

Malaria in South Sudan 1: introduction and pathophysiology

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This is the first in a series of articles on malaria. It is intended for everyone in South Sudan who diagnoses and treats malaria, and advises on how to prevent it. This article gives an overview of the epidemiology of malaria, the parasite's lifecycle and the pathophysiology of the disease. There is more information in items listed at the end of the article. Also in this issue of the journal are two articles on the diagnosis of malaria. Treatment and prevention will be covered in future issues.

Introduction

Approximately half of the world's population is at risk of malaria and most cases occur in sub-Saharan Africa (1) where 20% of childhood deaths result from this disease. African children have between 1.6 and 5.4 episodes of fever caused by malaria each year (1). In 2008, there were 247 million cases of malaria and nearly one million deaths. Malaria is an important cause of prenatal anaemia and of preventable low birth weight.

Malaria is a major health problem in South Sudan. The peak period of transmission is during the rainy season - mainly April to October (2). *P. falciparum* is the dominant species of parasite and responsible for more than 90% of the cases (and for all cases of cerebral malaria) in South Sudan.

Factors affecting susceptibility, symptoms and the progress of malaria

- The host's genetic makeup. For example, the association between sickle cell trait and protection from malaria is well known. As more information emerges from the genetic analyses of malarial disease more associations are being discovered (3).
- The variable virulence of different strains of the malaria parasite. This may account for the wide variation in clinical symptoms.
- The number and frequency of mosquito bites that transmit the parasite and hence induce a (semi-) immune status.
- Other effects on the immune status of the host including HIV infection.

Recent studies (3) indicate that there are clinical and pathophysiological differences in severe malaria in populations of different ages, geographical locations and

genotypes.

Immunity to malaria increases after each malaria attack. The following groups are reported to have partial immunity to malaria:

- Newborns - who are protected due to foetal haemoglobin (HbF).
- Those with glucose-6-phosphate dehydrogenase (G6PD) deficiency.
- Children with sickle cell trait who have low parasite rates and fatality rates.
- Those with thalassaemias who get some protection due to HbF
- West Africans because they lack the Duffy antigen needed for the *P. vivax* attachment; so they have immunity against the *P. vivax* species.

The role of maternal immunity in newborn susceptibility

The most recent evidence indicates that maternal immunity to malaria does not strengthen the neonate's immunity but instead predisposes the child to severe attacks of malaria later in life (4).

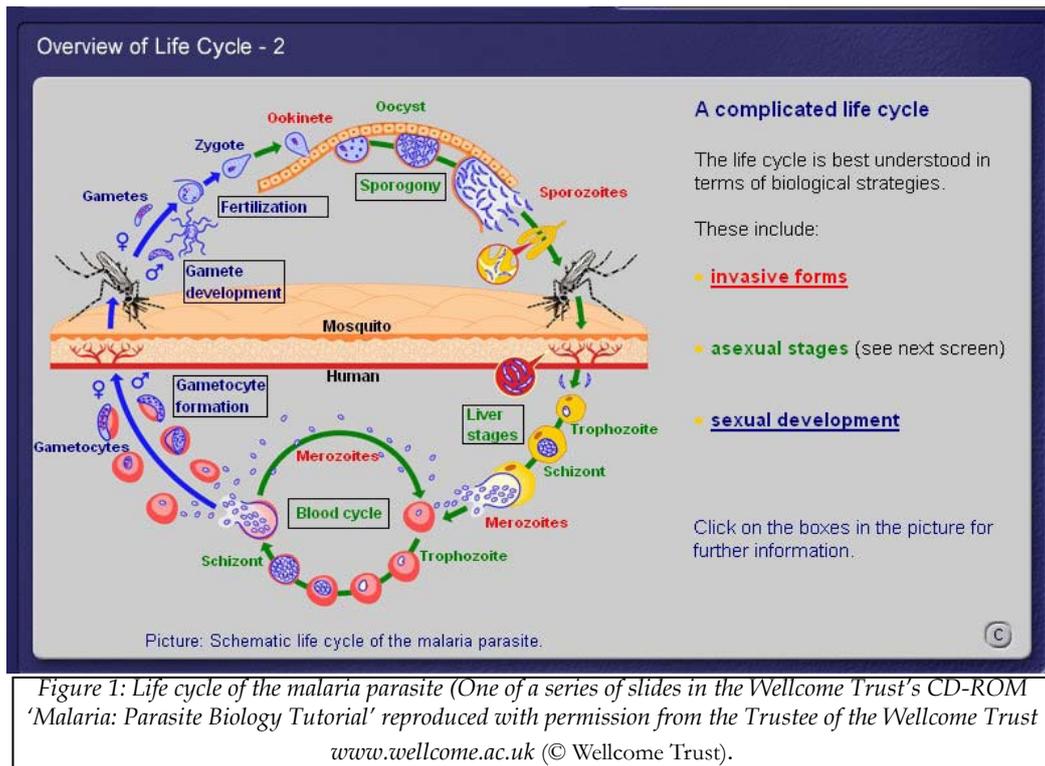
Groups at risk

Within South Sudan the groups at most risk of severe malaria are:

- Young children who have not yet developed their own protective immunity against the most severe forms of the disease (and HbF is reduced). Most of the deaths from malaria are those of young children.
- Semi-immune pregnant women. Pregnant women have a decreased level of immunity making them more susceptible to malaria. The placenta is a good breeding area for plasmodium due to the presence of the adhesion molecules. The hormonal changes during pregnancy make parasite penetration easy.

