# Malaria: old infections, changing epidemiology

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## Abstract

**The epidemiology of malaria has always varied between different parts of the world because of widely varying vectorial capacity. Mortality from malaria can be measured from clinical records or the rise of mortality during an epidemic, but better from observing the fall of mortality during control or from the population frequency of protective host genes. Holoendemic malaria may have doubled the infant and young-child mortality rate in Africa in the recent past, but death rates have fallen because of chemotherapy. The epidemiological pattern is changing. In the Sahel, water-resource developments tend to lengthen the transmission season, though less than might be expected, and urbanization tends to decrease transmission in Africa, not in Asia. The spread of multiple drug resistance of the parasites is making case management harder and deaths may rise. Malaria control has always been unsatisfactory in sub-Saharan Africa owing to the highly effective vector. The main current hopes for control are the use of the effective insecticide-impregnated bed nets and better case management. No simple concept of an epidemiological transition can reflect the very diverse changes occurring in human malaria worldwide.**

## Introduction

Malaria is, and has been, the most important parasitic disease of man in terms of mortality, morbidity and effects upon life generally, using 'parasitic' in its narrower meaning of the animal parasites: worms and protozoa. The malaria parasites are of great antiquity: they evolved along with man so that there are four malaria parasites specific to man, and other related parasites specific to the various great apes, monkeys, and other mammals. In spite of this long-term host-parasite relationship, there have been major epidemiological changes in human malaria over the last fifty years and they are taking place at an accelerating rate. This paper sets out the basic principles of quantitative malaria epidemiology, without which any attempts to understand changes would be meaningless; and describes the main epidemiological changes that are taking place.

An important genetic polymorphism in man, the sickle-cell gene, appears to be maintained by the protection it affords against human malaria and this is used to estimate the mortality due to human malaria, particularly in Africa, in the past. This is compared with the limited historical data on recorded mortality, and the possible causes of falling mortality are discussed. The results are related, though uncomfortably, to the concept of the health transition. The complex interaction of biology of the vector, present health-care, history of the use of medicines and insecticides, migration and environmental change does not fit simply into the idea of a single unidirectional process. There is considerable epidemiological material before these last issues are reached. The presentation focuses on the historical and health-transition issues.

## Malaria: background to epidemiology

There are four malaria parasites of man. Three of them, *Plasmodium vivax, P. malariae* and *P. ovale*, are the cause of intermittent high fevers in man that can make a person very ill but are rarely fatal. The remaining species, *P. falciparum*, is the cause of malignant tertian, or *falciparum*, malaria which has a substantial mortality if it is untreated, especially in the first or an early attack. Following a single infection, there is intermittent presence of the parasites in the blood for several months. In people subject to frequent infective mosquito bites, the parasitaemia will continue throughout childhood.

**Figure 1**
**The cycle of malaria transmission and course of disease, with determinants**

The basic transmission cycle of the malaria parasites is seen in the central part of Figure 1. The sexual stages of the parasite develop in the blood of someone who has been infected for some time. Mosquitoes of the genus *Anopheles* become infected by feeding on that person. The parasites develop in the mosquito at a rate dependent on the ambient temperature but in the tropics usually take about twelve days before the maturing parasites have reached the mosquito's salivary glands ready to infect

the next person on whom the mosquito feeds. It will remain infective for the rest of its life. The interval between the mosquito becoming infected and being first able to pass on the infection is known as the duration of the extrinsic cycle. When someone is bitten by the infective mosquito the parasites pass to the liver, develop in the cells there, and then burst out to infect the red cells of the blood. The parasites multiply, usually synchronously, in the red cells and go through this cycle every 48 hours except for *P. malariae* in which the duration is 72 hours. With each red-cell cycle the parasites increase logarithmically and as the cells burst the classical attacks of fever occur, hence the intermittent fever pattern known as far back as Hippocrates. As the proportion of infected red cells increases, so do the fevers. In *falciparum* malaria the infected red cells become sticky and adhere to the lining of the capillaries of the brain. They use up the blood's oxygen and prevent it reaching the brain so that the patient may go into a coma and die: cerebral malaria.

People who become infected, and are not immune, suffer a classical unmodified attack of clinical malaria with a severe intermittent fever. Their attacks get worse, usually occurring every other day in *Plasmodium vivax* infections, and on alternate days but more irregularly in cases of *P. falciparum*, which gives rise to more severe disease and a mortality of five to ten per cent in those remaining untreated. Malaria morbidity in very highly endemic areas is mainly a feature of infancy and may account for 30–35 per cent of the cases seeking health care at rural dispensaries. It is evenly spread through the year in the forest form and may vary between ten per cent and 80 per cent of childhood fevers in the savannah zone. Some data suggests that mortality may reach its peak in the savannah, where malaria may be combined with malnutrition, maternal overwork, and lack of drugs in the season of maximal transmission.

## The basic quantitative epidemiology of malaria

Malaria varies dramatically in its epidemiological pattern. In some places it appears as massive epidemics affecting people of all ages and causing temporary social disruption comparable to a very severe influenza epidemic. This pattern, alternating between large epidemics and scarce malaria, is called unstable malaria. At the other extreme is very stable malaria, where transmission is continuous, or regularly seasonal, and everyone is being infected and reinfected by mosquitoes. Unstable and stable malaria not only differ in their mortality and public-health effects, they are also very different in their responses to attempts at control. In particular, similarly energetic control measures may have completely different outcomes in different areas. These differences are biologically determined and must be understood if naive generalizations are to be avoided: for example, there was a tendency to blame the failure of malaria eradication in Africa on defective health services, whereas the problem was biologically intractable even with good health services.

