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The burden of malaria

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outdated malariotherapy) purposes, or accidentally through blood transfusion or sharing of injection needles; *e.g.* localized malaria outbreaks have been reported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 (wrigglers), 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 40-42C) 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 postrating 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 recrudesce 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 sequestred 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 highest in areas of year-round high transmission. A recent study in two large hospitals in Malawi, one serving an area with perennial high transmission and the other an area with marked seasonal fluctuations, indicated that malaria associated severe anaemia was 8.5% of all paediatric admissions and accounted for 54% of of malaria related deaths in the former, and 5.2% and 32% respectively in the latter, while the proportion of deaths due to malaria was rather similar in both places – 17.5% and 20.4% respectively – and in both places malaria associated severe anaemia peaked at the age group 6-11 months (Slutsker *et al.*, 1994).

In the highly endemic areas of tropical Africa, where the risk of death is practically limited to children between 6 months and 5 years of age, both sickness and death appear as highly seasonal, peaking at the end of the rainy season or seasons. There is a striking difference in the age at which the two main fatal syndromes occur; while severe malaria anaemia occurs at an early age, between 22 and 27 months, cerebral malaria occurs in children who are between 40 and 45 months old and may already be semi-immune (Marsh, 1992).

Severe disease and fatal outcome may also be the result of **rupture of the spleen** in *P. vivax* infections and of **quartan malaria nephrosis** in *P. malariae*, in which it is possible to detect depositions of antibody complexes on the basement membrane of the glomeruli; in highly malarious areas, new cases of nephrotic syndrome may represent about 2% of hospital admissions (Kibukamusoke, 1973).

Circulating malaria parasites can be eliminated from the blood with effective specific drugs, called schizontocides, which include quinine, chloroquine, amodiaquine, sulfadoxine-pyrimethamine, mefloquine, halofantrine, artemisinin, artemether and artesunate; all these drugs, at the appropriate doses, will completely cure a malaria disease episode with a short treatment (between a single dose of -sulfadoxine-pyrimethamine to ten days of quinine), unless the *Plasmodium* is resistant to the given drug. None of these drugs will destroy hypnozoites of *P. vivax* or *P. ovale* in the liver, for which other drugs like primaquine and longer treatments of 14 days or more are needed.

Resistance to drugs has become a very serious problem with *P. falciparum*; during the last decades there has been an increasingly rapid selection and dispersal of *P. falciparum* parasites resistant to antimalarial drugs, as more and more frequently these drugs are used as prophylactics and for automedication, often in insufficient doses. Resistance to chloroquine, first discovered in South America (Colombia-Venezuelan border) and in South-East Asia (Cambodia-Thai border) in the late 1950's, spread through South America, Asia and the Pacific and, since the late 1970's, has shown a particularly alarming evolution in Africa where, during the 1980's, it has spread through the continent. Resistance to amodiaquine, a related drug, and to sulfadoxine-pyrimethamine followed a similar pattern and is now also very widespread, and resistance to mefloquine has also started to develop in South-East Asia. The continuous intensification of this problem is hampering the efforts to provide adequate treatment in peripheral areas. It is difficult to assess how much of this phenomenon is due to migration of resistant parasites and how much to local selection, as both mobility and drug consumption have increased considerably in the recent past. There are many places in Africa where people use chloroquine more often than aspirin for minor fevers and aches.

Malaria mortality has been estimated at between 10 and 20 per thousand in children in the 1-4 years age group. In 1962 W.H.O. Regional Office for Africa estimated that every year between 200 000 and 500 000 African children die from malaria (Pampana, 1969); Bruce-Chwatt in 1969 estimated that figure at about one million. The latter figure has been extensively quoted ever since. Molineaux (1985), reviewing the impact on infant mortality of some malaria control projects, in particular those of Kisumu (Kenya) and Garki (Nigeria) concluded that malaria was responsible for about 20 to 30% of infant mortality. Studies in the Gambia show a malaria mortality in the order of 6.3 per thousand per year in infants and 10.7 per thousand per year in children 1-4 years old (Greenwood *et al.*, 1987), representing 10% of deaths before one year of age and 25% of those in the 1-4 years age group.

There have been nevertheless indications that at least in some areas of Africa, general infant and malaria specific mortality may be declining, often independently of specific interventions and more in line with social development and general education. Studies in Congo and Burkina Faso in the late 1970's indicated that malaria specific mortality could be lower than expected in areas where some decades ago malaria constituted a major cause of infant mortality. The authors (Carme *et al.*, 1984; Trape, Quinet *et al.*, 1987; Trape, Zoulani *et al.*, 1987; Vaise *et al*, 1981) attributed their findings to the widespread, even if indiscriminate, use of antimalarial drugs, often at doses which may not be adequate to ensure parasite clearance, but may achieve clinical cure and prevent death, even if collectively they will increase the drug pressure over the overall parasite population and may, therefore, be contributing to the selection of resistant parasites. The wide availability of antimalarial and other active drugs has also been blamed as a potential contributing factor to the general decline of infant mortality that was observed in the Kisumu area of Kenya, where between 1972 and 1976 overall infant mortality was reported to have declined between 157/1000 and 93/1000 while an effective malaria control programme using fenitrothion indoor house spraying was being conducted; later a slight decline in post neonatal mortality (from 73 to 67/1000) and a marked drop in mortality of children 1-4 years old (from 25 to 18/1000) were recorded between 1981-2 and 1982-3, following the implementation of a programme of community based antimalaria treatment. The bulk of such a decline was explained by the influence of a measles epidemic in 1981-2, the malaria specific mortality, being relatively low, did not show significant change in the year of intervention. Interestingly, this study appears to confirm in a small rural area the general observation that child mortality differentials can largely be explained by differences in maternal education, which will no doubt also influence use of medical care and drugs, but is more likely indicative of better hygiene and general living standards. Differences in infant mortality between districts in Kenya, as reported in the 1979 census, ranged from 38 to 153. It should also be noted that the withdrawal of the spraying in Kisumu in 1976 did not represent a complete return to the previous infant mortality rates; the general decline in the district in which this area is located was between 220 per thousand in 1959 to 181 in 1969, and 147 in 1979 (Spencer *et al*, 1987).

The influence of socioeconomic risk factors in the incidence of cerebral malaria has been highlighted by Carme *et al.* (1994), in Brazzaville showing that for 1988-89, the level of education and socioeconomic standard of households with a child hospitalized for cerebral malaria was significantly lower than the average. Similar factors may have contributed to the decline of malaria mortality among Europeans in Africa illustrated by Duren (1951) for the Belgian Congo where from 6.39/1000 in 1918-20, mortality dropped to 3.1 in 1921-30, 1.23 in 1931-40 and 0.9 in 1941-49. As Greenwood *et al.* (1991) points out, it would be important to explore further the particular influence of occupation, housing, use of local medicines, access to medical care or availability of appropriate drugs in creating these differences.

While it is very important to identify the major factors responsible for the different outcomes of malaria, in order to find possible lines of prevention, it is equally important to assess the distribution of these factors in a given population before being able to estimate the final effect of a given intervention and its potential penetration to the periphery. A number of studies have addressed the issue of actual treatment practices in malarious areas, indicating that a large proportion of cases are treated without contacting the health services. Several studies indicate that the majority of fever episodes are treated at home with drugs acquired in local markets, *e. g.* 58% in Guatemala (Ruebush *et al.*, 1992), 83% in Togo (Deming *et al.*, 1989), dosages being mostly insufficient and drugs being often of poor quality or counterfeits. Even

in urban areas self treatment is very frequent, *e. g.* 36% in Yaoundé, Cameroon (Louis *et al.*, 1992); problems of accessibility, ignorance of the existence of the facility, poor attention, absenteeism of health worker, lack of drugs, fear of fingerprick were among the reasons given for not attending health facilities. A recent nation-wide malaria survey in Malawi, *Knowledge, Attitudes and Practices*, (Slutsker *et al.*, 1994) indicate that only 9.7% of the 52% of febrile children who attended a clinic received prompt appropriate treatment, while only 4.5% of the 48% who did not attend a clinic received similar treatment. Other important factors which hamper appropriate treatment are biases, at least in some societies, in the utilization of health services; *e.g.* the under-representation of children and women among users of malaria clinics reported in Thailand (Ettling *et al.*, 1989), or the important male biases reported in rural India (Ganatra & Hirve, 1994), not only in seeking treatment by registered medical practitioners as opposed to paramedics, but also in following recommendations for referral, expenditures for treatment and distances travelled to obtain it.

