

Chapter 4
EPIDEMIOLOGY OF HUMAN MALARIA PLASMODIA
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Malaria is a common and serious tropical disease. It is a public health problem in some 90 countries worldwide, inhabited by nearly 40% of the world population, i.e. over 2 billion people (1993 figures). It has been estimated that malaria incidence may be in the order of 300-500 million clinical cases globally each year. Countries in tropical Africa account for more than 90% of these. Estimates of malaria mortality vary from 1.5 to 2.7 million deaths worldwide per year, with some 100 000 deaths occurring outside Africa.

In this chapter, human and parasite factors influencing malaria transmission will be presented, followed by an example of how these factors intertwine in the historical evolution of the malaria distribution over the last century. In the second half of the chapter the present geographic distribution of the malaria problem is described along with the epidemiology of drug-resistant malaria. The chapter concludes with epidemiology in practice: major epidemiological types, high risk population groups, management information needs for malaria control, and the bare epidemiological necessities for district health officers.

Human malaria parasites and factors influencing malaria transmission

Plasmodium parasites, people, *Anopheles* mosquitos, and the environment all have a profound influence on the transmission potential for malaria infection. Some of the factors influencing transmission are inherent to the malaria species, their mode of transmission and the physical environment. Other factors are man-made, including development and malaria control efforts, which can have positive or negative effects on the transmission potential. Man-made factors such as war, migration, vector resistance to insecticides and parasite resistance to drugs invariably enhance malaria transmission, or at least make its control more difficult and expensive.

a. Malaria species and mode of transmission. Four species of *Plasmodium* protozoa cause malaria in humans: *P.falciparum*, *P.vivax*, *P.ovale* and *P.malariae*. The species differ in many ways, some of which have a direct bearing on transmission and distribution patterns. Malaria parasites are normally transmitted from one person to another through infective bites of *Anopheles* mosquitos. The source of infection can be either a sick person or an otherwise symptomless carrier of parasites. The form of the parasite that can infect mosquitos is the gametocyte. Gametocytes start developing in red blood cells in capillaries of the inner organs of infected persons after the invasion of the blood by merozoites. Mature gametocytes appear in the peripheral blood some 3 days (*P.vivax*) to 10 days (*P.falciparum* and *P.malariae*) later, ready to be picked up by a mosquito. In *P.vivax* and *P.ovale* infections a non-immune patient will thus be infectious to mosquitos at or shortly after the onset of clinical symptoms. In *P.falciparum* infections the patient becomes infectious only after several days when the mature gametocytes appear in the peripheral bloodstream. Persons in highly endemic areas who have been repeatedly infected with malaria acquire a degree of immunity to malaria which

suppresses most clinical symptoms. These people may still carry gametocytes in their blood that will infect the mosquitos biting them. Antimalarial drugs such as chloroquine and mefloquine that are prescribed to cure malaria infections do not eliminate mature *P.falciparum* gametocytes from the bloodstream. A person who has been successfully treated with antimalarial drugs may thus be healthy but infective for up to two months until the *P.falciparum* gametocytes die off naturally, or until another drug such as primaquine is given that does eliminate the mature gametocytes.

The incubation period in malaria covers the time between infection and first appearance of clinical signs, of which fever is most common. The length of the incubation period depends on the infecting species and is usually between 9 and 30 days, shortest for *P.falciparum*, longer for *P.malariae*. In some strains of *P.vivax* the incubation period may last 8-9 months: perfectly suited to seasonal transmission in colder climates with a short transmission season.

In the case of *P.vivax* and *P.ovale*, some parasites remain dormant in the liver for many months. Relapses caused by these persistent liver forms (hypnozoites) may appear months, and occasionally up to 4 years after exposure, bringing with it the risk of delayed transmission of the infection to others. *P.malariae*, like *P.falciparum*, does not have persistent liver forms. However, un-treated or partially treated blood infection with *P.malariae* may be present for many years, perhaps for life with or without clinical symptoms. Untreated *P.vivax* and *P.ovale* infections may linger on (and remain infectious) for 1 1/2 to 5 years, untreated *P.falciparum* 1-2 years. In areas with emerging drug-resistant *P.falciparum*, recrudescences of the infection may occur up to a month or more after what initially seemed to be a successful clinical cure.