The reasons for this epidemiological variation can be understood in terms of the basic-case reproduction rate (BCRR) of malaria, a convenient measure of transmission. The BCRR is the mean number of new cases of malaria to which one case will give rise directly after a single passage through the vector mosquitoes, under conditions of no immunity in the human population. Thus with a BCRR of five, one case will give rise to five cases in the next generation and 25 in the succeeding generation of cases; spread will continue potentially until all the people are infected. Conversely, should the BCRR fall below one, the disease will tend to gradually die out: the goal of malaria-transmission control may be formulated as keeping the BCRR below one. In an endemic malaria situation, the supply of uninfected susceptibles will run out and acquired immunity will play a key role. Three characteristics of the female anopheline mosquito largely determine the BCRR: the density of mosquitoes, man-biting habit and longevity.

Mosquito density is conveniently measured in terms of the number of female mosquitoes per human inhabitant of the area. Malaria transmission is proportional to mosquito density, as might be

expected. However, the effects of changes in the man-biting habit and longevity upon malaria transmission are greater. The man-biting habit is the chance that a given female mosquito will feed on man on any one day. Mosquitoes may feed as often as alternate days, and if all meals were upon man, the man-biting habit would be 0.5. For a mosquito that fed only every third day and with only 20 per cent of meals upon man (the rest upon domestic stock) the man-biting habit would be less than that of the other species by a factor of 7.5. However, since transmission is proportional to the square of the man-biting habit because it takes two bites to transmit malaria—one to infect the mosquito and one to infect man again—the second mosquito is 56 times less effective as a malaria vector. Mosquito longevity affects malaria transmission even more. It takes time for the parasite to develop within the female anopheline. The minimum time is temperature-dependent but even in the hot tropics at least ten days must elapse between the bite that infects the mosquito with malaria and the first time the mosquito is able to pass on the infection. Mosquitoes are often quite short-lived, with a steady daily mortality of five to 25 per cent of the population, so that very few mosquitoes that catch malaria survive to pass it on in many vector species. A really long-lived species can however be extremely effective at passing on the infection. In a sense the 'geriatric' mosquitoes are responsible for malaria transmission.

The preceding discussion shows that, for effective malaria transmission, a mosquito species needs to be long-lived and have a high man-biting habit. Both the vector-species complexes that are largely responsible for African malaria transmission feed preferentially on people, feed frequently, and are long-lived in nature. They include the world's most efficient malaria vectors. Any value for the basic-case reproduction rate of malaria (BCRR) in excess of one will allow spread of the infection. In parts of Asia such values as three and five are not uncommon in malarious areas. In sub-Saharan Africa values for the BCRR in excess of 1,000 are found. There is therefore in many parts of Africa a vast excess of capacity for malaria transmission above that required to maintain endemicity.

This very high BCRR is responsible for the key features of malaria in much of Africa: it is extremely hard to control transmission effectively since so great a proportionate reduction in transmission, perhaps a thousandfold, is needed before the infection dies out; secondly, everyone tends to become infected at an extremely early age and exposures to infection are usual in the first year of life; thirdly, because of the high level of transmission, the natural variations in the determinants of transmission from one year to another never bring the BCRR down close to one so that malaria is always highly endemic. This situation is called 'stable' malaria because it varies so little, and malaria epidemics are unknown in much of the continent: in other words it is 'too unhealthy for epidemics'! The chief determinant of the pattern of malaria seen in Africa is thus the pattern of acquired immunity to human malaria. If this did not occur, in many regions of Africa all the inhabitants would have malaria parasitaemia every day of their lives. The pattern of infection under the extreme of stable perennial transmission is called holoendemic malaria.

## Malaria transmission and community impact

The relation between malarial transmission and its disease effects on the community has been the subject of some of the most vehement controversy in tropical health. This has centred on the problems of African holoendemic malaria—the effects of epidemics have been relatively unequivocal—and conflict was probably heightened by underlying differences of philosophy between the two schools of thought involved. One view was that an equilibrium is reached between parasites and the human community under the conditions of holoendemic malaria; this was most thoroughly propounded by Wilson, Garnham and Swellengebel (1950). They were impressed by the limited morbidity and lack of mortality among indigenous adults, conscious of the difficulty of interrupting transmission with residual insecticides, and fearful of the increased lethality of the disease that might follow unsuccessful control attempts. Their philosophy could be represented as not interfering with a naturally-established

equilibrium and had conservationist implications. By contrast, the other group, led by Macdonald whose 1951 paper is a model of forensic logic, and including Russell and Soper, were convinced of the need to vanquish malaria, and were confirmed interventionists with a strong commitment to eradication.[1] Their philosophy saw nature as red in tooth and claw, and they were conscious of the price in infant deaths that had been paid to achieve equilibrium by adult life. Macdonald in particular had been immensely impressed by the fall in infant mortality in Freetown, Sierra Leone, that followed larviciding operations, as he had worked there (Macdonald and Chowdhuri 1926). The 'interventionists' can be said to have won the day in 1950, and their research on the effects of control measures has provided much of the best evidence for the impact of malaria upon mortality, discussed below.

