

Ministry of Defence

Synopsis of Causation

Malaria

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Disclaimer

This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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1. Definition

- 1.1. Malaria is the commonest tropical parasitic illness, with approximately one third of the world's population at risk¹, and an annual mortality estimated at more than one million deaths.² It is caused by infection with one of 4 types of malaria parasite. Human malaria is divided into benign malaria, caused by *Plasmodium vivax*, *P. ovale* or *P. malariae*, and the more serious and potentially fatal falciparum malaria, caused by *P. falciparum*. Very rarely, human infection can occur due to animal malarias.³ Transmission between humans is via the bite of a female anopheles mosquito, with the parasite undergoing an essential part of its lifecycle while in the mosquito.⁴ Thus, transmission by mosquito requires specific conditions that are usually only found in the tropics.

2. Clinical Features

- 2.1. Following the bite from an infected mosquito, there is a latent incubation period which may last from 3 days⁵ to many months. In the case of falciparum malaria, symptoms usually occur within one month of exposure, whereas benign malarias may take several months. In both benign and falciparum malaria, presentation may be delayed if an individual has been taking antimalarial prophylaxis. In rare instances, malaria may present many years after exposure.⁶
- 2.2. Symptoms may be initially mild and flu-like with headache, myalgia, lassitude, abdominal discomfort and fever. These symptoms may remit and relapse with periods of relative well-being lasting 1-3 days before symptoms return.³ Previously, malarias were divided clinically into tertian and quartan fevers depending on the periodicity of the fever in the untreated infection. This classification is not useful diagnostically, particularly where prophylaxis or treatment is used, and has largely been abandoned.
- 2.3. All forms of malaria can give flu-like initial symptoms, but only falciparum malaria is likely to progress to give more serious features. These include delirium or coma (cerebral malaria), hypoglycaemia, seizures, severe anaemia, bleeding disorders, acute renal failure, pulmonary oedema, hepatic failure, associated bacterial septicaemia with shock (algid malaria) and death.
- 2.4. The development of clinical infection can be prevented by the prophylactic use of antimalarial drugs. Drugs currently in common use are listed below. The continued development of resistance to antimalarial drugs means that the advice regarding the correct drug for prophylaxis in any region is liable to change over time, and should always be checked with a reputable, up-to-date source such as the UK Health Protection Agency (www.hpa.org.uk), or a specific travel website for physicians such as www.travax.scot.nhs.uk.
 - 2.4.1. Mefloquine: Once weekly tablet, which requires 3 doses prior to entry to a malarious area to ensure maximal efficacy. Must be continued for 4 weeks after leaving the malarious area. Rarely associated with severe side effects, including convulsions and psychosis.
 - 2.4.2. Doxycycline: Once daily tablet, should be started one week prior to entry into the malarious area, and must be continued for 4 weeks after leaving the malarious area. May cause rashes, which can be rarely associated with sun exposure, limiting its usefulness for affected persons in the tropics. Contra-indicated in pregnancy.
 - 2.4.3. Atovaquone-proguanil (Malarone): Once daily tablet which can be started 2 days prior to entry into a malarious area, and should be continued for one week after leaving. Severe side effects very rare.
 - 2.4.4. Chloroquine-proguanil: Older regime now only useful in certain areas where chloroquine resistance is not a problem. Two chloroquine tablets once weekly and 2 proguanil tablets once daily. Should be started one week prior to entry into a malarious area and continued for 4 weeks after leaving. Severe side effects very rare. Regarded as safe in pregnancy, unlike other regimes above.

