

## **Malaria: 2007**

### **Malaria, Mozzies and a Mzungu. Part 1**

Christmas is coming, the bazungu are getting fat, and all the new arrivals will be off to the game parks with visitors from Europe and America escaping the cold and rain. Or snow. And all asking the same question: what about malaria?

The next few articles will be the latest information we have on malaria in Uganda, what is malaria, how do you get it and why is there so much confusion over what is essentially an easy disease to prevent, diagnose and treat.

Even the question "what is malaria" is actually complicated and difficult to answer! If malaria means someone who is infected with malaria parasites, then in seriously endemic areas that means an awful lot of perfectly healthy people. The latest research has shown that in some areas of Uganda, and apparently Pakwach is the worst found so far, the average child is bitten by an infected mosquito 1,500 times a year. That is 4 or 5 bites a night. So why is the average school child up country perfectly well most of the time? (Other than being noisy, snotty, running around playing football and getting into trouble like any child from Bristol, Berlin or Boston?) He either has "malaria" all the time, or he is always on treatment, or dead in 2 weeks or something else is happening.

So what is malaria? How can a child up country be infected with malaria every day yet is perfectly well most of the time, and why is a Mzungu bitten once in the airport on the way home in intensive care for a week? We have to start from the beginning. With a mosquito

### **Mosquitoes**

Most mosquitoes do not have malaria so they can bite you all night for a month and cause nothing but a few itchy bumps. In our houses most mosquitoes are Aedes or Culex. Unless, it seems, you live in Pakwach. I spent a month trying to catch malaria mosquitoes for a school project and never found a single one. There is no malaria on Makindye!

As everyone knows only the anophylene female can carry malaria. The males are vegetarian, a very healthy option so they do not get heart attacks, mad cow disease or spread any disease at all. Anophylenes are picky little beasts; they don't like houses, much, nor swamps, deep water, running water or dirty water. They leave that to the culex. They prefer shallow temporary puddles such as car tracks and footprints. How they survive I do not know, but maybe that is why there are no anophylenes on Makindye, it is too steep. What is more, some prefer goats to people; do not like coming indoors, and only bite between dusk and dawn. SO most mosquitoes you catch in your bedroom in Kampala are not anophylene. Have a good look at them. Most will be Aedes, delicate rather pretty little mosquitoes with black and white markings. They go for your feet, and at least for me itch like crazy: other species I don't even feel. The Culex are big brown hairy ones with the worst bites. And the nosiest. Anophylenes are rather nondescript, medium size with salt and pepper wings. They land on the wall, or you, with their bums up in the air like all the pictures on the malaria drug packets. The others bend in the middle and land flat to the wall, so easily identified as not anophylene. They all make a big red splodge when squashed so you cannot tell what they are that way. So in many parts of Kampala malaria is hardly ever seen as there are no Anophylenes about to give it to you.

### **The Parasite**

But let us assume you do not live on Makindye and are bitten by a female anophylene. What will happen? Probably nothing. Even most anophylenes do not carry malaria. Or it may inject about 15 to 20 sporozoites into your blood. These are invisible, and are carried around your blood until

they get to the liver. There they are actively taken up into liver cells. Each one quickly divides until they are about 40,000 little parasites called merozoites. What happens next depends on which species of malaria the mosquito had. I will consider only falciparum, the most common and the only one that can kill. After 5 days most of the infected liver cell burst, releasing around 600,000 merozoites into your blood. A few may wait a day or two and in rare cases up to another 2 weeks. However most of them come out in the first wave after 5 days. Some of them fail to find a suitable red cell, but the ones that do change their names to trophozoites, and spend the next 2 days growing. They still are causing no harm to us at all. After almost exactly 2 days they become sticky and "sequester" i.e. they stick in the narrow capillaries in the deeper warmer organs such as brain, kidneys, liver, lungs. They spend just a few hours stuck, and each divides into 32 new babies, then the red cell bursts and releases the next generation of merozoites into the blood. About 10 to 15 will find a suitable red cell and become trophozoites and start over.

When the cell bursts a lot of toxins from the excreta of the trophozoites and digested hemoglobin is released into the blood, and this is what causes the fever, headache and other symptoms of malaria. If you are an adult and have 1 bite then a bit of maths shows that to begin with, on days 5 to 7 you will have about 1 parasite in 30 million red cells, too few to cause any trouble at all. Every 2 days they sequester, burst and release toxins and start over with 10 times as many as before. That is why malaria symptoms come in waves every 2 days getting worse each time. On day 9 there may be enough toxins to cause a bit of a fever for a few hours. On day 11 the toxins will be enough to make you pretty ill, with fever, vomiting, headache lasting half the day. A lucky microscopist will find one parasite in 15 fields on a thick film but most would still miss them. The malaria rapid test would just be tripped, and will be a faint positive. Day 13 and with 10 times as many again, you are very ill, probably too sick to walk much further than the bathroom, and with 1 parasite in 3,000 cells that is almost 1 parasite per field on a slide and the Malaria rapid will be a strong positive. You may feel as sick as the sickest parrot that was ever sick, but this is still classified as a mild attack of malaria! It would take another 4 days of no treatment before the real trouble starts. The sticky red cells are now enough for there to be an odds on chance of the cells sticking together and blocking the capillaries when they sequester, so every deep organ goes into sudden failure due to blocked capillaries. This is "multi-organ failure", affecting the kidneys, lungs, brain, and often called "cerebral malaria". It is not a separate disease it is simply ordinary malaria that has not been treated, with the number of parasites increasing by 10 times every 2 days eventually the number of parasites reaches the critical mass of around 5%.

### **What happens when we take treatment?**

Remember the symptoms are due to the toxins released by the ruptured red cells. With a really fast acting drug like artemether, the parasites are almost all dead in about 4 hours. The red cell then gets eaten in the spleen and releases the toxins. So about 4 hours after treatment there is a new wave of symptoms and you will feel a lot worse. And there are now 10 times more parasites than in the last wave, so after treatment you will be feel far worse than you did before. People who say they have had malaria many times and take their favourite remedy and are better the next day have not had malaria. The next day you are not better you are worse. A lot worse. We will consider treatment in the next Eye.