**Sources of information on consequences of malaria**

The problems of diagnosis in rural clinics mean that routine reporting is not a source of reliable data. Nevertheless, information from numerous routine sources, particularly from West Africa, show 'malaria' to be one of the major clinical problems. Of eleven common diagnoses in Sierra Leone, malaria accounted for 18–35 per cent of the year-of-age specific diagnoses in young children at an outpatient department; it was the commonest cause both of hospital admission and of death in a hospital in north-west Uganda, though it occupied a much less prominent position in relation to adult patient diagnoses. In paediatric health-care facilities throughout tropical Africa, the three predominant causes of ill-health recorded are respiratory infections, diarrhoeal diseases and malaria, though the precise order in which they are placed depends on the region, the age-category under study and the type of health-care facility. Where more sophisticated approaches to the overall burden of ill-health are used, as has been done in Ghana (Ghana Health Assessment Project Team 1981), malaria emerged as the chief cause of loss of days of healthy life, an aggregate measure of the consequences of mortality, illness and disability. Malaria was responsible for 10.2 per cent of all healthy life lost from disease, amounting to 33 days per person per year, though of course much of this was due to deaths in infancy from malaria. Where attempts were made to transform this into economic loss in a fairly direct way, malaria remained the leading cause of loss with discount rates of zero and five per cent, falling to fifth place at a rate of ten per cent.

**Scale of malarial mortality**

There are three main ways of attempting to measure mortality due to a disease such as malaria: from clinical records as to the cause of death, from observing the rise in mortality during malaria epidemics and by determining the fall in mortality when malaria is brought under control. Molineaux (1985) has reviewed some examples of the consequences of malaria control and has also added a fourth method of assessing malaria mortality which depends on calculating the mortality necessary to maintain the observed level of the sickling gene in a balanced polymorphism.

The scarcity of post-mortem series in Africa and, more seriously, the extreme bias introduced because they only derive from tertiary-care facilities and very rarely include young children and infants, mean that what is usually viewed as the best possible source of accurate data is not useful for assessing malarial mortality in Africa or other developing countries. Clinical records of cause of death are equally unsatisfactory as most people die outside hospital; malaria is a very treatable condition unless it presents at hospital very late, and only those exceedingly ill are likely to be admitted. Add to this the scarcity of paediatric beds in many hospitals and it is clear that information on death certificates will be a poor guide to what is happening in the community. Nevertheless, malaria is the commonest cause

[1] In the case of Soper, well-founded in experience in Brazil and Egypt.

both of admission and of death in children under five years of age in a Ugandan community hospital (Williams, Hayes and Smith 1986). Epidemic malaria is rare in Africa, and relevant data come from outside the continent where the great epidemics of *falciparum* malaria in Punjab and Sri Lanka led to dramatic changes in mortality. In Sri Lanka the quarterly crude death rate at the height of the epidemic rose by a factor of 3.4, implying that two-and-a-half times more people died of malaria than of all other causes combined during that period. The Sri Lankan data on vital rates are sufficiently good to have been used in numerous, and controversial, analyses of the impact of malaria, discussed critically by Molineaux (1985). Perhaps the most informative picture comes by comparing the least and most malarious districts over a long period that includes the introduction of malaria control. This suggests that the crude death rate of the highly malarious district was consistently double that seen in the other, though the two had identical death rates after malaria control.

The best African data on malarial mortality derive from local field-research projects that have attempted to stop malaria transmission, usually by means of residual insecticides, though some recent projects have relied increasingly on chemotherapy and chemoprophylaxis. Of particular interest have been those where observation has continued after attempts at transmission control have been abandoned. All are research-scale because national-scale interruption of transmission has not been feasible in sub-Saharan Africa. The exceptions have been small islands, or areas at the edge of transmission due to temperature, in turn due to high altitude or location towards the southern limits of transmission; or at the northern limits from aridity. None of these situations is generally informative about the African situation. Three major field projects have used residual insecticides to lower drastically the transmission of malaria over substantial but research-scale patches of Africa.

The Pare-Taveta scheme was the earliest, with spraying from 1955, and in broad design the most elegant, since after several years the intervention ceased and the degree of reversion could be observed (Bradley 1991). Unfortunately, emphasis was originally placed on research areas other than infant mortality, there was a hiatus in demographic data collection, and the long-term demography was carried out subsequently in a slightly different but more detailed way. Striking findings on growth and morbidity were the apparent absence of malarial effect. Malaria was, however, clearly shown to be of importance in producing a substantial and widespread reduction of the haemoglobin level.

Mortality data, initially on a limited population, showed substantial year-to-year variation but a clear and large fall in the first year of full spraying, 1956; death rates remained down for the spraying years to 1958. After the spraying ceased and demographic-data collection had been resumed on a larger scale (1962–1966) there was a small mortality rise in the infant and over-40-years age groups, and a large reversion to the previous high death rates in the 1–4 years age group. It should be noted that malaria transmission only gradually resumed when spraying ceased and had not reached former levels even by 1966. Also, concern had been felt about stopping the spraying and there followed deliberate attempts to make antimalarials available to the population, so that not only was a complete reversion of vital rates highly undesirable, but efforts were made to prevent it. Other changes in socioeconomic progress were taking place, and drought also complicated the scene. Nevertheless, the immediate, precipitous fall in death rates, especially in infants and young children, as soon as spraying was complete, is very convincing. In particular, the infant mortality rate fell from a level of 165–260 before control to 78–132 after it had been instituted, a fall of 108 which amounted to a halving of the infant mortality rate. The young children aged 1–4 years also had a halved mortality, though it was of course much smaller than the IMR; falls in deaths in older people were less dramatic.