If wide availability and excessive use of chloroquine has no doubt contributed to lowering malaria mortality, maintaining this gain will require a better targetting of antimalarial drugs to those actually suffering from malaria, as the potential replacement drugs remain limited and resistance to new drugs is rapidly developing -- moreover, they are generally more toxic and less affordable. No doubt related to the spread of drug resistance is the increase in the overall proportion of *P. falciparum* in endemic areas outside of tropical Africa, which had reached 41% in 1991, compared with 15% in the early 1970's. In areas of continuous and intense transmission, like tropical Africa, where *P. falciparum* is by far the dominant species, the development of chloroquine resistance added to the widespread and indiscriminate use of the drug, will contribute to the increase in the proportion of parasitaemias in children which will not be completely cleared, and this has been recognized as perhaps the most important factor in producing life threatening severe anaemia (Slutsker *et al.*, 1994).

Malaria mortality outside tropical Africa as mentioned above occurs among non-immunes acquiring a *P. falciparum* malaria infection and becoming sick in situations where appropriate diagnosis and treatment is not available. This is the case of newcomers into endemic areas, such as agricultural workers, labourers, gold and gem miners, prospectors and settlers in new colonization or other frontier areas of economic development. In those circumstances the most affected are young adults, although, in the case of settlers, whole families may be affected. Typical examples of these situations are found in the colonization of the tropical jungles of South America, South-East Asia and the Pacific, particularly those of the basins of the Amazones and the Orinoco, Kalimantan and the Outer Islands (Indonesia), Sabah (Malaysia), the hills of the Indian subcontinent and the Indochinese peninsula and, in a smaller scale, throughout the tropics. Estimates from the Brazilian Amazon indicate a malaria mortality of the order of 6-10 000 people per year for a population of about 22 million (WHO, 1992).

1.2 Review of past attempts at measuring disease/injury burden

Malaria has been one of the very first diseases to be characterized as a **"social disease"**. Malaria epidemics have also been recognized, since antiquity, as being sensitive to certain human interventions, and organized malaria control was one of the earliest activities of emerging public health services in endemic countries.

It was also recognized that certain human activities, such as rice cultivation, triggered malaria epidemics and attempts were made to regulate those activities through health legislation. The development of health statistics during the XIX century, the economic motivations of the European colonial entreprise, the obvious recognition of malaria as a serious obstacle and the need of important investments for its control, lead to early efforts to define the malaria problem as a burden on society, measurable first in economic terms, such as lost productivity, and later including more general social values, such as learning ability and impact on education.

Sir Ronald Ross in 1911 proposed the calculation of the economic loss to the community caused by malaria, based on malaria mortality and morbidity and **"the local values of human life and labour at various ages and in various social classes".** He considered that **"from the preventive point of view this is perhaps the most important question before us; because, obviously, it governs the question of the expenditure which may be demanded for the anti-malarial campaign"**. He mentions that **"many such estimates have been attempted"** and quotes, as example the calculations of Dr Bolton, who added an estimation of **"hospital and other expenses"** to arrive at a cost of one million rupees (a rupee being about 1/15 of an English pound) for the population of Mauritius (383,000), that is 2.6 rupees per head, not counting **"enhancement of wages, cost of invaliding, and loss of market"**. Also quoted were Howard's (1909) estimates of the cost of malaria to the United States as **"surely not less than $100,000,000 per year"**. Perhaps the classical study in this line was that of Sinton (1935-6) entitled *What malaria costs India, nationally, socially and economically*, which estimated that malaria was directly responsible for **at least** 1,000,000 deaths and, including its indirect effects, of **at least** 2,000,000 deaths each year, representing *at least* 100,000,000 and **almost certainly** 200,000,000 cases, with a case fatality of 1%.

A certain conflict has always existed between the desire to make general estimates of the burden of disease, based on the study of the overall impact of the disease on the economy and economic development, on the local community, the household and the individual, and the recognition that the evaluation of this impact may make sense only for a particular local situation and that its simple extrapolation will often be very misleading.

In fact, public health action against malaria often consisted of the implementation of large scale programmes which required the use of considerable public funds; the justification for their political approval having either been fully based on economic arguments or on political desirability which, in most cases, was also presented as economically justified. Malaria has been, therefore, one of the diseases most studied from the socioeconomic point of view. There are nevertheless no fully satisfactory studies. It has been argued that economic analyses, made in the past, lacked the necessary scientific rigor as shown by the great variability in estimations of variables, such as the number of days lost per malaria episode, or the cost of saving a life or preventing illness. It may also be argued that the great range of variability of the different estimates of impact is the necessary consequence of the epidemiological variability of malaria and that past estimations were at least credible to the political authorities, who had an intuitive feeling for actual cost of sickness and control activities.

The following types of impact have been studied in different places:

Economic loss due to malaria

has been the most frequently attempted estimate. Most of these estimates focus on days lost from work or output foregone, which is already oddly narrow; calculations being based on the loss of wages during sickness, some including cost of treatments. Finally some estimates introduced the assignment of a monetary value for the lives lost, by attempting to calculate an actuarial value for a human life, *e.g.* Suarez Torres (1973) evaluates a life at 10,000 Mexican pesos, Padua (quoted by Winslow, 1951) at US $2,000.

The general approaches used for these estimations have been seriously criticized as they imply that human lives can be reduced to their work capacity, which can be bought for money (Franco Agudelo, 1981), or that man can be considered as an exchange value (Breilh, 1979). Even from the mere methodological point of view, Bruce-Chwatt (1978) criticized the narrow attempts to trace the influence of a single factor through all the mesh of the real economic world.

Nevertheless, these calculations were considered necessary to justify funds for malaria control, as argued by Sir Ronald Ross. Early estimates of total economic loss include: Carter (1919) $100 million for the U.S.A., Sinton (1935/6) $400 million for India, Winslow (1952) $30

million for Peru; Padua estimated that malaria and tuberculosis inflicted a loss to the Philippines of $600 million ($33 per person) each year. Similar estimates later became practically requisites of a control or eradication plan in the fifties and sixties. Suarez Torres (1973) estimated the economic loss to Mexico due to malaria during the period 1950-54 at more than 600 million pesos. Pampana (1969) reviewing the literature on the subject quotes $23 million for Indonesia (1958), $200 million for India (1942), $54 million for Paraguay (1957) and $50 million for Mexico (1955).

A different consideration was made by Russell (1948) to justify external assistance, estimating that any nation importing the products of a highly malarious country paid the equivalent of a 5% malaria tax and that, for the U.S.A., this represented $175 million a year.

Malaria and productivity

The justification of public health activities in pursuit of improving productivity has been a common argument since the debates on the "laziness disease" at the beginning of this century (Garcia, 1981). The image of malaria as the most prevalent disease of the poorest rural areas producing recurrent chronic infections, with fever attacks in spring and summer, and malignant tertian occurring in the late summer and autumn, when extra work is required for collecting the crops, is a classical example of a debilitating disease, impairing productivity. This image is typical of areas where people who also suffer from other infections, malnutrition and lack medical care, do not develop an early solid immunity, either because of low and seasonal transmission, or because of easy access to antimalarial drugs. In view of the coincidence of disease and need for intense agricultural work, which makes replacement more difficult, past estimates of the loss of work due to a malaria attack, which ranges between 5 and 15 days, do not seem too exaggerated. A recent study of 695 matched patient-control pairs in Nepal (Picard and Mills, 1992) indicated that *P. falciparum* was responsible for 10 days (95% CI 7.12-12.61) total disability and 2.5 days (95% CI 1.34-3.96) of partial disability and that *P. vivax* for 5 days (95% CI 4.49-5.47) total and one (95% CI 0.82-1.32) partial disability; the study also showed the substantial marginal value of patients labour (mean length of controls' working day being 8.32 hours) and the persistence, after reported complete recovery, of work time loss due to debility for several days, although there was important local variation; in some areas corroborating the assumptions of San Pedro (1967/8) of an equivalent loss of 10 days work or those of Khan (1966) of 20% reduction in work efficiency over 6 weeks.