### **Malaria, mozzies and a Mzungu. Part 2**

In the last Eye article we saw what happens when a non-immune is bitten by a female anophyline with malaria. A quick summary for new readers: The parasites first multiply in the liver for 5 days without any symptoms at all. Then they come out of the liver into the blood, the parasite is now called a "trophozoite" and each one grows in a red cell for 2 days. Then the red cells stick in the deep organs for a few hours, the parasites divide into 32 and release the new "merozoites" into the blood. About 10 of these will find a new red cell and again grow for 2 days. The parasites themselves don't cause much harm in these early stages, it is the toxins released from the ruptured red cells that cause the fever, headache and vomiting in a 2 day cycle, which

gets 10 times worse every 2 days. When the number of parasites reaches about 5 in every hundred red cells, the red cells sticking in the deep organs cause multiorgan failure and death. We asked the question why is a child in Pakwach who is bitten 5 times a night by infected mosquitoes, so is infected with malaria all the time, perfectly well? But a Mzungu, bitten only once, is desperately ill in a week and without treatment dead in a fortnight? Read on!!

What has been described is what happens in a complete non-immune adult bitten by one infected mosquito. 2 or more mosquitoes and the whole picture is brought forward 2 or 4 days, with you getting pretty sick in 9 days, and multi-organ failure and death if not treated by day 14. A new born baby, bitten by 5 mosquitoes and with 1 tenth the volume of blood could go from perfectly well on day 7 to dead in just 2 or 3 days without treatment. Or perhaps not. Life is not easy for a malaria parasite in Africa. At every stage danger lurks. The immune system. Without it, most of Africa would be uninhabitable.

### **Immunity**

Once you have had malaria, and have been treated, the immune system produces antibodies to the different stages of the parasite. Organs such as the spleen develop special cells that eat and destroy the cells with parasites in them, and enzyme pathways develop that clear away the toxins. The immunity is only partial and gets slowly more efficient each time it is stimulated by a new infection. So the Pakwach schoolboy is perfectly well most of the time. When he gets malaria the toxins don't make him so ill, he has a large spleen that eats the parasitized red cells before they sequester and release new parasites, and antibodies that kill the merozoites in the blood and possibly the sporozoites too. For him malaria is now a self-limiting disease, that most of the time he doesn't even notice.

However he is the source of the epidemic! Because we have left out one part of the cycle. The Mzungu, with no immunity either gets treated or dies. He cannot infect a mosquito, because the trophozoites in his blood are not infectious to the mosquito. However when the parasites realize that the immune system is giving them a hard time, they stop developing more trophozoites, but instead develop into male and female gametocytes, these are infectious to the mosquito.

### **Mating in the Mozzzy**

The male and female actually "hatch" in the mosquito's stomach, mate and produce the sporozoites. Trophozoites in the stomach of a mosquito simply get digested. So mosquitoes can only carry malaria if they are biting semi-immune people who have had malaria for a few days and are getting better without treatment. No immunes, no gametocyte carriers, means no transmission of malaria.

You can only become immune by getting malaria many times. Babies born to immune mothers and breast-fed have some immunity, and develop their own each time they get infected. So in most rural areas by the time they are 5 they are either immune, or dead. They are now carriers, infectious to mosquitoes and keeping the epidemic going. They may get sick every now and again when the number of parasites overwhelm the immune system, but will recover quickly with treatment. But not the Mzungu or a Ugandan who has lived all his life in Kampala. He may not have had malaria more than a few times, his immunity is weak or nonexistent, and without prompt and full treatment he is going to die.

So what use is this knowledge of the life cycle of parasites and the role of the immune system?

### **Practical application**

First of all, you cannot possibly have a diagnosis of malaria until you have been in the country at least 7 days. A diagnosis of malaria in the first week is wrong.

Secondly, visitors of less than 5 years are not going to develop immunity without being very ill every few weeks for many years. SO the excuse I often hear that I am here for 2 years so do not want to take prophylaxis because I can become immune is just plain daft. The reason none of my family have had malaria for 20 years is not because we are immune, it is because we don't get bitten.

Next, in some areas of Kampala malaria is so rare most of us do not take any precautions at all and never get malaria. But in most areas up country malaria is common. If you go to a game park or even a campsite in Jinja and don't take prophylaxis you are probably going to get malaria. And even the mildest of faint positives is going to make you as sick as a dog for a week.

Next, if a non-immune expat walks into a doctor with a slight headache and a bit of vomiting and has a slide and is told he has malaria that is very unlikely. Non-immunes with malaria are very sick indeed even with very few parasites. Those who think they have had malaria "lots of times" and just had a fever and a bit of a headache for a few days and get better after treatment have almost certainly not had malaria.

Lastly immunes are immune because they get a lot of malaria. So if they think they are getting malaria all the time, how come? Either they really do get malaria all the time and are immune and therefore don't get sick any more, or they don't get malaria very often and when they do they are sick. If you are sick every few months and always being treated for malaria, it is most unlikely to be malaria, because if it was, you would be immune and so malaria wouldn't make you sick, would it? Catch 22.

In the next article I will write in detail about diagnosis and treatment

### **Summary**

Malaria is a disease with 2 distinct extremes and a gray area in between. On one extreme the semi immune who gets infected every day but isn't sick. He is the carrier who keeps the epidemic going by infecting mosquitoes. On the other extreme, the non-immune. Just one bite and about 10 to 12 days later he is very ill, despite just a few parasites. Without proper treatment the number of parasites will increase 10 times every 2 days and he will die of multi organ failure. One disease, 2 extreme outcomes.

### **Malaria, mozzies and a Mzungu. Part 3**

#### **Diagnosis**

In the last 2 eye articles I have written about how we get malaria, what happens when an infected mosquito bites us, and the crucial role played by the immune system. Non-immunes get very sick about 8 to 10 days after being bitten and go into multiorgan failure and death after 12 to 14 days. Semi-immunes are either not sick at all and run around playing football all day with chronic mild malaria, or get a mild attack every few months if they are either bitten more than usual or have another condition which pushes down their immunity, such as an infection or pregnancy. So malaria is a potentially fatal disease to expatriates, visitors, pregnant women and very young children. However by the age of 5 someone who has lived in a malaria area all their life and been bitten by infected mosquitoes continually is semi-immune. For them malaria is either a mild easily treated disease or a self-limiting hardly noticed nuisance.