- 2.5. Drug prophylaxis against infection is highly effective if taken correctly, but it should be recognised that it is not 100% effective. Where malaria develops during or following prophylaxis, the clinical course may be altered, with a later onset and possibly less classical clinical features. However, severe malaria and death appear less frequent in travellers who take effective prophylaxis.^{8,9}
- 2.6. Military personnel may be 2-10 times more likely to contract malaria than civilian travellers.¹⁰ This may be due to increased exposure to bites due to the nature of military activities. The risk to personnel deployed in areas with a high chance of hostile action may be 10 times higher than that to personnel deployed in areas with a low chance of hostile action.¹¹ The reasons behind this have not been fully researched, but are likely to include greater exposure to biting mosquitoes with reduced awareness of bites, reduced use of protective measures such as mosquito nets and repellents which might compromise operations, and rapid deployment, with a decreased awareness of risks and preventive measures compared to situations where deployment is planned in advance and personnel appropriately trained. Also, chemical prophylaxis with mefloquine is not at full efficacy after only one dose, and thus, where deployment is not planned well in advance, personnel may have insufficient time to take the recommended 3 doses prior to entering a malarious area.

3. Aetiology

- 3.1. Malaria is caused by development of parasites in the blood of infected individuals. The 4 species of parasite are *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*. *P. falciparum* is the commonest species in sub-Saharan Africa, but occurs in many other tropical regions. *P. vivax* is commonest in Asia, with only a limited number of cases in Africa, where the predominant benign malaria is caused by *P. ovale*. *P. malariae* is widely distributed but relatively rare. The lifecycle of all 4 species is similar and is described below. For more detail on this complex process, see Manson's Tropical Diseases.⁴
 - 3.1.1. Female anopheles mosquitoes need a blood meal prior to laying eggs. Many species of anopheles mosquito feed from humans. If an infected mosquito bites an individual, it injects malaria parasites (called sporozoites) into the bloodstream. These migrate to the liver, where they mature for a variable period. (In the case of *P. vivax* and *P. ovale*, some of these liver parasites become latent as hypnozoites for potentially long periods of time.) In all species of malaria, the liver parasites multiply and are released into the bloodstream, where further multiplication takes place in red blood cells. At this stage the parasites are called merozoites. When this multiplication reaches a certain level, symptoms occur. The cause of the symptoms is the release of cytokines in response to the infection.
 - 3.1.2. In the benign malaras, all the merozoites circulate in the blood and can be seen under the microscope. In falciparum malaria, the merozoites adhere to the walls of the blood vessels, particularly in the brain, heart, kidneys and placenta, and thus the amount seen in peripheral blood may not correlate with severity of disease. This adherence to vessel walls causes direct damage to these organs, and is responsible for the serious nature of *P. falciparum* infection.
 - 3.1.3. During the infection in a human, some of the developing parasites develop into sexual forms, called gametocytes, which can then be ingested by a mosquito when it takes a blood meal. These male and female sexual forms then fuse together in the gut of the mosquito and migrate out of the gut before multiplying asexually again. These forms are the sporozoites which then migrate to the salivary glands of the mosquito where they are ready to be injected at the time of the next blood meal. This part of the lifecycle in the mosquito is essential for the natural transmission of malaria, and is highly dependent on ambient temperature, with mean temperatures between 20°C and 30°C being ideal. The development takes longer outside these temperatures, and may not be complete within the life span of the mosquito, hence the lack of transmission in cooler climates.
- 3.2. Malaria can also be transmitted by blood to blood contact. There are recorded instances of this occurring in medical situations such as blood transfusions and use of intravascular devices.¹² It is possible that in the military setting blood to blood contact between individuals may occur in training or on the battlefield.
- 3.3. Regions affected by malaria are constantly changing. The factors affecting the distribution of malaria are largely due to climate and habitat for mosquitoes.

- 3.3.1. The duration of the development of the parasite within the mosquito is temperature dependent. Although the species of mosquito required for malaria transmission are widespread through the world (including the UK), in cooler regions the temperature-dependent development of the parasite is so retarded that it is longer than the lifespan of the mosquito, rendering transmission virtually impossible. This is why some regions only have seasonal malaria at certain times of year. Changes in climate, particularly global warming, may see an expansion of the areas currently affected by malaria.
- 3.3.2. The other main factor affecting the distribution of malaria is the availability of suitable habitats for mosquitoes. Changes in the availability of swampy ground and water affect the breeding of anopheles mosquitoes. Attempts to eradicate mosquito breeding sites may be adversely affected by unrest or war and may rapidly increase in such areas.

