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Focus

Combating Malaria Morbidity and Mortality by Reducing Transmission

J-F. Trape and C. Rogier

Jean-François Trape and Christophe Rogier present epidemiological data and an analysis of the relationship between transmission, morbidity and mortality from malaria which suggest that any intervention aiming to reduce transmission will not, on a long-term basis, reduce the burden of malaria in the majority of epidemiological contexts observed in tropical Africa.

Malaria control in tropical Africa is principally based on the presumptive treatment of fever cases using anti-malarial drugs. In the past decade, the rapid spread of chloroquine resistance has stimulated the exploration of other control methods. Several studies have now shown that insecticide-impregnated bednets can reduce morbidity and mortality[1–4], and this method is generally considered to be an efficient means of combatting malaria. Aided by substantial funding from several international agencies, intervention programmes based on insecticide-impregnated bednets and curtains are either under way, or being planned, in many African countries. Other strategies aimed at reducing malaria transmission (such as the genetic manipulation of mosquito vectors[5] or the development of a transmission-blocking vaccine[6]) are also actively being explored.

Generally speaking, can we hope that interventions that aim to reduce malaria transmission can reduce, on a long-term basis, malaria morbidity and mortality whatever the epidemiological context? The answer lies within the general framework of relationships between the entomological inoculation rate, the incidence rate of malaria attacks and the frequency of severe forms of the disease. The average level of transmission varies considerably with the endemic area, from about 10^{-2} to 10^3 infective bites per person per year. The degree of acquired immunity in indi-

viduals living all their lives in a given endemic area depends on transmission intensity and age. This has marked consequences for the absolute and relative importance of the burden of malaria at a given age[7], but also, probably, on the immediate and delayed evolution of the incidence of malaria morbidity and mortality after a reduction in transmission.

Transmission and mortality

The results of a large study covering the 500 000 inhabitants of Brazzaville (Congo) provide an initial indication that extreme differences in malaria transmission may be associated with only minor differences in malaria mortality rates[8–11]. This study is the only published comparison of malaria mortality rates between populations that were identical in their genetic and socio-cultural backgrounds and that benefited from equal opportunities for therapeutic care, while differing dramatically in their exposure to malaria. Depending on the district of Brazzaville, the entomological inoculation rate varied from more than 100 infective bites per person per year to less than one infective bite per person every three years, which represents almost the entire scale of malaria transmission rates observed in Africa[9]. Despite this, the incidence of severe malaria cases was essentially identical for all the districts, the only significant difference being the younger average age of severe malaria attacks in the high-transmission districts (Fig. 1). It is important to note that the parasite rate in schoolchildren varied from 3% to 81%, depending on the district of the town, and that two-thirds of the schoolchildren from the low-transmission districts had no detectable anti-*Plasmodium* antibodies at the age of seven, which clearly indicated that the circulation of children between different districts was limited and could not, therefore, explain the homogeneity of the risk of severe malaria[11]. Recently, other studies have compared severe malaria rates in areas with different entomological inoculation rates. Similar levels of severe malaria were observed in two areas of markedly different malaria transmission in East Africa: one in

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Tanzania, where transmission reached 300 infective bites per person per year; the other in Kenya, where transmission was about 10 infective bites per person per year[12]. As in the case of Brazzaville, the only important differences concerned the age distribution and the clinical patterns of the severe forms of the disease. Similarly, the incidence of severe malaria was not associated with transmission level at nine different sites in the Kilifi District in Kenya[13]. Finally, comparison of malaria mortality rates observed in 28 studies in Africa revealed that these estimated rates were generally of only limited variability and showed no relationship with the transmission level in the 11 studies where entomological data were available[14].

Fig. 1. Incidence of severe malaria as the number of cases per 10 000 people per year of observation in children aged 0–14 years living in Brazzaville (Congo) according to the entomological inoculation rate (EIR) in the district of residence. Cases occurring before age five are shown in black, and those occurring after age five are hatched.

Transmission and morbidity

If the level of transmission is not an important risk factor for malaria mortality in Africa, is the same true for malaria morbidity? In highly malaria-endemic areas, distinguishing malaria from other causes of fever poses difficult methodological problems because of the high frequency of asymptomatic infections and the lack of specificity of the signs and symptoms of the disease[15]. It is only recently that methods have been developed that permit a precise estimation of the incidence of malaria attacks in areas of moderate and high transmission[15-18]. By using these methods, we have compared the malaria morbidity of three Senegalese populations (from Dakar, Ndiop and Dielmo) exposed to approximately 1, 20 and 200 infective bites per person per year, respectively.