#### **So how to diagnose malaria?**

Recently we have seen far more malaria than usual, with many people talking about "new types" and "cerebral malaria" and how treatment doesn't work. All complete nonsense, of course, but anyone who has been here 6 months thinks they are an expert in anything medical and malaria in particular.

Among our patients all the fatalities and all those unconscious in ITU were out of the country. Almost all our cases have been moderate or mild, treated with tablets and home in a few hours. Almost all the malaria cases we have seen have been away for a weekend and almost certainly picked it up out of Kampala.

So that is the first thing to know about diagnosis. Where were you 8 to 10 days ago? If the answer is "Murchison" then that is a big risk factor for malaria. If the answer is "India" or "Europe" then malaria is almost impossible. If the answer is "night flight out of Entebbe" then that is a very big risk.

After being bitten the parasites go into the liver. Most of them come out 5 and a half to 6 days later. The first wave of parasites cannot mature and release the fever toxins until they are 2 days old so the first fever of malaria cannot come in less than 8 days. Most people will get their first

severe symptoms 10 days after being bitten. I have often had patients who have been told they had malaria after being in the country only 4 or 5 days. That is impossible. The diagnosis has to be wrong.

Is it ever possible? Well yes. In a semi-immune the disease could grumble on for a month or two, so it is possible to see malaria in a Ugandan returning from a short trip abroad. Vivax malaria relapses every month and I know a Doctor who had his first fever from vivax 10 months after leaving Uganda. "Plasmodium malariae" has been known to relapse 20 years after leaving a malaria area. So all these unlikely scenarios could mean that someone has visible parasites in the blood 6 days after arrival. But if you are new, never been to an endemic area before, and have been here less than 8 days it cannot be malaria.

So that is the first point in diagnosis: where were you 10 days ago?

Secondly. Are you taking prophylaxis?

Almost all cases of malaria that we see are taking nothing. I have not heard of a single reliable report of malaria in someone taking mephloquin or Malarone properly, and I have only ever seen 3 cases in someone taking doxycyclin. I have had many patients who have been told they have malaria when they have been taking a good prophylactic. I doubt the diagnosis in almost all of them! I can remember one group of gap year volunteers who were all on mephloquin and all had acute diarrhoea with fever and vomiting after eating the same meal, so obviously an acute attack of gastroenteritis. They all went to the same doctor and were all give Halfan for "Malaria". Halfan and mephloquin is a well-known potentially fatal combination, and these students were lucky they all survived. Many people are given artemether drugs for "malaria", and when they do not get better are told artemether drugs do not work and given a quinine drip. They then get better because many diseases get better in 5 to 6 days anyway.

Does it matter? Yes! I know many travelers who have stopped taking their prophylaxis because they kept getting "malaria", thinking the prophylaxis didn't work. This is dangerous, and in travelers a possibly fatal mistake. These drugs do work! In most cases, perhaps all, it is the diagnosis that is wrong.

SO that is the next question about diagnosis: are you taking a prophylactic? If you are taking a recommended one, i.e. mephloquin, Malarone, primaquin or doxycyclin, then it is possible but very unlikely you have malaria.

Next, what are the symptoms?

Someone with malaria can have any symptom, I agree. They can even have a rash, in-growing toenails or haemorrhoids. But malaria is not the only disease that makes you sick!

Most people with a cough, a runny nose, or a sore throat, or pus on their tonsils have a respiratory infection. Of course someone with a cold may also have malaria, but it is not very likely. Add up all the unlikelies, e.g. symptoms don't fit, you're taking mephloquin, you only left Kampala 7 days ago, and really, what are the chances you have malaria? Most people with acute diarrhoea, fever and vomiting have an acute gastroenteritis, probably shigella or salmonella. This is in our experience by far the commonest cause of a high fever in a visitor. Yes, someone with acute gastroenteritis may have malaria, but add up all the unlikelies, and once again it is incredible how many people accept the diagnosis without question. These acute gastro's can go on for a long time, which is why we hear the story "artemether doesn't work". A very dangerous untruth.

Are there any specific symptoms or signs of malaria? No, not really. Most people with malaria will have sudden onset of fever headache and joint pains, without much else. After 2 days the symptoms get very much worse, often with a sudden rigor, vomiting, high fever, headache and aching all over. An untold number of diseases can do this: dengue and a dozen other similar viruses, flu, Ebola, leptospirosis, all the different rickettsias, borellia, the list is quiet literally endless! There are NO specific signs or symptoms of malaria; hundreds of other diseases can be mistaken for malaria. This is why it is so dangerous to assume that every fever is malaria! We have seen TB meningitis treated as cerebral malaria for 3 days, the patient nearly died. Other ordinary meningitis diagnosed as malaria, some have died. Pneumonia, a bleeding peptic ulcer, hepatitis, septiceamia all we have seen diagnosed as malaria, when they didn't get better medivac'd as "resistant malaria", all potentially fatal diseases where the diagnosis was delayed because of wrong diagnosis of malaria. So YES it is important!

So where have you been, are you taking prophylaxis, and do the symptoms fit? All these play a role in diagnosis.

### **So how do you make the right diagnosis?**

The official correct answer is a thick blood film, looked at by an expert, and if negative repeated after 24 hours. The “gold standard” is two independent experts agreeing on a blood slide. That is how we measure the success of other methods.

Sounds easy. What about reality?

First of all, missing it. In the UK about 20 people die out of about 2,000 cases every year, almost all because of late diagnosis. Missing it in the first day or two is inevitable; you just cannot possibly find malaria in every early case, as the parasites simply are not visible in the peripheral blood. If there are not enough to be seen in the blood slide, then there are not enough to cause trouble. The next day there may be the same number but bigger and easier to see, or there may be 10 times as many. Still not anywhere near enough to cause trouble. So if the very early malaria is missed, it doesn't matter and you can find them without any danger the next day. Vivax is particularly difficult to find, and you can miss them for a week and it still doesn't matter, as it is never dangerous. So a good lesson: missing malaria is honest, normal, inevitable and if repeated the next day is not dangerous. “Don't treat it until you find it and keep looking until you do” is a good maxim to live by.

