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ESTIMATING THE EFFECTS OF SUCCESSFUL MALARIA CONTROL PROGRAMMES ON MORTALITY *

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SUMMARY

This paper proposes a new, empirically based model to measure the expected effects of successful malaria control programmes on human mortality levels and structure. In the model, the human population (which may be interpreted as a specific age group) is partitioned into four subpopulations: individuals never infected with malaria, individuals with fever from malaria, individuals currently infected with malaria but without fever, and individuals previously but not currently infected with malaria. Three kinds of malaria control programmes are considered: chemotherapeutic programmes (which attempt to reduce the mortality of fever cases); multifaceted programmes (which attempt to reduce both the prevalence of infection and fever, and the excess mortality of individuals with infection or fever); and eradication programmes (which attempt to bring the incidence and prevalence of malarial infection permanently to zero).

The model produces a range of estimated death rates. The range depends on uncertainty about the effective success of control measures. A numerical example, based on the data of the Garki project in northern Nigeria, is discussed. Some alternatives to the model are mentioned. Some strengths and weaknesses of the model are described and evaluated. And some recommendations are offered for the collection and analysis of data in the intersection of malarial epidemiology and demography.

INTRODUCTION: WHAT IS THE PROBLEM?

Large numbers of people are at risk of sickness and death from malaria. In 1986, the WHO Expert Committee on Malaria estimated that approximately 2.1 billion people live in "areas where a reduced level of [malarial] infection is maintained by the continued application of antimalarial measures" and another 370 million live in areas where malarial transmission continues without any organized efforts at control (World Health Organization, 1986, p. 9). Wyler (1983) gives a good general review of the situation of malaria and research on malaria.

The present paper, which describes an empirically based model to estimate the expected effects of successful malaria control programmes (mcps) on human mortality levels and structure, begins by reviewing previous empirical and theoretical studies of the impact on mortality of malaria and its control.[1] Empirical studies lead to three generalizations that a model must explain. The uses and limits of four theoretical approaches to measuring the mortality effects of successful mcps are identified.

An analytical portion of the paper suggests the elements that a model should relate: the human subpopulations that are differentially affected by malaria, and the kinds of mortality corresponding to each subpopulation; the major variants of mcps; and some major ecological and social variables.

The synthetic part of the paper integrates these elements in simple mathematical models that relate malarial epidemiology to human mortality. One model is illustrated by a numerical example based on the Garki project (Molineaux and Gramiccia, 1980). Finally, some strengths and weaknesses of the proposed models are described, some alternative approaches to modelling are sketched and some recommendations for action proposed.

The problem tackled in this paper is very difficult. Molineaux and Gramiccia (1980, p. 247) wrote that "Computation of the expected demographic consequences of malaria control could only be made with a relatively large error. Even so, it may be worth attempting with the limited data available." Ewbank and others (1986, p. 71) conceded frankly that "we are not even sure of the amount of mortality associated with malaria".

The difficulty arises in part, but not entirely, from limitations of empirical knowledge. For example, where malaria is suspected of causing many deaths, data on the causes of death are rarely satisfactory: usually, no medically trained individual observes a death and vital statistical systems may not provide reliable national data even when individual reports are correct. Moreover, if a physician, nurse or medical aide observes an acute illness

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caused by malaria, he or she is likely to interfere with the course of the illness. Though medical personnel may provide reliable data on the causes of those deaths that they observe, their very presence systematically alters the situation. The data they provide, though correct, may not characterize other parts of the country if the country is poor and has few medical personnel. Further, because the force and course of malaria depend on local environmental conditions, accurate information from one locality may not apply regionally or nationally. Finally, consider the difficulties of measuring the impact of malaria on mortality from an experimental mcp in the field, with well chosen and carefully observed treated and untreated populations. If malaria is a serious problem, it is likely that the untreated population will be able to buy antimalarial drugs and will, like the treated population, use them at least for acute episodes of fever, thereby diminishing the apparent impact of the mcp on mortality. On the other hand, if drugs or medical personnel are involved with the treated population, it is likely that they will reduce mortality due to other causes as well as malaria, thereby exaggerating the apparent impact of the mcp on mortality. Experimental field mcps, which might at first appear to be the ideal way to determine the impact of malaria on mortality, are fraught with difficulties of interpretation.

A deficiency as important as limited empirical knowledge is the lack of adequate theory. Inadequate theory limits the ability to organize available information and to guide the collection of additional data. Models could organize some of the available facts and indicate what additional facts would be most useful.

Empirical approaches to the problem

Molineaux (1985) reviewed comprehensively empirical knowledge of the impact on mortality of malaria and its control. Three of his major generalizations provide points of reference to be explained by the models that follow.

First, for a given prevalence of infection with the micro-organism that causes the most severe form of malaria (*Plasmodium falciparum*), the level of adult mortality from malaria depends critically on whether malaria in the given region is stable or unstable. Other factors, such as nutrition and concurrent infections, also affect adult mortality from malaria, but the local ecology of malaria is a dominant variable. Malaria transmission is said to be stable if transmission remains high year-round (though possibly with seasonal fluctuations) and high from year to year. Stable malaria is found, for example, in the Garki area of northern Nigeria (Molineaux and Gramiccia, 1980, p. 116). Malaria transmission is said to be unstable if transmission is essentially interrupted during at least one season of the year or fluctuates from a very low level to a very high level from year to year.

An area with sporadically recurrent epidemics of malaria, which strike unpredictably from year to year, has unstable malaria, but unstable malaria may also occur without epidemics. As Dietz pointed out (K. Dietz, personal communication, 30 December 1986), malarial transmission is interrupted for several months a year in some villages within the Garki area. It may be appropriate to treat those villages as having unstable malaria if they are isolated from the other villages, or as having stable malaria if there is enough migration among the villages for people to acquire malaria while out of their home village.

According to Molineaux (1985, p. 35), when the transmission of *P. falciparum* is stable and intense at a high level, adult mortality directly attributed to *P. falciparum* is probably very low (because the surviving adults acquire a clinical but not sterile immunity). By contrast, when the transmission of *P. falciparum* is unstable, then adult mortality directly attributed to *P. falciparum* may be very substantial during episodes of intense transmission, such as epidemics. In either case, intense transmission causes considerable mortality among infants and young children (ages 0-4).

Secondly, the mortality directly attributed to malaria may, under certain circumstances, be small compared to the enhancement that malaria causes in the mortality directly attributed to other causes. Molineaux (1985) cites Newman's (e.g., 1965, 1977) and Gray's (1974) analyses of mortality in Sri Lanka, which suggest that the indirect effects of malaria on mortality were two to four times as large as the direct effects; and Giglioli's (1972) analysis of mortality in Guyana, which suggests that *P. falciparum* increased mortality from respiratory disease there. According to this generalization, malarial control may be expected to reduce mortality directly attributed to malaria and should, perhaps with some lag, lead to a larger reduction in mortality due to indirect effects.

Thirdly, in apparent contradiction to the preceding generalization, malarial control that reduces mortality directly attributed to malaria may lead to a much smaller net reduction in overall mortality, because most of the individuals saved from death due to malaria rapidly die from another cause. This phenomenon is a reasonable interpretation of what was observed in Garki (Molineaux and Gramiccia, 1980). Similarly, in a Gambian village studied by McGregor (1964) and described by Molineaux (1985), the total number of deaths among infants and young children varied little from year to year, although the distribution of deaths by cause between malaria and measles varied greatly from year to year.[2]

The indirect action of malaria on mortality (Molineaux's second generalization) suggests that controlling malaria mortality would have a greatly amplified effect on overall mortality. The interaction of malaria with competing risks (Molineaux's third generalization) suggests that controlling malarial mortality would have a much smaller effect on overall mortality. How are these two generalizations to be reconciled?

One explanation, suggested by Preston (S. H. Preston, personal communication, 3 December 1986), is that both phenomena may be artifacts of poor reporting or coding of the cause of death. As he points out, if deaths actually caused by malaria were attributed statistically to another cause, then controlling malaria would lead to a reduction in mortality that had wrongly been attributed to other causes. If, on the contrary, deaths actually due to other

causes were attributed to malaria, then controlling malaria would lead to a smaller than expected reduction in deaths, as if competing risks were at work.

For analyses based on large numbers of cases assembled through the official system of vital statistics of a developing country, there is no denying that these sources of error may be at work. The relative magnitudes of these sources of error are likely to be unknown. When observed in small, special-purpose field studies, such as those of McGregor (1964) and Molineaux and Gramiccia (1980), Molineaux's second and third generalizations probably cannot be explained entirely as artifacts.

I accept these generalizations and go beyond the analysis of Molineaux to suggest tentatively the following. Where malaria control led to a reduction in mortality which was far greater than the reduction in mortality directly attributed to malaria, the country was undergoing a process of cultural, educational and economic development far more extensive than the efforts to control malaria. For example, in Sri Lanka, the crude death rate began to decline long before the post-Second World War antimalarial spraying campaign. It has been argued that the decline resulted from improved maternal and child welfare services, improved nutrition and improved medical services, among other causes (Meegama, 1986). By contrast, in the Garki research programme, the only interventions were mass drug administration and residual spraying, both directed primarily to malaria (Molineaux and Gramiccia, 1980). Other factors contributing to the population's high level of mortality were not directly altered.

This view of the findings of Molineaux (1985) leads to two conclusions. The first, also Molineaux's first, is that adult mortality directly attributed to *P. falciparum* is likely to be low where malarial transmission is stable, and is likely to be higher where malarial transmission is unstable. The second is based on a tentative reconciliation of two findings of Molineaux. In a setting of general development, the indirect mortality benefits of malarial control may be several times the reduction in mortality directly attributed to malaria. But when malarial control is carried out in isolation, the reduction in overall mortality may be considerably smaller than the reduction in mortality directly attributed to malaria.

As Singer pointed out, if this second conclusion is correct, it has a parallel in the conditions under which programmes intended to lower fertility are most effective (B. H. Singer, personal communication, 16 December 1986). Previous studies of the relation of socio-economic factors to mortality from malaria include those of Pampana (1955) and Banguero and others (1982). It would not be surprising if portions of the reality were more complicated than the two simple conclusions just offered.

Theoretical approaches to the problem

Several theoretical approaches to estimating the impact on mortality of malaria and its control have been proposed. The four reviewed here are the Bernoulli-Makeham procedure of demographers (e.g., Spiegelman, 1968), based on the assumption of independence among causes of death; Peterson's (1976) extension of this procedure to allow for dependence among causes of death; mathematical models of malarial transmission (e.g., Dietz, 1986); and regression analysis (e.g., Newman, 1977; Ewbank and others, 1986, p. 63).

The Bernoulli-Makeham procedure, reduced to its simplest form, classifies all deaths of individuals in a given age group into those deaths caused by malaria and those deaths with other causes. Some ambiguities in the concept of a death caused by malaria will be clarified later. The Bernoulli-Makeham procedure assumes that deaths caused by malaria are reduced by x per cent, through means left unspecified, and computes the overall reduction in deaths in the age group. The computation assumes further that the individuals who are saved from dying of malaria have a risk of death from other causes that is identical to that of all other individuals in the age group. Therefore, some of the individuals saved from dying of malaria will die of other causes, and the total number of deaths from other causes will rise accordingly. However, since not every individual saved from dying of malaria will die of other causes while in the age group, there will be a net decrease in the number of deaths in the age group. The age-specific death rate will decline by y per cent as a result of the x per cent decline in deaths due to malaria, where y is smaller than x.

Preston and others (1972) applied the Bernoulli-Makeham procedure to national statistics on broad classes of causes of death. They point out, as have others before and since, that the assumption of independence among causes, which underlies the method, cannot be tested using the data furnished in conventional tables of death by cause. The observations of Molineaux (1985) suggest that the assumption of independence between malaria and other causes is unlikely to be true. It follows that the Bernoulli-Makeham procedure, by itself, is not likely to be useful for estimating the mortality impact of successful mcps. The Bernoulli-Makeham procedure cannot accommodate the observation that in some cases the indirect reductions in mortality greatly exceed the reductions in mortality directly attributed to malaria. Neither can it accommodate the observation that in other cases competing risks (e.g., measles) completely counterbalance reductions in mortality directly attributed to malaria.