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Malaria can result in serious maternal and foetal health risks including anaemia, miscarriage (especially during the first and second pregnancies), abortion, stillbirths and a low birth weight baby. In highly endemic countries like South Sudan, many women have developed some immunity; consequently re-infection with malaria during pregnancy may be asymptomatic, therefore masking the need for treatment.

- Semi-immune HIV-infected pregnant women are at increased risk of malaria during all pregnancies. Women with malaria infection of the placenta also have a higher risk of passing HIV infection to their babies.
- People with immunodeficiency (for example, HIV/AIDS).
- Visitors/Immigrants from non-endemic areas are at high risk of malaria and its consequences because they lack immunity. This includes South Sudanese who have lived in non-endemic areas (and therefore lost their immunity) and return home.

Transmission

Malaria is caused by the Plasmodium parasite whose life cycle is in the Anopheles mosquito and humans. It is almost always transmitted to humans by female anopheles mosquitoes that bite mainly at night. The female mosquito needs a blood meal in order for her eggs to develop. The male feeds only on plants. Four main species of plasmodium cause malaria in humans:

- P. falciparum (causes the most severe illnesses and

deaths, and is the most common species in South Sudan.)

- P. vivax (causes mild disease)
- P. ovale (causes mild disease)
- P. malariae (causes a mild disease).

There are occasional rare infections with P. knowlesi and P. simium. It should be noted that both P. vivax and P. ovale can cause a dormant liver stage (hypnozoites) that may lead to manifestations of malaria plus a positive film after months or even years.

Malaria can also be transmitted through:

- blood transfusion
- the placenta
- parenteral accidents.

Life cycle and pathophysiology of the malaria parasite

The life cycle of the malaria parasite (see Figure 1) is divided into:

1. The sporogonic cycle in the mosquito. The mosquito acquires gametocytes when it bites an infected person. These fertilise in the gut and eventually migrate as sporozoites to the saliva.
2. The erythrocytic cycle inside human red blood cells (RBC).
3. The exo-erythrocytic cycle outside RBC.

The erythrocytic cycle of *P. falciparum*

Pre-erythrocytic cycle

When the mosquito bites, sporozoites are injected with the saliva into the blood stream.

Within 30 minutes they invade the liver cells and multiply there for 7-10 days forming thousands of merozoites.

The pre-erythrocytic stage of infection produces minimal histopathological changes, cannot be seen under the microscope and there are no detectable symptoms or functional disturbances in the host. (Other species have longer incubation periods with *P. malariae* being the longest - about 40 days at most. *P. vivax* and *P. ovale* species become hypnozoites from which relapses may occur months or even years later).

Erythrocytic cycle

After the pre-erythrocytic cycle, the merozoites burst out of the liver and invade the red blood cells (erythrocytes). Here they develop through ring forms to trophozoites and finally to multi-segmented schizonts.

The exo-erythrocytic cycle of P. falciparum

The infected RBCs rupture after about 12-16 days (for *falciparum*) but takes longer (up to 40 days) in species like *P. malariae*. Merozoites and gametocytes are released into the blood stream causing clinical signs. The released merozoites infect more RBCs (thus continuing the cycle of infection). The gametocytes also invade RBCs and are ready to be swallowed by the mosquito when it bites again.

The fever, febrile paroxysms, headache and a variety of other aches and pains, prostrations plus the familiar and consistent (flu-like) symptoms of an acute attack are probably due to the cytokines released from macrophages and RBCs when the schizonts rupture.

References

1. WHO. 2010 Fact Sheets on malaria. Available at <http://www.who.int/mediacentre/factsheets/fs094/en/index.html> (accessed August 2010) and <http://www.who.int/features/factfiles/malaria/en/index.html> (accessed December 2010).
2. Ministry of Health, Government of Southern Sudan. Prevention and treatment guidelines for primary health centres and hospitals. 2006.
3. Warrell DA & Gilles HM eds. *Essential Malariology* 4th edn. 2002; Ch 10:236-249.
4. Hartman TK, Rogerson S J, Fischer P R. The impact of maternal malaria on newborns. *The Annals of Tropical Pediatrics: International Child Health* 2010; 30 (4):271-282 (12). DOI: 10.1179/146532810X12858955921032

Further information

- Wellcome Trust. Malaria website at <http://malaria.wellcome.ac.uk>
- Wellcome Trust. Parasite Life cycle at <http://malaria.wellcome.ac.uk/interactive/parasitelifecycle/interactive.html>

Thanks to David Attwood for help in preparing this article.

Case History Quiz



'Face of baby'

'Stomach and thighs of baby'

Here are two photographs of a baby boy, aged 11 months, who was born in Nyala, Darfur. The mother is married to her direct first cousin. This is her 6th child – two of them were born with the same condition – a boy died at age 3 months and a girl at age 27 months. Her brother had two children with the same condition – both died.

Questions

- Q1. What is wrong with this baby? What signs of disease can you identify?
- Q2. What is the diagnosis?
- Q3. What further questions should the doctor ask?
- Q4. What causes this condition?
- Q5. What treatment should the doctor give?
- Q6. Do you think the child is likely to get better?

Have you seen children with this condition? If so, what treatment/advice did you give? What was the outcome?

Answers are on page 16

A case from Darfur presented by Dr Massimo Serventi