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The burden of malaria

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1. INTRODUCTION

1.1 Brief review of the biology, aetiology and pathogenesis needed to understand estimates

The term malaria designates the diseases produced by the infection with any of the four human parasites of the genus *Plasmodium* (*P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale*); these parasites are transmitted from man to man by the bite of a female mosquito of the genus *Anopheles*, and are very selective of their vertebrate host, so that human malarias have no animal reservoir; only exceptionally, mainly as laboratory accidents, some plasmodia of monkeys have infected man, and only chimpanzees and a few South American monkeys can be infected with human parasites, to serve as laboratory animal models of the malaria infection. By extension, the term malaria is also applied to the infections produced by other species of plasmodia in their respective hosts. It is also very likely that *Plasmodium rodhaini* from the chimpanzee, and *P. brasilianum*, from South American monkeys, are identical to, or very recent adaptations of, *P. malariae*; even if the malaria produced by this parasite could be considered a zoonosis, the very limited contact of habitats restricts considerably the epidemiological importance of this possibility.

Under natural conditions the infection is almost exclusively transmitted from man to man by the anopheline mosquito, in which the parasite has to undergo its sexual reproduction. Congenital transmission, although possible, is quite rare; antibodies traverse the placenta more readily than infected erythrocytes, so that congenital malaria disease is much more rare than congenital infection and is more frequent when the mother has no immunity; in contrast, in endemic areas infants inherit their mother's immunity, so that malaria seldom occurs during the first six months of life. Malaria parasites can also be transmitted from man to man by the inoculation of infected blood, either intentionally, with experimental or therapeutic (the outdated malariotherapy) purposes, or accidentally through blood transfusion or sharing of injection needles; e.g. localized malaria outbreaks have been reported among drug addicts transmitted in this way.

The life cycle of malaria parasites passes through a sequence of three different types of reproduction: a) a single run of sexual reproduction, called the "sporogonic cycle", taking place in the *Anopheles* host; b) a single run of asexual reproduction, called the "pre-erythrocytic cycle", in a liver cell of the human host; and c) an indefinite number of runs of asexual reproduction, called the "erythrocytic cycle", in the red blood cells of the human host; throughout this erythrocytic cycle some parasites differentiate into male and female gametocytes which, if taken in with the blood meal of an *Anopheles*, will initiate the sporogonic cycle.

The sporogonic cycle takes between 9 and 30 days or longer depending on the parasite species but, even more, on the temperature. The gametocytes present in the

blood meal mature in the stomach of the mosquito and, after fertilization, produce a motile egg that penetrates and encysts in the stomach wall, where it divides into about 1,000 motile sporozoites, which burst into the mosquito's body cavity and invade the salivary glands, where they are ready to infect a human host in each successive bite.

Not all species of anophelines are vectors of malaria and, even among those that are vectors, there are great differences in their ability to transmit the disease. Mosquito refractoriness to malaria may be essential, due to the inability of the *Plasmodium* species to develop or to invade the salivary glands of a particular species or strain of *Anopheles*, or conditional to insufficient mosquito survival for the completion of the extrinsic cycle of the parasite, or to inadequate man/vector contact, e. g. low attraction of the anopheline to bite a human, so that, even if infected, the probability of biting again after completing parasite development becomes negligible. There are about 400 species of *Anopheles*, but only about 60 are vectors of malaria under natural conditions, some 30 of which being of major importance.

The habitat of the immature *Anopheles* is water. Eggs are laid on or on the edge of water and hatch in 2-3 days to produce larvae (wigglers), which develop through four larval and one pupal aquatic stages to produce adult flying mosquitos. Only the female mosquito bites, as it requires blood for the maturation of the eggs; the male feeds on vegetable juices. Mating occurs soon after emergence of the adult female, it takes place only once, the female storing the spermatozoa in a deposit called spermatheca, from where they are released to fertilize successive egg batches. The aquatic stages commonly last between 7 and 20 days according to temperature, the adult female may live from a few days to well over a month, going through several cycles of blood feeds and egg laying (some 100-200 per batch), every 2-4 days; survival and egg development are mainly dependent on temperature and relative humidity; under extreme climatic conditions mosquitos may go into hibernation or estivation, which allows the survival of the species through the winter in temperate climates, or long dry seasons in tropical arid areas.

There are considerable variations in larval habitats, indicative of the great evolutionary adaptability of mosquitos. Different species will breed in water habitats ranging from permanent to transient collections, from fresh to brakish water, from standing waters to flowing canals and open streams, from large open marshes to the very small water collections between the leaves of bromeliads or plant axils, tree, rock or crab holes, cattle foot prints or discarded artificial containers, from open sun to deep shade, from very shallow pools to deep wells, from clean drinking water to water highly polluted with organic matter. The characteristics of breeding places are, nevertheless, rather narrowly defined for every particular mosquito species, so that larval habitat modifications can be used for mosquito species control.