Even in the most endemic areas of tropical Africa, where anybody surviving childhood presents often asymptomatic parasitaemias, people may suffer one or more clinical episodes resulting in 5-6 days of incapacity (Colbourne, 1955); recent studies in Rwanda, Burkina Faso, Chad and Congo give similar estimates, which are expected to rise due to the spread of drug resistance (Shepard et al, 1991). As mentioned above, repeated attacks of malaria constitute an important factor in the causation of severe anaemia and high fatality. In contrast the mere presence of a malaria infection does not seem to affect productivity; a study in Liberia showed no detectable loss of physical ability in people with malaria parasites in their blood; on the other hand a marked correlation was found between loss of physical ability and anaemia (Brohult *et al.*, 1981).

On the other hand, in places attracting labour from areas of lower endemicity, the impact may be very severe. In Southern Rhodesia it was estimated that the loss of manpower due to malaria was from 5 to 10% of the total labour force, with the greatest incidence at the peak of agricultural production (Winslow, 1952). Similar problems were observed in other parts of East Africa.

Impact of major malaria epidemics

Multiple examples could be quoted from the classical hydraulic works to control and prevent recurrent epidemics, from Empedocles of Agrigentum (V c. B.C.) to Lancisi (XVIII c. A.D.); the repeated prohibitions of rice cultivation around Valencia since 1342 B.C., sometimes under death penalty (Nájera, 1988); up to the more modern epidemics of Sri Lanka in 1968, those of India and Pakistan in 1976 and that of S.E. Turkey in 1977, all of which led to the mobilization of large financial resources for the re-establishment of extensive control programmes; the epidemic of Sri Lanka played an important psychological role in the abandonment of the global malaria eradication programme in 1969. Very recent large scale malaria epidemics, which have had important impact on the mobilization of national and international resources have been those of Madagascar in 1987-89, Sudan in 1989 and Northern Iraq in 1993-94.

Malaria as a major obstacle to important collective enterprises

such as economic development projects, the protection of armies at war, police forces or border posts in endemic areas. Malaria was one of the main factors which had to be overcome for the successful construction of the Panama Canal, most of the railways and roads in tropical countries, the agricultural development of the Roman Campagna, the Venezuelan Llanos, the building of colonial empires, the protection of Armies from the First World War up to that of Vietnam. Malaria control - or vector control to prevent its reintroduction – continues to be an important component in the execution of major public works in the tropics, *e.g.* highways such as the transamazonian, dams such as Itaipú on the Paraná, and numerous tourist resorts from Mexico to the Maldives or Indonesia.

Malaria is a remaining health problem in a socioeconomically developed area

Although the transmission of malaria had been interrupted in most temperate areas of the world by the environmental changes introduced by the process of economic development, there were places, such as some areas of northern Germany or the Netherlands, where malaria persisted in spite of economic development and its eradication required major investments. In these cases, particularly the elimination of the last foci of transmission in Europe in the 1960's, the impact of the remaining disease transmission had been more political than economical.

Effects of malaria on the individual and family

As health is being perceived as an objective of social development more than as an instrument of economic development, understanding of these effects becomes more important. Apart from the actual incapacitating effect of an acute attack, malaria has long been recognized as a major cause of ill-health and anaemia. Wernsdorfer and Wernsdorfer (1988) highlight the issue of its undermining the effectiveness of investment in education; in highly endemic areas, where adults are often asymptomatic, schoolchildren are severely affected and in many of these areas the number of children whose learning may be impaired by malaria may still range between 35-60%, as was estimated by Macdonald (1950). A recent study in a community of the Solomon Islands (Kere *et al.*, 1993) found that, on average, each child lost 5.3 days of school each year and calculated that this represents a loss of US$ 108,966 of the country's investment in education; Mharakurwa and Mugochi (1994) found, in an area of rising endemicity and increasing drug resistance in the highlands of Zimbabwe, school absenteeism as high as 28%.

Conly (1975) studied the microeconomic effects of a malaria epidemic in Paraguay, including the loss of economic potential, which averaged 75% in the most affected families, and the various compensatory adjustments, including increases in labour input per unit of output, increased work of healthy family members and children, help from neighbours and hired work, postponement of agricultural tasks, leading to a reduced yield per hectare 36% below normal. Other adjustments included: reduced ability to clear new land to add to their fields (41% less), reduced acreage planted (7% less) and reallocations of land, replacing relatively low value crops to be collected in a non-malarious season in lieu of higher value crops, requiring extra work in the malarious season. De Castro (1985) finds similar adjustments – particularly the increased work of healthy members of the family – which simply means that the costs of the disease are borne by others besides those who are ill.

Bonilla and Rodriguez (1992) found that the economic and social costs due to malaria were clearly perceived by rural Colombian households, that a third of the cost of illness was represented by the cost of treatment and 2/3 by time lost by the patient and the caretaker, and that the psychosocial costs were more difficult to compensate when the disease affected women.

Malaria and population pressure

The dangers of uncontrolled population growth have been a serious concern of demographers and public health specialists. The role of malaria as a major contributor to mortality rates raised the question that its control may contribute to the population explosion, particularly in the 1950's and 1960's when global eradication of the disease was envisaged. Russell (1955) comments on a question by Sir Charles G. Darwing, referring to the success of malaria control in Ceylon, "But is the world the better for having a large number of healthy people dying of starvation, rather than letting them die of malaria?", as being a "typical '*have-you-stopped-beating-your-wife? – Answer yes or no*' query"; finally, commenting that this issue should not be seen as a dilemma, but as a problem, concluded that "the world needs today not more disease but more vision!". Wernsdorfer and Wernsdorfer (1988) make a thorough review of the literature on the subject and, analyzing the multifactorial causes of mortality and fertility rates, show the relatively minor contribution of specific malaria control to the generally observed reduction in mortality rates, which are mainly, as Marshall (1974) said, the result of better food distribution rather than the effect of modern medical and public health techniques in the developing countries; they also showed that the evolution of crude death and birth rates in 109 countries between 1960 and 1979 has been uninfluenced by changes in their malaria situation, while there are quite clear signs of an inverse relationship between birth rates and life expectancy; it may be necessary to reduce death rates for birth rates to start declining.

The discussion of the problem of an increasing world population, which has greatly surpassed the figure of 4 000 million, projected in the fifties with aprehension, for the year 2000 (Russell,1955), is again being brought to a central position in the planning of international cooperation, and essential differences in core values present serious difficulties, as shown in the recent "round table" in the World Health Forum (Martin, 1993 and Discussion).

2. DEFINITION AND MEASUREMENT

2.1 Diagnosis and standard measures, disease and sequelae – data sources available

An acute attack of malaria, particularly if due to *P. vivax* or *P. malariae,* has sufficiently clear symptoms to allow a reasonably accurate clinical diagnosis, if complemented with epidemiological considerations, such as residence or visit to an endemic area, season and, in some areas, age or occupation.

The traditional "gold standard" for malaria diagnosis has been the detection of malaria parasites in a "thick blood film"; this is a very specific and sensitive test of **malaria infection**, since parasitaemias may only remain below the density of detectability for a short time. It may have rather low specificity for the diagnosis of **malaria disease** in highly endemic countries, where it is common to find positivity rates of 40-70%, in children of school age and adults, in the absence of any symptoms.

As mentioned above, in highly endemic areas, clinical immunity develops relatively early so that, around five years of age, children are capable of tolerating a continuous infection, with reinfection every few days, without symptoms; even in areas of medium endemicity, it is common to find high proportions of asymptomatic infections (Covell, 1960). Under these circumstances the diagnosis of the cause of a fever in order to treat a patient cannot be satisfied by the finding of a positive slide and, while it should be advisable to treat a malaria infection in a patient whose fever may have a different cause, it is of doubtful benefit to treat a completely asymptomatic infection in an immune person living in a highly endemic area who will continue to be exposed to very frequent reinfection. In fact the number of clinical attacks per year is highest in the 1-4 age group, while prevalence of parasitaemia reaches its peak in the 5-9 age group or even later; even during the period of maximum susceptibility to clinical disease children are most of the time parasitized but "well" (Marsh, 1992).

