

*Applied Field Research in Malaria Reports* No. 2

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**Epidemiological Aspects  
of Severe and Complicated Malaria:  
Research Needs**

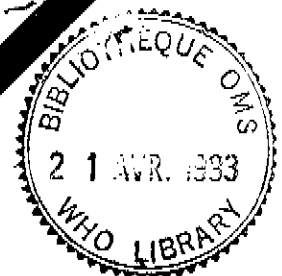
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*UNDP/WORLD BANK/WHO Special Programme for Research and Training in Tropical Diseases (TDR)*



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## FOREWORD

The United Nations Development Programme/World Bank/World Health Organization Special Programme for Research and Training in Tropical Diseases (TDR) held an informal meeting on Severe and Complicated Malaria in Kilifi, Kenya, from 1-4 July 1991.

The objectives of the meeting included presentation of results of completed studies of severe and complicated malaria, and of preliminary findings of studies under way in Kenya, Malawi and The Gambia. Discussions centered around the comparability of these studies and identification of research priorities in severe and complicated malaria. We hope that this paper, finalized at the meeting, will stimulate proposals to be submitted to FIELDMAL for funding.

## INTRODUCTION

Epidemiological approaches to understanding and controlling malaria have traditionally focused on the transmission of parasites by vectors and on the quantitation of parasites in the human population. Improved information on the clinical impact of malaria on communities, and especially information on mortality, is urgently needed for a number of reasons:

- 1) It cannot be assumed that disease and death rates from malaria parallel the rates of parasitaemia, splenomegaly, vectorial capacity or vectorial infectivity. In most areas there are more data on these traditional malariometric indices than on the clinical impact of the infection.
- 2) Interventions may require large expenditures of money and effort: they may need to be targeted on areas or groups with a particularly high risk from malaria.
- 3) Without epidemiological data on malaria-related disease and death, the benefit of an intervention cannot be assessed. In many parts of the world much effort and expense continue to be devoted to antimalarial measures that have not been evaluated for their efficacy in reducing sickness or mortality, because ways of measuring these outcomes have not been developed. Malariometry has been tailored largely to the needs of eradication programmes. In most countries where eradication has not already been achieved, it is not considered to be within immediate reach. There is danger that dogged adherence to established malariometric methodologies may actually work against the development of more appropriate approaches to both control and assessment of the results of control.
- 4) The pattern of malaria transmission is known to vary greatly between geographical areas, but the effects of different transmission patterns on disease and death in the community are very poorly understood.

In considering what questions require more attention we have excluded certain areas; malaria in pregnancy has recently been the subject of a comprehensive internal review (Brabin, 1991). We have not specifically considered the possibility that a proportion of 'malarial' deaths are not due directly to malarial disease but result from a variety of causes to which individuals are made more susceptible by the ill understood 'immunosuppressive' effects of parasitization. This is an important area of investigation, but clear answers are only likely to be obtained from large scale effective interventions requiring the development of some of the approaches discussed below. We have restricted ourselves to the severe clinical manifestations of malaria and have identified the following areas as requiring either more emphasis or new approaches:

- 1) The clinical features and natural history of malarial disease, particularly in children in endemic areas. Accurate information is essential for the development of appropriate case definitions for epidemiological studies.
- 2) Quantitation of the load of severe malaria and mortality; how many deaths are caused by malaria, and how are these deaths distributed among population age groups, geographical areas and seasons? New methods are needed both for research purposes and for operational purposes as part of control programmes.
- 3) The factors which determine the clinical severity of an episode of parasitization; why do only a minority of infected individuals develop life-threatening diseases? (Greenwood, Marsh and Snow, 1991).

## 1. PATTERNS OF CLINICAL DISEASE

Although studies in Thailand and elsewhere have provided a good picture of the disease in adults, there is a relative paucity of information on the clinical features and natural history of severe malaria in children, despite the fact that worldwide they bear the brunt of morbidity and mortality. Severe clinical disease in children exhibits a number of important differences compared with adults, including the relative rarity of certain features such as renal failure and pulmonary oedema, and important differences in patterns of recovery from cerebral malaria (WHO, 1990). There has been a tendency to concentrate exclusively on cerebral malaria, which is the most obvious dramatic manifestation of severity, however it is likely that other clinical syndromes are also important. In particular, although severe anaemia in endemic areas is often multifactorial in origin, there is nonetheless a clear impression of a distinct syndrome of acute severe malarial anaemia, probably with a different age susceptibility than cerebral malaria. The importance of malarial anaemia as a contributor to mortality in the community may be underestimated because it has a relatively lower case fatality compared with cerebral malaria in hospital settings. Furthermore, the clinical importance of severe anaemia in hospital has increased because of the risks of transmission of HIV by transfusion.