A second similar study, in the Kisumu area of Kenya, to the north-east of Victoria Nyanza, took place nearly 20 years later and used Fenitrothion to achieve a 96 per cent reduction in malaria

transmission. This was accompanied by a fall in the infant mortality rate of 40 per cent, from 157 to 93 per thousand. The malarial effect was greatest between three and ten months of age (Payne et al. 1976).

The third study, and that best documented and executed, was in the Garki area of northern Nigeria in 1971–1973, with extremely intense seasonal-malaria transmission. Intervention was by residual insecticide spraying with Propoxur, backed up by mass drug administration for part of the area, which had a very substantial effect in reducing transmission. Infants were not given drugs unless they were found to be infected (Molineaux and Grammiccia 1980; Molineaux 1985). The most dramatic findings were a large fall in the infant mortality rate from 255 to 55 and 102. Comparable unprotected villages had an IMR greater by 80 and 90 in the two intervention years. The death rate of children aged 1–4 years was less than half that in unprotected villages as was the crude death rate. Moreover, in the absence of protection there was a close seasonal parallel between the IMR and the rate of conversion of infants to parasite positivity, with the IMR about ten per cent of this rate-of-incidence measure. Under protection the IMR both fell and lost its seasonal peaks.

In Senegal, the first of three chemotherapy and chemoprophylaxis trials (Garenne, Cantrelle and Diop 1985) halved the mortality of those aged six months to 35 months, but had no effect on those older, or younger. Moreover, there was a large fall in the diagnosis 'fever and malaria' as the stated cause of death. As this was rather precisely balanced by a rise in the 'miscellaneous or not known' category for other causes of death, Carnevale and Vaugelade (1987) have cast some doubt on this interpretation.

Subsequent studies in the Congo at Kinkala, and in Bobo Dioulasso (Burkina Faso) as studied by Baudon et al. (1984), showed very little effect of intense chemoprophylaxis and chemotherapy upon mortality and are difficult to reconcile with the weight of other evidence except on some of the hypotheses considered below.

**Historical assessment of malaria morbidity: inferences from genetics**

The gene for sickle-cell anaemia, when present in homozygous SS form, is effectively lethal before reproduction. For this gene to be maintained in the population, the heterozygous AS form must have a selective advantage over the normal homozygous AA. It is believed that this advantage consists of a relative protection against the lethal effects of *falciparum* malaria. If the relatively conservative assumption be made that all AS individuals have a zero death rate from malaria, it is possible to calculate the minimum malaria mortality of the AA group, and thus of the whole population, needed to maintain the S gene at any observed equilibrium frequency. The sickling gene reaches a very high frequency in parts of sub-Saharan Africa and may reach a frequency of 40 per cent of sickle-cell trait carriers. At a level commonly encountered in East Africa of 18 per cent of sickle-cell traits, AS (or a gene frequency of 10% S), and assuming complete loss of sicklers before puberty, then an excess mortality of the order of 100 per thousand is required from malaria in the AA genotype people, or an excess of some 81 per thousand in the overall population. In other words, if the total cumulative mortality in the population by puberty is of the order of 300 per thousand, over a quarter of this mortality would be due to malaria to maintain the gene frequency in equilibrium. If any of the AS die of malaria, the proportion of malaria deaths would need to be greater.

An incidental consequence of the way in which the gene frequencies are maintained in balance by a 'proportional mortality of genes' is that where the non-specific infant mortality is high, a lower mortality from malaria per thousand live births will be needed to maintain the same gene frequency. To maintain the ten per cent sickle-cell gene frequency (18% sickle-cell trait) requires a mortality of 90 per thousand from malaria where this is the only cause of death, 81 at a non- malaria mortality of 100 per thousand before puberty and 72 at a non-malaria mortality of 200. To maintain 32 per cent heterozygosity in a population with 200 per thousand premature deaths from other than malaria,

requires a malarial mortality of 128 per thousand and 200 per thousand AA individuals, or doubles the mortality in the AA group.

**Interpretations of malaria mortality**

In reviews of differing aspects of malarial mortality, Molineaux (1985) and Carnevale and Vaugelade (1987) have considered the empirical evidence. Any attempt to put together the apparently conflicting evidence must take one of three broad approaches. One is to deny the validity of some of the data. This is not difficult as all the studies have methodological defects, some bristle with assumptions, and many have broad confidence limits even if the observations are correct. There is therefore much space for the author to choose the conclusions he prefers and to explain away discrepant results. This tends to be Carnevale's approach. The second way of dealing with the range of results on mortality is to assume the existence of confounding variables that affect the scale of the observed mortality that is ascribed to malaria. This view is adopted by Molineaux and developed by Cohen (1988). A third view, perhaps a variant of the second, is to assume heterogeneity of the consequences of equally endemic malaria due to interventions of other types, a position which can explain some of the problems confronting Carnevale.

Molineaux (1985), in an exceptionally careful and imaginative analysis of the data on malaria mortality, deals with two problems. The first is the much greater reduction in mortality observed after malaria control operations than the fall in deaths ascribed specifically to malaria would suggest. This is most apparent in non-African data, from Guyana and Sri Lanka, where an indirect effect of malaria control on mortality, 2–4 times the direct reduction of deaths from malaria, was observed.