Malaria can also be transmitted via blood transfusions. This can accidentally happen if a person donates blood before the onset of clinical symptoms, after merozoites have entered the blood stream from the liver. Blood donations from *P.malariae* carriers and (semi)immune persons without clinical symptoms may also contain malaria parasites. In certain cases this has given rise to malaria outbreaks in paediatric wards of urban hospitals, most notably concomitant with dengue haemorrhagic fever epidemics when many children receive transfusions. Similarly, malaria may be transmitted by contaminated needles and syringes. Relapses do not occur in relation to transfusion malaria. In congenital malaria, which is comparatively rare, parasites are transmitted from mother to child before and/or during birth.

All non-immune persons, regardless of age or sex, are susceptible to malaria infection. The only exceptions are the indigenous populations of Western and to some extent Central Africa, whose erythrocytes lack the Duffy blood group antigens which are essential for penetration of *P.vivax* into erythrocytes. Other genetic anomalies such as the sickle cell trait, ovalocytosis, glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, and thalassaemias alter but do not restrict malaria transmission. They may offer some protection against severe falciparum malaria.

Ambient temperature. Temperature is an important factor which, through its effect on the development of the malaria parasite in the vector and its effect on the development of the vector itself, greatly influences the geographical distribution of malaria transmission in general and malaria parasite species in particular. Female *Anopheles*

mosquitos ingest malaria gametocytes when taking a blood meal from an infected person. The parasite needs a period of development in the mosquito before it can infect other people again. The length of this extrinsic sporogonic cycle depends on the *Plasmodium* species and the ambient temperature. The development of *P.falciparum* in the female adult *Anopheles* mosquito requires a minimum temperature of 20°C whereas the other human malaria species can develop at temperatures down to a minimum of 16°C. Above the minimum temperature the development of the parasite in the vector accelerates with increasing temperature. The duration of sporogony at optimum temperatures for *P.falciparum* is 8-10 days. It is somewhat less for *P.vivax*. Sporogony of *P.malariae* and *P.ovale* takes longer, and only a minority of vectors live long enough to transmit them. Malaria epidemics may occur when conditions for malaria transmission are marginal in terms of temperature, rainfall patterns or altitude.

Development. There are many instances where socio-economic development has reduced malaria transmission through improvements in agriculture, housing construction, land use, etc. The concomitant development of health services will reduce morbidity and mortality and contribute to a reduction in transmission. However, uncoordinated development such as in slum areas of rapid urban growth may enhance malaria transmission. In ill-designed development projects the thoughtless creation of additional mosquito breeding places may combine with large-scale migration to cause malaria epidemics.

Control efforts. Control efforts aiming to substantially reduce transmission through unsustainable methods may put populations at risk of epidemic malaria when control efforts can no longer be kept up. Such may be the case in areas where the level of endemic malaria has been reduced through time-limited large-scale vector control programs.

War. Some recent epidemics occurred in areas of social and political upheaval or economic distress, where health infrastructure was destroyed, control efforts abandoned, and large populations had to leave their homes in search of security.

Migration. Migration of non-immunes into endemic areas may lead to malaria epidemics, as may migration of parasite carriers into non-endemic, receptive area. Receptivity refers to an abundant presence of anopheline vectors and the existence of other ecological and climatic factors favouring malaria transmission. Thus resettlement schemes and development projects involving an influx of labour forces may lead to malaria epidemics, as may refugee movements.

Resistance to drugs. Ineffective antimalarial drugs will not clear the parasites from the blood, thus potentially prolonging the infective period of patients. Also, as second line drugs tend to be more expensive, many people may no longer be able to afford a full treatment course.

Transmission patterns - two extremes

Stable malaria is caused by the presence of a vector with a frequent man-biting habit, with moderate to high longevity, at temperatures favourable to rapid completion of the sporogonic cycle. With such characteristics, only very few bites per person per night are necessary to maintain transmission. Seasonal changes will occur with changes in temperature. Transmission stops when the ambient temperature drops below some 15°C. A seasonal increase may occur during the warm weather, starting at a relatively low temperature and terminated by low temperature. Marked fluctuations other than normal seasonal changes are not likely except when due to obvious causes. Epidemics are very unlikely, except among non-immune populations arriving to the area. The regularity of transmission is likely to ensure stable immunity, varying in degree from place to place. Only the young children will not have experience with malaria and thus no resistance to it¹. In areas with stable malaria it is very difficult to reduce transmission. The first objective will be to reduce morbidity and mortality through early diagnosis and adequate treatment of malaria disease, especially in children, and through personal protection methods.