It is important that information on clinical patterns of severe malaria is available from a wide range of endemic settings and research is needed into possible means of obtaining such information through routine health care facilities, in addition to the few specialized clinical research units.

There have been several recent attempts to draw up criteria of severe malarial disease in children. Clearly, researchers should use defined criteria but caution must be exercised on several counts. Firstly, such criteria are at best based on extrapolations from limited experience in a small range of endemic settings. Secondly, the concept of 'severity' has a number of different legitimate meanings for researchers.

- 1) An aetiological concept - where the underlying hypothesis is that there are distinct pathological entities, such as cerebral malaria, which must be clearly separated from non-cerebral malaria.
- 2) A prognostic concept in which severe disease would be defined as those episodes which had greater than an (arbitrary) chance of leading to death. Such approaches have been heavily influenced by the need to identify bad prognostic groups, even under optimum treatment in hospital. They thus exclude subjects who do well in this setting, but who may have had a very poor prognosis outside hospital.
- 3) Severity may be defined in terms of load on the health care system, thus under this definition anyone who requires in-patient treatment for malaria is part of the problem.

Any single definition of severe malaria in children is therefore unlikely to be appropriate to every study. Nevertheless it is essential that the results of research findings by different groups can be related to each other. All who conduct research in this field should make clear the definitions they are using, and should present results in such a way that comparisons with the results of others can be made.

The following guidelines have been designed to help in the preparation of definitions for groups embarking on research in this field.

#### Clinical Categories of Malaria:

- a) 'Not malaria': absence of parasites from a specified number of oil-immersion fields on the thick blood film. 100 fields is commonly stipulated. In suggestive clinical circumstances, several negative results on samples taken at intervals may be required. In patients with fatal illness, negative autopsy results should be included if possible.
- b) 'Asymptomatic infection': parasites are present in the blood film, but the person is 'well'. Clarification of the latter term is necessary, and should include whether (and which) symptoms are to be actively inquired after, and what preceding interval should be taken as relevant. Objective assessments such as ability to attend school/work and the person's body temperature should be used whenever possible.
- c) 'Uncomplicated malaria': the patient has suggestive symptoms and/or fever (axillary temperature  $> 37.5$  C), with asexual *P. falciparum* parasitaemia at a density above a level chosen for the context of the study. In tropical Africa this minimum density will generally be between 1,000 and 10,000 parasites per ul, being at the higher end of this range in areas with most intense transmission; a figure should be chosen with the help of background information on the distribution of parasitaemia in the population in the area and season to be studied. There should not be another obvious cause of the symptoms or fever.
- d) 'Severe or complicated malaria': [Some or all of the following characteristics may be chosen as criteria for a particular study. Whichever defining characteristics are chosen, all of the following should be assessed and recorded, so that comparisons with the work of other research groups can be made ]: *P. falciparum* parasitaemia with any one of the following, in the absence of a non-malarial explanation for the clinical condition:

- **cerebral malaria**, i.e. loss of consciousness (Blantyre coma score 0-2) [exclude transient coma following a convulsion, or coma that is promptly reversed by treatment with glucose in a hypoglycaemic patient]

- **severe anaemia**, i.e. haemoglobin concentration = /  $< 5$ g/l, when other causes of anaemia have been excluded by stipulated methods. A minimum density of parasitaemia should be chosen to 'fulfil the definition of malarial anaemia' - e.g. 1,000 asexual parasites/ul (usually less than the density specified in the definition of uncomplicated malaria)

- **prostration**: the child, although old enough to sit, is too sick do to so without help

- **convulsions**: the current WHO guidelines stipulate three or more in a 24 hour period. Some current studies use a definition of two or more. The definition chosen should be clearly stated.

- acute renal failure
- pulmonary oedema/respiratory distress syndrome
- shock
- spontaneous or prolonged haemorrhage

Features which are important to record, but which may not define the clinical severity of malaria in the absence of any of the above features include:

- jaundice
- intravascular haemolysis
- hypoglycaemia
- density of parasitaemia

**Unexpected death** in a patient with apparently uncomplicated malaria, or death in any individual in whom malaria (sequestered parasitized red cells) is the only significant finding at autopsy, should be included in the definition when possible.