By contrast, in non-immunes all infections would produce symptoms and should therefore be treated, making infection and disease clinically synonymous in these cases; finally, in areas where malaria has been eradicated or considerably reduced it is important, from the public health point of view, to treat any infection, including the antirelapse treatment of *P. vivax* and even the search for asymptomatic infections, in suspected new or residual foci.

Actually, important changes in the meaning of a reported malaria case had occurred even before the discovery of the malaria parasite. Ross (1911) shows how the enforcement of medical certification of deaths introduced in two districts of Mauritius in 1899 had as a result "that the mortality ascribed to malaria fell in them at once from 45% of the total deaths to only 25%".

During the first half of the XX century malaria microscopy was slowly becoming available in endemic areas, although it remained more of a research tool than an aid to medical care. Health statistics compiled **malaria cases** reported by medical practitioners and diagnosed only on clinical and, sometimes, epidemiological criteria, as mentioned above; traditionally the response to quinine confirmed the diagnosis or induced the search for other possible causes of the fever, such as brucellosis, typhoid, tick borne relapsing fever, etc.; in some occasions, a patient could be referred to an antimalaria dispensary or a hospital where malaria microscopy could be available; in most endemic countries malaria was a disease of compulsory notification and the health departments added the notifications received, whether parasitologically confirmed or not, into recorded and published morbidity and mortality statistics.

It should be noted that specialized services often mistrusted official statistics and conducted epidemiological surveys to assess **prevalence of infection**, attempting to estimate **variations in incidence** by the experience of antimalaria dispensaries under their supervision. A similar situation with officially reported morbidity statistics very much below the most conservative estimates, persists in tropical Africa, where reporting is not only limited to a few institutions but tends to be irregular even there. Between 1983 and 1990, the total number of reported cases from the WHO African region varied between 2.0 and 23.2 million (WHO, 1994), while conservative estimates, based on longitudinal studies, prevalence surveys and clinical experience, bring this figure to at least 100 million; currently WHO estimates that the global number of malaria episodes per year is in the order of 300 to 500 million, 90% of them in tropical Africa (WHO, 1994).

These were the processes of defining a malaria case in most countries before the **global malaria eradication programme** transformed the case definition into the "occurrence of malaria infection in a person in whom, regardless of the presence or absence of clinical symptoms, the presence of malaria parasites in the blood has been confirmed by microscopic examination" (WHO, 1963).

The malaria eradication programme (MEP) was based on **total coverage** of all mosquito resting surfaces in human shelters with insecticide spray, for which a geographical reconnaissance and population census was maintained, updated with each spray round about every six months; in many malarious countries, this census and sketch maps were far more complete than any previous national census so far undertaken. The objective of eradication also required the setting up of a system to confirm the absence of infection, before claiming that malaria had been eradicated from an area. For this purpose a system of **case detection** was established around the third year of the programme, to visit every house once a month and to collect a blood slide from every fever case found, complemented by similar examination in patients attending any health service; this was based on the assumption that, after three or four years without malaria transmission, all infections would have died out, even without treatment, and people would have lost their immunity so that **any new infection would produce fever**.

By the early 1960's most of the endemic countries outside tropical Africa had adopted malaria eradication and, with it, the uniform standards of case detection, population coverage and case definition prescribed by the eradication norms; this produced data on malaria morbidity, for countries outside tropical Africa, of a coverage and comparability never achieved before.

With time, case detection systems became routinized and, as a result of economic constraints, lost a good part of their staff and coverage in terms of time/space/population, so that much of the previous intercountry comparability was being lost. Many countries, even after establishing their malaria eradication programme, did not abolish their old notification system and continued to collect malaria morbidity and mortality statistics from their old sources, with their very different case definitions and population base, at the same time as the MEP reported on their case detection. Most countries had, nevertheless, agreed to accept as official only the data from the MEP, but some of them, particularly those where the vertical programme was very independent of the general health services, continued to publish these reports separately.

The return to a strategy of malaria control, during the 1970's and 1980's, has changed the focus of control from infection to disease, therefore requiring a reconsideration of the malaria case definition. Some countries, *e.g.* Myanmar, have started to collect, and report, **suspected malaria cases**, even if the clinical definition(s) of a case has not been sufficiently standardised.

The great differences in the epidemiological situations with regard to malaria throughout the world would, therefore, require that there will continue to be different **case definitions** in different areas, and even for different purposes, *e.g.* the study of a population health problems and the general planning of public health interventions would require the assessment of actual **cases of malaria disease**; the logistics of health services supplies

would need to estimate **cases requiring antimalaria treatment**, and the planning and evaluation of transmission control interventions should study **cases of malaria infection**; planning of population based interventions would require assessment of **persons affected**, while planning requirements in resources, *e.g.* antimalarial drugs, would require assessment of **malaria episodes** in a given period. WHO actually changed its estimates of malaria morbidity in 1993 from an attempt to estimate people suffering clinical malaria to the estimation of malaria episodes; up to 1992 (WHO, 1992) estimates for tropical Africa were based on parasite prevalence surveys assigning an estimated frequency of clinical manifestations to each major age group; later estimates (WHO, 1993 & 1994) are based on studies of frequency of malaria attacks per population age group; morbidity outside Africa is estimated by applying to the reported number of cases a correction factor based on country experiences consolidated by WHO regional offices.

There have been in the last few years a number of technical improvements in the detection of malaria infections, by concentration of parasitized cells and staining procedures, to facilitate microscopical identification or by new methods of parasite detection, like DNA and RNA probes, PCR amplification, or by immunological reactions, detecting soluble antigens. These diagnostic tests may considerably facilitate the detection of malaria infections, and may bring such diagnosis to the routine clinical examination, but do not, as yet, solve the problem of differentiating between disease and infection.

The differential diagnosis of fevers would, therefore, remain a problem of clinical judgement, even with the help of the laboratory, and a number of criteria have been proposed to guide the interpretation of laboratory positivity, mainly by detecting a threshold of parasite density below which parasitaemia would not produce fever; for *P. falciparum* this threshold has been set between 600 to 10,000 parasites/mm^3, depending on area, season, age and expected level of immunity (Miller, 1958; Trape *et al.*, 1985). Such definitions would again not solve the problem of diagnosis at the periphery where microscopy is seldom available; attempts to a widespread deployment of peripheral laboratories in tropical areas have had to face serious problems of microscope maintenance and quality of work, particularly when the microscopist has no feed-back of the clinical importance of his work; a study in India showed low performance of microscopic diagnosis, particularly for *P. falciparum* (Beljaev *et al*., 1985).

Clinical diagnosis, particularly by paramedical health workers will continue to be the rule at the periphery; it would be facilitated by the development of locally relevant algorisms for differential diagnosis of common fevers, taking into account not only clinical but also epidemiological considerations such as season or age (*e.g.* Rougemont *et al*., 1991; Richens *et al.*, 1992). WHO is currently developing guidelines for the peripheral diagnosis of *a sick child*.

In contrast with all these developments, there are a number of observations indicating that, at least in many malarious areas, people are able to recognise the disease, which may even have a distinct name. Ejezie *et al.* (1988), observed that mothers were able to recognise malaria correctly by identifying combinations of fever, headache, vomiting, convulsion, dizziness, diarrhoea, loss of appetite, joint pains and bitterness of the mouth; they confirmed that these diagnoses had, in fact, a high degree of accuracy, by parasitological examination.

Similarly **verbal autopsies** have been extensively used to estimate malaria mortality, although there are indications that this method has a low specificity for malaria, below 50% (Snow *et al.*, 1992), mothers tending to report malaria symptoms as present during terminal illness in 43% of cases where these symptoms were absent (Snow *et al.*, 1993).