Peterson (1976) considered the extremes of possible dependence between two competing risks of death, which are "malaria" and "other" in the present context. At one extreme, if malaria and other causes are positively dependent, then every individual who would have died from malaria before control would die at the same age from another cause if death from malaria were prevented. Hence, under this extreme hypothesis, a "successful" mcp could result in no decrease in the age-specific death rate. This extreme hypothesis of positive dependence among causes represents precisely the compensation between malaria and measles that McGregor described in a Gambian village. For an mcp in isolation from economic and social development, the net mortality benefit of an mcp that succeeded in eliminating or reducing deaths from malaria could be as low as zero.[3]

At the other extreme, if malaria and other causes are negatively dependent, then every individual who would have died (in a given age interval) from malaria before control would not die (within the age interval) from any other cause after control. Under this extreme hypothesis, every death due to malaria that is postponed beyond the end of the current accounting period by a successful mcp would contribute to a reduction in the net death rate. This negative dependence among causes leads to complete survival, within the specified age interval, of individuals saved from dying directly of malaria. This hypothesis fails to represent the indirect effects of successful mcps described by Molineaux and others; it does not allow the elimination of malaria to lower the risks of death from other causes. It may be useful to compute the extreme reduction in death rates implied by Peterson's hypothesis of negative dependence among causes, but it will be important to recognize that still larger reductions are possible.

Both the Bernoulli-Makeham procedure and Peterson's extension to dependent causes take as given the number of deaths from malaria that are averted in each age class by a successful mcp. Where are these numbers to come from? Control programmes, successful or not, are usually specified by administrative and technical inputs and are monitored by epidemiological measures of coverage. It seems natural to expect that mathematical models of the transmission dynamics of malaria link the activities of an mcp with its achievements in reducing mortality from malaria. Unfortunately, the available models do not. Bailey's book (1982) on mathematical models of malaria indexed neither "mortality" nor "death rates". Dietz's (1986) comprehensive review and analysis concentrated mainly on a discussion of the relation between equilibrium prevalence of infection and vectorial capacity depending on simplistic assumptions about density-dependence in man and vector. No linkage with malaria-specific or general death rates was discussed. It therefore is necessary to build a linkage between malarial epidemiology and mortality on top of or in parallel with existing mathematical models of the transmission dynamics of malaria. A way to do this is suggested below.

Ewbank and others (1986) used regression to estimate the mortality consequences of successful mcps. For each province in Kenya, they used as the independent variable (X) the percentage of out-patient cases (in 1979) that were diagnosed as malaria. As the dependent variable (Y), they used the infant mortality rate per thousand. They then estimated a linear regression $E(Y) = a + bX$ for the average or expected infant mortality rate $E(Y)$ in a province with percentage of malaria X. When X is replaced by 0 in this equation, the expected infant mortality rate is just $E(Y) = a$. Ewbank and others (1986, p. 63) concluded: "This analysis suggests that in high mortality districts, eliminating malaria would reduce the infant mortality rate by 15 points. If an equal number of deaths were prevented at all other ages, malaria would be responsible for about 8 per cent of all deaths in districts with a high incidence of malaria."

The use of the word "suggests" is appropriate because there are well-known problems with using regression equations for prediction (e.g., Tufte, 1974, pp. 80-81). As Ewbank and others pointed out, it is doubtful whether the percentage of malaria cases diagnosed in out-patients bears any reliable relation to the prevalence or incidence of malaria in the population from which the infant mortality rate is measured. But suppose, in order to focus on other, more important questions, that an appropriate measure (X) of malarial incidence or prevalence and an appropriate measure (Y) of age-specific mortality could be defined and measured reliably. When Ewbank and others added to the regression equation variables representing ecological zones, the malaria index was no longer a significant predictor of infant mortality. Reducing malarial incidence or prevalence X to zero in reality, as opposed to the regression equation, might have no effect on infant mortality. On the other hand, if malarial incidence were reduced to zero by extensive programmes of environmental alteration, public health education and economic development (leading, for example, to screened windows), then the reduction in infant mortality might be far greater than that predicted by the regression equation.

Another problem with extrapolating from the given regression equation is that the observed percentage X of out-patient cases diagnosed as malaria ranged from 6 per cent to 30 per cent. It is notoriously unreliable to extrapolate regression equations outside the range of data for which they are estimated, in this case to $X = 0$, because there is no way of knowing whether X and Y are linearly related, or, if so, with the same values of a and b, outside the observed range of data.

Ewbank and others (1986, p. 63) were careful to point out reasons why the proportion of deaths caused by malaria might be much smaller or much larger than the 8 per cent they estimated. The conceptual difficulties described above, and many others, make regression equations a doubtful tool for estimating in advance the effects on mortality of successful mcps.

However, it is important to distinguish prediction from measurement. While the above arguments suggest that regression equations are an unreliable way to estimate the future reduction in mortality that would follow from a hypothetical mcp, there is nothing implausible about using regression equations to summarize observed effects of an mcp on mortality, as Newman (e.g., 1977) and Gray (1974) have done with Sri Lankan data.

In summary, the classical life-table analysis of Bernoulli and Makeham, its modern extension by Peterson to dependent competing risks, mathematical models of malaria transmission, and regression equations all suffer from serious defects as models to predict the impact of mcps on mortality. What follows is an attempt at a fresh analysis and some new models.

Analysis: control programmes, mortality, environment

How will a successful mcp affect the level and structure of mortality? In this question, the independent or input variable is "a successful mcp" and the dependent or output variable is "the level and structure of mortality". This analytical part of the paper specifies the meas-

ures of input, output and environment that a model needs to relate.

First, this paper will describe how the people affected by malaria are identified. It will then categorize deaths associated with the presence of malaria in a population. Then it will describe the possible forms of mcps and connect these forms with the deaths caused by malaria. Because given mcps have different effects on mortality, depending on the human and natural situation, it will also specify the environment in which the input and output variables interact.

Specifying the people affected by malaria

The aim of mcps is to protect people at risk of malaria. The aim of this paper is to estimate the reduction in mortality that will follow successful mcps. Both aims require operational means of identifying the people affected by malaria.

This section describes three major methods of identifying the people affected by malaria. For each method, the risk of false negatives (failing to identify a person who is affected by malaria) and the risk of false positives (identifying a person as affected by malaria who is not so affected) are described. On the basis of these methods, a partition of the malaria-affected population into four subpopulations is proposed: never infected, fever cases, currently infected (but not fever cases) and previously infected.

Parasitemic cases. A drop of blood is taken from a person and malarial parasites are identified by some standardized procedure. The procedure has traditionally been microscopic examination of the blood (Hunter and others, 1966) but DNA probes for the genetic material of the parasite are under development (e.g., Wirth and others, 1986). The variants on the microscopic and diagnostic techniques employed are not germane here. What will be considered here are diagnostic techniques that detect the presence of the parasite, rather than the immune reactions of the person.

Routine microscopic examination may miss some infections (in the Garki project, roughly 5 per cent to 25 per cent, depending on the species of malarial parasite (Molineaux and Gramiccia, 1980, pp. 112-114)), but it is unlikely to identify anyone without malaria as a malarial case. On balance, the reported number of parasitemic cases is likely to understate the number of individuals infected with malaria.

Where malaria is endemic, malarial parasites may appear in the blood of many people who consider themselves healthy. Thus, most "parasitemic cases" are not "fever cases", as defined next. However, malaria-infected individuals, even if they do not consider themselves sick from malaria, have a higher risk of death (World Health Organization, 1975) than they would have if they were not infected with malaria.

The fraction of people who are parasitemic cases will be called the parasite rate. The parasite rate may be crude (referring to an entire population in a defined area), age-specific or age-standardized. The parasite rate may refer to a particular species of *Plasmodium* (the genus of the various species of malarial parasites), to particular stages in the life cycle of one species (e.g., *P. falciparum* gametocytes), or to all malarial species.

Fever cases. Breman and Campbell (1986) propose that "a probable case of malaria is a person having fever (above 38°C, 100.4°F, if a thermometer is available) associated with the current illness. Chills, sweats or other signs and symptoms consistent with malaria may also occur but are not required for treatment. The person should live in or come from a malarious area, and there should be no other apparent cause of illness". A person meeting these criteria will be called a fever case.

Molineaux and Gramiccia (1980, p. 258) report that "screening the [Garki] population for temperatures of 37.5°C or more would have detected only 14.6% . . . of the [parasitological] positives below 9 years and only 3.4% . . . of the positives above 9 years of age. These findings are probably characteristic of a situation of intense transmission and relatively strong immunity of the survivors". On the other hand, fever cases probably include people who have no malarial infection but who do have fever from other causes, such as viral infections, that are not easily identified under field conditions. Molineaux and Gramiccia (1980, p. 144, figure 38) found that, in the Garki project, the most intensive malarial control efforts reduced the percentage of children less than 9 years old positive for *P. falciparum* in the wet season from approximately 80 per cent to approximately 5 per cent, while, at the time of the latter measurement, the prevalence of body temperatures of 37.5°C or more among children less than 9 years old was 11 per cent in an unprotected village and 4 per cent in the most intensively protected villages (Molineaux and Gramiccia, 1980, p. 256, table 28). The reduction in the prevalence of fevers was far less than the reduction in the prevalence of infection. Of course, it is possible that fever cases were atypically resistant to the efforts to control malaria.

On balance, the figures of Molineaux and Gramiccia suggest that there are many more parasitemic cases than fever cases under stable, intense malarial transmission.

The number of fever cases measures the acute burden of malarial disease perceived by the population. The criteria used to define fever cases may be workable in the field where microscopy is not possible. As a first approximation, it will be assumed that all fever cases are parasitemic cases. The fraction of people in a population who are fever cases will be called the fever rate.

Immune cases. Malarial infection challenges the immune system of people who survive long enough to develop a functioning immune system (e.g., Voller and others, 1980). Examination of the spleen and of the blood serum are the two main immunological approaches to determining whether an individual is affected by present or prior infection with malaria.

The spleen helps form antibody to antigens which, like malarial parasites, are particulate and distributed via blood (Humphrey and White, 1970, p. 263). Splenomegaly (enlargement of the spleen) often follows chronic malarial infection. Splenomegaly is determined clinically by palpating the spleen. Clinical scales exist for measuring the extent of enlargement. The spleen rate is the

prevalence of (fraction of people in a population having) a specified degree of splenomegaly. The population on which a spleen rate is based may be the entire population or a particular age group (Hunter and others, 1966, p. 337). The spleen rate has been widely used in malarial surveys to estimate the chronic intensity of malarial transmission in a population.

Individuals whose spleens have not yet enlarged in response to malarial infection, or whose spleens have enlarged too little to be palpable, or whose enlarged spleens have subsided to normal size, will not be numbered as having splenomegaly. Individuals without malarial infections whose spleens have enlarged in response to non-malarial (e.g., schistosomal or other helminthic) antigens will be numbered as having splenomegaly. The balance of false negatives and false positives, resulting from using splenomegaly as an indicator of chronic malarial infection, is not clear. However, it is consistent with past practice and reasonable until better indicators are available to suppose that spleen rates are positively associated with the prevalence of chronic malarial infection in malarial areas (cf. Newman, 1965, 1977).

Another principal approach to measuring the impact of malaria is via the blood serum. Many different immunological assays may be performed using serum. The assays produce a titre, that is, a measure of the concentration of a specified serum antibody. Commonly, one titre is chosen by the investigators as a threshold and individuals whose titre exceeds the threshold are considered positive for that assay.

Different assays measure different features of the immune response. To illustrate, the Garki project (Molineaux and Gramiccia, 1980, chap. 6) performed six assays: measurements of immunoglobulin G (IgG) and immunoglobulin M (IgM), a precipitin (Ouchterlony) test, two indirect fluorescent antibody (IFA) tests, and an indirect haemagglutination test. No relation was found between IgG and infection by the malarial parasite (as determined by microscopic examination of blood) nor, after the first few years of life, between the IFA test for *P. falciparum* and malarial infection. All but the IgG tests were positively associated with malarial infection among the young. "For 3 tests (IgM, precipitin and IHA) the relationship [to malarial infection] became negative in older children and adults, indicating that the test results were associated with protection" against infection (Molineaux and Gramiccia, 1980, p. 212). The three assays that are associated with protection in older children and adults also indicate the intensity of prior infection, since that infection induces the protective response. Finally, the IFA test for *P. malariae* was positively associated with infection throughout life. Other serological assays are under development (e.g., Wirth and others, 1986); their epidemiological characteristics remain to be determined.