Unstable malaria occurs where malaria is transmitted by a vector which feeds on humans only infrequently. Consequently, high densities of *Anopheles* are needed to maintain transmission. Endemicity and the immunity status of the population will differ markedly by area and over time, depending on the presence of other factors favourable for propagation of mosquitos and thus malaria transmission. When conditions for transmission become favourable, epidemics may occur.

Epidemic malaria is the "malaria of non-immunes"². Epidemics occur when non-immune and partially-immune populations are exposed to high rates of transmission. Malaria epidemics, if uncontrolled, follow a natural course. The epidemic grows in a series of steps representative of the incubation interval (the period between the occurrence of infective gametocytes in the primary case and their reappearance in a secondary case), which is about 20 days for *P.vivax* and 35 days for *P.falciparum*. The length of the incubation interval and the degree of the reproduction rate determine the rate of multiplication of transmission, which is much faster in *P.vivax* epidemics than in *P.falciparum* epidemics. In areas where both *P.vivax* and *P.falciparum* are present, the initial stages of an epidemic will be determined by a predominance of *P.vivax* infections and a very gradual increase in severity of the epidemic, while in later stages *P.falciparum* is likely to be abundant. The peak of new infections due to *P.falciparum* epidemics will only be reached when some 50% of the population at risk is infected, unless climatic changes (notably colder temperatures) prevent further transmission.

Potential epidemic situations can often be identified through knowledge of the epidemiology of malaria in a

given area combined with an awareness of socio-economic trends. Many epidemic prone situations will, by their nature, stretch across national boundaries. Over the last years, epidemics occurred in countries such as Botswana, Ethiopia, Turkey, Uganda and Viet Nam, and in various refugee populations. Control of malaria epidemics involves relieving the immediate clinical consequences, preventing the progress of the epidemic in time and space, and preventing future recurrences. This means improving disease management and providing some form of transmission control. Control of epidemics and reduction of mortality become difficult as epidemics tend to occur in less accessible areas without regular health services.

Historical evolution of malaria distribution^{3 4}

Ancient records suggest that a disease similar to malaria was long known. References to seasonal and intermittent fevers exist in ancient Assyrian, Chinese, Egyptian, and Indian religious and medical texts. Whether they actually describe malaria remains uncertain. Hippocrates, in the fifth century B.C., made the link between the appearance of the disease and the season of the year or the places where his patients lived. He described in detail the clinical picture of malaria and some complications of the disease. Well over 2000 years later, in 1880, Laveran, a French army surgeon in Algeria, was the first to see and describe malaria parasites in the red blood cells of man.

Where the malaria parasite originated from has not been generally agreed upon. Bruce-Chwatt (1985) concluded that the disease probably originated in Africa, where man acquired the infection from primates and spread it to Europe, Mesopotamia, India, and SE Asia. The reverse has also been argued: that the origin of primate malarias was in Asia and that man has been responsible for the spread of the parasites to African and New World primates⁵. To the present date chimpanzees and gorillas remain the natural reservoir for *P.malariae*. How malaria arrived in the New World remains unclear. It is speculated that *P.vivax* and *P.malariae* were brought from SE Asia to S America by pre-Columbian travellers. *P.falciparum* was then introduced much later by Spanish colonizers and African slaves.

Geographical boundaries of malaria transmission are not constant: they have changed over the centuries with changes in global climate, migration of populations to previously uninhabited areas, and the mode of life. The distribution of malaria within the geographical boundaries of transmission is similarly changing.

Malariological surveys carried out around the turn of the century suggest that malaria at that time probably approached its broadest range of distribution (Map 1). The disease was recorded as high as 2850m above sea level in Tajikistan, and as low as 400m below sea level in the Dead Sea area. At that time, the impact of anti-malarial