A converse effect appears to prevail in two West African studies, where the removal or massive reduction in deaths from malaria has led to a much smaller fall than expected in infant and young child mortality. This was seen in Garki, Nigeria (Molineaux and Grammiccia 1980), where malaria control removed the seasonal peaks of malaria deaths but mortality remained high overall, and in The Gambia when a measles epidemic shifted the peak season of infant mortality from the malaria season without massive effects on total mortality. The most economical hypothesis to explain these results is that of competing risks: a certain number of children are postulated as likely to die anyway, possibly with low birth weights and for other ultimate reasons, and the immediate cause of death may be malaria if present and some other infection if malaria is absent. Both malaria and, say, measles may be sufficient causes and only one is necessary. In either situation, deaths averted by malaria control are not equal in number to deaths due to malaria. With the twin explanations of indirect malarial mortality and competing risks, it is of course dangerously easy to explain most sets of paradoxical results. In a long-term study many other variables also change; this fact limits the ability to refute some of these possible explanations of observed data.

Carnevale and Vaugelade (1987) are primarily concerned with African data that suggest a fall in adult as well as infantile mortality after malaria-control operations, and with the relatively small effects seen in some recent control projects, mainly using chemotherapy, in francophone Africa. Although they argue from the earlier campaigns forwards, it is reasonable to infer that the main starting points were their own and colleagues' recent work in Burkina Faso and in the Congo which showed very little reduction in mortality among children subject to a vigorous chemoprophylactic and chemotherapy regime. The earlier Senegalese study is open to criticism on diagnostic grounds. Carnevale and Vaugelade (1987) then attempt to undermine the conclusions of the three major control programs in Pare-Taveta, Garki and Kisumu, arguing that, first, the decline in mortality is general and progressive, owing to social and economic development along with a broad-based improvement of medical care, and secondly the insecticidal and chemotherapeutic programs are non-specific, contrary to what has been generally asserted.

It is certainly true that several of the communities studied have improved economically and in access to health care over the periods studied and this is likely to have been responsible for some of the changes observed, as discussed above, and the Kisumu changes are difficult to explain on any grounds. But the rapidity of the effects in Pare-Taveta and Garki argue strongly for a specific antimalarial intervention as the primary determinant of the main changes observed and described above.

The argument that residual insecticiding is non-specific in its effects is unconvincing. A more likely hypothesis is that the earlier studies did indeed demonstrate substantial malarial mortality; that the ones, intermediate in time, at Kisumu and at Ngayokhem in Senegal, have methodological problems that make them hard to interpret reliably; and that the recent francophone-country studies showed little benefit from organized chemoprophylaxis or chemotherapy because mortality from malaria had already been reduced by various forms of progress but chiefly by individuals purchasing chemotherapy for their families when febrile.

The studies are all compatible with heavy infant mortality in uncontrolled holoendemic malaria, greatly reduced by individual access to chemotherapy in recent years.

## Epidemiological trends

In spite of its epidemiologically 'stable' nature, African malaria is undergoing substantial and rapid change at present in its basic epidemiology, in the pattern of mortality and in the pattern of resistance displayed by *P. falciparum* to antimalarial drugs. It is possible that in the medium-term immunization methods may become available to produce a fourth and massive type of change.

Several types of change in malaria transmission are taking place at present. In the Sahel and savannah areas where lack of surface water prevents transmission for several months of each year, the development of water-storage dams and of irrigation, particularly for rice production, is extending the breeding season for anophelines and increasing mosquito populations. Few new large dams are now being built, but small dams proliferate, often without any form of health assessment, and though their effect on malaria should not be exaggerated, they will have some effect in the more arid areas. Urbanization is proceeding rapidly and it has been predicted that up to 43 per cent of the population of Africa may live in urban areas by the year 2000. Usually the effect of urban development has been to decrease anopheline densities substantially. Pollution of urban surface waters has led to a marked increase in the 'dirty water'-breeding culicines such as *Culex quinquefasciatus* and a fall in the mosquitoes that flourish in clean water, such as the anophelines, and this has been well documented in Dar es Salaam. In South Asia, however, urban malaria is common because of the urban anopheline, *An. stephensi.* which is also a very good vector.

The widespread availability of some antimalarials, chiefly chloroquine, has undoubtedly affected the mortality from malaria in children. In some places, few fevers, whether due to malaria or not, escape partial if not complete courses of chloroquine and this has brought down the number of fatalities. Within the remaining areas of chloroquine sensitivity this trend will continue. It has already been argued above that this provides a better explanation of the apparently changing effects of malaria control on population mortality than do the suggestions of lack of specificity of the earlier insecticidal programs. Sir Ian McGregor (personal communication) has described the appearance of cerebral malaria in teenagers in Banjul, The Gambia, where it was previously a disease of infants. The combination of urbanization in reducing transmission, and frequent chemotherapy or even chemoprophylaxis in diminishing individual duration of parasitaemia, have probably been responsible for this.

If the malaria parasites had remained unchanging, the steadily increasing availability of antimalarials at health-care facilities and shops, and consequently in the home, would be expected to have led to a progressive decease in malarial mortality so that it would have remained a major cause of

disease but become of limited importance as a cause of death. However, the spread of drug-resistant strains of *P. falciparum* is greatly altering this optimistic picture. Resistance to the folic-acid antagonists proguanil and pyrimethamine emerges rapidly after their widespread use, and pyrimethamine resistance is common in many parts of the tropics. But the crucial resistance has been to chloroquine which has dominated the treatment of malaria in the past because it is efficacious, cheap, relatively non-toxic, and easy to administer. The spread of chloroquine-resistant *P. falciparum* since 1950 has created a new situation. It spread from foci in Colombia and on the Thai-Vietnam border to envelop Southeast and South Asia, and then reached Africa a decade ago. The last five years have seen very rapid spread across Africa. It is common in East and Central Africa and has reached Cameroon, Ghana, and other West African states. It will soon have reached all the states of West Africa.