2.2 International Classification of Disease (ICD) 9 and 10 codes

There has been a considerable increase in the classification space allotted to malaria in ICD 10, allowing a code for each species of malaria parasite, as follows:

ICD 10 classification (WHO, 1992):

B50 *P. falciparum*
- B50.0 cerebral malaria
- B50.8 severe
- B50.9 unspecified

B51 *P. vivax*
- B51.0 with rupture of spleen
- B51.8 other complications
- B51.9 without complication

B52 *P.malariae*
- B52.0 with nephropathy
- B52.8 other complications
- B52.9 without complication

B53 Other parasitologically confirmed malaria
- B53.0 *P. ovale*
- B53.1 Simian parasites
- B53.8 other non specified

B54 Unspecified malaria, clinically diagnosed

Malaria is included in other codes:

B94.8 Sequelae of other specified infections or parasitic diseases

O98.6 Protozoal diseases complicating pregnancy, childbirth and the puerperium (B50-B64)
P37.3 Congenital falciparum malaria
P37.4 Other congenital malaria
T80.2 Infections following infusion, transfusion & therapeutic injection.

In contrast ICD 9 provided only one code for malaria, the 084, which excluded congenital malaria (code 771.2). The malaria code was subdivided into:

084.0 Falciparum malaria (malignant tertian)

084.1 Vivax malaria

084.2 Quartan malaria

084.3 Ovale malaria

084.4 Other malaria (monkey malaria)

084.5 Mixed malaria

084.6 Malaria, unspecified

084.7 Induced malaria
Therapeutically induced. Excludes:

- accidental infection from syringe, blood transfusion, etc. (084.0-084.6, above, according to parasite species).
- transmission from mother to child during delivery (771.2)

084.8 Blackwater fever

084.9 Other pernicious complications of malaria
Algid malaria
Cerebral malaria
Use additional code, if desired, to identify complication, as malarial hepatitis (573.2), nephrosis (581.81)

Other codes, including malaria:

573.2 Hepatitis in other infectious diseases classified elsewhere

581.81 Nephrotic syndrome in diseases classified elsewhere

647.4 Other specified infections and parasitic diseases, complicating pregnancy, childbirth, or the puerperium

771.2 Congenital malaria

ICD 10 uses a single code (043 Malaria) for the "Special tabulation of morbidity", equivalent to the (052 Malaria) in the "Basic tabulation list" of ICD 9.

3. REVIEW OF EMPIRICAL DATABASES

As mentioned in the discussion on "definition and measurement" malaria has been an important subject of attention of the health authorities of most of the endemic countries since the earliest stages of development of specific morbidity and mortality statistics. Many endemic countries have, therefore, some information on malaria morbidity and mortality going back, at least, to the early years of the XX century; these data served to evaluate control efforts and, subject to the problems of changing definitions, population coverage and systems of data collection and consolidation, constitute time series which retain, for relatively long periods, reasonable comparability for an specific area.

A more serious problem has always been that of intercountry comparability. As mentioned above, comparability, although limited to the number of malaria infections, was greatly facilitated by the standardization of definitions and procedures by the malaria eradication programmes; perhaps the main contribution of the malaria eradication programmes to public health practice was the emphasis on *total coverage* which, as mentioned above, contributed in several countries to the geographical reconnaissance and the introduction of vital statistics into areas of difficult accessibility. With the abandonement of the eradication strategy, malaria programmes could not maintain, as mentioned above, the same operational standards everywhere and, therefore, the previous intercountry comparability was progressively lost. WHO has, in recent years, tried to estimate incidence per country, based on malaria programme reports corrected by a factor which is established, in consultation with the programme concerned; in SEAR this factor has been mainly based on an appreciation of deficiencies in coverage by the system of epidemiological surveillance, while in AMR this correction is based on information about antimalaria drug use; finally in Africa South of the Sahara, malaria eradication programmes never acquired national coverage and official statistics have little continuity and coverage; their interpretation requires, thus, a more intimate knowledge of local conditions, and any generalization becomes a projection of limited experience and, therefore, largely subjective.

In spite of all their deficiencies, the official malaria statistics provide the best information on geographical distribution of the problem and constitute a good base to make gross estimates of disease burden outside tropical Africa; nevertheless, they lack information on duration of incapacity and differentiation of clinical forms and, although age and sex have almost always been recorded, they seldom appear in national consolidated data.

While official statistics provided the best global estimate of *incidence of malaria infection*, reliable data on **mortality** has always been difficult to obtain. Malaria was often assumed to be the cause of any fatal febrile process in malarious areas before the opinion spread, between the 1960's and 1970's, that the disease had practically been eliminated in most of the endemic countries; moreover, eradication programmes focussing their attention on detecting residual infections neglected to collect information on mortality. Malaria deaths passed rather rapidly from being overreported to highly underreported, but again the timing and intensity of this change varied considerably from area to area; modern programmes have serious difficulties in interpreting data on mortality and in establishing some form of

interpretable reporting. In SEARO, for example, it is estimated that malaria mortality may be between 2-3 to 25 times the officially reported figures (Orlov, 1993).

Actually, malaria mortality occurs almost exclusively in *P. falciparum* infections and, even if the disease may have a very rapid fatal course in certain children (Greenwood *et al.*, 1987), mortality rapidly declines when treatment becomes widely available and used. Outside tropical Africa, high *P. falciparum* incidence, high levels of drug resistance, lack of health facilities and inaccessibility to education and information tend to occur most frequently in remote areas and among displaced populations or among temporary workers in frontier areas of economic development, which are therefore the most likely to die from malaria, but also to remain unrecorded. In tropical Africa *P. falciparum* is ubiquitous infecting practically the whole population, since early childhood, so that by about five years of age people acquire a solid immunity; malaria mortality is practically limited to children under five years in tropical Africa, while in the rest of the world's malarious areas, where infection rates are considerably lower and accessibility to antimalaria treatment considerably higher, solid acquired immunity is very rare, so that the risk of death may be considered as evenly distributed. General case fatality rate was traditionally considered between 1% and 2% in areas of low immunity and practically no availability of antimalarial treatment; based on the above considerations, it may therefore be considered that malaria mortality outside tropical Africa may now be of the order of 1% of the estimated number of *P. falciparum* cases.

As mentioned above, **age and sex distribution** has seldom been reported at the national level, but has been the subject of a number of studies; Kondrashin & Rashid (1987) summarized such studies in Southeast Asia. These examples seem to indicate a higher incidence of malaria among males in some areas, like West Bengal, and a higher incidence in adults, with a possible tendency to the increase of these two characteristics in later years (India, 1977-1985; Sri Lanka, 1971-1973); this type of age and sex distribution, corresponding to increased transmission in areas attracting adult males, is difficult to delimit from the more common type of uniform risk where transmission occurs at home. The experience of malaria control programmes indicates a tendency for malaria risk to concentrate in economic frontiers, nevertheless this does not seem to be equivalent with an overall marked concentration of risk in adult males; colonists, displaced populations, and even migrant labourers, may include both sexes and, perhaps with the exception of young children as labour force, all ages. For this reason it may still be estimated that, outside tropical Africa malaria incidence is evenly distributed among age groups.

The emphasis of the malaria control strategy in disease management requires more information than mere incidence of infection and even mortality; this and the lack of a regular source of epidemiological information on malaria in tropical Africa has stimulated, particularly in the last few years, a number of local analysis of hospital and other health statistics as well as population based studies and historical analyses of the literature.

The Appendix presents, in tabular form, a review of specific studies, published in the literature, aiming at the measurement of relevant indicators for the quantification of the mortality and disability caused by malaria in tropical Africa. This represents the beginning of a database which will be expanded in the future and extended to other parts of the world with the hope of becoming a useful reference; at present, as a collection of references, it is quite preliminary and incomplete; in spite of these deficiencies, it is presented here as an indication of the great variability of the impact of malaria not only in quantitative, but also in qualitative terms.

4. ESTIMATIONS OF MORBIDITY AND MORTALITY

From the discussion presented above, it may be obvious that any attempt to make global estimates of malaria morbidity and mortality is a rather hazarduous exercise, requiring a number of subjective assumptions on which it is rather difficult to achieve a consensus.