4. Diagnosis and Treatment

- 4.1. **The ABCD approach to malaria.** The ABCD approach to malaria has been advocated by the UK Health Protection Agency.¹³ This is summarised as:

Awareness: know about the risk of malaria, (particularly the risks affecting the area being visited and during the season of visiting).

Bites by mosquitoes: prevent or avoid (using insecticide-treated bed nets, mosquito meshes in buildings, long sleeved garments and trousers and a repellent containing at least 30% DEET).

Compliance with appropriate Chemoprophylaxis.

Diagnose breakthrough malaria swiftly and obtain treatment promptly.

4.2. Diagnosis

4.2.1. Malaria has traditionally been diagnosed by looking at thick and thin blood smears under a microscope, and in experienced hands, this is probably still the most sensitive diagnostic tool. However, it should be remembered that particularly in non-immune travellers, malaria may give symptoms when parasite numbers are too low to detect by any method.

4.2.2. Two other methods are now also in general use. The Quantitative Buffy Coat method uses a fluorescent dye which stains the parasites, and a centrifuge to separate the blood, such that the red blood cells containing parasites are concentrated together in one part of the centrifuge tube, allowing for easier identification but not speciation. The most recent addition is a group of tests based on detection of malaria antigens. These are available as card or stick tests, (similar to urine pregnancy tests), and can be designed to differentiate the dangerous *P. falciparum* from the benign malarias.

4.3. Treatment.

4.3.1. Treatment of uncomplicated malaria is usually possible with oral medication, and may even be instituted without a definitive test for malaria in areas of high transmission when someone has symptoms suggestive of malaria. It is important that anyone responsible for treating malaria is up to date with local patterns of resistance to antimalarial drugs, as this is constantly changing. Many of the drugs used in prophylaxis, and thus carried by people in the field, can be used at higher doses for treatment, but it may be appropriate to switch to a different drug from that which the patient was using for prophylaxis.

4.3.2. Treatment of severe malaria should ideally be done in a hospital setting by experienced staff. Coma and organ failure may require intensive support in an intensive therapy unit. However, therapy of severe malaria should not be delayed until the patient reaches an appropriate establishment. Commencing therapy with intramuscular or rectal preparations of drugs is commonly done in resource-poor settings and can be life-saving.

- 4.3.3. Quinine remains the mainstay of drug therapy for falciparum malaria, and is also effective against the benign forms. It can be given orally, but may require to be given intravenously in severe cases. Quinine may cause significant side effects, particularly when given intravenously, including hypoglycaemia and cardiac arrhythmias.
- 4.3.4. The development of new antimalarial drugs is slow, but a class of drugs known as artemisinins has been developed from a Chinese herbal remedy. While readily available in many parts of the world, these drugs are not yet widely available in the UK. This is likely to change as they become increasingly important as resistance to quinine and related drugs increases.