The second-line therapeutic drug is Fansidar (a mixture of pyrimethamine and a long-acting sulphonamide) which is more toxic and much more expensive, and to which resistance has been clearly described in East and part of Central-Southern Africa as well as in Asia. Alternatives for treatment are also expensive, resistance emerges quickly to mefloquine, and quinine is both toxic and more difficult to administer than other antimalarials. Chloroquine resistance and Fansidar resistance will surely continue to spread and the scanty number of new drugs to be available in the near future (halofantrine, artemether, etc.) suggests that mortality from malaria may cease to decline, and in areas where drugs are already used may begin to rise. The outlook is not good, in the absence of major innovations, among which a vaccine is the item on which most hopes are based.

**Changes in approaches to control**

The history of malaria was for many centuries about an increasing understanding of the circumstances under which it flourished, together with some preventive action, and a concurrent clinical understanding of the pattern of fever and association with splenomegaly that goes back to ancient China. Therapy improved substantially in the seventeenth century with the introduction of quinine, but otherwise the modern era began in the 1880s. As with all infectious and communicable diseases, in the late nineteenth century the field became dominated by microbiology and the causative *Plasmodium* was described in 1882. Although description of the stages of the life cycle in the mosquito by Ross soon followed, malaria was remarkable for concealing some of its parasitological secrets so that the whole life cycle, including the hypnozoite stages, took a complete century to unravel. However, malaria was equally remarkable for the very rapid translation of parasitological research to preventive action. This was mainly due to the orientation of Ross towards practical control. On demonstrating the mosquito transmission of *Plasmodium*, Ross turned from parasitological research to field control at once and the 'mosquito theory' was put to use within a few years, with great success, particularly by Watson in Malaysia and Gorgas in Panama. The subsequent rate of malariological research steadily increased, and while the frantic pace of modern molecular biological research is a very recent phenomenon, enormous progress was made in the first half of this century in many aspects of malaria, and also of control.

The nineteenth century saw great improvements in the control of communicable disease, chiefly as a consequence of environmental improvements. The provision of a safe piped water supply to every household was the most striking of a series of measures to improve the health of the population as a whole. This may be described as the public-health approach. The public-health approach (in this limited sense) to malaria is reduction in transmission, aiming to protect everyone. An alternative approach to disease control has been to seek to protect the individual. In malaria, this goes back to the use of quinine as a prophylactic and is most clearly seen today as the use of chemoprophylaxis by travellers to malarious areas and the provision of chemoprophylaxis to pregnant women in endemic areas. It is more concerned with preventing death or disease than with protecting the whole community.

It bears a closer relation to clinical medicine than does transmission control, and lends itself to distribution through a curative primary health-care system.

The broad public-health approach of our ancestors looked to environmental control leading to a man-made landscape under careful control and a fertile economy. Into this fits species sanitation: the selective alteration of the environment to prevent breeding of the local anopheline vectors of human malaria, which was so successful in areas of relatively lower vectorial capacity and especially organized plantation agriculture in the tropics. For the first two decades of this century, both environmental control of mosquito breeding and various patterns of chemotherapy were tried. Successes on the grand scale for the Panama Canal, Zambian copper belt, and South Asian tea plantations made the public-health approach dominant for areas where organized control of the environment was feasible, usually where there was a commercial opportunity and investment for development. The elaboration of a sophisticated species-sanitation approach provided a sound basis for this.

The discovery of the residual insecticidal properties of DDT changed the method of control completely and made large-scale area-wide control feasible from the 1940s (Table 1). It also shifted any previous focus on individual protection from bites by personal action towards centralized public-health efforts and strengthened the predominance of transmission control.

**Table 1**
**An attempt to epitomize the decades since 1930 in malaria control**

| | Malaria |
|---|---|
| 1940 | |
| | Control |
| 1950 | |
| | Eradication: attack |
| 1960 | |
| | Eradication: consolidation |
| 1970 | |
| | Resurgence |
| 1980 | |
| | Chaos |
| 1990 | |
| | Hope |

Eradication took this further still in the 1950s onwards. Not only was the interruption of transmission the central goal, but chemotherapy of individuals in the consolidation phase was viewed as an attack on transmission rather than as therapy for individual benefit. There was an extreme loss of interest in the malaria patient as such, and also in research. Eradication of malaria was treated rather as a military campaign; many of the workers were not from the health-care system and the program was usually kept separate from the remainder of the health services, at any rate until well into the consolidation phase.

Malaria became, in a unique sense, the World Health Organization's disease. It staked its reputation and half its staff on eradicating malaria. The initial successes of the eradication policy, the lasting benefits for many countries, and the subsequent difficulties in the consolidation phase over time, are well known and need no repetition here. The resurgence of malaria in India (Figure 2) illustrates what was seen elsewhere throughout Asia, while eradication was scarcely attempted in much of sub-Saharan Africa.

**Figure 2**

In the long and disorderly sorting out of policies during the decades of resurgence and chaos (see Table 2) there has been a shift towards a risk approach, in several steps. This approach of preventing deaths and shortening illness was conceded initially with reluctance to communities otherwise unable to cope with controlling malaria, and has gradually become more vigorously advocated by WHO. Much of this has been related to resolving tensions between malaria-control strategies and the primary-health-care concept which succeeded malaria eradication as a driving ideology at WHO, though both ideas are now moving to more empirical approaches, partly driven by economic pressures.