In Dakar, among individuals that have lived since birth in a district of the town where the transmission intensity was about one infective bite per person per year, the clinical incidence rate was identical to the parasitological incidence rate in children aged seven to 11 (Ref. 7) and was three times less than thè parasitological incidence rate in adults (J-F. Trape and L. Konate, unpublished). These observations show that a high proportion of infections are symptomatic in individuals of all ages exposed since birth to about one infective bite each year. By the age of 60, these individuals have probably accumulated an average of 27 to 30 malaria attacks since birth, of which about half will have occurred in adulthood.

Since 1990 (Dielmo village) and 1993 (Ndiop village), we have uninterruptedly followed up the population of two villages in Senegal where malaria transmission intensity differs considerably[19,20]. In the first village, transmission is intense and perennial due to the presence of a stream which serves as a permanent breeding site for Anopheles gambiae s.l. and An. funestus. In the second village, transmission is about ten times lower, as the Anopheles-breeding sites only exist during the rainy season, which lasts about four months. For these two populations, identical and strict clinical surveillance programs have been carried out. These include a daily home visit to each person and the pres-
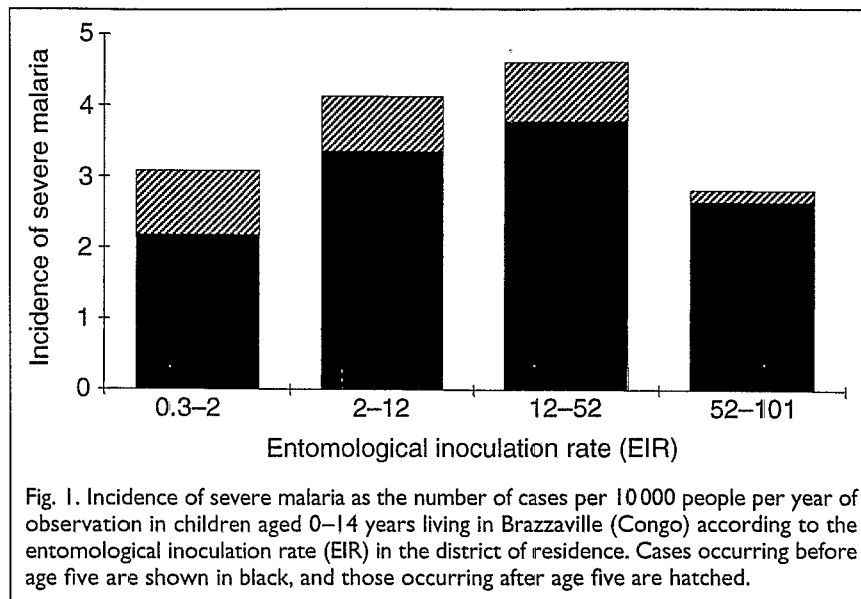
ence, night and day, of a medical team in the village to diagnose and treat any pathological episode. As shown in Fig. 2, these two populations differ markedly in terms of the pattern of age-dependent variations in malaria attack incidence rates. From these data, it can be estimated that, at the age of 60, the Dielmo inhabitants, who are exposed to about 200 infective bites per person per year, average a total of 43 attacks since birth, with only 23% of these arising during adulthood. For the Ndiop inhabitants, who are exposed to about 20 infective bites per person per year, one can estimate an average total of 62 malaria attacks by the age of 60, of which 41% occur during adulthood.

The comparison of these three Senegalese populations suggests that there is little difference in the total number of attacks over an entire lifetime in individuals residing in areas that vary by as much as a factor of 200 in transmission intensity. If this is correct, how do we explain the decrease in malaria morbidity and mortality following the implementation of bednets programmes which has been observed in most studies in Africa? Figure 3 compares the fluctuations of the entomological inoculation rate and the incidence density of malaria attacks in chidren in Dielmo. Clearly, these fluctuations are closely correlated, and a tenfold decrease or increase in malaria transmission is associated, in the following weeks, with a twofold decrease or increase in malaria morbidity. The decrease of malaria transmission in Dielmo each year at the end of the rainy season can be compared to the implementation of a bednet programme, as a tenfold reduction of transmission is close to the maximum reduction in malaria transmission that has been achieved by impregnated bednets in tropical Africa. In the short term, it is followed by a decrease of malaria morbidity. There are no existing data on the medium- and long-term efficacy of bednet trials. However, they can be predicted using data from areas where malaria transmission is lower because of natural conditions.