If parasitemic cases are taken as the standard, the serological assays may produce false negatives because the threshold titre is set inappropriately high, because the reagents used in the assay are insensitive, or because the immune response is delayed relative to infection, that is, because a newly infected individual may not have had time to develop or display an immune response. The assays may produce false positives (relative to parasitemic cases) for diverse reasons: because a high IgM or IgG response is produced by some other infection; because the reagents for antimalarial antibodies cross-react with antibodies against other antigens; because the positive immune response measured by the assay is protective, having eliminated previous malarial infections and prevented reinfection; or because a non-protective immune response measured by the assay outlasts a malarial infection.

Notwithstanding the complexities of interpreting different serological assays, Molineaux and Gramiccia (1980, p. 207) concluded: "At the total population level, it is likely that all 6 tests used here are indicators both of contact with malaria and of partial immunity to it, that is, there is more malaria and a higher level of immunity in populations showing higher test results."

The serum rate of a population may be defined as the fraction of the population whose titre, on some specific test, exceeds a given threshold. The detailed interpretation of a serum rate depends on which test is used. The distribution of titres in a population tells more than the serum rate, but requires considerably more sophisticated analysis.

An immune case is defined as an individual who gives evidence of an immunological reaction to malarial infection. Such an individual may be said to be immunopositive (to malaria). As a first approximation, it will be assumed that every parasitemic case is an immune case.

In summary of this subsection, the size of the population affected by malaria may be described by the parasite rate, the fever rate, the spleen rate and several serum rates. These rates in fact describe different subpopulations.

On the basis of the biological facts just reviewed about malaria and its measurement, the population will be partitioned into four subpopulations. Individuals who are not fever, parasitemic or immune cases will be called "never infected" and the population in this category will be denoted p_0. The proportion of the population who are fever cases will be denoted p_f.[4] Individuals who are parasitemic cases but not fever cases will be called "currently infected" and the proportion of the population in this category will be denoted p_b. (The subscript b is a reminder that blood is drawn to diagnose parasitemia.) Finally, immune cases who are neither blood nor fever cases will be called "previously infected" and the proportion of the population in this category will be denoted p_i. Obviously, $p_0 + p_f + p_b + p_i = 1$. (The symbols introduced here [p_0, p_f, p_b, p_i] and in the remainder of this paper are listed and defined in the annex to the present article.)

In practice, although this partitioning of the population into four subpopulations could be done on the basis of a single cross-sectional survey, it would be preferable to estimate the point-prevalences of the four subpopulations from data collected using repeated observations of identified individuals over a period of time. The reason is that the fraction of individuals who are parasitemic (by

microscopic examination of blood slides) at a single observation appears to understate substantially the true prevalence of parasitemia in the population (e.g., Bruce-Chwatt, 1963; Molineaux and Gramiccia, 1980). Improved diagnostic procedures (e.g., Wirth and others, 1986) may alleviate this problem in the future.

Let P be the parasite rate and S the spleen or seropositive rate. Assuming that all fever cases are parasitemic cases, $P = p_f + p_b$; then p_b may be found from $p_b = P - p_f$. Similarly, assuming that all parasitemic cases are immunopositive, $S = P + p_i$, hence $p_i = S - P$. Under these assumptions or using direct measurement, the fractions p_0, p_f, p_b and p_i can in principle be estimated directly or indirectly from epidemiological measures commonly taken in malaria surveys.

Specifying mortality

In a population affected by malaria, people never infected with malaria have death rate d_0; fever cases have death rate d_f; currently infected people have death rate d_b; and people previously infected have death rate d_i. The death of an individual from each of these four subpopulations may be called, respectively, a death without malaria, a death from malaria, a death with malaria, and a death following malaria.

In principle, any death could be classified as one of these four kinds on the basis of information or material collected at or shortly before the time of death. In practice, in the developing countries where malaria remains a major problem, it is too much to hope that every death could be classified in this way, but it is not too much to hope that a carefully planned sample of deaths could be so classified to assist in planning and forecasting for an mcp. Hence, the four death rates are in principle measurable or estimable in conjunction with information about the relative sizes of the four subpopulations.[5]

If d is the death rate of the population, then

$$d = p_0 \cdot d_0 + p_f \cdot d_f + p_b \cdot d_b + p_i \cdot d_i. \qquad (1)$$

This equation may be used to check the consistency of the estimates of the fractions and death rates of the four subpopulations. The excess mortality of fever cases is $d_f - d_0$, of currently infected cases is $d_b - d_0$ and of previously infected cases is $d_i - d_0$.

All the above death rates and fractions refer to a population that can be pooled or specific, that is, heterogeneous or homogeneous, with respect to age or any other demographic characteristic. If the population contains all age groups, then the death rates are called crude rates; if a specific age group, then age-specific rates. If the population is a specific age group, the proportions p_0, p_f, p_b and p_i will obviously depend on the age. If the population consists entirely of individuals aged five years and older in an area where malaria is endemic and transmission is intense, it is reasonable, unless evidence to the contrary is available, to take $p_0 = 0$, since virtually everyone under such conditions has been infected with malaria.

In addition, malarial infection may be defined to include all species of malaria found in an area or any single species. From a biological perspective, it would be desirable to define malarial infection in terms of a single malarial species or of a specified combination of species, since the impact on mortality of an infection of *P. falciparum*, for example, differs from that of *P. vivax*.

However, the more homogeneous the population (in terms of age or malarial infection), the more detailed the demographic and epidemiological information required to measure or estimate the proportions and death rates of the subpopulations. When the model that follows is used for a real population, a want of data will quickly limit the possibility of using equation (1) for very narrowly defined populations.

Specifying malaria control programmes

After malaria eradication was abandoned in large parts of the world, the World Health Organization and the United States Agency for International Development outlined four approaches to malaria control, which are known as "tactical variants". The following presentation, based on Breman and Campbell (1986) and World Health Organization (1986), emphasizes the means that these tactical variants employ rather than their goals.

Tactical variant 1: chemotherapy. Sick people are treated with drugs. Attention focuses on children 0-4 years old who are acutely ill (and on pregnant women).

According to Breman and Campbell, this tactical variant "should be used in areas with high malaria prevalence, severe clinical illness and high case fatality rates, low socio-economic status, and limited experience in malaria programme administration. Most of rural Africa fits into this category." For convenience, an mcp following tactical variant 1 will be referred to as a chemotherapeutic programme.

Tactical variant 2: chemotheraphy, limited chemoprophylaxis and low-cost vector control. The acutely ill are treated with drugs. Drugs to prevent malaria are distributed to selected groups such as pregnant women. Vector control is initiated by voluntary measures such as mosquito netting.

Tactical variant 3: intensification and extension of tactical variant 2. In addition to all the activities of variant 2, a national or regional organization is used to apply more extensive vector control measures, and trained epidemiological personnel evaluate the actions taken and the results achieved.

An mcp based on tactical variant 2 or tactical variant 3 will be referred to as a multifaceted programme.

Tactical variant 4: eradication and surveillance. Expanded vector control operations are added to the activities of tactical variant 3, with a view to long-term eradication of malaria. Where malaria has been eradicated or is naturally absent, surveillance is undertaken to assure the continued absence of malaria. Asymptomatic carriers of malaria pose special problems for surveillance (Yekutiel, 1960); it may not be easy to decide when malaria has been eradicated from an area.

An mcp based on tactical variant 4 will be referred to as an eradication programme.

Recently, the WHO Expert Committee on Malaria reviewed the four tactical variants and suggested that

antimalarial programmes could be described more simply as using two major approaches: first, the treatment of people with malaria; and second, the long-term control of malaria transmission, in addition to the treatment of people with malaria. Both approaches are supposed to be carried out as part of the improvement in the general health services and control of the other major causes of preventable deaths (World Health Organization, 1986, pp. 48-49). What was defined here as a chemotherapeutic programme corresponds roughly to the first of these two approaches, while a multifaceted programme and an eradication programme correspond to different degrees of intensity of the second approach.

Various vaccines may eventually be available for use in mcps (e.g., Dame and others, 1984). However, as Halloran pointed out (M. E. Halloran, personal communication, 14 December 1986), vaccines are not currently available, it is not known when they will be available and their effects on mortality are unknown.

What constitutes a "successful mcp" (a term used often above and in what follows) requires definition. It would be convenient but useless to define a successful mcp as one that completely and permanently eliminates excess mortality in its target subpopulations (fever cases for chemotherapy programmes etc.). By this definition, there would be little uncertainty about the impact on mortality of successful mcps, but large uncertainty about whether an mcp should be considered successful. A less convenient but more useful definition would be that a successful mcp reaches completely and permanently its target subpopulations (so that, for example, all fever cases continually receive chemotherapy, whether or not chemotherapy saves their lives). Unfortunately, among real mcps, complete coverage is rare.

I propose that a successful mcp be defined as one that is both self-conscious and sustained. A self-conscious mcp has reliable procedures to measure the efforts it expends and the results (administrative, epidemiological and demographic) it attains. As Singer pointed out (B. H. Singer, personal communication, 1 May 1987), a self-conscious mcp also has reliable procedures to measure antimalarial activities other than the activities it initiates. For example, where chloroquine is already widely sold over the counter or by pedlars, an additional chemotherapy programme might have little effect on the mortality of fever cases, even though, in the absence of chloroquine, malaria was a major source of mortality. Proper evaluation of the impact of malaria on mortality requires a comprehensive picture of control activities. A sustained mcp adapts the control efforts applied to maintain malaria at some chosen level lower than that prior to the mcp; equivalently, it prevents a resurgence of malaria after a reduction is achieved. A sustained mcp need not constantly apply the same control measures, since the control measures appropriate to surveillance differ from those appropriate to an initial attack. By this definition, the Garki project (Molineaux and Gramiccia, 1980) was a successful mcp during its intervention phase. It was a successful research project, but not a successful control project, even after the intervention phase, as the transmission of malaria again increased.[6]

Connecting people affected by malaria with malaria control programmes

This section will attempt to link the tactics of mcps with the people affected by malaria. The proposed linkage is subject to revision by further information.

A chemotherapeutic programme is (by the above definition) directed to people who are acutely ill and to pregnant women. Therefore, apart from the pregnant women, a chemotherapeutic programme would presumably reduce malaria as a cause of death only among fever cases, since only they would be identified as acutely ill.

Chemotherapy might have diverse other effects, depending on whether drug treatment of an individual with malarial fever was or was not sustained over a long period and depending on whether the dosages applied were or were not sufficiently high to clear parasites from the treated individual. Taking account of both duration and dosage, there are four cases to consider.

Long-duration, high-dosage chemotherapy of an individual with a malarial fever could clear parasites. It would reduce substantially the p_b and p_i subpopulations in addition to the p_f subpopulation, because the treated individual would be prevented from becoming reinfected and would gradually lose his immunity. Nevertheless, other individuals might acquire infections without a period of fever and might shed those infections without either fever or drug treatment; thus, the p_b and p_i subpopulations would not necessarily vanish.

Long-duration, low-dosage chemotherapy would not clear parasites from treated individuals but would only lower the density of infection enough to remove fever. Such chemotherapy would convert individuals directly from fever to parasitemic cases.

Short-duration, high-dosage chemotherapy that cleared infections could convert fever cases to previously but not currently infected individuals, or could effectively convert fever cases to never-infected individuals by depriving them of the immunity resulting from prior malarial infections (Pringle and Avery-Jones, 1966). Such chemotherapy would provide only short-term protection against reinfection.

Finally, short-duration, low-dosage chemotherapy sufficient to interrupt a fever, as might be expected with self-administered drugs sold commercially, would temporarily convert fever cases to currently infected cases but would have little effect on the size of either subpopulation since nothing would prevent a recurrence of fever. This last case seems to be the most realistic description of actual chemotherapy programmes, unless they are part of a well-run research project.

This attempt at analysis suggests that chemotherapy could have multiple and non-obvious effects. The analysis could profit from more explicit and detailed modelling using a dynamic model of malarial infections, and should be considered subject to revision.