4.1 Traditional estimates

As mentioned above, WHO had based its estimates of global morbidity on regional estimates based on reported cases for all areas outside tropical Africa, and on extrapolations from point prevalence surveys for tropical Africa; in both situations the attempt was to estimate the number of persons suffering from malaria. This approach gave estimates for 1990 of "nearly 120 million clinical cases each year, with nearly 300 million people carrying the parasite. Countries in tropical Africa are estimated to account for more than 80% of all clinical cases and more than 90% of all parasite carriers" (WHO, 1992). Estimates of mortality continued to quote the estimate of about one million deaths worldwide; the status report for 1990 quotes "a figure of 800,000 deaths per year in African children", as estimated by the WHO African Region for 1991 (WHO, 1992).

4.2 Consolidation of estimates of morbidity and case fatality

Following the Ministerial Malaria Conference in Amsterdam and the adoption of the global malaria control strategy, emphasizing improved case management as the main priority, WHO made an effort to estimate the number of actual clinical malaria attacks per year, arriving at an estimatation of 300-500 million clinical cases each year for 1991 to 1993 (WHO, 1993; WHO, 1994; WHO, 1996). Estimates of malaria mortality were quoted as varying from 1.5 to 3 million for 1991 (WHO, 1993) and from 1.5 to 2.7 million for 1992 and 1993 (WHO, 1994; WHO, 1996).

These estimates were based on revised country's estimates, coordinated by the WHO Regional Offices, and a number of assumptions which, by groups of countries, may be sumnmarized as follows:

4.2.1. Established Market Economies (EME) and Formerly Socialist Economies of Europe (FSE):

During the period from 1985 to 1989, when most countries sent reports to WHO, reported incidence varied between 7 272 and 9 117 cases (nearly all imported). Studies have shown that there is considerable under-reporting of morbidity. In Switzerland, only 44% of cases registered during surveys were notified to the authorities (Steffen *et al.*, 1990). In the USA, only 50% of non-fatal cases are notified (Lobel, unpublished observation, 1986, quoted by Papaioanou *et al.*, 1988). In France, retrospective national surveys showed that about 25% of diagnosed cases are notified. Everywhere, clinicians rarely think of malaria as a diagnosis of a febrile process, so that mild malaria attacks often go undiagnosed and severe cases are frequently diagnosed late. As a "guesstimate" it has been assumed that only one out of two cases will be notified which leads to an annual incidence of about 16,000 cases in the EMC and 3,000 in the FSE area.

Reporting on mortality is believed to be more complete that reporting on morbidity. The falciparum case fatality rate varies from 0.5% to 7% in countries of this areas (Lobel *et al.*, 1985; Phillips-Howard *et al.*, 1988; Molineaux & Hempel, 1989), but it is likely that the higher rates are too high, not only due to underreporting of incidence but also to increased severity, as a consequence of late diagnosis, even post mortem diagnosis continue to occur.

4.2.2. India (IND):

In the WHO South-East Asia Region, to which India belongs, the true malaria incidence is thought to be several times higher than the reported incidence, giving an estimation of about 15 to 20 million cases annually (Orlov, 1993). This would represent 11 to 15 million cases in India which represents 74% of the malaria cases in this Region. An in-depth evaluation of the Indian Malaria Control Programme, in 1985, revealed that the problem of malaria was greatly underestimated and that case detection was absent or inadequate in large areas. The incidence figures used for global consolidation are based on estimates made by the regional office which take into account the reported incidence, adjusted to correct for inadequate surveillance coverage and programme execution.

In each consecutive year from 1988 to 1991, the number of reported deaths due to malaria were 209, 268, 353, and 406 (provisional), respectively (NMEP, 1992). Only the confirmed malaria deaths were included in these reports. However, malaria deaths occur mostly in remote and inaccessible areas away from any health infrastructure for reporting. The vital statistics report for India includes 137,846 deaths in 1985 and 75,285 deaths in 1987 due to malaria. As for the other countries outside Africa, malaria mortality has been estimated to be 1% of the estimated falciparum malaria incidence.

4.2.3. China (CHI):

The reported incidence is based mainly on microscopical blood examination. In some areas, the number of unreported cases could reach even 70-80% of the real number (Xu Shuhui, paper presented at WHO Inter-Regional Meeting, Kunming, 1993). The number of cases was estimated to be in the order of twice the reported incidence.

4.2.4. Other Asia & Islands (OAI) Middle Eastern Crescent (MEC):

The overall incidence in this area was derived from estimates made on a country by country basis, including reported figures, adjusted reported figures as well as expert estimates from reports on advisory missions, etc.

4.2.5. Africa south of the Sahara (SSA):

Incidence – As mentioned above, the numbers of malaria cases reported from countries in this area refer in their great majority to clinical cases of malarial disease, but there are few reporting institutions. During the period from 1983 to 1990, the total number of such cases varied between 2.0 and 23.2 million. Reporting is irregular and fragmentary and the coverage of consolidated figures is seldom known. The number of cases reported represents only a small and changing fraction of the actual amount of clinical malaria cases (WHO, 1994).

As mentioned above, the estimates of the incidence have been based on the population in areas with malaria risk and on the number of malaria episodes that a person is expected to suffer every year, depending on age group and endemicity. The following assumptions are used to make those estimates:

- About 90% of the population is exposed to malaria risk:

- **For children less than 5 years**, Breman and Campbell (1988) estimated a fever rate between 1 and 9 attacks per year, partially caused by malaria. Half of the febrile episodes were prevented by malaria chemoprophylaxis (Björkman *et al.*, 1986; Morley, 1971). In an area of Tanzania, 56% of fever attacks were considered as due to malaria (Rooth & Björkman, 1992); 3 to 6 fever episodes of which 50% are typically due to malaria have been chosen to calculate the estimates giving a malaria attack rate of 1.5 to 3.0 per year. This is in agreement with other findings indicating that the incidence of clinical malaria in children in rural Africa is in the range of 1-5 attacks per year (Greenwood *et al.*, 1987; Trape *et al.*, 1987).

- **For older children and adults** there are few observations on actual morbidity; Bruce-Chwatt (1963) found attack rates between 0.4 and 0.52/man/year in adults in a suburb of Lagos, classified as holoendemic. Rates will no doubt vary considerably, but it may be assumed that general immunity if anything may have declined, as mentioned above, with severe cases occurring more frequently among older children and young adults.

It has been estimated in order to consider the great differences in immunity that:

a. In areas of hyper and holoendemicity, where it is estimated that 60% of the population at risk lives, about 90% of people are infected and, for the reasons given above, attack rates have been estimated as varying between 0.45 and 0.65/person/year.
b. In meso and hypoendemic areas, estimates are even more speculative, based on the following assumptions:
    - In mesoendemic areas, with 30% of the population at risk, it is estimated that 40% may be infected but, due to their partial immunity, only 80% of them will suffer a clinical attack; these areas are being subject to an increasing frequency of outbreaks, while there has been some important intensification of malaria in highland areas due to extension of agriculture in these areas (Matola *et al.*, 1987).
    - In hypoendemic areas, where it is estimated that 10% of the population at risk lives, 5% of people may acquire malaria and, lacking immunity, all will suffer from clinical disease.

Consolidating these two assumptions an estimated attack rate is obtained of 0.25/person/year for 40% of the population at risk in this large age group.

Mortality estimates are based on the following assumptions:

- It is assumed that all malaria cases are caused by falciparum infections; the proportion of other species among the infections being rather small. Overall, this simplification should not strongly influence the results.

- **For children under 5 years of age**:

a. 3% of all clinical cases will show signs of severe malaria.
b. Case fatality rates of 10-30% have been noted among children referred to hospitals with severe malaria (Greenberg *et al.*, 1991; Brewster *et al.*, 1990), and malaria mortality is likely to be substantially higher in children in rural areas with little access to specialized treatment. It might be in the order of 50% (Greenwood *et al.*, 1991). For the estimates it has been assumed that 25% of all severe malaria cases will die.

These two assumptions result in a fatality rate of 0.75% , which is in the order of previous estimates, 0.5 – 1% (Greenwood *et al.*, 1991) and with the generally accepted estimate of 1% (Pampana & Russell, 1955) before the global eradication campaign, and concomitant development of trade and communications, considerably increased peripheral availability of antimalarials.