What about the other way, finding malaria where none exist?

This is very easy! The gold standard is an expert, with a good microscope and a new slide with clean stains. Reality is quite different. A busy microscopist in a hurry, a scratched slide reused 20 times, stains that should have been changed hours ago and are now growing bacteria which look like parasites, with a microscope that hasn't been cleaned for a week! Add to that thinking squashed platelets are parasites, and it is no wonder that all over the world finding malaria when none exist is extremely common. One research I read was in UN soldiers in Angola where if I remember correctly about 1,600 had been diagnosed as malaria over a 2-year period, and antibody tests showed that only 3 had ever had malaria. The diagnosis was wrong in 99.8% of cases!!

So what can the poor sick traveler do?

In the next Eye we will look at the self-test kits and come to a common sense answer. Or you can look on the website and find the whole article!

### **Malaria, mozzies and a Mzungu. Part 4**

Rapid tests.

This is the 4th article in our series on malaria, if you want to read the others go on The Eye website and you will find the full or even expanded articles. We have covered the life cycle, the disease, the effect of immunity and diagnosis. We asked the question, why is a Pakwach school boy who is bitten 5 times a night completely well most of the time, yet a Mzungu bitten once on a weekend in Murchison is very ill in 10 days and without treatment dead in another week? More importantly, why are so many travelers told they have malaria even when they are taking prophylaxis and don't even have a fever, or have only been in the country 4 days?

We looked at the reality of malaria diagnosis, the difficulty of relying on a blood slide and the results of some research highlighting the very real problem of over diagnosis.

One about to be published article shows some research in Tanzania where in one area 98% of people diagnosed and treated for malaria did not have malaria. So how do you know if you have malaria and not another cause of fever, a virus, or meningitis, or a hangover? If you are on holiday, away from home, or sitting worrying in your house at midnight with a hot cross 2 year old and desperate for a good night's sleep, what do you do? Your friends confidently tell you the child has malaria, but you really don't think so. Is the child going to go unconscious before morning? Is it safe to carry on our trip? Is it safe to be pregnant in Uganda, won't malaria cause a miscarriage and the treatment harm the baby?

Article 3 finished asking, “What is the answer?” Read On!

First common sense! Ask the 3 questions looked at in detail in the last article: where were you 10 days ago, am I taking prophylaxis, do the symptoms fit. Common sense can take you a long way in medicine!

The next best answer is the malaria rapid test. They have a sensitivity of finding malaria if there is 1 parasite in 25,000 cells. In theory The Gold Standard lucky expert could find one parasite in 50,000 if he looked for long enough. However as the number increases by about 10 every 2 days, then the worst that can happen is that 2 days later there are 1 parasite in 2,500 cells. Not a big deal. You need to wait another 4 days, i.e. a total of 6 days, to get the potentially fatal 5% parasite count. So a good malaria rapid test, repeated the next day if negative, is going to find your malaria long before you get seriously sick. It will pick up as a faint positive while you still have a slight headache and a fever that you hardly know is there.

Magic

### **So what is the problem?**

First. There are some very poor tests on the market. We found one that missed malaria even with one in 2,000 parasites. It will find them before the fatal amount, but still far too insensitive to be of any use in the field. We wrote to the importer requesting them to take it off the market. We cannot name it! But the following we can recommend. Becton Dickinson, ACT, and MR made in Cape Town and distributed by The Surgery. Those are genuinely sensitive to one in 25,000.

Next problem. They go out of date. If in doubt trade it in for a new one.

Next. Too much heat ruins them. They may give a false positive, telling you that you have malaria when you don't or miss it when you do. If it has been cooked, chuck it.

Next. The reagent evaporates. It does not happen if the top is screwed down properly! We have tried it, we kept them upside down for weeks and they do not leak if properly tight! If your bottle is empty, get it refilled. It is only buffered water, and we have litre bottles of it.

Next. They will miss vivax and p. malariae. It doesn't matter, as neither can cause severe malaria, but can be a big nuisance. So if you get a 2-day or 3-day recurrent fever with a persistently negative rapid, think other species. One good clue: urobilinogen in the urine. It makes it very dark even if you are drinking plenty. There are vivax rapid tests, even some that pick up all 3. They cost a bit more but if you live in a vivax area, i.e. a bit cooler, get the kit that tests for both.

Next. They stay positive for a very long time after cure. It picks up a protein called the F protein that is released by the parasites. It carries on circulating in the blood for weeks after the parasite is dead and gone; until it is removed by enzymes that cut it up and metabolize it. So in a semi-immune with a stimulated and efficient enzyme pathway it goes negative in a few days after treatment. In a traveler it takes up to 6 weeks. So a positive rapid 3 weeks after treatment does not mean you have another bout of malaria. It might! Or it might still be fading. All you can do is repeat the next day. If it is an even stronger positive that means you have a new malaria. If it is fainter then it is the old one still showing positive.

However this is not only a problem; it is also one of the good things about the rapid tests. It means we can tell if someone really did have malaria after treatment. So if someone has "malaria" and is treated and doesn't get better, we can see if they really did have malaria or we need to look for another disease causing the symptoms. Every day we see people who have been treated for "malaria" with very unlikely symptoms. In about 9 out of 10 cases we find the rapid is negative.

### **Summary.**

Diagnosis of malaria is not as straightforward as you may think. The symptoms are not specific, very many different diseases can be wrongly diagnosed as malaria, and blood slides are easily misinterpreted.

If the diagnosis is missed for too long it can be fatal. However treating every disease as malaria can also be fatal.

A really expert microscopist with new slides, clean stains and a properly serviced microscope, with negatives repeated a day later, is the best method of diagnosing malaria, as they can tell if it is falciparum vivax or p. malariae, how many parasites there are and if the number is close to being dangerous.

In practice in most places the most reliable method is the do it yourself malaria rapid test. It can be done at home, on the road, or on holiday back in Europe. It can save a lot of lives as well as lots of hassle. It will pick up malaria at very low densities of 1 in 25,000, including the time when they are “sequestered” in the deep organs and therefore not seen in a slide. They also need to repeat negatives in 24 hours. They will miss the other species unless it is a multi species test, and give false positives for up to 6 weeks after treatment. They can also be spoilt; out of date and done wrongly, they are not the perfect answer.