activities and social and economic development was still limited, and the boundaries of malaria distribution were determined by natural factors relating to the propagation of *Anopheles* mosquitos and the malaria parasites in them. *Anopheles* was absent in Antarctic, parts of Arctic region, and higher mountain ranges, due to unfavourable conditions for their propagation. Natural barriers prevented the spread of *Anopheles* to Pacific Ocean Islands such as New Zealand, American Samoa, Tonga, Cook, Guam, Fiji and New Caledonia. Indigenous malaria was also absent from areas where, although *Anopheles* was present, the average ambient temperature was too low for the parasite to complete the sporogonic cycle, and thus for the vector to transmit malaria ("Anophelism without malaria"). Within these broad geographical boundaries the distribution of the malaria problem was very uneven, underlining the focal nature of the disease. The most intensive malaria transmission occurred in areas of tropical Africa and Papua New Guinea where the equatorial climate provided year-round favourable conditions for mosquito survival, man-mosquito contact and completion of sporogony. Marked seasonal variations in malaria intensity were observed in other parts of the (sub-)tropical belt, and an epidemic tendency was recorded in areas towards the edge of the malaria distribution. Malaria was concentrated on the plains, in mountain valleys, and foothills where an abundance of breeding places favoured the propagation of *Anopheles* populations. With increasing altitudes the mosquito fauna became less diverse and mosquito breeding places and densities decreased. This, in combination with a reduction in temperature with altitude, made that malaria ceased to exist at altitudes over 1500m above sea level in most malarious areas. Malaria was also absent in desert areas where conditions for mosquito breeding and survival are particularly difficult. However, it was present in oases where underground water caverns enable mosquito survival.

Both the first and second World War (WWI and WWII) influenced the distribution of malaria. Soon after WWI an extensive epidemic occurred in Russia. Other malaria outbreaks occurred in countries such as England, France, Germany, and Italy. Social upheaval caused by the war combined with favourable climatic conditions to enhance transmission. Between WWI and WWII considerable social and economical development took place in Europe, parts of Asia, and N America. Changes included improvements in agriculture, housing construction, increased urbanization, and land reclamation notably in Italy and Holland. This, together with wider availability of quinine, resulted in a considerable reduction in the intensity of the malaria problem in Europe and N.America. As a result, by the start of WWII the malaria conditions of Europe and N.America were quite different to that at the time of WWI. Following WWII the spread of malaria was greater, but of lower intensity than the spread which followed WWI. WWII extended well into N.Africa and Asia. Military personnel acquired malaria in these areas and brought *P.vivax*, *P.falciparum* and *P.malariae* back to Europe and America. The difference

in intensity of malaria following the two World Wars can be attributed to social and economic changes and to improved chemoprophylaxis and personal and group protection among the troops, particularly after 1944 with the advent of DDT for malaria control. Prior to WWI the spread and intensity of the malaria problem within its boundary of distribution was mainly determined by natural factors. Between the two World Wars, at least in Europe and N.America, this distribution was to a considerable degree determined by the pace of social and economic development and to a lesser extent by organized malaria control operations.

After the end of WWII the situation changed drastically. Residual insecticide spraying was introduced for malaria control, and new synthetic antimalarial drugs became available for treatment. As a result of the selective use of these new powerful tools, together with the progress in socio-economic and health services development, malaria practically disappeared from Western and Central Europe, N.America, Chili, Japan, and from the northern and central parts of the USSR. By the end of the 1950s a population of about 220 million, some 20% of the total population living in malarious areas, had been freed from the risk of the disease. This, together with successes with residual insecticides for malaria control in some countries with (sub-)tropical climates (notably British Guyana, Greece, Italy, Taiwan, and Venezuela), led to the belief that malaria could be eradicated in a relatively short time from most of the malarious areas in the world.

In May 1955, the 8th World Health Assembly decided that WHO should take the initiative in developing an international programme aimed at the worldwide eradication of malaria. The possibility of interrupting malaria transmission with residual insecticides in the most intense malaria foci of tropical Africa was still unproven, and this part of Africa was temporarily excluded from the global programme. Thus the most severe malaria problems in the world were left unattended, while the more "doable" areas were approached first. The concept of malaria eradication depended heavily on the use of DDT and the availability of chloroquine. The extensive vertical eradication programmes used a "blanket" approach, oblivious to the focal nature of the epidemiology of malaria disease. The global malaria eradication programme, an effort of unprecedented magnitude, attracted over 200 million US\$ in international assistance during the ensuing 10 years.