- **For the age groups of 5 years and older**:

a. in areas of hyper and holoendemicity case fatality rate is very low, but it is not negligible in the lower limits of the group and during pregnancy; it may also be increasing due to the delay in the development of immunity in some areas; therefore **a case fatality rate** of 0.1% for these areas has been estimated;
b. in meso and hypoendemic areas it has been estimated that severity will resemble endemic areas outside tropical Africa and **case fatality rate** has been estimated as 1% of all cases.

4.2.6. Latin America and the Caribbean (LAC)

During the period from 1990 to 1992, an average number of 1,158,000 confirmed malaria cases were reported. Based on the amount of drugs consumed, the PAHO/WHO Office estimated the actual number of cases occurring to be about 3.8 to 7.9 times higher (PAHO/WHO, 1993). The estimated number of cases is then in the order of 4.4 to 9.1 million.

4.3 Estimates based on proportional mortality

General demographic information is becoming increasingly reliable and population and mortality estimates, per sex and age groups are being considered reasonably reliable for all geographical areas. It has been noted that the estimated malaria deaths presented above appear excessive when compared to the total number of deaths, particularly in tropical Africa.

In addition, data on proportional mortality are more widely available and perhaps more reliable than those on morbidity and therefore on case fatality rates.

It is therefore possible to make an alternative estimate of mortality, at least for tropical Africa, where malaria deaths represent an important proportion of total mortality.

- For children under 5 years, it may be estimated that :
- in holo and hyperendemic areas, representing about 60% of the population, malaria is responsible for 25% of the deaths of children 1-4 years old and 4% of those less than one year old, making a general proportion of 20% for the age group 0-4 years; and
- in meso and hypoendemic areas, where there are fewer observations on which to base estimates, it may be possible to assume, based on observations in other mesoendemic areas of the world, that 10% of deaths for the whole group 0-4 years, may be due to malaria.

- By combining these estimates it is possible to arrive to an estimation that **16% of all deaths of children less than 5 years of age are due to malaria.**
- For the age group 5 years and older, it may be assumed that:
- in holo and hyperendemic areas, solid immunity is built up by late childhood, but more and more frequently adults search employment in towns where they may lose some of their immunity and be exposed to higher morbidity on visits to their villages. It could, rather tentatively, be assumed that this may reduce the relative mortality to a sixth of that in chilhood, and that, therefore, 3.3% of all deaths of people over 5 years of age are due to malaria;
- in meso and hypoendemic areas there may be some slow build up of immunity, justifying the idea of declining incidence with age, but immunity is seldom very solid and high morbidity and severity may occur in epidemic years, often affecting all age groups; also morbidity and risk of death are greatly associated with travel to areas of high endemicity, often in search of work or trade. It could, therefore, be assumed that the proportional mortality does not change very much from that of children and that 10% of all deaths are due to malaria.

  These assumptions give an overall estimate that **6% of all deaths, for adults and children 5 years and older, are due to malaria.**

This method of estimation will give a total number of malaria deaths for Africa south of the Sahara of 895 000 and a global estimate of around one million deaths.

5. OTHER CONSIDERATIONS IN CALCULATING BURDEN

As mentioned above, malaria has been the subject of a quasi continuous debate on the relative merits of important investments in its control or eradication, mostly based, or at least justified, on estimations of the socioeconomic burden of the disease; it is possible, nevertheless, to detect some sort of historical periodic oscillation, at least since the discovery of the mosquito transmission, between the strategies of control based on aggressive specific attack and those based on general development, including the improvement of health services; within these alternations, the promoters of specific interventions requiring new financing, were those who needed to make serious attempts to estimate disease burden.

Although the variables studied were very similar – *i.e.* morbidity, mortality, days of incapacity – they seem to have had much higher convincing power when they were addressed to concrete projects, which had real control of their funds, than when they addressed long term development invoking government funding; this contrast was illustrated by Wilson and Wilson (1936), malariologist of British East Africa, in their report of a visit to India to observe the success of malaria control there, "the only examples of effective malaria control that were shown to us were those conducted by private or semiprivate enterprise... The work of the Bengal-Nagpur Railway was a revelation of what can be done in intensely malarious country, given sufficient inducement coupled with persistance, ingenuity and unfailing resource. But the cost (sums such as three thousand rupees per annum for a single small station) was a further discouragement to any thought of applying such measures in poor rural areas."

It should be highly desirable that choices, involving the use of public funds and having an impact on public health, should be based on a precise and objective measurement of those impacts. Unfortunately, the encapsulation of all the complexities of an epidemiological phenomenon, such as the impact of malaria on a population, in a single indicator, would require a perfect knowledge of all its components and the dynamics of their interactions. In real situations such thoroughness of knowledge is far from being approached, therefore decisions have to be made on an imprecise knowledge of an incomplete range of variables. If it is true that most public health decisions are made on a final reduction to a *perceived value* by the decision-maker(s), the subjectivity of this reduction may remain visible. By contrast, the replacement of all the partial estimates, with all its lacunae, by a single "impact estimate" may remove the need for a final subjective judgement at the end, but only by the previous consolidation of a large number of subjective judgements; this process does not add any objectivity, but would distance the eventual decision-maker from the anguish of uncertainty and, therefore, from the preparation for the unexpected.

The current interest in estimating lost DALY's (disability adjusted years), as the single indicator of the burden of disease, ignores that:

1. The burden of disease on a society is much more than the sum of the specific burden of identified individual diseases on each of its members; a chronic disease of the bread winner of a family, reducing the family income and requiring a large amount of time from other family members for its care, has more dire consequences than the death of a young child, although it can claim less DALY's.
2. One or two weeks of incapacity due to a malaria attack during the critical crop season, has much more damaging effects than the same duration of incapacity due to an acute respiratory infection during the winter or the dry season.
3. The failure of an agriculture colony in a forest area due to disease has not only a social impact much greater than the addition of individual incapacities but, pushing the survivors to try their luck in another area, contributes to extending deforestation and starts a process of land degradation, leading to the consolidation of failed agricultural farms into extensive cattle ranches.
4. Focal epidemic outbreaks, as are common with malaria in hypoendemic areas, and with a number of other mosquito-borne diseases, can disrupt the life of a whole community at the time when most work is needed in agriculture.

5. With regards to the planning of public health activities, the distribution of the social burden of disease, among individual diseases, may lead to the selection of priority diseases for action, and induce the temptation of favouring specific control activities, which will rapidly reduce the incidence of these diseases, over more developmental type of activities aimed at making health care accessible to all the population. These type of interventions, such as mass chemoprophylaxis or insecticide spraying for malaria control, produced, in the past, very spectacular successes, but with **diminishing returns**, due to loss of popular collaboration and compliance, attrition of discipline and operational performance, as well as development of parasite and vector resistance. Moreover, interventions of this type have been frequently too dependant on external funding which, at least in the past, has been more ready to support the provision of supplies than the building of sustainable local capabilities to manage problems, and often ended with a programme collapse when external funds were withdrawn.
6. A common unjustified expectation is that socioeconomic development will automatically follow the control of a disease which is producing a very high burden on society in an endemic area; again an expectation which has, in most cases, failed to materialize.

6. DISEASES AS RISK FACTORS FOR OTHER DISEASES

From the first characterizations of malaria as a nosological entity, it was recognized as a debilitating disease, which greatly affected the capacity of the organism to resist to concomitant diseases, stress or even demanding physiological events, like pregnancy or its outcome. Epidemiologists, making estimates of mortality due to malaria, often attribute as much weight to the indirect as to the direct effects of malaria as a cause of death (Sinton, 1935-6). Malaria as a cause of anaemia would explain both the effects on other diseases and the general state of ill-health suffered by repeatedly infected people; this, plus the seasonality of the disease and its coincidence with needs for agriculture work, would explain most of its effects on maintaining poverty, as its effects extend beyond the sick to other members of the family.

It has been a general observation that the control of malaria in any endemic area has resulted in a greater improvement of health than could have been expected from the contribution of malaria to morbidity and mortality. These improvements are due not only to the indirect nosological effect of malaria, but also to the contribution of the health services, created for malaria control, to the management of other health problems as well as to the general health information and education of the population.