The absolute best is both! A rapid and a slide. If in doubt, remember common sense. And the most important piece of health equipment you can have with you is your mobile phone.

In the next eye we look at treatment

### **Malaria, Mozzies and a Mzungu. Part 5**

Treatment.

We have already seen that malaria is a complex disease, with individuals responding in different ways according to their immune status. A Ugandan living in a rural area may be bitten by an infected mosquito 3 or 4 times a night, and therefore constantly has malaria. He is not sick as his immune system kills the parasites before they develop. However the constant battle may make him vaguely unwell and susceptible to other diseases, as his immune system is busy fighting malaria. Some good research has shown that if all children in a district are treated for malaria just after the beginning of the rainy season, including those who are not sick at all, then all cause mortality, which basically means deaths from diarrhea and pneumonia, is reduced by up to 30%. However a Mzungu, or someone who lives in Kampala where malaria is rare, has no immunity. When he is bitten he gets sick after 7 days, becomes very ill over the next 2 or 3 days and is dead in a week. Clearly he needs more radical treatment than someone who is not sick at all.

#### **So what is the best treatment?**

Fortunately the wheel has been invented and there is no need for anyone to rush around looking for a new better cure. The WHO has quiet rightly persuaded most governments in malaria areas that ACT's are the preferred treatment. Unfortunately in most of Europe and America they still use the awful quinine. More about that later.

#### **So what are ACT's?**

It stands for Artemether combination therapy. There are many Artemether derivatives with nothing much to choose between them. They are mostly tasteless, extremely well absorbed after an oral dose and start to work within 2 hours. They kill almost all parasites after about 4 hours, and they have a very short half life, with most of it excreted in 4 hours. Magic! So what's the problem?

The problem is the very short half life. Any remaining parasites, and any new ones coming out of the liver, are free to grow again unimpeded 8 hours after you swallowed the tablets. So you need to keep taking them daily for at least 7 days. The other problem is monotherapy. If you try and treat a parasite with just one drug, eventually there is a risk of resistance. Hence combination therapies are in.

There are 3 common ACT's available in Uganda. One of the many Artemether derivatives mixed with lumafantrine, piperaquin or amodiaquin. There is little to choose between them, all have the same idea, the fast acting “kill'em quick” Artemether with a long acting drug in combination to prevent relapse.

#### **So why should anyone have any problem with malaria when we have the near perfect treatment? And why so many injection abscesses?**

First of all as we have already seen in the previous articles, good research has shown that in some places in the world up to 9 out of 10 people diagnosed and treated for malaria do not have malaria. We see it over and over. A visitor up country gets acute fever, diarrhea and vomiting. Any one with a titter of wit can see this is acute gastroenteritis, and it will either get better with plenty to drink, or it can be treated with an appropriate antibiotic. We recommend norfloxacin. But

“malariaphobia” is a powerful force to reckon with. Off they go to a health worker, or they get advice from their friend the IT specialist! They confidently diagnose malaria, perhaps after looking down a microscope in desperate need of a service, at a dirty, scratched slide stained with bacteria contaminated reagents, seeing something vaguely purple that is probably a squashed platelet and reporting it as “MP+”.

They are then given the ACT and they don't get better. Not surprising, as they don't have malaria. Then they are told that ACT's don't work and they need quinine. As this is often given as a drip, at least the fluids are useful and they get better. The visitor is now convinced that diarrhea and vomiting is malaria, that the recommended treatments don't work and that he needs a quinine drip every time. Bad news.

### **So what is the truth?**

ACT's work. There is no true resistance in Uganda, in fact none in Africa. They work extremely quickly. We have used nothing else for the last 10 years, except combi tabs were not available so we gave Artemam and doxycyclin as our combination, and we have never had a single failure. They work so fast that most of the parasites die in 4 hours. This results in a sudden exacerbation of symptoms. You see, the fever and vomiting and other symptoms of malaria are due to the toxins released from the ruptured red cell, as described in the first article. So after treatment, the parasites die in about 3 to 4 hours, and the red cell is ruptured, releasing all the toxins. So this causes a new wave of symptoms, and because there are more parasites than there were in the last wave, you actually feel a lot worse. Someone who is quite well with a headache and not much fever can become very ill indeed 4 hours after treatment. They may have a fever up to 40, vomit, hallucinate, and even go unconscious. This is not because the treatment isn't working, it is because it is! For that reason people with a lot of parasites in the blood we usually keep in for 4 hours to see how they are after that time, and we warn everybody that if they really have malaria, they will get a lot worse 4 hours after the first dose.

Most of our patients say they do not like the new ACT's. I agree!! The “other drug” often has a lot more side effects than the Arthemether alone, and those used to Artemam and doxycyclin usually say they feel worse after ACT's. Sorry! But they are extremely effective, so put up with it

There is however a more serious problem. Duration. In Falciparum malaria most of the parasites come out at the same time about 5 to 7 days after being bitten. This is why the first symptoms, corresponding with rupture of the first wave of parasitized red cells, are usually after 8 days. However a few may dribble out of the liver up to 14 days, maybe even longer, after being bitten. So a 5 day course of Artemam will result in a relapse in about 10 to 20% of cases. The combination drugs have longer half lives, Piperazine weeks, and lumafantrine a bit variable but around 3 days, so the standard 3 or 4 day course will give a therapeutic level up to maybe the 7th or 8th day after starting treatment. This will make 100% of patients better, but there is still the possibility of a clone coming out of the liver very late, and starting a relapse a week later. (If you want to be pedantic, it is a recrudescence, not a relapse!) For almost all Ugandans this doesn't matter, the packets come with a 4 or 5 day course and they will all be cured. Why? Because the immune system slows the progress down, they get symptoms later, the chances of a clone coming out of the liver after the packet is finished is remote, and the immune system will probably polish it off anyway. However I have seen research that in Kampala children there is still some relapses after the standard dose, so maybe for children the duration of lumafantrine ACT's should routinely be longer. I leave that to the experts to decide!