Individuals relieved of malarial infection by a multifaceted programme are still exposed to a (reduced) risk of reinfection. Individuals who had acquired protective immunity against malaria as a result of prior chronic

exposure to infection would not lose that protective immunity immediately. Hence, a multifaceted programme would be expected to have a much greater prompt effect on the parasite rate than on immunological indicators, for example, the spleen rate, or a serum rate associated with protective immunity, such as those (in the Garki study) based on IgM, precipitin and IHA assays.

The longer-term effect of a multifaceted mcp on protective immunity depends on how the programme works. For example, suppose the multifaceted programme lowered the parasite rate to 25 per cent of its former level and held the parasite rate steady at that level. If only one quarter of the population were infected at any one time but all individuals were infected at some time, then it is possible that no one would lose his or her protective immunity and the serum rates (based on assays for protective immunity) might remain constant. On the other hand, if the multifaceted programme really consisted of malarial eradication in areas where three quarters of the population lived and no control at all where one quarter of the population lived, then the serum rate of the protected three quarters would eventually drop to zero, while the serum rate of the unprotected quarter would not change. Under the latter hypothesis, because malaria control meant eradication in one region and no control in another, the serum rate would mirror the parasite rate. I will assume henceforth that major geographical differences in control would be identified and the effect of control on mortality in different regions would be analysed separately. I assume that partial control, that is, control short of eradication, will eliminate neither chronic exposure to malarial infection nor the possibility of maintaining a partially protective immunity.

A successful eradication programme would affect fever cases, parasitemic cases and immune cases, though the effects might differ depending on whether malaria were stable or unstable. For example, following eradication of stable malaria, previously infected individuals would, after some time, lose the immunity (and the sometimes pathological auto-immunity) produced by the antigenic stimulation of a chronic malarial infection. Thus, a successful eradication programme would eliminate the excess mortality associated with splenomegaly or malaria-induced auto-immune diseases, as well as any other mortality resulting from stable malaria.

Specifying the environment

As a first approximation, the environmental variables that modulate the effect of mcps on mortality may be classified as ecological and social.

The primary ecological variable that influences the effect of mcps on mortality is whether malaria is stable or unstable. First, suppose malaria is stable. Parasitemic cases old enough to have developed an immune response and to have survived many attacks of malaria (say 5 years and older) would be expected to have a small excess mortality $d_b - d_0$, relative to a situation of unstable malaria. But the excess mortality $d_i - d_0$ of previously infected individuals might be large, relative to a situation of unstable malaria, because of the weakening and auto-immunity caused by chronic malarial infection with *P. falciparum*. (The likely pathogenic effect of chronic *P. malariae* infection, for example, would be much less.) A plausible upper bound on the excess mortality $d_i - d_0$ is $d_f - d_0$. Now suppose malaria is unstable. The excess mortality of parasitemic cases $d_b - d_0$ may be quite substantial, especially at the older ages, while the excess mortality $d_i - d_0$ of previously infected individuals may be relatively small, because such individuals have not suffered chronic malarial infections. It is suggested below that this difference between stable and unstable malaria may lead to different patterns of falling mortality after malaria control.

The primary social variable modulating the effect of mcps on mortality appears to be whether the mcp is a single-purpose, isolated control programme (which may be a research programme, a demonstration programme or a single-purpose public health programme) or is part of an ongoing and comprehensive process that includes education, environmental and sanitary improvement, primary health care infrastructure and economic development. Where the mcp is isolated, it appears that, especially at the youngest ages, lives saved from malaria are often lost to other risks of death. (The same phenomenon has been demonstrated for lives of children vaccinated against measles in Zaire (Kasongo Project Team, 1981).) Where the mcp is part of extensive social development, it appears that the maximum possible improvements in mortality from mcps are realized. The difference between isolated mcps and mcps that are part of social development will be reflected in the value of a parameter that describes the action of competing risks in the models to be presented next.

SYNTHESIS: EFFECTS OF MALARIA CONTROL PROGRAMMES ON MORTALITY

Equation (1) expresses the death rate of a population as the mean of the death rates of four subpopulations, weighted by the relative sizes of those subpopulations. As already mentioned, for an analysis of age-specific death rates, equation (1) may be applied separately to different age groups.

Equation (1) focuses attention on how different kinds of mcps will affect the death rates and relative sizes of each of the four subpopulations. The models proposed now express the variables on the right side of equation (1) as functions of variables that describe the success of mcps and of ecological and social variables.

There is considerable uncertainty in both the structure of the models and the values of the parameters. Given the models' structure, the uncertainty in the parameter values implies a range of estimates of the death rate following mcps. This range of estimates has no meaningful interpretation as a confidence interval. However, if the models prove useful, it may be of interest, as Nedelman pointed out (J. Nedelman, personal communication, 3 December 1986), to assign subjective probability distributions to the parameters and to compute subjective distributions for the predicted death rate.

Let d' denote the death rate of the population after the implementation of an mcp. Throughout, the prime $'$ dis-

tinguishes a quantity after an mcp from the same quantity before an mcp.

Chemotherapeutic programmes

A chemotherapeutic programme affects the excess mortality, and could affect the size of the subpopulation of fever cases.

Chemotherapy averts the death of a fever case, except where the malarial parasite is intractably drug-resistant or where the fever is unrelated to malaria. A chemotherapeutic programme that treats successfully a fraction s_f of the fever cases will be said to have a "success coefficient" s_f, which is a fraction between 0 and 1. It may be useful to think of s_f as the product of the coverage of the programme times the effectiveness of the programme in treating those individuals included in it. Assuming that all the excess mortality of fever cases is from malaria, a chemotherapeutic programme that effectively treats a fraction s_f of the fever cases could lower the excess mortality in the population of fever cases from $d_f - d_0$ to $d_f' - d_0' = (1 - s_f)(d_f - d_0)$. (I do not assume $d_0' = d_0$: the death rate of the never infected may change for exogenous reasons.)

However, competing risks of death may kill those fever cases saved from dying of malaria. To describe the action of competing risks, define c as the "competing risk control coefficient". The operational meaning of c is that competing risks reduce a chemotherapeutic programme's effective success so that the excess mortality in the population of fever cases is, on average,

$$d_f' - d_0' = (1 - c \cdot s_f)(d_f - d_0).$$

One may think of $c \cdot s_f$ as the effective success, in terms of mortality, of a chemotherapeutic programme that has apparent epidemiological success s_f. That is, the chemotherapeutic programme reaches a fraction s_f of fever cases and averts their deaths from malaria. But competing risks take away some of those lives saved, as if the programme reached only a fraction $c \cdot s_f$ of the fever cases in the absence of other causes of excess mortality.

For example, if all fever cases, whose death from malaria is averted by chemotherapy, die immediately from another cause, then competing risks are not controlled at all, and by definition $c = 0$. If all fever cases, whose death from malaria is averted by chemotherapy, die not immediately but within the year (or other unit of accounting) from another cause, then c would be small but strictly positive so that the death rate of the fever subpopulation would correctly reflect the person-years lived. A value of c between 0 and 1 means that fever cases saved from dying of malaria have some excess mortality, but less than untreated fever cases. At the other extreme, if fever cases, whose death from malaria is averted by chemotherapy, have only the risks of death of individuals never infected by malaria, then by definition $c = 1$ and competing risks are completely controlled.

In principle, c could be measured by longitudinal observations of treated fever cases. However, such a special-purpose study is likely to be impractical. It is still possible to estimate c crudely because, as noted, the action of competing risks appears to depend on the social context of the mcp. Where a chemotherapeutic programme is an isolated effort, it would be reasonable to make c small. Where a chemotherapeutic programme is part of a multifaceted or eradication programme, and these in turn are part of extensive social development, it would be reasonable to estimate c large, and close to 1. In any event, it would be desirable to compute d' twice, by considering the extreme cases $c = 0$ and $c = 1$, to see whether the uncertainty about c materially affects the estimate d'.

Another possible form of sensitivity analysis would be to consider other formulations of the success coefficient. The above formulation of the success coefficient and of effective success is additive because excess mortality is measured by the difference $d_f - d_0$. If excess mortality were measured by the mortality ratio d_f/d_0, a multiplicative version of the success coefficient could be defined, as pointed out by Horiuchi (S. Horiuchi, personal communication, 19 December 1986). For the extreme values 0 and 1 of the effective success coefficient, the results of using the additive and multiplicative versions are identical. The additive version is used here because the formula for it is simpler.

Chemotherapy prevents reinfection of the subpopulation of fever cases, only for a negligible period of time. During the period when a treated individual has no or few parasites in his peripheral blood, he has a reduced risk of infecting a mosquito that bites him, and that mosquito therefore has a reduced risk of infecting another human on which it feeds later. Thus, there is some impact, in principle, of chemotherapy on the subsequent incidence of human malarial infection. However, unless the chemotherapy programme reaches most of the population at risk nearly simultaneously, the impact of chemotherapy on subsequent malarial incidence seems likely to be small. In any event, it is virtually unmeasurable as a separate effect. At the same time, chemotherapy of fever cases does not diminish the flux of parasitemic cases into the subpopulation of fever cases. Hence, I suppose, as a first approximation, that in areas of intense transmission a chemotherapeutic programme has no effect on the size of the subpopulation of fever cases.

In summary, under a chemotherapeutic programme, the death rate and relative size of the subpopulation of fever cases are

$$d_f' = d_0' + (1 - c \cdot s_f)(d_f - d_0),$$

$$p_f' = p_f.$$

The mortality d_0' among never-infected individuals after the programme may differ from that d_0 before the programme for reasons unconnected with the mcp. Then the death rate d' of the population after the programme is in place, continually treating fever cases, is predicted to become

$$d' = p_0 \cdot d_0' + p_f \cdot d_f' + p_b \cdot d_b' + p_i \cdot d_i', \qquad (2)$$

with d_f' given above. Where no information to the contrary is available, it is parsimonious to assume that $d_0 = d_0'$, $d_b = d_b'$ and $d_i = d_i'$.

Though age is not mentioned in this model, the model is intended to be applied separately to age groups that have notably different values of the death rates or subpopulation proportions. As suggested by Ewbank (D. C. Ewbank, personal communication, 10 December 1986), suppose, for example, that if an attack of malaria coincides with weanling diarrhoea, the child has a high risk of death from or with malaria, but if the child suffers a malarial infection after the weanling diarrhoea is past, the mortality from or with malaria is much reduced. To anticipate the impact of a chemotherapeutic programme on children in this situation, it would be appropriate to apply the above model separately to pre- and post-weaning age groups, in combination with standard demographic cohort projection. Chemotherapy in the pre-weaning group would leave more children alive to benefit from the lower malarial death rates of the post-weaning group.

Multifaceted programmes

The success of a multifaceted programme may be measured by four average "success coefficients": s_f, the fraction of excess mortality from malaria that is prevented by chemotherapy among fever cases (exactly as in a chemotherapeutic programme),

$$s_f = 1 - [d_f' - d_0']/[d_f - d_0];$$

s_b, the fraction of excess mortality with malaria that is prevented by chemotherapy and chemoprophylaxis among currently infected cases,

$$s_b = 1 - [d_b' - d_0']/[d_b - d_0];$$

s_F, the fractional reduction in the size of the subpopulation of fever cases,

$$s_F = 1 - p_f'/p_f;$$

and s_B, the fractional reduction in the size of the subpopulation of currently infected cases,

$$s_B = 1 - p_b'/p_b.$$

How are these success coefficients to be estimated, short of carrying out the mcp and waiting to see what happens? The fractional reductions in excess mortality s_f and s_b could be estimated crudely from the mcp plan as the programme's anticipated coverage of the subpopulations of, respectively, fever cases and currently infected cases. The fractional reductions in the subpopulations of fever and currently infected cases could be measured after the fact, in the course of epidemiological surveillance once the mcp is in place. Alternatively, mathematical models of malarial transmission (see, e.g., Dietz, 1986; Gonzalez-Guzman, 1980) could be used in advance to derive a predicted post-control parasite rate P'; a "success coefficient" s_P for reducing the parasite rate could then be estimated from

$$s_P = 1 - P'/P$$

and, until better information is available, one could take $s_F = s_B = s_P$. The model presented here does not provide a prediction of the size of the subpopulations of fever and currently infected cases after a multifaceted programme is in place.