## 2. QUANTITATION OF SEVERE MORBIDITY AND MORTALITY

The pattern of malaria-related mortality differs between geographical settings. Quantification of these differences requires studies in a number of sites using standardized methods so that results can be compared. Two approaches are discussed below in sections (a) community mortality determined by verbal post-mortem techniques and, b) data collection from existing health facilities. The first method of assessment is more comprehensive but it is time-consuming and expensive and despite increasingly widespread use there remains major problems of validation; it is therefore probably best applied in a limited number of specific areas in programmes which are capable of tackling the inherent methodological issues. Health unit diagnoses are likely to be more reliable, and in some areas the majority of deaths occur there (53% of childhood deaths in a study in Papua New Guinea (Moir *et al.*, 1988)); on the other hand in some communities most deaths occur at home (90% paediatric malaria-related deaths in a study in The Gambia (Greenwood *et al.*, 1987)). Research is required in both areas to solve methodological problems and assess their use for quantitating clinical malaria.

### (a) Estimation of malaria mortality in a community by the use of verbal autopsy techniques

The approach requires the accurate enumeration of a large population and a system of recording all deaths in the age range of interest. Families are then visited and interviewed using a standardized questionnaire and the death is ascribed to a diagnostic category. Questionnaires have been used to record cause-specific mortality in number of studies; (reviewed in Report on a Workshop on the Verbal Autopsy, 1989 (Gray, Smith and Barass, 1990)). The application of verbal autopsy methods specifically to malaria has been described in two papers (Greenwood *et al.*, 1987 and Moir *et al.*, 1989).

Before any study using the VA technique is undertaken, the limitations of the method should be considered (Snow and Marsh, 1992).

i) The sensitivity, specificity and positive predictive value of a VA may be different for different causes of death. All may be high for trauma, neonatal tetanus, measles and malnutrition, i.e. conditions with characteristic symptom-complexes, but the VA may perform less well with conditions which exhibit overlapping symptom complexes, such as severe anaemia and respiratory tract infections. Deaths from cerebral malaria may not be distinguishable from those due to meningitis or viral encephalitis. Preliminary validation of a VA, by initial assessment in hospital, may help to maximize its value and quantify its limitations. The hospital-based mortality data so derived will also help to indicate the relative contributions of different disease to in-patient mortality, but this cannot be assumed to be the same in the community. A VA study in the community may not give precise figures for actual causes of death, but at least may allow death to be classified by symptom complex and thus allow estimates of minimum possible incidences for each cause, which may be valuable for comparison between places or times.

ii) Local vernacular terms for disease or symptoms must be studied before a VA can be properly planned or interpreted.

iii) Preliminary assessment of VA's should include clinical features characteristic of particular causes of death, the ability of parents to recognize and describe those features, the terms they use for such descriptions, and their ability to recollect features at appropriate intervals after the event. Visual aids (photographs, films) can be helpful in teaching interviewers or in eliciting information from relatives; such methods must be evaluated in the context of a particular study.

iv) Hospitals may be the only suitable sites for the preliminary validating of VA's (i.e., for comparing mother's responses to known diagnoses); but the pattern of mortality and the composition of the population in hospital may differ from those in the community.

v) Death rates only have meaning in the context of the known size and age-structure of the population within which they occur. Information about this denominator population should be sought from all possible sources. Official census in some countries are exhaustively and accurately carried out, and reported data should be made full use of. Additional information may be obtained from indirect demographic techniques, from local authorities, or even from aerial photographs showing the number and distribution of houses in an area. It can be valuable to gather information from several sources and compare the figures obtained.

Community-based estimates of malaria-specific mortality should be performed in the context of studies into deaths due to causes over a specified time in a defined population because, (i) the size of the malaria problem can be seen in relation to that of other diseases, (ARI, diarrhoeal disease, etc.); (ii) classification by cause of death is more likely to be accurate if other possible causes are considered; (iii) when the

technique is used to assess the consequences of intervention against malaria, the contribution of malaria to deaths from other causes may come to light, and (iv) knowing cause-specific mortality will be of value to the health services in disciplines other than malaria.

### Study Sites

Existing data suggest that there are differences in the patterns of malaria-related mortality between geographical areas, probably in relation to the intensity of transmission. It would be valuable to obtain data from sites with different transmission patterns.

### Age Selection

In some areas it may be desirable to record deaths throughout all age groups of the population. This is particularly necessary in areas where the impact of malaria is not known. Elsewhere, a study may be targeted at a particular age group if it is already known that most malaria deaths occur in that group (e.g., young children in highly endemic areas).

Different categories of certainty with which death may be attributed to malaria may be used in a verbal autopsy study; e.g., 'definite malaria', 'probable malaria' (Moir *et al.*, 1988), but it is essential that studies taking place in different locations make their criteria explicit so that data can be compared and pooled for analysis.