By 1968, as a result of the intensive international efforts, the geographic area of malaria between its northernmost and southernmost boundaries was considerably narrowed, and within these boundaries the distribution and intensity of the malaria problem were greatly reduced. Malaria was eradicated from Europe, the USSR, Australia, Tunisia, Libya, Lebanon, Jordan, Israel, the Korean Peninsula, from all islands with a sub-tropical climate and from many islands with a tropical climate, including the Caribbean islands (except Haiti), Mauritius, Reunion,

Taiwan, etc., and from most of the malarious areas of Argentina and South Africa. *P.falciparum* was the first species to disappear from the former fringe areas of the geographic range and from many areas or countries with a sub-tropical climate (N.Mexico, Argentina, S.Brazil, Algeria, Morocco, Turkey, Syria, Iraq, N.Iran, Afghanistan, Nepal, N.China, Korean Peninsula, N.Viet Nam). In many tropical countries the proportion of *P.falciparum* infections was markedly decreased, to the level where *P.vivax* became the dominant species. Only in areas where malaria was not amenable to control with residual insecticides, due to exophily of vector populations, poor housing and/or intensive population movements, *P.falciparum* remained the predominant species. *P.malariae* usually fell into the same pattern of disappearance as *P.falciparum*, though occasional indigenous *P.malariae* cases continued to be reported even from areas where malaria was eradicated long ago. With some exceptions (Amazonian Region of Brazil, Colombia, Haiti, Surinam, and some areas of Laos, S.Viet nam, Cambodia, Myanmar and Thailand), *P.vivax* became the major species. In tropical Africa the malaria distribution and prevalence remained practically unchanged with the majority of malaria cases being due to *P.falciparum*.

In the early seventies the concept of malaria eradication had to be abandoned for various reasons, including technical problems, as parasites became increasingly resistant to drugs, and mosquitos resistant to insecticides. Besides, the logistics and resources involved in eradication programmes were too heavy a drain for many national health budgets. When the World Health Assembly in 1969 decided to re-examine the malaria eradication strategy, donors quickly responded with a withdrawal of funding from the programme. Many national programmes in developing countries had already exhausted their capabilities to improve the situation further or maintain the malaria-free status. The economic crisis at the beginning of the 1970s, which heavily affected the developing countries, led to a another considerable reduction in antimalarial activities. Prices of insecticides and drugs became unaffordable, even more so where DDT resistance and chloroquine resistance necessitated the purchase of more expensive alternatives. As a result, malaria started a gradual and in some instances dramatic comeback in many Asian and Latin American countries from where malaria had not been completely eradicated. The majority of "post-eradication" malaria epidemics were due to *P.vivax*. However, within a short period of time after the re-establishment of malaria transmission *P.falciparum* usually reappeared, with the exception of countries in Asia Minor.

Recent years have seen an intensification of malaria transmission in many previously less affected or unpopulated areas: agricultural development areas, jungle areas with open mining, industrial and agricultural development projects, peri-urban settlements of explosive population growth, areas with socio-political disturbances, civil wars and refugee movements, and so forth. In most of

these areas *P.falciparum* has become the predominant species. The northern and southern limits of *P.vivax* and *P.falciparum* distributions are now almost identical. *P.malariae* has a very patchy global distribution, and is common along the equatorial belt in Africa with relative prevalences as high as 25%. *P.ovale* is restricted to tropical Africa, with rare cases recorded from countries in SE Asia and the Pacific. Its relative prevalence is generally low (between 0.1 and 10%), but may be somewhat higher in forest and coastal regions. The relative prevalence of malaria species is fairly stable through the year in areas with perennial transmission, but may vary in areas with seasonal transmission⁶. Thus the distribution and intensity of the malaria problem are currently governed by natural factors, by the pace and direction of social and economic development including the health sector, and by a country's capability to organize and sustain epidemiologically sound malaria control activities.

In 1945, only 30% of the world's population was estimated to live in areas free from malaria transmission. By 1959, just after the start of the world-wide malaria eradication campaign, this percentage had increased to 43%. In 1968, at the height of the malaria eradication campaign, 53% of the world's population was free from malaria risk. By 1982 this percentage had gone down again to 44%. In 1993, mainly on account of the eradication of malaria from the most populated areas of China, 64% of the world's population was estimated to live in areas free from malaria transmission. Obviously, since the world population has been growing from 2.9 billion in 1959 to 5.5 billion in 1993, the absolute number of people exposed to malaria risk is still a staggering 2 billion, compared to 1.7 billion in 1959.