Seasonal variation in the availability of specific breeding places as well as the great influence of weather conditions on mosquito activity and survival are, to a large extent, responsible for the marked seasonality observed in mosquito densities and malaria transmission in most areas, outside of permanently humid tropical areas.

Mosquitos also show specific behavioural characteristics, which may affect their vectorial ability. Mosquitos preferences to feed on man or animals and their feeding frequency are very important determinants of the probability of their transmitting malaria. Human habitations or domestic animal shelters, particularly those with thatched roofs, abundant cracks in wall surfaces and dark corners, provide good and, for some species, preferred resting places for mosquitos to digest their blood meals and mature their eggs; as such, they favour mosquito survival. The use of indoor spraying of residual insecticides for the eradication of malaria was based on the expectation that indoor resting was the most common behaviour of malaria vectors.

Sporozoites inoculated with the saliva of a biting mosquito into the blood of a susceptible human host reach within about half an hour a liver tissue cell, where each successful sporozoite will develop into a mature liver schizont, which will burst and liberate into the blood as many as 20,000 merozoites, small forms capable of invading red blood cells. The time needed to multiply in the liver varies with the parasite species: 6 to 12 days for *P. falciparum*, 14 to 30 days for *P. malariae*, 8 to 20 days for *P. vivax* and 12 to 20 for *P. ovale*, although some *P. vivax* and *P. ovale* parasites remain dormant in the liver for months, or even some years, in a form called hypnozoite, responsible for the true relapses, characteristic of the two latter species. *P. vivax* has adapted to areas of very short seasonal transmission (because of long winters or dry seasons) by developing patterns of long incubation or interrelapse periods, when hypnozoites assure the survival of the parasite.

Merozoites penetrate red blood cells initiating the erythrocytic cycle by maturing into blood schizonts which burst, producing between 8 to 24 (depending on the parasite species) new merozoites that rapidly invade red blood cells. This development is accomplished in 48 hours for the so-called tertian malarias (benign in the case of *P. vivax* and *P. ovale*; malignant in the case of *P. falciparum*) and 72 hours for the quartan malaria (*P. malariae*); *P. vivax* and *P. ovale* selectively invade young erythrocytes and *P. malariae* selects the old, while *P. falciparum* indiscriminately invades any. This is why the former three species are self limiting while the latter may reach any density; parasitaemias over 5% should be considered as severe and exchange or partial exchange transfusion has been recommended, if it is possible to ensure pathogen free blood and to prevent transfusion related infections, in parasitaemias exceeding 10%. As the parasite grows, the surface of *P. falciparum* infected erythrocytes becomes adhesive and they are sequestered in the capillaries of internal organs, such as the brain, producing the severe manifestations typical of this parasite; this is the reason why in the peripheral blood only very young forms and gametocytes of *P. falciparum* are found (presence of mature schizonts is a sign of severity), while all the developmental forms of the three other species are commonly found.

The disease manifestations are the result of the parasitization and destruction of the red blood cells, while the development of the parasite in the liver, or its persistence as hypnozoites, do not produce any symptoms. Initial symptoms of the disease are quite variable, particularly in children, and may include irregular fever, malaise, headaches, muscular pains, sweats, chills, nausea, vomiting, some diarrhoea.

If untreated the fever acquires a tendency to periodic bouts alternating with days with less or no fever. The classical fever paroxysm, lasting 8-12 hours, goes through three typical stages: cold shivering rigor, hot with burning dry skin reaching high temperature (up to 40-42°C) and sweating with drenching sweat and lowering temperature; it is more typical of *P. vivax* (tertian periodicity) and *P. malariae* (quartan) than *P. falciparum*, which shows prostrating fever, with brief and incomplete remissions of a tertian periodicity, but which can be quite irregular. The untreated acute attack of *P. falciparum* is shorter than that of *P. vivax*; in fatal cases death often happens in 2-3 weeks, although in some cases it may occur as early as 2-3 days after onset of symptoms. Repeated infections give rise to the immune response of the host, which eventually controls the disease and the infection. Common antimalarial drugs are effective against the parasites developing in the blood, but not against hypnozoites in the liver, so that while *P. falciparum* and *P. malariae* could be fully cured, *P. vivax* and *P. ovale* may produce true relapses by new invasion of the blood from latent hypnozoites, even after complete clearance of parasites from the blood. The elimination of hypnozoites requires a long treatment (14 days or more) with primaquine or related drugs. In any case, untreated or incompletely treated infections will produce several recrudescences, after more or less long symptomless periods, from parasites surviving in the blood. In the absence of reinfection, untreated *P. falciparum* may persist for 1-2 years, *P. vivax* for 3-4, while *P. malariae* has been reported to recrudescence up to 52 years after last exposure.