The people who leave the subpopulations of fever cases and currently infected cases as a result of multifaceted control may be allocated, in this model, to either of two subpopulations: those never infected, or those previously infected. Although age has not entered the model explicitly up to this point, it seems necessary to introduce age here.

For the youngest individuals (say, 0-4 years), a reduction in prevalence P is likely to be achieved largely by reducing the incidence of infection, thereby enlarging the pool of people never infected. Moreover, such young children appear biologically incapable of mounting a protective immune response like that of an adult chronically exposed to malarial infection. So for never-infected children, the size of the subpopulation changes from p_0, before multifaceted control, to

$$p_0' = p_0 + s_F \cdot p_f + s_B \cdot p_b \qquad \text{(0-4 years only)}$$

after multifaceted control.

For older individuals, the opposite allocation seems more sensible. Assuming the population is geographically homogeneous (or, if not, redefining the population so that it becomes geographically homogeneous), I will assume that everyone who would have been infected by malaria before control becomes infected with some steady mean frequency after control, and therefore maintains some immune response. This assumption is most plausible in an environment of stable malaria with fairly intense transmission, where older individuals experience chronic malarial infection. When the steady mean frequency of malarial infection is low, as in an environment of unstable malaria, I am assuming that there is at least some immunological memory of prior malarial infection among older individuals.

People who lose a malarial infection as a result of a multifaceted programme may be quite different from people who mount a protective immune response on their own. But it seems more reasonable that the excess mortality of formerly infected individuals saved from infection by a multifaceted programme would resemble the excess mortality of immune cases than that the formerly infected individuals saved from infection by a multifaceted programme would have no excess mortality at all, like the individuals never infected with malaria.

On the basis of these arguments and assumptions, among individuals aged five years and older, the relative size of the subpopulation of previously infected cases changes from p_i, before multifaceted control, to

$$p_i' = p_i + s_F \cdot p_f + s_B \cdot p_b \qquad \text{(5 years and older only)}$$

after multifaceted control.

There is no simple relation between the activities of a multifaceted control programme and the success

coefficients s_f, s_b, s_F and s_B. Indeed, the effects may be counterintuitive. Some activities affect only one measure; for example, chemotherapy of fever cases probably affects mainly s_f. Other activities affect more than one measure. For example, measures directed against the mosquito population, such as larviciding and altering breeding habitats; measures aimed at separating the mosquitoes from people, such as using mosquito nets, screening windows and spraying the insides of homes with residual insecticides; and chemoprophylaxis, aimed at preventing parasites from establishing the asexual life cycle in the human host, diminish the incidence, and thereby the prevalence, of malarial infection. But the measures aimed at the mosquito population and its attacks on people also diminish the frequency of superinfection (repeated inoculation of malarial parasites into individuals already infected with malaria).

In a population with endemic malaria, it is plausible that a reduction in superinfection would lower the mean interval between periods of being free of malaria, that is, would reduce the mean duration of a spell of malarial infection, which would in turn lower the excess mortality with malaria, especially among infants and children, "if chronic malaria affects adversely the general underlying condition of persons, which is likely" (Molineaux and Gramiccia, 1980, p. 246). The point is that an activity such as vector control or screening, which might appear aimed at incidence or at prevalence, may also affect excess mortality. Still other activities, such as mass drug administration, especially at a sufficiently high frequency, must affect all measures of success: s_f, by curing fever cases who would otherwise die; s_b, by reducing the density of parasites and the consequent pathology; and s_F and s_B, by terminating bouts of infection.

With currently infected cases as with fever cases, competing risks of death may reduce the demographic net effect of success in averting both deaths from malaria and deaths with malaria. The death rates in these two subpopulations become, after multifaceted control,

$$d_f' = d_0' + (1 - c \cdot s_f)(d_f - d_0),$$

$$d_b' = d_0' + (1 - c \cdot s_b)(d_b - d_0).$$

In summary, using the preceding steps, the death rate after multifaceted control is estimated to be

$$d' = [p_0 + s_B \cdot p_b + s_F \cdot p_f]d_0' + (1 - s_F)p_f d_f' \qquad (3a)$$

$$+ (1 - s_B)p_b d_b' + p_i' \cdot d_i' \qquad \text{(0-4 years only)}$$

$$d' = p_0' \cdot d_0' + (1 - s_F)p_f d_f' + (1 - s_B)p_b d_b' \qquad (3b)$$

$$+ [p_i + s_B \cdot p_b + s_F \cdot p_f]d_i' \text{ (5 years and older only)}$$

where d_f' and d_b' are given in the previous equation. Assume $d_0' = d_0$ and $d_i' = d_i$ unless there is information to the contrary. The logical requirement that the proportions of the four subpopulations sum to 1 both before and after control implies that $p_i' = p_i$ in (3a) and $p_0' = p_0$ in (3b). But if facts show that after multifaceted control individuals aged 0-4 years have been previously exposed or individuals aged 5 years and older have never been exposed, the simplifying assumptions made in constructing (3a) and (3b) should be modified accordingly.

A high death rate would be estimated by setting $c = 0$, so that competing risks neutralize any successes in reducing mortality from or with malaria. A low death rate would be estimated by setting $c = 1$, so that individuals reached by the programme attain the mortal risks of individuals never infected with malaria.

The same notation c is used for competing risks affecting both the p_f and the p_b subpopulations (as well as for all age groups, if age groups are to be considered) not because competing risks will have the same effect in all cases but because it is highly unlikely that data will be available that would justify assigning different values to c in different subpopulations. In the happy event that such data are available, different values of c could, of course, be introduced.

Eradication programmes

Like multifaceted programmes, eradication programmes lower the parasite rate. However, by reducing incidence to 0, eradication programmes, unlike control programmes, eventually eliminate the subpopulation of people previously infected. At the older ages, as time passes, the decline in the p_f and p_b subpopulations will be compensated by a rise in the P_0 subpopulation (never infected), rather than in the p_i subpopulation (previously infected).

The reason for the difference is that in a control programme, with a positive steady-state prevalence of malarial infection, individuals shuttle irregularly between a state of being infected and a state of being previously but not currently infected. The proportion infected is $P = p_f + p_b$ and the proportion previously but not currently infected is p_i. Individuals in the subpopulation p_i suffer the after-effects of sporadic (unstable) or chronic (stable) malaria. Under malarial eradication, the subpopulation p_i gradually loses members by death, and the excess mortality of individuals originally in p_i gradually declines as any constitutional weakening and immunological stimulation of prior malarial infection fade into the past.

Unfortunately, I do not know of quantitative information about the post-eradication rate of decline or asymptote of the excess mortality of previously infected individuals. As Singer pointed out (B. H. Singer, personal communication, 16 December 1986), it may be possible to extract generalizations about the post-eradication decline of excess mortality of previously infected individuals from the numbers of cases of malaria and numbers of malaria deaths in European countries (Bruce-Chwatt and de Zulueta, 1980). The difficulties of interpreting the available numbers are serious (for example, are the reported malarial deaths from, with or following malaria?) but the possibility of extracting useful information from them deserves study.

Because the decline in the subpopulation of previously infected people depends on the passage of time, it is natural to embed this model for the mortality effects of successful meps in a standard demographic cohort-

component projection (e.g., Keyfitz, 1968). For concreteness, suppose the entire human population is treated as a collection of age-specific populations of individuals aged 0-4 years, 5-9 years and so on. These age groupings are conventional in demography.

Let $t = 0$ be the year eradication is achieved, so that $t \geqslant 0$ is the number of years since the last endogenous malaria case. Also, let (t, n) refer to the population of individuals aged n to $n + 4$ years in year t. Eradication means that there are no more fever cases and no more currently infected individuals, that is, for $t \geqslant 0$, $p_f'(t, n) = p_b'(t, n) = 0$, for $n = 0, 5, 10, 15, \ldots$

It remains only to describe $p_0'(t, n)$ and $p_i'(t, n)$. For $t > n + 4$, the age group n to $n + 4$ contains only individuals born after eradication, and such individuals have never been infected, by the definition of eradication (and ignoring migration from other regions where malaria may still be endemic). Hence,

$$d'(t, n) = d_0'(t, n),$$

when $t > n + 4$. In this equation, the death rate of individuals aged n to $n + 4$ who were never infected with malaria is denoted as a function of time $d_0'(t, n)$ to allow for the possibility that this death rate may change as a result of factors having little to do with malaria or its control.

At $t = 5m$ years post-eradication ($m = 0, 1, 2, \ldots$), where $t \leqslant n$, the age group n to $n + 4$ contains individuals who were alive at the time of eradication and who were aged $n - t$ to $n - t + 4$ at that time. Let $p_0(0, n - t)$ denote the proportion of never-infected individuals in the age group $n - t$ to $n - t + 4$ just prior to eradication; similarly for $p_f(0, n - t)$, $p_b(0, n - t)$ and $p_i(0, n - t)$. Let $p_0'(t, n)$ and $p_i'(t, n)$ denote the proportions of never-infected and of previously infected individuals t years after eradication (when $t = 0$, this means just after eradication) in the age group n to $n + 4$. As stated above,

$$p_f'(0, n) = p_b'(0, n) = 0.$$

Immediately after eradication,

$$p_i'(0, n) = p_i(0, n) + p_f(0, n) + p_b(0, n),$$

for every n,

because eradication does not remove the fact of past malarial infection from the p_i subpopulation, and after eradication the fever and parasitemic cases join the ranks of the previously infected. After $n + 5$ years have passed since eradication, the population aged n to $n + 4$ years will have no previously infected individuals, because all individuals aged n to $n + 4$ will have been born after eradication. In symbols,

$$p_i'(n + 5, n) = 0, \quad n = 0, 5, 10, \cdots$$

Consequently, the excess mortality of the p_i subpopulation becomes 0 by $n + 5$ years post-eradication, because the p_i subpopulation vanishes.

What is uncertain, as I stated before, is how the aggregate excess mortality of the p_i subpopulation declines from $p_i(0, n)[d_i(0, n) - d_0(0, n)]$ just before eradication to 0 after $n + 5$ years. This ignorance will be described quantitatively, dealing first with the decline in per capita excess mortality $d_i'(t, n) - d_0'(t, n)$ and then with the decline in the size $p_i'(t, n)$ of the p_i subpopulation.

Just prior to eradication, $d_i(0, n) - d_0(0, n)$ is the average per capita excess mortality of previously infected individuals aged n to $n + 4$ years. After t years, this same cohort, now aged $n + t$ to $n + t - 4$, will, by definition, have per capita excess mortality

$$d_i'(t, n + t) - d_0'(t, n + t) = [d_i(0, n) - d_0(0, n)]f(t, n)$$

where the unknown function $f(t, n)$ describes the decay in excess mortality: $f(0, n) = 1$ and $f(t, n) \geqslant 0$ for all t and $f(t, n)$ is non-increasing with t. For practical applications of the model, it might be reasonable to assume that $f(t, n)$ declines exponentially and independently of the initial age n, for example, $f(t, n) = \exp(-Dt)$. Under this assumption, $(\ln 2)/D$ is the half-life of excess mortality of previously infected individuals, that is, the number of years required for the excess mortality of previously infected individuals to fall by half.

Two bits of evidence may be indirectly relevant to estimating the half-life of excess mortality of previously infected individuals. First, the half-life of the immunoglobulin IgG is estimated at 23 days, and other immunoglobulin classes (IgA, IgD, IgE and IgM) break down much more rapidly (Davis and others, 1973, p. 483). Secondly, schoolchildren living in a highly malarious area of East Africa who were protected from infection for between one and two months by the administration of antimalarial drugs displayed a substantial loss of clinical immunity to malaria when drug treatment was terminated, as many of the new infections caused more severe clinical symptoms and parasitemia than had prevailed before treatment (Pringle and Avery-Jones, 1966). The concordance between the half-life of IgG and the decay-time of clinical immunity to malaria is remarkable. Unfortunately, a direct link between these two facts and the decay of excess mortality of previously infected individuals remains to be made.

If t were measured in years, and excess mortality decayed exponentially with the same half-life as IgG, then $D = 11$ and the excess mortality of the previously infected would be unmeasurably small even half a year after eradication. The form of this decay may depend on the eradication programme; for example, medical care for previously infected individuals could accelerate the decline of their excess mortality. In the absence of directly relevant data, other functional forms and parameter estimates for the decline function $f(t, n)$ are equally plausible.