The totally non-immune expat is a different story. He gets the symptoms earlier, has more parasites, sometimes gets treatment very early on, and the 5 days plus 3 is often over before the last clone has come out of the liver. So relapses are more common. For this reason we recommend either an extra 2 days of treatment or doxycyclin for 10 days starting on the last day of the course. That way we have seen no relapses since we started using ACT's. This should not be a problem with Piperazine ACT's, as the Piperazine component should carry on killing parasites for well over 10 days after the course is finished, but I don't have enough experience with it yet to see if theory translates into practice.

### **Can everyone take ACT's?**

Probably. However they are not fully recommended for small babies, and I would be hesitant to give all of them to pregnant women. Also children may find them pretty bitter. So for those who cannot tolerate ACT's and for stubborn Bazungu who say they make them feel ill, Artemam is still an alternative. Artemam alone can be given for 7 days to small children under 10kg, or to children who absolutely refuse to swallow the ACT. It is also a good alternative for pregnant women. But remember what we said about monotherapy? So I would still give pregnant women doxy afterwards for 10 days. (OK, so it stains the teeth. Maybe after the 5th month, but is that really an issue if the first baby tooth has a minute invisible brown line on it?)

### **Are injections better?**

Usually not. In fact they are slower to work! The oil based injections may not give you a therapeutic level for 4 hours, whereas after an oral dose they are busy killing parasites after one to 2 hours. In a totally collapsed patient absorption of drugs IM can be even slower. An injection of Artemam or Artesunate may be indicated if you can't swallow, vomit, and they can't get a line in. Even then we prefer to give drugs to stop vomiting and give the ACT by NG tube if necessary. We hardly ever give antimalarials by injection.

### **Are there any alternatives?**

Here is a theoretical list

Homeopathic treatment. Only works if you don't have malaria. We have a special name for those who treat real malaria with homeopathy, we call them corpses.

Quinine. Drug of choice in UK, USA and maybe still some other countries, and in Africa is sometimes used as IV for patients who are unconscious.

It is very slow, often after 24 hours there is still the same number of parasites under the microscope (though they are probably dying). It doesn't stop sequestration so you can go into full blown multiorgan failure many hours after the first dose of quinine. Most of the cases I know who got quinine in the UK last year finished up on intensive care and with renal dialysis. Not surprisingly I prefer Arthemether derivatives!! In fact I really don't know why they still insist on using it.

Quinine given IV is at least safe, if slow, causes temporary deafness and makes you feel as sick as a dog. However IM it is truly horrible. It causes the most awful abscesses and really should never be given IM if there is any alternative. The pictures in New Vision last month of people needing reconstructive surgery after IM quinine necrosis reinforced my prejudice! My advice, if someone comes near you with a syringe of Quinine, and you are still conscious, say thank you very much but can I have artesunate please?

Malarone. Licensed for treatment, but why bother? Takes longer to get better, has more side effects, expensive, and ACT's beat it in every department. At least for the next few years, leave it as prophylaxis for the rich

Chloroquin and fansidar. Doesn't work. May slow the parasites down in immunes long enough for the immune system to gobble them up, but still no longer recommended in most of Africa. Other fansidar look-alikes the same applies: if you get better it probably wasn't malaria!

Mephloquin. Great drug if you don't mind being off your head for 10 days. Also sometimes used as the "other drug" for single dose ACT mass treatment in some countries, but why bother when other ACT's are better? Leave it for prophylaxis.

### **Best advice for travelers?**

Carry 5 malaria rapid test kits and a packet of ACT with doxycyclin. If the children find it too bitter, Artemam for 7 days is still OK. If you are going to Europe or America take it with you and insist that the doctors allow you to use it; they cannot legally refuse you to "treat yourself" and it could save you a week on renal dialysis!

## Summary

Arthemether derivative combination therapies are the latest recommended treatment for malaria for almost everybody almost everywhere.

There are many different combinations on the market with little to choose between them, but some popular brands may need a longer duration of treatment than the packet suggests.

Monotherapy is frowned upon but may sometimes be best for babies and pregnant women.

A Quinine drip is an alternative for unconscious patients, but intramuscular Quinine is unnecessary and can cause huge destructive necrotic muscle damage.

## **Malaria, mozzies and a Mzungu. Part 6**

### Prevention.

We are now on the last lap of our Malaria marathon. This month and the next article are about prevention. The first 5 articles have looked at what is malaria, how we get it, what happens to us, and why a schoolboy in Pakwach gets bitten by an infected mosquito every night yet is perfectly well, while a Mzungu bitten only once is sick after 8 days, very sick in 10 days and without treatment dies after 2 weeks in multiorgan failure.

The key to understanding malaria is immunity, and without consideration of the immune status of the mosquito's dinner option, you will not understand malaria. Last month we looked at the different treatment options, and why the treatment that works for the Pakwach schoolboy may not work for the traveller. This month we are looking at prevention and why what works for our famous schoolboy may not work for you.

I am writing this from the Kenya coast, that well known literary venue that has inspired most of Kampala's annual pantomimes! This year I am not taking prophylaxis. At least not yet. I haven't seen a single mosquito, it is too windy, and the local anophylene doesn't like salt air. 100 metres inland and I am sure the situation changes. Those who live out of the range of the sea breeze may enjoy sitting out on the veranda in the evening but so does our friendly female mozzie. And that is the first consideration of prevention. Where are you? Are you going to get bitten, and is your dinner guest likely to be infected?

### Location.

Malaria has to develop inside a malaria mosquito that has bitten a semi immune human and ingested the male and female gametes. They meet and mate in the mozzie tummy, usually while she rests on the house wall, and the babies, called sporozoites migrate to the salivary gland. When she has digested her meal and her eggs are ready, she goes off to look for a puddle to lay her eggs in. On coming off the water, she is met by the males who hang around the pools waiting for the girls. So she is pounced on by the male, and starts to grow eggs. This is energy consuming (the egg growing I mean, not the mating which is over in seconds.) So she needs a blood meal, and goes looking for you. The male meanwhile has a much easier life and so is vegetarian. So he goes off to look for a nice juicy plant shoot, then straight back to the gutter again to look for another nice juicy female. Sound familiar?