Several international regulations remain to help contain the spread of malaria and its vectors. These include the disinsection of aircraft before departure or in transit; disinsection of aircraft, ships and other vehicles on arrival if the health authority at the place of arrival has reason to suspect importation of malaria vectors; and the enforcement and maintaining of rigid antimosquito sanitation within the mosquito flight range of all ports and airports. In special circumstances antimalarial drugs may be administered to potentially infected migrants, refugees, seasonal workers, and persons taking part in periodic mass movement into areas or countries where malaria has been eliminated⁷.

Present geographic distribution of malaria problem (Map 2)⁸.

In Africa south of the Sahara malaria remains one of the worst public health problems. It is estimated that 270 to 480 million clinical malaria cases occur annually, some 140 to 280 million of them occurring in children under 5 years old. Only a fraction of malaria cases are reported. More than 90% of the population in the WHO African Region live in areas where they are at risk of getting malaria, with

74% of the population living in highly endemic areas where malaria transmission is intense and perennial (equatorial and tropical forests and Sudanese savannas at altitudes up to 1000 m with an average rainfall over 2000mm/year). At altitudes over 1500m and rainfall below 1000mm/year, endemicity decreases and the potential for epidemic outbreaks increases. *P.falciparum* is the predominant species in the highly endemic areas, where some 30% of febrile illnesses are attributable to malaria. Mortality is concentrated in the younger age groups. Among children referred to hospitals with severe malaria, case fatality rates of 10-30% have been reported. In rural areas with little access to adequate treatment these rates might be even higher. Overall, malaria produces considerable impact on the health of young African children, leaving neurological sequelae, increasing susceptibility to other infections, and hampering development.

In the WHO Eastern Mediterranean Region, a group of countries stretching from Morocco to Pakistan, about 45% of the population live in areas where they are at risk of *P.falciparum* and *P.vivax* transmission. Another 15% is at risk of *P.vivax* alone. It is estimated that some 13 million cases of malaria occur annually in the region, the large majority caused by *P.falciparum*. Some 35,000 deaths are estimated attributable to malaria, occurring chiefly in Sudan, Somalia and Yemen. Over 95% of malaria cases occur in just five countries: Sudan, Somalia, Yemen, Afghanistan and Iraq. In these countries, as well as in Djibouti, widespread poorly controlled malaria is due to extremely favourable conditions for transmission, and/or disruption of control programmes due to war and political instability. In the remainder of countries malaria is under more or less firm control or has been interrupted altogether. In Iraq, Morocco and Syria *P.falciparum* has been selectively eradicated, with *P.vivax* transmission remaining⁹.

Malaria transmission is a public health problem in 21 countries and territories in the Americas. During 1993, a total of almost a million microscopically confirmed malaria cases (*P.falciparum* and *P.vivax*) were reported, a slight decrease compared to previous years. However, records of the actual number of malaria treatments administered through the health services indicate incidences some five times higher. Taking into account that the private sector and self-treatments are not included in these data, officially confirmed malaria cases appear to be only a small portion of the actual number of patients with malarial disease. Nearly half of the cases were registered in Brazil; a third originated from the Andean countries (Bolivia, Colombia, Ecuador, Peru, Venezuela) and almost one sixth from Central America and Mexico. While the overall proportion of registered *P.falciparum* infections declined slightly to some 30% in 1993, their proportion increased in Bolivia, Ecuador, French Guiana, Guatemala, Mexico, Peru and Venezuela. Almost two-thirds of all falciparum infections detected in the Americas occurred in Brazil.

During the last 3 years, the overall number of malaria cases reported in the WHO South East Asia Region remained stable at 2.6 to 2.7 million cases annually. India represents some 80% of these recorded cases. The real malaria incidence may be about 6-7 times higher, representing between 16 and 19 million malaria cases annually, of which more than half are falciparum malaria. Most of the malarious areas, accounting for nearly half of the total number of cases, are situated in forests, forest-fringe areas, forested hills, development project areas and their surroundings. Due to the exploitation of natural resources forests become more accessible and movements of populations with low immunity into such areas result in malaria epidemics. Many such areas are close to the international borders. Their population is very mobile and the peripheral health structure is lacking and inadequate for the early diagnosis and treatment of malaria. The world's worst multi-drug resistance problems occur in such areas, especially in border areas between Thailand and Myanmar and Thailand and Cambodia. Some areas in South East Asia rely for malaria control on extensive vector control operations, leaving the malaria situation precariously influenced by the quality and extent of such operations and the development of insecticide resistance.