Acute severity and mortality, in the absence of other complicating factors, occurs almost exclusively in *P. falciparum* infections. Besides its rapid multiplication and therefore its capacity for massive destruction of erythrocytes, this parasite causes the surface of infected red blood cells to become adhesive and to be sequestered in the capillaries of internal organs, hampering blood flow and leading to local hypoxia and damage of the vascular endothelium. The main forms of severe malaria are: cerebral, hepatic, renal, pulmonary oedema, gastrointestinal, severe anaemia and haemoglobinuria or blackwater fever.

P. falciparum malaria can proceed very rapidly to extreme severity and death. It is very important, therefore, that there is very early recognition of signs of severity which should require immediate referral for medical care; such signs include impairment of consciousness, anaemia, renal failure, respiratory distress, shock, spontaneous bleeding, convulsions, macroscopic haemoglobinuria, jaundice and hyperpyrexia. Health services should treat suspected severe malaria as a medical emergency, instituting immediate treatment; whenever possible, patients should be immediately transferred to services capable of intensive care and laboratory monitoring of signs of severity, such as parasite density, hypoglycaemia, fluid and electrolyte balance (Warrell *et al.*, 1990; Gilles, 1991).

The risk of malaria severity and death is almost exclusively limited to non-immunes, being most serious for young children over six months of age, when they have lost the immunity transferred from their mothers, in highly endemic areas in Africa and the Western Pacific; in rural areas, surviving children develop their own immunity between the age of 3-5 years. It has been reported by African health authorities that in the last few years, cerebral malaria is being seen with increasing

frequency in older children and even in young adults; it has been suggested that this may be the result of increasing urbanization and use of antimalarials and personal protection, which would reduce infection risk and delay development of immunity, compounded with increasingly ineffective treatment of disease, due to drug resistance and the proliferation of fake and counterfeit drugs (Elesha, 1993). The decline in prevalence of parasitaemia in some urban areas of Africa has been illustrated at the University College Hospital of Ibadan (Nigeria) from 70% of outpatient children in 1960 to <30% in 1968 (Hendrickse, 1976).

Severity in adults is seen in areas of low endemicity, where people may reach adult age without immunity. During epidemics all age groups are affected; equally at risk are immigrants and travellers from non-endemic into endemic areas, particularly labourers, who are often concentrating in camps, where non-immunes and infected live in overcrowded conditions with high risk of transmission. Severe malaria in adult local populations has, therefore, had a rather focal distribution, mainly in South-East Asia, the Amazon and Orinoco basins in South America and some areas of East Africa (e.g. Elamin, 1981).

Also at risk are pregnant women, possibly due to the natural immune depression in pregnancy. During pregnancy, *P. falciparum* malaria in the non-immune may lead to death, abortion, prematurity or low birthweight; in the semi-immune inhabitants of highly endemic areas malaria represents a serious risk in the first and second pregnancy as they are more frequently infected, and are susceptible to anaemia, hypoglycaemia and other complications. The placenta being a preferential site for parasite development, malaria is an important cause of low birthweight and high neonatal mortality in first and second born in endemic areas.

Cerebral malaria is the most common complication and cause of death in *P. falciparum* infections, and could represent as much as 50% of all cases of falciparum malaria admitted to hospital and 80% of fatal malaria cases. Case fatality of cerebral malaria is always high, even in hospital (10-40%), depending on a complex of factors not clearly understood, hypoglycaemia being a common complication of bad prognosis. Recovery from cerebral malaria is often complete, but some survivors retain a wide range of neurological sequelae, such as cortical blindness, hemipareses, extrapyramidal syndromes and severe mental impairment (Brewster *et al.*, 1990). While cerebral malaria is the most frequent serious manifestation, there are clinical differences in severe malaria between African children and South East Asian adults, which include the higher frequency of profound anaemia, hypoglycaemia and frequency of neurological sequelae (>10%) in the former, and the higher frequency of jaundice, pulmonary oedema and renal failure among the latter, who have lesser neurological sequelae (< 5%) (Warrell, 1992).

Severe anaemia is the second most important complication which, in some parts of Africa, may be even more common than cerebral malaria and it may also be a serious complication in pregnancy, particularly in primigravidae after the first trimester; it depends, to a large extent, on the severity and duration of parasitaemia and may predispose to secondary bacterial infection and puerperal sepsis. The relative importance of severe anaemia varies considerably from place to place, being