Relationships between transmission, morbidity and mortality

We have attempted to quantify the relationships between transmission, the incidence of clinical attacks
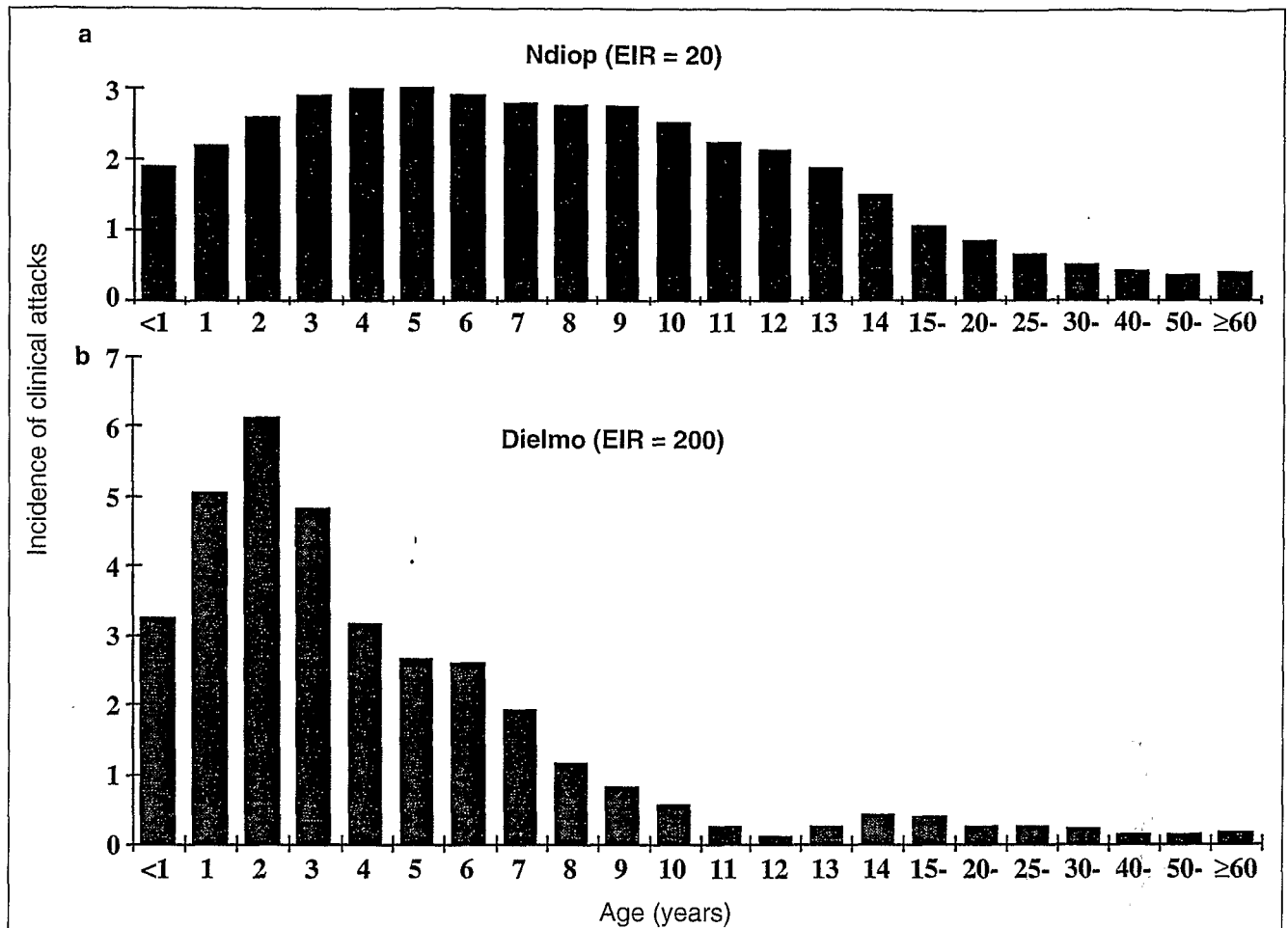
Fig. 2. Annual incidence of malaria attacks according to age in permanent residents of two Senegalese villages with markedly different *P. falciparum* transmission: Ndiop (EIR: 20 infective bites per person per year) (a), and Dielmo (EIR: 200 infective bites per person per year) (b).
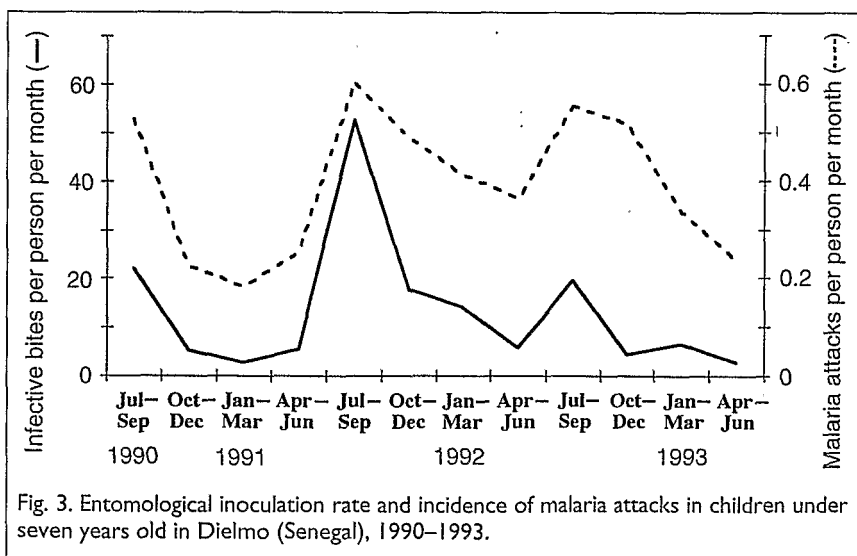

