with fever are brought for care, less than 26% of all children with malaria received an ACT.

584 000 malaria deaths (range 367 000–755 000) occurred worldwide; 78% of malaria deaths occurred in children aged under 5 years.
By 2015 If the annual rate of decrease over the past 13 years is maintained, malaria mortality rates are projected to decrease by 55% globally and by 62% in the WHO Africa Region.
56–69 million children with malaria did not receive an ACT.
528 000 malaria deaths (range 315 000–689 000), 90% of the global total, occurred in the WHO African Region.
Malaria mortality rates in children aged under 5 years are projected to decrease by 61% globally and 67% in the WHO Africa Region.

Blackwater fever: from Beryl Markham, West with the night

A man can be riddled with malaria for years on end with its chills and fevers and its nightmares but if one day he sees that the water from his kidneys is black, he knows he will not leave that place again wherever he is, or wherever he hoped to be. He knows that there will be days ahead, long tedious days which have no real beginning or ending but which run together into night and out of it without changing colour or sound or meaning. He will lie in his bed feeling the minutes and the hours pass through his body like an endless ribbon of pain because time becomes pain then. Light and darkness become pain; all his senses exist only to receive it, to transmit to his mind again and again with ceaseless repetition the simple fact that now he is dying.

Call for "'adical action' on drug-resistant malaria" 30 July 2014
Drug-resistant malaria is spreading in South East Asia, and has now reached the Cambodia-Thailand border, according to a study.
"Radical action" is needed to prevent further spread of malaria parasites resistant to key drugs, say scientists.
The spread could undermine recent gains in malaria control, they report in **the New England Journal of Medicine**.
No evidence was found of resistance in three African sites - Kenya, Nigeria and the Democratic Republic of Congo.
The study analysed blood samples from more than 1,000 malaria patients in 10 countries across Asia and Africa.
It found the malaria parasite had developed resistance to front-line drugs known as artemisinins, in western and northern Cambodia, Thailand, Vietnam, and eastern Burma, also known as Myanmar.
There were signs of emerging resistance in central Burma, southern Laos and north-eastern Cambodia.
Of particular concern was the corner of Asia on the Cambodia-Thailand border, where resistance to other anti-malarial drugs has emerged in the past.
"Resistance is now present over much of South East Asia," said lead scientist Prof Nicholas White, of the University of Oxford.
"It's worse than we expected.
"We have to act quickly if we are going to do anything."
Prof White said it might be possible to prevent further spread, but conventional malaria-control approaches would not be enough.

"We will need to take more radical action and make this a global public health priority, without delay," he added.
Meanwhile, a separate study, also published in the New England Journal of Medicine, reported early results of an anti-malarial drug in the pipeline.
Commenting on the research, Dr Brian Greenwood, from the London School of Hygiene and Tropical Medicine, said: "The emergence of artemisinin-resistant parasites is a major threat to further advances in malaria control.
"Every effort needs to be made to contain their spread while at the same time pushing forward with the development of effective alternative treatments that are almost certainly going to be needed in the future."