The question of whether malaria contributed to some form of predisposition to other life threatening diseases has also been debated; a recent study in the Gambia (Greenwood *et al.*, 1989) failed to find any difference in mortality from acute gastroenteritis and acute respiratory infections between children protected and not protected with malaria chemoprophylaxis, although there was an important reduction in mortality – approximately 35% – mainly due to the decline in deaths due to malaria and malnutrition. These results, as the authors recognize, should be interpreted with caution, due to the limitations of the study and the seasonality of malaria in the Gambia, which would not justify their direct extrapolation to areas of continuous transmission; they nevertheless indicate that a relation, if it exists, is indirect and mediated by factors not automatically corrected by the mere reduction of malaria infection; to a certain degree this relation may be similar to that between malaria and productivity discussed above.

7. BURDEN AND INTERVENTION

7.1 Access to, and impact of treatment

As mentioned above, even in areas of high prevalence of infections resistant to common antimalarial drugs, practically all cases of uncomplicated malaria can be successfully treated, if diagnosed at that stage, even if it is necessary to use combinations, such as quinine/tetracycline for seven or more days. Nevertheless, chloroquine being the only drug commonly available at the periphery, its loss of efficacy has been accompanied by an increase of malaria mortality in some areas. Acute severe and complicated malaria due to *P. falciparum* still has a very high case fatality, even in the best equipped and competent centers, which is generally considered to be due to lack of appropriate treatment at the periphery and therefore the delay in initiating effective therapy becomes critical for some of the more severe complications, such as cerebral malaria, particularly if accompanied with hypoglycaemia, renal failure or pulmonary oedema, which may rapidly evolve to a lethal outcome. It has been reported that, in some children, malaria can evolve from apparent health to death in less than two days (Greenwood *et al.*, 1987), and it has been argued that mere accessibility to treatment may not save these children and that only preventive measures, such as impregnated bednets or chemoprophylaxis may solve the problem. In contrast, Lepers and co-workers succeeded in a study village in Madagascar, during the recent epidemic in 1987-89 in reducing malaria monthly mortality from 12% to 0.7%, by establishing an outpatients clinic in the village.

7.2 Potential current burden in the absence of currently financed interventions

Malaria has been eradicated from previously malarious areas with a population of 1 960 million people (35% of the world's population), and was considerably reduced or even eliminated in further areas with 1 620 million people (29% of the world's population), but the latter have since suffered resurgences and are considered to be under unstable or deteriorating situations; further areas, comprising a population of 400 million (7% of the world's population), mainly in tropical Africa maintain a rather unchanged high malaria endemicity (WHO, 1996). Areas, which were estimated (WHO, 1993) to be inhabited by about 50 million people (1% of the world population) suffer new severe malaria problems arising from major ecological or social changes due to a variety of causes, including anarchical exploitation of jungle areas, sociopolitical unrest or large scale use of migrant, often illicit, labour forces.

It is recognized that, although the great improvements in the malaria situation in the areas included in the first two groups mentioned above were achieved following intense deployment of specific antimalaria interventions, their success – and particularly the maintenance of it – was also largely due to the concomitant development of health services and general socioeconomic development; these latter developments ensuring the maintenance of some unspecific vector control as well as disease care services which permit the discovery of incipient outbreaks and the mobilization of local control interventions.

Areas in the second group maintain, in general, routine specific antimalaria interventions, which are often insufficiently financed and not fully effective. The Malaria Control Strategy, adopted in the Amsterdam Conference in 1992 (the Amsterdam strategy), requires a reorientation of these interventions to improve their cost effectiveness, in terms not only of malaria control but essentially in terms of their contribution to the health improvement of the population.

Areas in the third group have never benefitted of large scale antimalaria activities, except for some vector control in some urban areas, while penetration of health care services into the periphery has been very slow and irregular. They have been under the influence of an also

irregular but often deep penetration of the drug trade, which has resulted in an extensive use of antimalarial drugs, most often in inadequate doses, which might have contributed to the reduction of malaria mortality, at least in some areas, but also to the rapid spread of drug resistance, as mentioned above. A similar commercial development has resulted in an equally extensive use of insecticides and repellents for personal protection, mainly targetted to nuisance mosquitos. It is therefore necessary to speed up the development of diagnostic and treatment facilities and to improve the use of public and private resources in order to attain their preventive potential; most countries would require to increase their health resources from internal sources and/or international collaboration.

7.3 Estimated actual burden which could be avoided by the application of currently available interventions

The implementation of the first element of the Amsterdam malaria control strategy would lead to the elimination of most of the current malaria mortality and to a considerable reduction, expected to be at least half, of the current incapacity caused by malaria.

The reorientation of existing transmission control interventions, and the further implementation of selective vector control, would result in the progressive elimination of residual incapacity.

Technological improvements derived from current and future research may considerably speed up the attainment of these goals.

7.4 Cost-effectiveness of interventions

It has been recognized that assessment of health benefits is a very complex issue, involving subjective value considerations, while cost/effectiveness might be based on more measurable variables. In any case, the cost component of malaria control is as, if not more, variable and difficult to estimate than the economic impact discussed above. Previous studies of cost analysis gave such different values, that it would be hard to make any generalization about them, except the confirmation of that variability. A recent review of the literature (Nájera, Liese and Hammer, 1991) shows estimates of costs per year of life saved from US $2.10 to $259, and benefit/cost ratios from 2.4 to 146.

As with the assessment of disease impact, methodological problems affect the comparability of data from different studies. Differences in data quality, in assumptions used in the analyses (*e.g.* the estimation of mortality avoided), in the definition of the relevant costs, in the duration of the study, the discount rate applied and in the coverage and purpose of the original intervention, all account for much of the observed variation; but again variability of local conditions would have a great influence.

Another factor which affects the appreciation of costs and benefits, as time passes, is the diminishing returns of health expenditure. In spite of the warnings of the 8th report of the WHO Expert Committee on Malaria (W.H.O., 1961) about the need to plan for the proportionally high cost of late attack and consolidation, most malaria eradication programmes found themselves unable to justify the required expenditures when reaching "near success in an environment with an excess of problems clamoring for attention. As malaria recedes to a low level, other pressing health and social problems exert irresistible demands for available resources" (Scholtens *et al.*, 1972).

Gabaldón (1969) noted that the arguments used to justify a control programme lose their value as success is achieved, "this means that health expenditure produces diminishing returns, and its economic status should change from capital to current expenditure... If

because of misunderstanding of economic conditions, too much money is spent on health, there may be a delay in development which sooner or later will worsen the general state of health". In the case of malaria control, the concept of diminishing returns should be extended beyond the increasing cost per unit of output, to the attrition of effectiveness of the control measures themselves, as noted by Molineaux (1988).

Unwarranted extrapolations have been responsible for many unfulfilled expectations of malaria control. Not only were the effectiveness of interventions in the early successful programmes in a few countries uncritically extrapolated to all malarious areas, but also the expectation of economic benefit. Most of the estimations of economic loses inflicted by malaria were the result of studies of economic development projects, colonial or foreign agricultural, mining or prospecting enterprises in tropical countries or of the impact of malaria epidemics. It is seldom noticed that, while a malaria epidemic will seriously affect the economy of the affected population, as documented by Conly (1975), the mere removal of endemic malaria will not automatically represent an equivalent economic improvement in a population whose economy is adjusted to whatever debilitating effect malaria may have. Similarly, it should be obvious that the mere elimination of malaria does not represent a decrease in mortality equivalent to the specific malaria mortality, when all the other diseases associated with poverty continue.

A distinction which is seldom made is that between cost and affordability, which is related to the difficulty mentioned above, of reaching those in greatest need. While in planning preventive measures, cost/benefit analysis are made projecting costs of treatment to the total estimated cases, during execution coverage and quality of operations are considerably better in those areas or population groups, which originally had access and could afford treatment. As a general result of the accumulation of these tendencies most of the resources spent today for organized malaria control remain concentrated in areas which have only small or considerably reduced malaria risk.

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