Fig. 3. Entomological inoculation rate and incidence of malaria attacks in children under seven years old in Dielmo (Senegal), 1990–1993.

which is acquired by a person exposed to malaria, is lost after several years without exposure. Thus, for low levels of transmission, ie. 0.01 and 0.1 infective bites per person per year, the incidence of malaria attacks is probably directly proportional to the level of transmission, in adults as in children. For levels of transmission of 1, 10, 100 and 1000 infective bites per person per year, the data that we have collected in Senegal suggest that global malaria morbidity, which is always very high, varies at maximum by a factor of two to three according to the level of transmission (Table 1).

Quantifying the relationship between transmission levels and potential malaria mortality is a much more uncertain exercise as almost all of available data, even old data, deal with populations who had access, albeit varying, to antimalarial drugs. For populations benefitting from identical possibilities of treatment, we have previously seen that all available data in Africa suggest that there is no marked variation in malaria mortality according to transmission when this is transmission of at least one infective bite per person per year. In the case of populations with

and potential malaria mortality, on the basis of available data for six different levels of transmission representing, on a logarithmic scale, the complete range of epidemiological situations observed in endemic areas (Table 1). At least half of the bites from an *Anopheles* which carries sporozoites of *Plasmodium falciparum* in its salivary glands will give a blood infection followed by a clinical attack in non-immune subjects[21], and it is generally acknowledged that protective immunity,

Table 1. Annual number of malaria attacks and malaria deaths according to the level of transmission in an imagined population of 10 000 people (125 individuals per year of age 0–79 years) who would have no available means of treatment

| | Entomological inoculation rate (EIR) (no. infective bites per person per year) | | | | | |
	0.01	0.1	1	10	100	1000
Number of attacks	100	1000	3700[a]	8800[a]	5800[a]	?
Number of malaria deaths	2–20	≥20	25[b]	25[b]	25[c]	25[c]

[a] Estimated figure based on studies carried out in Pikine[7], Ndiop[20] and Dielmo[19,20].
[b] Hypothesis: no more than 20% of newborns are at risk of death from malaria.
[c] Maximum estimate derived from previous field studies in holoendemic areas of central Africa[27] and from the prevalence of sickle-cell trait in these areas[28].

no access to antimalarial drugs, we have attempted to estimate the maximum or minimum malaria mortality rates at different levels of transmission. In people without immunity, such as tourists, cases of severe or complicated malaria (always fatal without treatment) are observed in 1% to 5% of clinical infections. However, historical data suggest that the complications of untreated malaria in a non-immune subject often occur several weeks after the onset of clinical symptoms[22], and it is relatively infrequent nowadays that a diagnosis would be so delayed. To our knowledge, the most documented data on malaria mortality in non-immune populations with little or no access to anti-malaria drugs are those of the epidemics of Mauritius in 1867 (Refs 23,24), Rio Grande do Norte and Ceara (Brazil) in 1938 (Ref. 25), and Ethiopia in 1958 (Ref. 26). Data from these three epidemics are consistent in suggesting that in the absence of any treatment, lethality due to P. falciparum in non-immune people occurs between 5% and 20% of cases. This latter rate is close to the maximum estimates of global malaria mortality that were reported in the most highly endemic regions of Central Africa[27] or which are derived from the frequency of the carriers of the sickle-cell gene in these areas[28]. For these populations exposed since birth to numerous malaria infections, there is strong evidence that genetically determined factors protecting against the severe forms of malaria have been selected and that in that way the risk of death following a malaria attack may vary considerably according to individuals. However, even in retaining the low hypothesis that only 2% of malaria attacks are potentially lethal in a non-immune African population[29] and that this lethality is in fact concentrated in only 20% of genetically susceptible individuals, Table 1 suggests that it is necessary to reduce transmission to very low levels – probably one infective bite per person every 10 years, or even less – to hope to obtain a long-term impact on potential malaria mortality.