The decline in the size of the p_i subpopulation can now be described by simple equations. At time t, where $0 \leqslant t \leqslant n + 5$, the population aged n to $n + 4$ years

contains a fraction $p_0'(t, n)$ of individuals never infected, who suffer per capita mortality $d_0'(t, n)$, and a fraction $p_i'(t, n) = 1 - p_0'(t, n)$ of individuals previously infected, who suffer per capita mortality

$$d_i'(t, n) = d_0'(t, n) + [d_i(0, n - t) - d_0(0, n - t)]f(t, n - t).$$

As a rough approximation (better approximations are given by Keyfitz, 1968), using five-year death rates, and ignoring immigration and emigration, the number of never-infected individuals aged $n + 5$ to $n + 9$ y at time $t + 5$ is proportional to $p_0'(t, n)[1 - d_0'(t, n)]$ and the number of previously infected individuals aged $n + 5$ to $n + 9$ at time $t + 5$ is proportional to $p_i'(t, n)[1 - d_i'(t, n)]$. Consequently, the proportion of never-infected individuals aged $n + 5$ to $n + 9$ at time $t + 5$ is

$$p_0'(t + 5, n + 5) = p_0'(t, n)[1 - d_0'(t, n)] / [p_0'(t, n)[1 - d_0'(t, n)] + p_i'(t, n)[1 - d_i'(t, n)]].$$

The proportion of previously infected individuals is then

$$p_i'(t + 5, n + 5) = 1 - p_0'(t + 5, n + 5).$$

From these last two equations, given some assumed form for $f(t, n)$, the proportions $p_0'(t, n)$ and $p_i'(t, n)$ can be calculated for all times t post-eradication and all age groups n to $n + 4$. The crude death rate $d'(t, n)$ of the age group can be calculated as a weighted mean,

$$d'(t, n) = p_0'(t, n)d_0'(t, n) + p_i'(t, n)d_i'(t, n),$$

and the cohort can be projected by the standard cohort-component method.

The method depends, of course, on facts or assumptions about the decay function $f(t, n)$. Regardless of uncertainty about the form of $f(t, n)$, the end points at $f(0, n) = 1$ and $p_i'(n + 5, n) = 0$ are clear.

This very simple model can explain how the mortality gains from eradication can substantially exceed the direct reduction in mortality from or with malaria, as Molineaux (1985) observed. Ignoring age structure for a moment, and assuming that the background death rate d_0 of individuals never infected with malaria is constant before and after control, the aggregate post-control reduction in mortality, after all previously infected individuals have died, is $p_f(d_f - d_0) + p_b(d_b - d_0) + p_i(d_i - d_0)$. This reduction may greatly exceed the sum of the averted deaths from malaria $p_f(d_f - d_0)$ and averted deaths with malaria $p_b(d_b - d_0)$. The model not only explains this effect qualitatively, but shows that the size of the effect should depend on the time since eradication (cf. Giglioli, 1972). The model gives a way of estimating the size of the effect quantitatively, given facts or assumptions about the decay $f(t, n)$ of excess mortality of individuals previously infected.

It is plausible that an eradication programme can be put in place and made to hold only amid considerable social development. If so, it is equally plausible to evaluate the competing risk control coefficient c as $c = 1$, pending data to the contrary (particularly evidence of drug resistance).

Will an eradication programme cause a larger eventual decline in mortality where malaria is intense and stable or where malaria is epidemic and unstable? The answer depends on the relative size of the excess mortality in the p_i subpopulation versus that in the p_f and p_b subpopulations. Recall that the excess mortality of the p_i subpopulation is likely to be substantial in stable malaria compared with that in unstable or epidemic malaria. By contrast, the excess mortality of the p_f and p_b subpopulations is likely to be substantial in unstable or epidemic malaria compared with that in stable malaria. Eradication eventually eliminates both the p_i subpopulation and the $p_f + p_b$ subpopulations, and the magnitude of the population's mortality decline depends on the balance of the sizes of these subpopulations and the excess mortalities in them.

Numerical example: the Garki project

One of the most carefully planned and reported field experiments in malaria control is the Garki project (Molineaux and Gramiccia, 1980). The project was carried out in Kano State, northern Nigeria, by the World Health Organization in co-operation with the Government of Nigeria. Malarial transmission in this area is intense and stable: prior to any intervention, the crude parasite rate for *P. falciparum* infection for all villages combined exceeded nearly 50 per cent year-round, while the crude parasite rate for *P. malariae* infection exceeded 10 per cent year-round. Because eradication was neither a goal nor a result of the project, the Garki project is an example of a multifaceted programme. No effort was made to provide comprehensive social and economic development.

In the baseline phase of the project, the parasitology, immunology, clinical signs and demography of the study population were observed. In the intervention phase, several malaria control strategies, including mass drug administration and spraying of residual insecticides, were carried out in different combinations in different villages. Data from the villages that received the most intense treatment (follow-up units 5 and 7) will be the subject of attention here. During the intervention phase, some villages also received no treatment (follow-up units 1 and 2).

On the basis of differences in immune function and in the prevalence of infection with *P. falciparum* malaria, three age groups will be treated as separate populations: 0-4 years, 5-18 years and 19 years and older. Table 1 shows d, the death rates (from all causes) of these three age groups before control, and d′, the corresponding estimates after control (estimated from the statistics on follow-up units 5 and 7). The post-control death rates (d′) are uniformly and substantially lower than those

TABLE 1. DEATH RATES OF MALARIA SUBPOPULATIONS IN THE GARKI PROJECT

Line	Parameter	Population (age group in years) 0-4	5-18	19+
	Villages where treatments were applied (follow-up units 5, 7)			
(1)	d, death rate per year before control	.190	.014	.018
(2)	d′, death rate per year after control	.063	.007	.009
(3)	p_0, proportion never infected	.20	0	0
(4)	p_f, proportion of fever cases	.11	.07	.04
(5)	p_b, proportion currently infected	.69	.78	.36
(6)	p_i, proportion previously infected	0	.15	.60
(7)	P, parasite rate	.80	.85	.40
(8)	d_0, death rate of never infected	.163	.012	.015
(9)	d_f, death rate of fever cases	.253	.019	.024
(10)	d_b, death rate of currently infected	.187	.014	.018
(11)	d_i, death rate of previously infected	unknown	.012	.018
	Villages where no treatments were applied (follow-up units 1, 2)			
(12)	d, death rate per year before control	.187	.008	.027
(13)	d′, death rate per year after control	.124	.004	.017
(14)	F, factor of exogenous decline in d	.663	.5	.630

NOTES:

The estimates in table 1 are based on two sources (see references):

A World Health Organization (1975)

B Molineaux and Gramiccia (1980).

Other abbreviations used are:

F figure

T table

p page.

Lines (1) and (2). Source A, T 2, gives the infant mortality rate (IMR) of follow-up units 5 and 7 before and after control. T 10 gives the death rates of age groups 1-4 years, 5-28 years and 29 years and older before and after control. I computed d and d′ for 0-4 years as the weighted mean of the corresponding IMR and death rate for 1-4 years, using the weights 63/240 and 177/240 given in A, T 1. I set d for age groups 5-18 years and 19 years and older equal, respectively, to those given in A, T 10, for age groups 5-28 years and 29 years and older. For the post-control death rates in the two older age groups, I smoothed the data as follows. There were one death in 5-28 years and 12 deaths in 29 years and older, giving a death rate for the two groups combined of 13/(813 + 801) = .008, where 813 and 801 are the sizes of the two groups. I then required $d'(5\text{-}18)/d'(19+) = d(5\text{-}18)/d(19+)$ and $[813 \cdot d'(5\text{-}18) + 801 \cdot d'(19+)]/(813+801) = .008$.

Line (3). $p_0(0\text{-}4) = 1 - P(0\text{-}4)$. $p_0(5\text{-}18) = p_0(19+) = 0$ on the basis of B, p. 121, F 25.

Line (4). B, p. 256, T 28. Fever is defined as body temperature of 37.5°C or more. $p_f(0\text{-}4)$ is the per cent with fever in village cluster 2 at survey 15, age less than 9 years. Village cluster 2 is the only untreated follow-up unit for which data on fever prevalence are presented in B, p. 256, T 28. $p_f(19+)$ is the same for age 9 and older. $p_f(5\text{-}18) = [p_f(0\text{-}4) + p_f(19+)]/2$. These figures on the prevalence of fever differ a little from those quoted above from Molineaux and Gramiccia (1980, p. 258) when "fever cases" are defined in this text because the latter data are pooled over surveys and village clusters.

Line (5). $p_b = P - p_f$ = line (7) − line (4).

Line (6). I set $p_i(0\text{-}4) = 0$. For the two older age groups, $p_i = 1 - P$.

Line (7). Read from B, p. 144, F 38.

Lines (8), (9), (10), (11). Source A, T 6, gives the IMR in the baseline phase according to the infants' parasitological status at the beginning of an interval of observation. Infants who were uninfected had IMR = .202. Infants infected with *P. falciparum* who had fewer than 25 per cent of thick film fields positive for asexual stages of the parasite had IMR = .231. Infected infants who had 25 per cent or more of fields positive had IMR = .311. Now, the greater the proportion of fields positive for *P. falciparum* asexual stages, the greater the probability of fever (B, p. 256, T 29). Hence, I set the ratio .231/.202 = 1.15 equal to the ratio d_b/d_0, and the ratio .311/.202 = 1.55 equal to the ratio d_f/d_0. Then, I assumed, for all age groups,

$$d = p_0 \cdot d_0 + p_f(1.55d_0) + p_b(1.15p_0) + p_i \cdot d_i. \quad \text{(Ta1)}$$

(In principle, d_0, d_f, d_b and d_i could all be computed directly from the Garki data tape.)

For 0-4 years, $p_i = 0$, so (Ta1) determines d_0, since d, p_0, p_f and p_b are given by lines (1), (3), (4) and (5) respectively. From d_0,

$$d_f = 1.55d_0, \quad \text{(Ta2)}$$

$$d_b = 1.15d_0. \quad \text{(Ta3)}$$

For 5-18 years and 19 years and older, (Ta1) is not sufficient to determine either d_0 or d_i. Therefore, I made the further assumption that

$$d_0(19+)/d(19+) = d_0(5\text{-}18)/d(5\text{-}18) = d_0(0\text{-}4)/d(0\text{-}4) = .163/.190 = .858. \quad \text{(Ta4)}$$

In combination, (Ta1) and (Ta4) determine the values shown.

As line (3) shows $p_0(5\text{-}18) = p_0(19+) = 0$, it is important to point out that $d_0(5\text{-}18)$ and $d_0(19+)$ are hypothetical estimates of the death rates of those age classes in the absence of malarial infection.

An unanticipated consequence of the calculation is that $d_i(5\text{-}18) = d_0(5\text{-}18)$. Young people who lose their infection are estimated to have the same mortality as those never infected, that is, their mortality appears to recover to normal once they are freed of infection. However, $d_i(19+) = d_b(19+)$. Older people freed of infection suffer excess mortality that is as adverse as if they were still infected. Qualitatively, these findings seem realistic.

Lines (12), (13). The same procedures and sources were used as for lines (1) and (2), without the smoothing procedure used there.

Line (14). F = line (13) divided by line (12). The ratio .663/.5 of the largest to the smallest F is much smaller than the ratio (.187 − .124)/(.027 − .017) of the largest to the smallest of the corresponding differences between line (12) and line (13); hence, it seems more economical to summarize the exogenous change in mortality as a multiplicative change (multiplication by a factor F) than as an additive change (subtraction of a constant amount).

before control (d). The present section is devoted to the question of how well the model of a multifaceted mcp can predict d′, using only information available prior to control. All the calculations presented here, being based on heroic assumptions and good but limited data, are approximate.

Table 1 gives an internally consistent set of estimated values for the parameters of the model of a multifaceted mcp. The notes to table 1 describe in detail how these values were obtained. In brief, some of the values are taken directly from Garki measurements, and the rest of the values are calculated from measurements under assumptions intended to be reasonable or at least plausible. The measurements are taken from Molineaux and Gramiccia (1980) and from an unpublished report of the World Health Organization (1975), which was used in preparing their study.

A magnetic tape of the Garki project's raw data is available, and careful analysis of those data would make

it possible to replace some calculations or guesses in table 1 with measurements. Because table 1 is intended only as a realistic numerical illustration, I have been content here with existing tabulations.