The total malaria incidence of East Asia and the Western Pacific declined by some 20% between 1992 and 1993. Australia, Brunei Darussalam, the Korean Peninsula, Hong Kong, Japan, Macao, Mongolia, Singapore, large areas of China and most of Oceania remained free of malaria altogether. The majority of cases were reported in Viet Nam, the Solomon Islands, Myanmar, and Thailand. Several countries experience severe and deteriorating falciparum malaria problems, especially in peripheral parts of the country, often combined with the occurrence of multidrug-resistant *P.falciparum*. Malaria is for instance a major cause of illness and death in Cambodia, Laos and Viet Nam.

99 000 confirmed malaria cases and 1100 deaths due to malaria were recorded in Cambodia in 1993, but real figures are estimated to be over five times as high: some 0.6 million clinical cases and 5000 to 10 000 death annually. In Laos an estimated 14 000 deaths due to malaria occur each year. Viet Nam has an estimated number of clinical cases in the order of 1.5 million per year. Levels of antimalarial drug resistance in some parts of these countries are so high that chloroquine and sulfadoxine-pyrimethamine are useless against falciparum malaria. In addition, there is localized resistance to both quinine and mefloquine. In some provinces the main treatment for falciparum malaria is now artemisinin or artesunate. Malaria is holoendemic in parts of Papua New Guinea, very similar to parts of Africa. Vanuatu and the Solomon Islands have the highest overall malaria morbidity of this region with 66 and 364 malaria cases per 1000 population respectively, some 60% due to *P.falciparum*.

Europe experiences a steady influx of malaria cases

imported from tropical countries. A substantial portion of these occur in nationals from endemic countries, who upon living in Europe for some time, and thereby losing their immunity, subsequently become infected when visiting their relatives back home. Isolated cases of local transmission in Europe (excluding Turkey) occur rarely, including some cases of "airport malaria". In Turkey, malaria incidence has increased over five-fold since 1990. The provinces most affected are located in south-east Anatolia, most of them bordering Iraq. In this area of extensive population movements one of the largest development projects in the Middle East is under way, including some 22 new dams for electricity production and irrigation.

Present epidemiology of drug-resistant malaria

P.falciparum. Strains of *P.falciparum* resistant to chloroquine were first reported in S America and SE Asia in the early 1960s. Since then they have swept across the globe. Among the countries where falciparum malaria is endemic, only those of Central America have as yet not recorded chloroquine resistance. Chloroquine resistant *P.falciparum* spread over almost all of tropical Africa in the 1980's. In many African countries, especially in eastern Africa, high levels of resistance pose increasing problems for the provision of adequate treatment. Surveillance has indicated that the development of resistance to chloroquine has been accompanied by an increasing incidence of severe malaria. An increase in the prevalence of anaemia in very young children may be one of the early signs of chloroquine failure. Resistance to sulfadoxine/pyrimethamine is widespread in South-East Asia and South America but focal and uncommon in other parts of the world. In certain border areas of Thailand over 50% of falciparum infections no longer respond to mefloquine therapy. Reduced sensitivity of *P.falciparum* to mefloquine has only rarely been reported in *in vivo* studies in Africa. It has not been reported from the Americas. In several countries of South-East Asia as well as in Brazil quinine plus tetracycline is used for treatment for uncomplicated malaria, and sensitivity to quinine is diminishing. Consequently, artemisinin and its derivatives are increasingly being deployed for first-line treatment in these areas.

P.vivax. Resistance of vivax malaria strains to chloroquine, first documented in 1989 in infections from Papua New Guinea, has now been confirmed in Indonesia, Myanmar and Vanuatu. In some localized foci in Indonesia and Papua New Guinea, 20-30% of patient infected with vivax malaria suffer recurrences of parasitaemia 1 to 3 weeks after a course of 25 mg chloroquine base/kg. Elsewhere chloroquine resistance does not yet pose an operational problem.

P.ovale and *P.malariae*. Occasional reports of drug resistance exist, as yet without operational significance.

World maps depicting the geographic distribution of drug-resistant *P.falciparum* are somewhat misleading. The mere reporting of drug resistance does not imply that all parasite strains in an entire country show resistance; chloroquine may well be operationally effective treatment for the large majority of malaria cases. Similarly, the absence of reported drug resistant *P.falciparum* may only point to the absence of a regular monitoring system. However, on a country basis the accurate monitoring and mapping of *in vivo* drug resistance is an important, essential part of the national malarial drug policy.