The female if the timing is right bites you just when the sporozoites are mature enough to infect you and start off another cycle of malaria. This timing is temperature dependent: over 15 degrees centigrade, the malaria can develop inside the mozzie within her breeding cycle. If not, it can't. You either get another species that can develop at slightly lower temperatures, Vivax, or no malaria at all.

Half of southern Europe could have Malaria, and indeed used to in the past, and half the southern USA. But there are no semi-immune humans to infect the Italian or Californian mosquito. So no malaria. The Kenya coast within a few metres of the sea has no mosquitoes. Nairobi is above 6,000 feet so too cold at night. Kampala is perfect, but some of the hills are too steep for the shallow puddles that anophylenes prefer to breed in, and less than 1% of the mosquitoes in some areas are infected.

So prevention no.1. Live on Makindye! No one ever gets malaria on Makindye (except one family and we made them move.) Other peculiarities of our local anophylene, photophobia, preferring to bite after 10.00pm and before dawn, an odd preference for puddles rather than lakes, tin cans,

toilet cisterns and dirty ditches, and they don't like heights. More than 10 feet above ground and they get dizzy, so there is no malaria above the second floor of hotels. That is why we never see malaria from people living in the Golf Course Apartments. (Unless your mother is a doctor).

So that is the first option for prophylaxis. Nothing. If you live in Kampala, or above 6,000 feet, or are always on the second floor after dark, this is a legitimate option. It is tasteless, no side effects, cheap and you never forget to take it. However it certainly is not 100% effective, and we see about half a dozen bazungu a year who have slept only in Kampala and have got malaria. Up country it is not a sensible option! Many of the old eye readers will remember the fishing trip to Murchison about 10 years ago. One couple took prophylaxis, but 7 out of 10 of the Old Kampala boys who took nothing got malaria, most of them for the first time in their lives. Murchison is rightly notorious. And Entebbe airport night flights are high risk too: most of the patients I know who have died or have needed intensive care and renal dialysis flew out of Entebbe 2 weeks earlier! One evening in Entebbe seems to be as much a risk as 2 years in Kampala.

A lot of people tell me they don't take prophylaxis because they are here for a long time. First of all a "long time" is 5 years not 2. Next the mozzzy doesn't care how long you have been here, you may smell pretty bad to the rest of us but you still smell like dinner to one interested female! Immunity takes at least half a dozen attacks of malaria in a year to be of any use at all, plus a bite at least once a week to keep it boosted. How much of your short time in Africa do you want to spend vomiting to develop any useful immunity?

Others tell me they don't take prophylaxis because they don't work. I hope the last 5 articles have explained why. Someone takes malarone or mephloquin and they get an acute fever and diarrhoea, and the local expert, perhaps the garden boy or their favourite IT specialist, tells them they have malaria. He knows of course, because he has had malaria 100 times in the past year and recognizes it immediately. Or perhaps you are not that gullible, and go to the local clinic for a blood test. There your blood is put on an old scratched slide, stained with old reagents that haven't been filtered for hours and looked at down a microscope that hasn't been cleaned for a week. Someone may see a squashed platelet that looks a little bit like a parasite and may report it as "MP + seen" or but even if reported as negative the doctor then calls it "clinical malaria" and treats you anyway. Meanwhile your acute gastroenteritis that caused the fever gets better on its own. Every honest microscopist is bound to miss malaria sometimes on the first day of fever because there are simply too few to be seen in a blood slide. The right thing to do is repeat the slide, or the malaria rapid test, the next day, NOT say my prophylaxis doesn't work and stop taking it.

So nothing is an option in Kampala, perhaps in other places where malaria really is rare, but not a sensible option for travellers and 2 year wonders living up country.

Other options

### **Homeopathy.**

Homeopathy is perfectly safe because it contains only water or inert powder. The active ingredient is diluted by a factor of 10 at least 16 times, and shaken so that the "life force" of the drug goes into the water or inert powder. Of course anyone is welcome to believe in life forces, but unfortunately malaria parasites do not! Amazing how few people use homeopathy to prevent pregnancy, isn't it?

Boiling and filtering your water.

Wrong disease. Doesn't prevent pregnancy either. As effective as the first 2.

Nets, mozzzy repellent, long sleeves etc.

Your choice. Like most men my age I have to get up to pee every night and can't stand mosquito nets. And I forget the repellent. And the little b....s get my ankles anyway. So I use option 1. Live on Makindye.

Next month we look at the various drug options. The full article is available on the web site.

## **Malaria, mozzies and a Mzungu. Part 7**

### Prevention

And now some philosophy. If something works most of the time, but isn't 100%, is it a good option? The Pakwatch school boy gets bitten every night by 3 or 4 infected mosquitoes, so he always has malaria. This makes him immune, so he may be a bit tired most of the time, and he gets a clinical attack of malaria every now and again when he gets a cold or bad diarrhoea due to lowering his immune threshold. Preventing malaria will probably make him healthier, cleverer, and bigger, and has been shown that he is less likely to die from pneumonia and diarrhoea as getting rid of his malaria strengthens his immune system. BUT, and this is a big But. (Oops, pun not intended.) Now he sleeps under a net. So for a year or 2, or 3, he doesn't get malaria and he is fitter, bigger and cleverer. Then the system fails. He gets up for a pee in the middle of the night and gets bitten for the first time in 3 years. His immunity has now waned. So he gets a really awful attack of malaria, and without treatment he is going to be like the non-immune mzungu, multi-organ failure and dead in 2 weeks. And as he doesn't have immunity, or at least a lot less immunity than before, he needs full total treatment, not partial. See last month. Just a thought for the health planners. If we are serious about prevention, we had better do it properly or not at all!

### **And now the biggy! DDT**

One lecturer at the Liverpool School of Tropical Medicine, what where clever doctors go, used to swallow a teaspoon full of DDT powder in front of the students to demonstrate how safe it is. Yes I agree with "Silent Spring", but hey, that was millions of tons of the stuff sprayed on crops indiscriminately every year. So as we all know it builds up in the food chain and birds lay soft eggs. But a tiny amount sprayed on the walls is as safe as houses. Maybe the vultures may get a little too much when they eat us, but as long as we are buried, I don't think it matters!! Now I am not daft, I know the real issue is that the EU and USA have zero tolerance for organophosphates in fish and coffee. OK. So what about their tolerance for mercury in tuna? Could it possibly be that European and American fishermen catch poisoned Tuna from European and American pollution, but not tilapia with one part per million of DDT? I don't know much about politics, but do I smell hypocrisy?