The most vulnerable assumptions made in computing table 1 are expressed in equations (Ta1) to (Ta4), which are found in the note to lines (8) to (11) of that table. A first assumption is that the ratios d_f/d_0 and d_b/d_0 are the same in all age classes as among infants, and may be estimated from the ratios of death rates among individuals with high and low densities of *P. falciparum* infections. A second assumption is that the ratio d_0/d for the two older populations is the same as the ratio d_0/d for the 0-4 years population. These assumptions are not part of the general model, but are temporary adjuncts that make it possible to obtain numerical estimates of the model's parameters from available tabulations of the Garki data.[7]

When the estimated death rate d_0 of individuals never infected with malaria (line 8) is compared with the post-control death rate d' (line 2) in each population, d' is seen to be lower than d_0. Even if the mcp could restore to all individuals the pre-control mortality of the never infected, it could not lower the mortality of each treated population as far as the observed mortality fell.

At least three factors could possibly explain how the post-control mortality of a population might have fallen below the pre-control mortality of its never-infected subpopulation. First, the multifaceted mcp probably reduced causes of death in the treated villages in addition to malaria. Secondly, exogenous factors probably caused a decline in mortality independently of any mcp. Thirdly, the numbers of recorded deaths might be so low that the difference is due to sampling fluctuation. The evidence pertinent to these factors will be described below.

First, as Vaugelade pointed out (J. Vaugelade, personal communication, 22 January 1987), in the treated villages, the antimalarial drug pyrimethamine was administered in combination with sulphalene, a long-acting sulphonamide (Molineaux and Gramiccia, 1980, pp. 23-25). Independently of malaria control, sulphalene would have reduced mortality, and most strongly among infants and young children. Indeed, comparison of lines (1) and (2) shows that the decline in the death rate, both absolutely and relatively, was largest among children aged 0-4 years. It is impossible to say whether this difference among populations should be attributed to sulphalene or to the mcp.

Secondly, exogenous changes in mortality lowered death rates in villages that were left untreated in both the baseline and intervention phases (lines 12 and 13). Without any intervention, death rates declined in those villages (line 14) to one half to two thirds of the original level. Since the untreated villages received no drugs or other treatments, the effects of malaria control and sulphalene contribute jointly to the difference in mortality between the treated and untreated villages.

Thirdly, the numbers of deaths used to calculate the estimates in table 1 are low (World Health Organization, 1975). For example, if the rates are given as (the number of events)/(the population at risk), the infant mortality rate in follow-up units 5 and 7 was 14/61 during the baseline phase and 9/112 during the intervention phase, while the death rates of those aged 1-4 years during the corresponding phases were 25/142 and 11/194, respectively; the rates $d = 0.190$ and $d' = 0.063$ in lines (1) and (2) of table 1 for children aged 0-4 years are weighted means of these fractions. To test the null hypothesis that there is no difference between the infant mortality rates of the baseline and intervention phases, I assume Poisson sampling of deaths and compute X^2 corrected for continuity, with one degree of freedom, as 6.38, which has a probability between 0.01 and 0.025. For children aged 1-4 years, the difference in death rates is significant beyond the 0.005 level. Thus, there is very little likelihood of no real decline in the death rate of the 0-4 years population associated with the intervention phase. The sample sizes of the other estimates in table 1 are similarly small. While it would be possible to test every asserted difference for statistical significance, it seems more productive, for this example, to suppose that the sample sizes are sufficient for valid inferences. Henceforth, attention will be limited to the first two factors.

The model cannot, and is not intended to, explain either exogenous changes in mortality or effects of a control programme on causes of death unrelated to malaria. At best, it can hope to explain changes in excess mortality associated with malaria. An independent model or measurement is required to estimate other changes in mortality.

Because there is no quantitative information about the effects of sulphalene on mortality in the treated villages, this numerical illustration will consider only the exogenous change in mortality. The exogenous change can be estimated by comparing death rates in the untreated villages before and after control.

Suppose that, in the absence of treatment, the exogenous decline in mortality experienced by the untreated villages would have affected in the same multiplicative way each subpopulation of the treated population. Table 2 gives the hypothetical death rates expected during the intervention phase for each subpopulation, in the absence of multifaceted control, adjusting only for the exogenous factor of mortality decline (lines 15 to 18).

Even after this adjustment, for the population aged 0-4 years, the estimated death rate 0.108 of the never-infected subpopulation (line 15) still exceeds the death rate 0.063 actually observed (line 2) after multifaceted control. This suggests that the sulphalene supplied in combination with pyrimethamine contributed to the decline in mortality of the children aged 0-4 years, or that the exogenous decline of mortality in the treated villages was greater than that in the untreated villages for the population aged 0-4 years, or that the excess of 0.108 over 0.063 could at least partly be due to sampling variability in the estimates of the death rates.

For the populations aged 5-18 years and 19 years and older, the estimated death rate d_0 of the never-infected subpopulation is smaller than the death rate d actually observed after multifaceted control.

The death rates adjusted for exogenous mortality decline (the upper half of table 2) and the proportions of the subpopulations (in table 1) may be combined to give

TABLE 2. PREDICTED MORTALITY FOLLOWING MALARIA CONTROL IN THE GARKI PROJECT

Line	Parameter	Population (age group in years) 0-4	5-18	19+
	Villages where treatments were applied (follow-up units 5, 7)			
(15)	d_0F, adjusted rate of never infected	.108	.006	.009
(16)	d_fF, adjusted rate of fever cases.....	.168	.010	.015
(17)	d_bF, adjusted rate, currently infected ..	.124	.007	.011
(18)	d_iF, adjusted rate, previously infected	unknown	.006	.011
(19)	d' with multifaceted control success 0.	.126	.007	.011
(20)	d' with multifaceted control success .5	.112	.006	.011
(21)	d' with multifaceted control success 1.	.108	.006	.011
(22)	d' with eradication, compete success ..	.108	.006	.009
(2)	d', death rate observed after control ...	.063	.007	.009

NOTES:

Lines (15), (16), (17), (18). Subpopulation death rates from lines (8), (9), (10), (11), respectively, multiplied by the factor F of exogenous decline from line (14).

Line (19). $d' = p_0 \cdot d_0F + p_f \cdot d_fF + p_b \cdot d_bF + p_i \cdot d_iF$, based on lines (3) to (7) and (15) to (18).

Line (20). d' based on text equations (3a) for 0-4 years and (3b) for 5-18 years and 19 years and older, using adjusted death rates from lines (15) to (18) instead of actual rates and $c \cdot s_B = c \cdot s_F = s_b = s_f = 1/2$.

Line (21). d' based on text equations (3a) for 0-4 years and (3b) for 5-18 years and 19 years and older, using adjusted death rates from lines (15) to (18) instead of actual rates and $c \cdot s_B = c \cdot s_F = s_b = s_f = 1$.

In lines (19) to (21), the subpopulation-specific death rates were first adjusted for exogenous decline by the factor F and then the impact of the mcp was computed using (3a) and (3b). As may easily be verified algebraically and numerically, the results are identical if the impact of the mcp on the original subpopulation-specific death rates is computed first using (3a) and (3b) and the results are then adjusted for exogenous decline by the factor F. The reason is that either way F appears linearly in all terms on the right sides of (3a) and (3b). Hence, our numerical procedure makes no implicit assumption about the order of action of the mcp or the exogenous decline.

Line (22). All individuals have the adjusted death rate of those never infected. Identical to line (15).

Line (2). Estimated actual death rate, from line (2) of table 1.

the predicted post-control death rates (the bottom half of table 2) under various assumptions about the success of multifaceted control or eradication. To facilitate comparison of these predicted rates with those actually observed, table 2 repeats the observed post-control death rates d'.

When the success of multifaceted control is 0 (line 19), the predicted death rate corresponds to no mcp at all, and is the result of applying equation (1) to the estimated subpopulation proportions and the adjusted death rates. For the populations 0-4 years and 19 years and older, no success is predicted to have resulted in death rates higher than those observed. For the population aged 5-18 years, the observed death rate is indistinguishable from that estimated assuming no success.

Setting the success of multifaceted control equal to 1 (line 21) is a hypothetical extreme, because it corresponds to the complete elimination of fever cases and of currently infected cases. This extreme may be viewed as the limit of a highly successful multifaceted control programme; the Garki project, for example, did succeed in reducing the prevalence of infection by 95 per cent or more (Molineaux and Gramiccia, 1980, p. 144). The same set of model parameters may be interpreted to describe an eradication programme just after eradication has been achieved, before the previously infected cases have died out or lost their excess mortality due to prior infection.

For the youngest population, 0-4 years, the greater the success of multifaceted control, the lower the estimated death rate. However, eradication offers no further lowering of mortality beyond that attained by completely successful multifaceted control, because, according to the model, the youngest population has no subpopulation of previously infected.

For the oldest population, 19 years and older, the success of multifaceted control, whether 0 or 1, makes a negligible difference in mortality. The reason for this perhaps surprising finding is that, with no individuals never infected and very few fever cases, this population consists overwhelmingly of individuals currently infected or previously infected. Multifaceted control shifts individuals from the currently infected subpopulation to the previously infected subpopulation. But according to table 1, these two subpopulations are estimated to have nearly identical mortality. Hence, there is no change in mortality with more successful multifaceted control. However, eradication would eventually assure that the entire population was never infected by malaria. This shift would lower the estimated death rate to that actually observed.

Finally, for the population of intermediate age, 5-18 years, increasingly successful multifaceted control and eradication are estimated to cause very small declines in mortality because the adjusted death rates d_0F, d_bF and d_iF of the largest subpopulations are so similar.

The range of estimated death rates for the populations 5-18 years and 19 years and older does include the actual death rate observed after control, but the range estimated for the population aged 0-4 years is too high (as previously mentioned).

In a real use of the model, as pointed out by Rabinovich (J. Rabinovich, personal communication, 26 December 1986), it would be important to carry out a thorough sensitivity analysis to determine how vulnerable the predictions are to sampling or observational errors, such as false positives and false negatives. Since the numbers used here are based partly on bold assumptions, a sensitivity analysis of them is justified only to illustrate the method. Suppose, for example, that the population aged 0-4 years had not 20 per cent never infected (as in line (3)) but 10 per cent, and that 5 per cent had been previously infected (instead of 0 as in line (6)) and 74 per cent were currently infected (instead of 69 per cent as in line (5)). Suppose also that the death rate d_i of the previously infected was 0.012, the same as for the age group 5-18 years in line (11). These assumptions lead to a pre-control death rate $d = 0.183$, slightly below the $d = 0.190$ shown in line (1). The predicted post-control death rates are also slightly lower. The predicted values of d' for lines (19), (20) and (21) become 0.121, 0.108 and 0.103. Thus, even assuming that half of the infants and young children are false negatives does not lower the predicted death rate with complete success as far as the death rate $d' = 0.063$ observed after control.

The present section began with the question of how much useful information the model could give about the

post-control death rate of a population, given only estimates of the model's parameters prior to control and estimates of the planned control efforts. The numerical example given here suggests that the model can do quite well at predicting the post-control death rate, provided the exogenous change in mortality and the effects of the mcp on other causes of mortality in the treated population are known. The change in mortality that would have occurred in the absence of the mcp can be predicted, prior to control, by an independent theory derived from some other source; or it can be measured, after control, in an untreated population whose death rates are known or believed to behave like those of the treated population. For example, routine vital statistics in an ecologically similar country neighbouring the treated country, or in a yet untreated portion of the treated country, might be used to evaluate exogenous mortality. The effects of the mcp on non-malarial sources of mortality seem more difficult to estimate, especially if those causes are likely to interact with malarial mortality. However, without good information about exogenous and non-malarial programme-related changes in mortality, the model presented here cannot be expected to offer much predictive power.

Conclusion

This section sketches alternative approaches to estimating the impact on mortality of mcps. It then reviews some of the strengths and weaknesses of the models proposed here. Finally, it offers some recommendations for the collection and analysis of data in the intersection of malarial epidemiology and demography. These recommendations can be generalized to efforts to predict the mortality impacts of other major diseases.