**Table 2a**
**Recent estimates of the numbers of people exposed to or suffering from malaria within a year, expressed as an annual period prevalence**

| | |
|---|---|
| Exposed | 2,073 million |
| Infected | 270 million |
| Ill | 110 million |

| | |
|---|---|
| Died | 1 million |

**Table 2b**
**Current risk of malaria in relation to past eradication efforts in the world. There is considerable lumping of data by countries which exaggerates the 'reduced' category. Population in each of four categories**

| | |
|---|---|
| Never malarious | 1,300 million |
| Eradicated | 800 million |
| Reduced | 2,120 million |
| No control | 370 million |

Nobody can look at the list of available antimalarials today with any complacency: the safe drugs are rapidly becoming ineffective, and the more effective drugs are either new or relatively toxic or both, and are expensive. New drugs may well be followed by parasite resistance, or previously inadequately perceived toxic effects may emerge, as was the case when amodiaquine was used for prophylaxis on a larger scale. And the list of candidate new drugs is tiny. As chloroquine resistance spreads to cover Africa, what remains that is both safe and cheap? The situation cannot change overnight as the gestation period for a new drug is long—nearer a decade than a year—and few join the queue to enter.

Hopefully, the present decade will see a transition from chaos to hope in malaria control. Vaccines could transform the scene, but even if not, there are advances taking place in many aspects of malaria control, such as the use of insecticide-impregnated bednets. As we learn the new, we must not forget the old. It is now necessary to combine these various accounts of epidemiological and control processes and of historical events into a coherent whole and in relation to the idea of a health transition.

In summary, there have been substantial changes in the mortality from malaria both in the African holoendemic situation where availability of personal chemotherapy has increased, and in Asia and Latin America where eradication attempts greatly reduced transmission and where mortality from resurgent malaria has again been handled by chemotherapy.

In finer detail, transmission has only fallen in those parts of Africa where urbanization has polluted the vector-breeding sites, where desertification has greatly curtailed the transmission season and where malaria control has been practised at the altitudinal or latitudinal limits of transmission. As transmission persists at a much higher level than is needed to maintain all the population infected (or subsequently partly immune), there continues to be a great threat to life of the young, comparable to that observed in the past in the Pare-Taveta study or inferred from the sickling frequency. This is only held in check by early chemotherapy of those ill from malaria. With the spread and intensification of chloroquine resistance, followed by multidrug resistance, in *P. falciparum*, malaria mortality is tending to rise again and this is likely to continue with the relative paucity of new drugs entering the market, and their high cost, unless an effective and cheap vaccine becomes available.

In the other malarious areas of the world, transmission was dramatically reduced, and almost halted in places by the eradication programs of the period 1950–1970. Both mortality and infection became very low. In Europe, the USA, and several small islands eradication was successfully achieved. In South Asia, Indonesia, and other large areas a massive resurgence of transmission took place following the collapse of the eradication programs, so that, for example, the annual incidence of malaria

in India, around 100 million cases a year in the 1930s, fell to 200,000 at the best year for eradication, and then rose again to reach levels of the order of 20–40 million annually after allowing for underreporting of cases. Urbanization did not reduce malaria as *An. stephensi* is an urban breeding mosquito and a good malaria vector. Mortality did not rise proportionately with the resurgence of transmission, presumably because of chemotherapy, but the spread of chloroquine resistance is making this more difficult. Nevertheless, the level of transmission is lower than in sub-Saharan Africa and this makes control an altogether more tractable proposition.

**Changes in malaria 1930-1991**

The course of malaria as a world problem has therefore been one of massive incidence and prevalence with great mortality up to the 1940s, with control taking place in limited areas of commercial agriculture or urban development where funds were available and the level of transmission was not too high. Some of these situations, such as parts of the USA and Europe, were in the demographic and health transitions, but others such as the tea-gardens of South India could not meaningfully be so described. No impression was made on sub-Saharan African lowland malaria where malaria mortality might approach 50 per cent of infant and young-child deaths, or a rate of over 60 per thousand births.

The decade following the Second World War saw the use of DDT on an increasing scale. Around the Mediterranean almost total control was achieved in countries of very varied standards of living, as also happened on various small islands in the Caribbean and elsewhere, regardless of where they were in relation to a demographic transition. Success in control, short of eradication, then followed in many relatively poor countries of Asia and Latin America through the use of residual insecticides, chiefly DDT, often paid for by foreign-aid funds. Good results needed a rudimentary health service capable of being improved and a low or medium BCRR. Temporary successes were recorded in countries as poor as Bangladesh, Sri Lanka and India.

From 1970, eradication had been achieved in European countries and the USA, places with relatively high-income, well-organized health services, and also less efficient malaria transmission or a short transmission season. Successes were also attained on some islands without those criteria. In Asia, difficulties in getting rid of the last cases through problems at the consolidation phase first prolonged that phase and eventually were followed by collapse of the eradication programs, which were rigid, and conspicuously lacking in research support. Failure was variously blamed on insecticide resistance of the mosquitoes, administrative failure of the consolidation case-finding program, resistance to drugs by the parasites, generally weak health services, and so on. The process was complex and often country-specific. Eradication is a high-risk activity that has to be oversold to have any hope of success and then must maintain activity and funding in the face of a disappearing health problem, and push eradication to completion in less than a decade, before political will is exhausted. In many poorer countries the remarkable fact is not that eradication failed but that it came so close to success. The outcome also depended on the BCRR as this determined the difficulty of the task. The same effort in Sri Lanka and Sierra Leone would eradicate malaria from the former while having a negligible effect on the latter. For practical purposes, sub-Saharan tropical Africa wisely did not participate in the eradication program and the holoendemic malaria there persisted.