In this succinct quantitative approach of the relationships between transmission, morbidity and mortality from malaria, several data and hypotheses that we used were approximate or uncertain. Furthermore, the real populations' age structure and the competing causes of death within these populations are also to be considered, because they are fundamental to ascertaining the number of potential deaths due to malaria in high- and moderate-transmission areas. However, whatever hypothesis is considered, it appears clearly that variations of the burden of morbidity and potential mortality from malaria are weak compared with the considerable range of transmission levels.

Concluding comments

It is generally estimated that over 80% of the deaths due to malaria in the world occur in tropical Africa, although this region represents only one quarter of those populations exposed to P. falciparum[30]. Clearly, a huge mortality from malaria exists in tropical Africa, and is often attributed to the very high transmission levels, since the entomological inoculation rate ranges generally from five to 1000 infective bites per person per year in rural areas, whereas in other endemic areas in the world (except in New Guinea) the entomological inoculation rate is almost always less than one.

Our analysis suggests that in most epidemiological contexts observed in tropical Africa, only a considerable reduction of transmission (much higher than that which it is presently possible to obtain on a large scale, or to maintain for more than several years) would be able to reduce, on a long-term basis, the burden of malaria for the whole community.

The health sectors in African countries have few means at their disposal, are often badly managed and their staff frequently lack motivation. Hoping to work round these difficulties, the main funding agencies are now strongly encouraging the setting up of programmes to combat malaria with insecticide-impregnated bednets, basing such programmes on the results of short-term studies, and thus reflecting the general disarray with regard to the continual aggravation of the problem posed by chemoresistance. We believe that the only effective ways of fighting malaria in Africa with currently available means are (1) improvements in health services, and (2) health education to facilitate better use of antimalarial drugs.

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Control of Lymphatic Filariasis by Annual Single-dose Diethylcarbamazine Treatments

E. Kimura and J.U. Mataika

It has long been stressed that diethylcarbamazine citrate must be given at a total dosage of 72 mg per kilogram of body weight in 12 divided doses of 6 mg kg^{-1} to obtain maximum effect against Wuchereria bancrofti. *However, recent studies revealed that only a single dose at 6 mg kg^{-1} could reduce microfilaria (Mf) counts by 90%, and that the effect would persist for 12–18 months. The annual repeat of the single-dose mass treatment was shown to be effective in reducing Mf prevalence and density in large-scale, long-term field trials. The scheme is simple and economic, and could be sustainable in many endemic areas, where health manpower and resources are often not sufficient. Annual single-dose mass treatments can be an effective weapon against human lymphatic filariasis, as discussed here by Eisaku Kimura and Jona Mataika.*

There are an estimated 78.6 million cases of lymphatic filariasis in the world[1], and only a small proportion of them is fortunate enough to be treated with the first drug of choice, diethylcarbamazine citrate (DEC).

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For more than 40 years, DEC has been used, worldwide, as the most effective and safest drug. The standard treatment scheme recommended by WHO[2] is to administer the drug at a dosage of 6 mg per kilogram of body weight daily, weekly or monthly for a total of 12 times in order to obtain the required overall dose of 72 mg kg^{-1} for the treatment of *Wuchereria bancrofti* infection, or a total dose of 36–72 mg kg^{-1} for *Brugia* spp infections. The standard treatment can effectively reduce filariasis and suppress its transmission, but ensuring that 12 doses are given poses considerable practical difficulties in a large-scale campaign. Recently, annual single-dose treatments with DEC at 6 mg kg^{-1} were reported to be effective in reducing the microfilaria (Mf) prevalence and density. The effect of each single dose is not very strong but is steadily progressive in a course of repeated treatments. In a filariasis control campaign in Samoa involving 160 000 people over eight years, three single-dose treatments decreased the Mf prevalence from 5.6% to 2.5%, showing that single-dose chemotherapy is a practical strategy for filariasis control.

What is the aim?

Annual single dose is given for mass treatment, eliminating the laborious and costly step of blood