Epidemiology in practice

Arm chair epidemiology of local malaria situations. On the basis of easily recognizable ecological and social characteristics, most malaria situations in the world can be identified as falling within a few major epidemiological types. For each of these, certain risks are particularly important, and certain approaches to control are more likely to succeed than others. Planning malaria control for a given area starts with identification of the major epidemiological types within it, followed by collection of information on the particular risks and on control approaches that might be realistic (see Table).

High risk of malaria disease and death. To get an overview of the malaria problem in any given area, and to target control activities towards a reduction in morbidity and mortality, it is important to realize who are most likely to be affected by the disease, and who are most likely to die of it. The individual risk of serious illness and death is closely related to the absence of acquired immunity. Immunity to malaria is only partial and for a duration that is a function of the intensity and frequency of prior infections. In areas with seasonal or epidemic malaria where disease is infrequent, adequate protective immunity may never build up and the disease will affect all age groups. This will also be the case in previously endemic areas that have become epidemic, for instance as a result of increasing urbanization. Even "fully immune" adults who are no longer exposed to infection lose their immunity over 1-2 years.

High risk population groups. The vast number of malaria deaths occur in endemic areas of tropical Africa among children aged 6 months to 3 years, especially in remote rural areas with poor access to health services. In these areas *falciparum* malaria may kill up to 5% of children before the age of five years. The surviving children who continue to be exposed to infection gradually acquire partial immunity. Malaria is a major cause of anaemia in children, and increases their vulnerability to other diseases. It is estimated that malaria kills about 1

million children below the age of 5 every year. For some of them malaria will not be the only cause of death. Another group at high risk of malaria are pregnant women. In the majority of developing countries these will be young women in their teenage years. They are at higher risk of clinical disease, and at higher risk of severe disease. In endemic areas malaria substantially increases the risk of maternal anaemia, abortion, stillbirth, prematurity and low birth weight during a woman's first pregnancy. With subsequent pregnancies this risk diminishes. The risks of malaria infection in non-immune pregnant women include spontaneous abortion in up to 60% of cases and a maternal mortality rate of up to 10%. Other high risk groups include non-immunes such as travellers, refugees, displaced persons, or labour forces entering into endemic areas.

High risk occupations. In some areas, including parts of SE Asia and S America, malaria transmission may be geographically linked to specific activities and occupations, such as wood cutting or gem mining in forest areas. In these areas the disease affects specific segments of the population. Low immunity combined with inappropriate and delayed treatment may lead to high mortality and severe morbidity in those affected. In addition, some of the world's worst antimalarial drug resistance problems occur in these areas.

High risk environment. Persons who should normally not be at risk of serious life-threatening disease are put in danger when they have no access to early diagnosis and adequate treatment of malaria disease. This can be due to inadequate health infrastructure, inadequately trained health staff, or scarcity of resources (of the patient and/or health services). Socio-political unrest, population movements and civil war may make health facilities inaccessible or non-functional.

Fine tuned management information needs for malaria control. Assessment and analysis of local malaria problems are a prerequisite for targeted control activities. An appropriate epidemiological information system is thus an essential part of a control programme. The Global Strategy on Malaria Control recommends that epidemiological information should include morbidity and mortality data, as well as information on underlying factors relating to the human population, the parasite, the vector and the ecosystem, and on the impact of malaria. In addition, the status of health services and of existing vector control activities should be taken into account in planning, as should the constraints and opportunities posed by resources and the physical and administrative infrastructure.

d. The bare epidemiological necessities. For district health officers, the bare necessity will be to have descriptive information on "person, place and time" relating to malaria morbidity and mortality. In short: WHO,

WHERE, WHEN, HOW MUCH and WHAT KIND OF? The district officer needs to know who gets affected (age, sex, occupation), which villages or areas are most affected, and during which times of the year. To target effective first line treatment with antimalarial drugs, the patterns of different malaria species present in the district must be known (*P.falciparum* or other species), and their patterns of response to treatment. For the latter, WHO has developed a simplified *in vivo* monitoring system, based on the active follow-up of malaria patients for signs of drug failure. In the absence of such *in vivo* monitoring, treatment failures reported by health centres will give a rough and ready indication of the effectiveness of first line antimalarial drugs.

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