Alternative approaches

The essential idea of the models proposed here is that a large part of the heterogeneity among individuals in the effects on mortality of mcps can be accounted for by stratifying the individuals into four subpopulations based on prior or present experience with malaria. For example, a chemotherapeutic programme could be expected to reduce the mortality of a malarial fever case substantially, but the mortality of a never-infected person hardly at all. Stratifying to recognize major elements of heterogeneity could be pushed much further, as has already been done by Manton and Stallard (1984) for human mortality data unrelated to malaria.

In the context of malaria control, as pointed out by Molineaux (L. Molineaux, personal communication, 9 December 1986), one could determine the cause, such as malaria and "other", and other characteristics, such as age, sex and residence, in a sample of deaths. From counts of the population at risk in each cross-classified stratum of age, sex and residence, one could estimate cause-specific death rates by stratum. One could assume that malaria and "other" causes act independently within each stratum, and use the Bernoulli-Makeham procedure to estimate the impact of removing malaria, stratum by stratum. Though independence between malaria and "other" causes of death would be assumed within strata, malaria and "other" causes could be correlated overall (this should be considered as spurious correlation).

This approach demands considerably more, and more detailed, data than the models proposed here. Because of the limited number of deaths observed, the data of the Garki project are not likely candidates for this mode of analysis. The idea deserves to be kept in mind if more extensive sets of data become available.

A second alternative approach, as noted by Dietz (K. Dietz, personal communication, 30 December 1986), would be to begin with an existing dynamical model of malarial transmission (e.g., Bailey, 1982; Dietz, 1986) and consider different death rates for different strata of people. Interventions that shift the numbers of people in different strata would lead to changes in death rates. An advantage of this approach is that it offers the possibility of describing the transient effects of mcps. A possible weakness is that estimates of the parameters of such a model may require more data than the approach taken in this paper.

Critique of the model

Not one but a family of models has been proposed: one model for chemotherapy programmes, one for multifaceted programmes and various possible models for eradication programmes (depending on the function chosen for the decay of excess mortality of the previously infected). Since the underlying ideas of all models in this family are very similar, it is convenient in the following critique to speak of "the model", keeping in mind that various forms are possible.

The model proposed and illustrated here has several strengths: extreme simplicity, a foundation in the biology and epidemiology of malaria and a requirement only for variables that can be measured in the field.

Because the model is extremely simple, it is intellectually transparent. It rests on no hidden simulations, no hidden variables, no complex but obscure equations. The assumptions on which the model is based can be clearly identified. These assumptions can be modified or improved as warranted by additional facts or theories.

A second strength of the model is that it attempts to capture the main biological, epidemiological and demographic features of malaria in the field. The strategy of the model, explicit in equation (1), is to stratify the population into demographically more homogeneous subpopulations based on how the individual is affected by malaria. The structure of the model is guided by what is known of how different kinds of mcps affect the various subpopulations.

Third, the variables in the model have clear operational definitions. Almost all of the variables in the model could be measured directly, or estimated with very few inferences, from the raw data of the Garki project. Knowing in advance what variables are of interest, future mcps could measure directly all the variables, with the exception of an exogenous change in mortality, from data routinely gathered by mcps. Even the exogenous change in mortality could be estimated from routinely gathered vital statistics.

The model also has several weaknesses, some of which are rooted in its strengths. It assumes homogeneity

within subpopulations. It assumes that mcps affect only individuals affected by malaria. It ignores seasonality. With the partial exception of the model for an eradication programme, it compares only a static "before" with a static "after", ignoring the duration and dynamics of the transition. It requires more detailed epidemiological and demographic information than is routinely available now. The model for a multifaceted programme does not predict the sizes of the post-control subpopulations of fever cases and currently infected cases.

The extreme simplicity of the model means that many of its assumptions are only approximations to reality. For example, each of the four subpopulations in equation (1) is treated as homogeneous (possibly after age stratification). In fact, the mortality of a fever case may depend strongly on how often or how long the individual has had fever, but the model omits any duration dependence. The mortality of an infected individual without fever depends on the density of infection, that is, the fraction of blood cells parasitized by malaria, but the model omits any density dependence. The mortality of a previously infected individual without fever or parasites may depend strongly on his or her immune titre, but the model omits any dependence of mortality on titre other than an all-or-none classification as positive or negative. The model omits heterogeneity in residence, as an example of an easily measured demographic variable, although an individual living near a rural swamp is exposed to a different intensity of reinfection from an individual living in a city.

The model treats the mortality of the never-infected population as independent of the mcp, though possibly subject to exogenous changes. However, Gramiccia and Hempel (1972, p. 191) mention that, following a malarial eradication programme in Venezuela, Gabaldon found decreased death rates among infants and young children due to diarrhoea and enteritis, "this being probably due, to some extent, to the action of the anti-mosquito insecticide on flies and other contaminating insects". Similarly, antimalarial spraying of DDT in India led to the near-disappearance of kala-azar in India during the 1950s (e.g., Sanyal, 1982). Thus, an mcp could affect the mortality of individuals never infected by malaria. The model omits any such effect.

The model ignores seasonality in the ecology of malaria. The season in which control measures are applied will materially affect their impact on incidence, prevalence and mortality. As presented, the model considers only averages over a year. However, the model could in principle be adapted to deal with one season as the unit of time, at the expense of additional complexity.

Beyond ignoring seasonality, the model ignores the process and impact of the transition from pre- to post-control. It simply assumes a transition from one steady-state ecology to another. It offers little guidance, for example, about how long to wait before measuring the post-control parameters for comparison with the model's predictions.

It is perhaps both a weakness and a strength of the model that the model requires more detailed epidemiological and demographic measurements than are now routinely provided by most demographic systems of vital registration. The model cannot predict the mortality impact of mcps where the required information is lacking. The model fosters no illusions that the mortality impact of mcps can be predicted without the required measurements or estimates.

However, as Horiuchi pointed out (S. Horiuchi, personal communication, 19 December 1986), when partial information is available, it would be sensible to modify the model to profit from it. For example, if a parasitological survey had been carried out but the prevalence of fever cases could not be estimated separately, it would make sense to modify the model to combine the fever and currently infected subpopulations. Similarly, if a serological survey identified all individuals with recent or current malarial exposure, it would be reasonable to simplify the model further by combining the fever, currently infected and previously infected subpopulations. In short, though the model asks for additional data, it should be adapted for use under real conditions.

The model for a multifaceted control programme does not predict the post-control sizes of the subpopulations of fever and currently infected cases. The numerical example based on the Garki project circumvented the need to predict the sizes of these subpopulations by considering a range of possible effects of the mcp (lines (19)-(21) of table 2). For some practical purposes, such a procedure may be sufficient. However, it would be useful to be able to predict the fever and currently infected subpopulations that will result from a multifaceted programme on the basis of mathematical models of malarial transmission (e.g., Gonzalez-Guzman, 1980; Bailey, 1982; Dietz, 1986). The further development of such dynamic models, suggested above as a second alternative approach, is really a necessary complement to the simple models proposed here.

Recommendations

Several recommendations for action follow from this study.

First, it would be informative to analyse the raw Garki data, and existing data from any other studies with the required detail, to see whether the predictions of the model improve or deteriorate when the variables in the model are measured more directly, with a smaller component of conjecture than here.

Secondly, if the results of these analyses are encouraging, it would be informative to test the model further in countries where malaria may be a major cause of death. One would need to record, for each dying person, whether the person was at the time of death feverish, or was known (preferably on the basis of microscopy) to be malarially infected, or had been previously malarially infected. If it is impossible to collect such information on a national scale, it might be possible to collect it in suitably designed samples of deaths. The data collection could be patterned after recent efforts to assess the causes of deaths in Bangladesh (Zimicki, 1986) and Senegal (Garenne and Fontaine, 1986); these efforts rely entirely on non-medical personnel to collect data from

the field. Sample surveys could be used to estimate the prevalence of malarial fever, malarial infection and prior malarial infection. These prevalences, in combination with data on the cause of death, give estimates of the specific death rates and sizes of the subpopulations described by the model. Countries considering mcps could then use the model to try to anticipate the impact of malarial control on death rates. The considerable effort and expense required to use the model would be far less than that required for the Garki project and could largely be absorbed in the planning phase of an anticipated mcp.

Thirdly, if the cumulative experience with the model remains encouraging, the model's simple strategy, namely, stratifying the population into epidemiologically more homogeneous subpopulations, based on the biology of the disease, might be extended to other diseases with a major impact on mortality.

This analysis will remain an idle exercise unless people in the countries affected by malaria use it, improve it and adapt it to their own needs. Able epidemiologists in the countries where malaria is endemic appear to be in short supply. The steering committee of the scientific working group on epidemiology of the Special Programme for Research and Training in Tropical Diseases (sponsored by the United Nations Development Programme, the World Bank and the World Health Organization) described the special problems of epidemiology in the endemic countries (World Health Organization, 1983, pp. 3 and 4) as follows: ". . . of all disciplines needed in public health in the tropical countries, epidemiology is perhaps the most severely neglected. If the tools that are being developed . . . are to be put to use, then the epidemiological [and, I would add, demographic] capabilities of the disease control programmes in endemic countries must be strengthened. . . . a vital function of the epidemiologist in developing countries is often that of obtaining basic data." The future of the ideas in this paper lies with people in the endemic countries who can put the ideas to work and make them evolve.

Notes

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[2] However, measles and other causes of death may not always be complementary as McGregor (1964) reported for measles and malaria; see, for example, Pison and Langaney (1985).

[3] It might be argued that the spraying of households with DDT and other toxic residual insecticides, and the mass administration of potent antimalarial drugs, some with adverse side-effects, open the possibility that a successful mcp might actually raise death rates eventually. The potential benefits so far outweigh the minuscule potential risks of mcps that this theoretical possibility will not receive further analysis here.

[4] When it is possible to distinguish malarial fevers from fevers of other origins, then only malarial fevers should be counted. When this distinction cannot be made, then the clinical definition quoted above from Breman and Campbell (1986) should be followed.

[5] These definitions refine the proposal of Breman and Campbell (1986) that "a patient with probable [fever case] or confirmed [parasitemic case] malaria who dies becomes a death due to malaria". The refinement seems justified by the likelihood that the death rate among fever cases is higher than the death rate among parasitemic cases without fever, and by the probability that these two groups of individuals will be differently affected by different tactical variants of mcps.

[6] An interesting and important question, which I shall not attempt to answer here, is what happens to mortality if a hitherto successful mcp is interrupted. This model is premised on the assumption that the mcp is sustained.

[7] It is interesting to compare the fraction of deaths among children 0-4 years from or with malaria in rural northern Nigeria, according to the figures in table 1, with an estimate of the fraction of infant and child deaths in which acute malaria can be incriminated as the cause of death [Bruce-Chwatt, 1952, p. 198] in Lagos, Nigeria. From lines (1) and (8) of table 1, the fraction of deaths from or with malaria prior to the Garki mcp is $1 - d_0/d = 1 - 0.163/0.190 = 0.14$. Analysing records of autopsies performed on children in Lagos during the years 1933-1950, Bruce-Chwatt (1952, pp. 198-199) identified acute malaria as the cause of death in 9 per cent of infants and 14 per cent of children aged 1-4 years. Considering the differences in origin between the Garki project's population-based data and Bruce-Chwatt's autopsy records, the agreement is remarkable, though possibly coincidental.

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ANNEX

Symbols

Symbols without a prime refer to pre-control conditions. Symbols with a prime (′) refer to post-control conditions.

c	competing risk control coefficient
D	coefficient that describes the decay of excess mortality
d	death rate of the population
d_0	death rate per year of individuals never infected with malaria
d_b	death rate per year of individuals currently infected, without fever
d_f	death rate per year of fever cases
d_i	death rate per year of previously infected individuals
F	factor of exogenous decline in mortality
f(t, n)	decay function for excess mortality of previously infected persons
P	parasite rate = $p_f + p_b$
p_0	proportion of individuals never infected with malaria
p_b	proportion of individuals currently infected, without fever
p_f	proportion of fever cases
p_i	proportion of previously infected individuals
S	spleen rate or sero-positive rate or serum rate = $P + p_i$
s_b	success in reducing the excess mortality of parasitemic cases
s_B	success in reducing the proportion of parasitemic cases
s_f	success in reducing the excess mortality of fever cases
s_F	success in reducing the proportion of fever cases
s_P	success in reducing the parasite rate
t	years after eradication