5. Prognosis

- 5.1. **Benign malarias.** Benign malarias can give severe symptoms and incapacitate affected individuals in the short term, but are rarely a cause of severe illness on their own. *P. vivax* and *P. malariae* can remit and relapse over many years (up to 20 in the case of *P. malariae*).⁶
 - 5.1.1. Sequelae from benign malarias are rare. Children in malarious areas may have severe anaemia, growth retardation and splenomegaly, with very rare fatalities due to splenic rupture.³ Adults may get recurrent bouts of debilitating acute illness, but are unlikely to suffer any serious consequences. However, it should be remembered that they may be unable to perform even simple tasks when an acute attack occurs.
- 5.2. **Falciparum malaria.** In non-immune individuals, falciparum malaria is always a serious disease. Untreated, cerebral malaria is almost universally fatal. Even with treatment, cerebral malaria has a mortality of up to 10-30%.¹⁴ With prompt recognition (before severe malaria develops) and correct treatment, healthy individuals will normally make a full recovery within weeks. However, the main factor affecting prognosis in falciparum malaria is the promptness of its recognition and treatment. Untreated, the individual may develop any or all of the severe clinical features detailed above, and once severe malaria has developed, treatment becomes more difficult, requiring intravenous drugs and the potential for toxic effects of the drugs.
- 5.3. People living long-term in malarious regions with high transmission rates may develop partial immunity and tolerance to infection (premunition) and may not develop clinically apparent infection, but this is usually confined to people who have grown up in malarious regions and lived there constantly. This partial immunity wanes rapidly if the individual leaves the malarious area, and on return to a malarious zone these individuals are at nearly as great a risk as travellers from non-tropical areas.
- 5.4. Malaria in pregnancy carries a poor prognosis for both mother and baby. Severe malaria is much more likely, and even if this does not develop, low birth weight is very common¹⁵ as is spontaneous abortion.
- 5.5. Malaria is much more common and more likely to be severe in people who have had their spleen removed¹⁶ because the spleen functions in removing abnormal (parasitised) red blood cells from the circulation. People who have no spleen or a non-functioning spleen should be cautioned about the special risks of tropical travel.
- 5.6. Research into malaria vaccines has been going on for many years, but there is as yet no effective vaccine. This work is ongoing and may eventually yield an effective vaccine which could at least ameliorate the disease if not help in its eradication.¹⁷ A vaccine could be particularly useful for military personnel who may have difficulty complying with bite avoidance strategies while in high risk situations.

6. Summary

- 6.1. Malaria is a potentially fatal tropical infection, presenting initially with non-specific flu-like symptoms, which if not treated promptly can lead to multi-organ failure and death. Treatment with appropriate antimalarial drugs should be instituted immediately the diagnosis is made. The benign malarias, particularly *P. vivax* and *P. malariae* can relapse many years after exposure.

7. Related Synopses

Hepatitis

HIV

8. Glossary

algid malaria	Severe clinical stage of falciparum malaria, with shock and prostration, often with associated bacterial sepsis.
anopheles	The genus of mosquito containing many species that act as vectors of human malaria.
artemisinins	Antimalarial drugs derived from the plant <i>Artemisia annua</i> .
cytokines	Regulatory proteins produced by cells of the immune system which act as signals in an immune response.
gametocyte	Sexual form of the malarial parasite. Occurs in male and female forms in human blood. These forms fuse in the gut of the mosquito, resulting in a new generation of parasites.
hypnozoite	A form of the malarial parasites of <i>P. vivax</i> and <i>P. ovale</i> , which can remain dormant in the human liver for months to years, before giving rise to the blood phase of the parasite.
malaria	A parasitic disease causing fever.
merozoite	The blood stage of the malaria parasite. This develops in the host red blood cells.
myalgia	Muscle pain.
plasmodium	The genus of parasite which contains the 4 species of parasite responsible for malaria in humans.
<i>Plasmodium falciparum</i>	The species of malarial parasite which can cause the serious and potentially fatal forms of malaria.
<i>Plasmodium vivax</i> <i>Plasmodium ovale</i> <i>Plasmodium malariae</i>	The 3 species of malarial parasites which cause benign malaria in humans.
premunition	A state reached by an individual after repeated exposure to malaria, in which they do not develop signs of infection despite having detectable parasites in the blood. This is not true immunity, but a form of immune tolerance.
prophylaxis	The prevention of disease.
quartan fever	A traditional way of describing one pattern of fever seen in untreated malaria, where fever occurs every third day. Now a largely obsolete term.

quinine	An antimalarial drug derived from the bark of the Chinchona tree.
red blood cell	Cells in the blood which contain haemoglobin, the chemical which carries oxygen to the tissues. It is these cells which are parasitised by the blood phase of malaria.
sporozoite	The stage of the malaria parasite which develops in the female anopheles mosquito and is injected in to the human when the mosquito takes a blood meal.
tertian fever	A traditional way of describing one pattern of fever seen in untreated malaria, where fever occurs every second day. Now a largely obsolete term.

9. References

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