I also know that if the District health officer has a few drums full of DDT for perfectly safe spraying on house walls to save a lot of lives, then it is very tempting to spray a bit of it on his tomatoes or his cotton too, and sell a bit to his mates as well. Dangerous!! I also know that if the poor old farmer simply leans his bag of coffee beans against the sprayed wall, it will pick up the one in a million parts of DDT that will get our whole crop rejected by the EU. So the programme needs a lot of honesty and a lot of education. The challenge is on! However to me the biggest challenge is, destroy the immunity built up over years, and everything about malaria changes. When the Pakwatch schoolboy does get malaria he is going to need far more vigorous treatment than he used to.

Enough Philosophy, on with the drugs

There are many each with pros and cons.

### **Malarone.**

Excellent drug, 100% effective, there is no record of proven malaria in Africa in someone taking malarone correctly. It is the only drug that works in the liver, actually preventing malaria from developing at all, and in the blood killing it if it escapes from the liver. For this reason it only needs to be started the day you arrive and for 5 days after you leave. It probably has more side effects than the others, none particularly dangerous. Your hair may fall out, you may get mouth ulcers, you may be dizzy and sick, you may get diarrhoea, but then who doesn't? Prove it is the malarone! However the main side effect is the very serious effect on your wallet. The stuff is ridiculously expensive. Great for a weekend away, as you only need to take it for 5 days. Costs a fortune if you are here for 3 months. Maybe that is another way that it works: once you have bought the malarone, you can't afford to go to Murchison! If you miss a dose it doesn't matter, probably works if you take a dose alternate days, though I wouldn't try it! If you are leaving the country we will buy any leftover malarone from you at 4,000/= a tablet.

### **Mephloquin**

Great drug. For 90% of us. Another 100% effective drug in Africa, i.e. no proven case in those with adequate blood levels, but 10% of people get serious psychiatric side effects. Don't let this put you off: the drug has a very long half life of 3 weeks, and hangs around for 7 weeks; it builds up slowly, so you get some warning. If after 3 tablets you start to get bad dreams, wake up at night screaming with emotional swings and paranoia, (they are out to get you, but you're not supposed to know) then stop the drug. The full blown picture of psychosis, and laughing and crying at the same time, comes slowly over the first few weeks. If you have taken over 4 tablets and start to get mild problems, then reduce the dose to 3 a month, i.e. skip a dose and skip the last Sunday every month. And the skipping will make you fit, too. Good option for those who can tolerate it for long term use, not really useful for weekends away as you need 3 doses to begin to get an effective blood level.

It obviously doesn't matter if you forget to take a dose, and you only have to take one more dose after you leave, as it lasts for 3 weeks. It works only in the blood, not in the liver, so although it kills all species, Vivax can still come out of the liver and get you up to a year later. It is now the CDC recommended drug for pregnant women.

### **Doxycyclin**

Like mephloquin works only on the blood stages, so you can develop some immunity to malaria without ever getting sick if you live in an area of high transmission. Unfortunately it is no longer 100% effective for everyone; we have seen a few cases of malaria from some areas of the country even in those taking it properly. However it slows the malaria down, so instead of getting the classical alternate day rigors and fever getting worse every cycle, the few patients we have seen have been vaguely ill with little fevers coming and going, but mostly just ill and tired for weeks. It is very difficult to find in such cases, the slide is negative, even the malaria rapid the first few days, but usually the urine is dark, and that is a good clue. Treatment is the same, with ACT's, but do carry on with the doxy, it is still mostly effective.

It is a great drug, with few side effects, and very cheap, about 2\$ a month. Main problem is that blue eyed blondes and the Irish can get terrible sunburn. The sensible option is try it and see. The most important warning is take it standing up with a lot of water or followed by food. If it sticks half way down your oesophagus, it will make an ulcer and give you pain swallowing for 10 days. 2 of my children have managed to do that!! It can give ladies thrush, but only for the first few weeks, then the lactobacillus gets resistant to it and it doesn't happen again. Ditto the "pill doesn't work" story. Oestrogen absorption depends on a bacteria killed by antibiotics, but again it gets resistant after a week or 3, and anyway the progesterone component isn't affected. Have you ever seen anyone get pregnant on the pill while taking doxy? I haven't!

It is safe in pregnancy. If taken in the last 4 months, the baby teeth may be stained brown. Won't happen if taken for a weekend away. It works only on the blood stage, so needs to be taken for at least 2 weeks after leaving the malaria area. If used to cover the Entebbe night flight scenario, take it for a full 2 weeks, and when you stop, if you do have a grumbling chronic malaria, it will now take off as a classic full blown malaria attack, so a fever a week after stopping doxy must be properly assessed.

### **Primaquin**

Great drug, very cheap, about 3 dollars a month. Trials show pretty good efficacy, but not enough yet to know the full picture. I have never seen a case of malaria in Uganda on someone taking primaquin. Like malarone, it works in the liver, actually preventing malaria rather than killing it in the blood after it comes out. Also like malarone it kills vivax, so if taken on departure, you will not get a dose of vivax a month after coming home. The only significant side effect is that it causes haemolysis in people with G6PD deficiency. Er...it does what? Don't worry about it! If you are of true northern European descent, it is safe for you! However if you, or the father of your unborn baby, is genetically from the Mediterranean, Africa, the middle and far east, then you may have the gene for this fairly rare blood group, and if you take primaquin or half a dozen or more other drugs, then there is a risk of the blood self-destructing. Simple. If you are at risk, get a cheap blood test done before you take primaquin.

It is an excellent weekend away drug as you only need to take it for 5 days, if you forget a dose it doesn't matter, and a good choice for pregnant women as long as you know who the father is!

**Summary**

Read the other 6 articles online so you know what I am talking about.

Get a map, so you know where Makindye is

People living up country, travellers, Kampala residents going away for the weekend, or taking a night flight out of Entebbe should take prophylaxis.

The drugs work, if you are told you have malaria be very suspicious