During the 1970s and 1980s resurgence of malaria occurred in those countries where eradication had not succeeded. *P. vivax* preceded *P. falciparum*, as is usual in malaria epidemics. The level of endemicity reached was usually lower than in the 1930s and in particular the mortality appeared much lower, though official reluctance to acknowledge the failure of the program and the general collapse of morale and malaria control may have greatly impeded reporting. The overall impression gained is that malaria mortality is substantially reduced, probably from widespread self-medication with chloroquine.

With the massive spread of *P. falciparum* resistance to chloroquine, and often multi-drug resistance, it is likely that mortality will rise again, certainly in Africa.

## Malaria and the demographic and health transition

Clearly, the relation between malaria and the so-called health transition and the demographic transition is complex. In African holoendemic malaria, significant control clearly affects the demographic transition because malaria is such a major cause of infant mortality. Even where this is less obvious, as in Sri Lanka, the near-eradication period was characterized by a great rise in fertility and population growth.

Apart from the direct contribution of malaria to mortality and fertility, where it is driving the demographic processes that lead to the transition, malaria control is relatively autonomous as a health variable. Its feasibility is determined by the biological BCRR which depends on local mosquito biology. Certainly, because control requires resources and a health-care delivery system, it is related to economic development. It does not, however, disappear 'spontaneously' as incomes rise, it requires a specific and well-organized effort to control transmission, though mortality does tend to fall once the appropriate chemotherapy is widely available.

But the malaria parasite is also capable of adaptation, and drug resistance may result in malarial increases that would not tidily fit a health transition that went one way. Conversely, moderate effort on islands with a relatively low BCRR can eradicate malaria at a stage long before the other aspects of the health transition would occur.

Thus, for malaria, as for other vector-borne infections, any simple concept of a demographic and health transition fits uncomfortably. It is truer for malarial mortality than for malarial infection. But biological factors which show immense areal variation play a major role, and both recent technical advances and ancient genetic mechanisms confuse the simple picture. Malarial mortality reduction may be part of the health transition, but the richness and diversity of malaria epidemiology and control cannot be contained within so simple and general an idea.

## References

Baudon, D., J. Roux, P. Carnevale, J. Vaugelade, C. Boudin, J. Chaize, J.L. Rey, M.B. Meyran and O. Brandicourt. 1984. Etude de deux stratŽgies de contr™les des paludismes, la chimiothŽrapie systŽmatique des acc• s fŽbriles et la chimioprophylaxie hebdomadaire dans 12 villages de Haute-Volta, en zone de savanne et zone rizicole de 1980 ˆ 1982. *Technical Document* No. 8450. Bobo Diolasso: Organisation de Coordination et de CoopŽration pour la Lutte contre les Grandes EndŽmies.

Bradley, D.J. 1991. Malaria. Pp. 190–202 in *Disease and Mortality in Sub-Saharan Africa*, ed. R.G. Feachem and D.T. Jamison. New York: Oxford University Press.

Carnevale, P. and J. Vaugelade. 1987. Paludismes, morbiditŽ palustre et mortalitŽ infantile et juvŽnile en Afrique sub-saharienne. WHO/MAL/87.1036. Geneva: World Health Organization.

Cohen, J.E. 1988. Estimating the effect of successful malaria programmes on mortality. *Population Bulletin of the United Nations* 25:6-26.

Garenne, J., P. Cantrelle and I.L. Diop. 1985. Le cas du SŽnŽgal (1960-80). Pp. 307–330 in *La Lutte Contre la Mort*, ed. J. Vallin and A. Lopez. Travaux et Documents no. 108. Paris: Presses Universitaires de France.

Ghana Health Assessment Project Team. 1981. A quantitative method of assessing the health impact of different diseases in less developed countries. *International Journal of Epidemiology* 10:73-80.

Macdonald, G. 1951. Community aspects of immunity to malaria. *British Medical Bulletin* 8:33-36.

Macdonald, G. and K.L. Chowdhuri. 1926. Malaria in the children of Freetown, Sierra Leone. *Annals of Tropical Medicine and Parasitology* 20:239-262.

Molineaux, L. 1985. La lutte contre les maladies parasitaires: le probl• me du paludisme, notamment en Afrique. Pp. 111–140 in *La Lutte Contre la Mort*, ed. J. Vallin and A. Lopez. Travaux et Documents no. 108. Paris: Presses Universitaires de France.

Molineaux, L. and G. Grammiccia. 1980. *The Garki Project: Research on the Epidemiology and Control of Malaria in the Sudan Savanna of West Africa*. Geneva: World Health Organization.

Payne, D., B. Grab, R.E. Fontaine and J.H.G. Hempel. 1976. Impact of control measures on malaria transmission and general mortality. *Bulletin of the World Health Organization* 54:369–377.

Williams, E.H., R.J. Hayes and P.G. Smith. 1986. Admissions to a rural hospital in the West Nile District of Uganda over a 27 year period. *Journal of Tropical Medicine and Hygiene* 89:193-211.

Wilson, D.B., P.C.C. Garnham and N.H. Swellengrebel. 1950. A review of hyperendemic malaria. *Tropical Diseases Bulletin* 47:677-698.