### Duration

Since the incidence of malaria deaths may vary with season, and between seasons, any study of this kind should cover a period of at least two years. Since setting up such a system involves a large amount of work, it is desirable that there be a long-term intention to monitor the population. It is also important that overall and cause-specific mortality rates obtained be compared with the results of other available methods, such as civil registration, and particularly with hospital based monitoring (see section 6).

### Making Use of Other Programmes

Before embarking on a community mortality study, it is important to identify whether any comparable studies are in progress or are planned, either by demographers (outside the health service), or by investigators studying mortality due to other diseases (e.g., ARI, AIDS, diarrhoeal diseases). Such projects might be utilized through introduction of suitable slight changes, to provide information on deaths due to malaria.

### Relation to Health Service Data

When possible, it is advisable to combine verbal autopsy studies with analysis of records from local clinics and hospitals. This will indicate how representative these institutions are of the community as a whole and allow approximate estimates of community deaths to be made on the basis of hospital data (see (b)).

## Population Data Needed

In association with a verbal autopsy based study of malarial mortality, it would be valuable to have other information about the population studied; e.g., use of antimalarial drugs (which ones - when), quantities of antimalarial drugs consumed (based on health service and private sector distribution data), and indices of the intensity of malaria transmission-parasite rates, vector information, etc.

## Retrospective Verbal Autopsy Studies

It may be that an abbreviated retrospective verbal autopsy study could be a cheaper way of providing some, albeit less comprehensive and less reliable, data on mortality. By this method a team makes a single visit to all individuals and households in a defined area and inquires about deaths over a specified preceding interval. It may be worth assessing the validity of data on malaria mortality obtained in this way in an area where hospital attendance and records are comprehensive and can be used as a basis for comparison.

## Advice on Study Design

In some areas verbal autopsy techniques may appear to be the only feasible way to obtain some of the most important community data needed for an adequate assessment of the impact of malaria or the impact of an intervention. However, it is important to avoid the uncritical adoption of a technique which may be complex and expensive and which still has major limitations (Snow and Marsh, 1992).

Because of this and the need for studies which can be compared with one another, it may be appropriate for TDR to arrange for a visit to the proposed site by an individual with experience in projects of this kind. It may also be valuable for investigators to travel to and participate in an existing study in order to learn methods and pitfalls.

### **(b) The use of health facilities to collect clinical and epidemiological data on severe malaria**

The aim of malaria control activities is the reduction of morbidity and mortality due to malaria. Rational planning and assessment of control programmes requires quantitative data on the incidence of severe disease and deaths. The collection of such data is fraught with difficulties - in the areas where the malaria problem is worst, problems of case definition and incomplete coverage are likely to be most pronounced. This is apparent in Africa where, with the exception of a few specialized research programmes, few accurate data are available. It is clearly important for this problem to be addressed using rigorous methodologies in a number of epidemiological settings, and possible approaches using verbal post mortem questionnaires in closely monitored large populations are discussed above. However, such approaches are demanding and expensive; they are appropriate for special projects, but could not form the basis of routine data collection.

At present, the only obvious sources of data on severe disease and deaths are secondary and tertiary level health facilities. The main objection to developing a monitoring system based on such facilities is that in many cases only a small (and unknown) proportion of total cases even enter the system and this is compounded by difficulties with verifying diagnostic accuracy. These present major problems, and it is clear that, except in countries with highly developed health-care systems, a hospital based monitoring system could not provide definitive rates. However, it may be possible to develop simple systems for data collection which provide useful comparative information and which may, with the application of crude correction factors, be used to estimate rates of severe disease and malarial deaths which are considerably more accurate than those presently available (Greenberg, Ntumbanzondo, Nutula *et al.*, 1989). Such a system could also be used as a base from which more extensive data collection systems could be developed. The availability of semi-quantitative species-specific DNA probes offer the prospect of retrospective quality control of diagnostic categories, if such a system were to be instituted at multiple 'sentinel' sites. Similarly, recently developed techniques suitable for handling numbers of specimens stored on filter paper, would enable the same approach to be taken to monitoring anti-malarial drug usage.

The essential aim of such a system would be the collection of data on severe disease and deaths from defined populations. Development of methods will need to concentrate on two areas in particular: the definition of populations served by 'sentinel' sites, and the improvement and standardization of simple ways of classifying severe malarial disease.

#### (1) Definition of populations

When the number of cases of severe malaria seen at two hospitals differs, it may be because one area has a bigger 'malaria' problem, alternatively, it may simply be that the hospitals differ in their true drainage populations. It is therefore necessary to estimate a population denominator. Although many factors affect health care utilization, it is probably a reasonable assumption that in the case of a life threatening disease the chances of seeking hospital treatment remain fairly constant for quite a distance away from the hospital, and then decline. With an estimate of population distribution in the area served by the hospital (from available census data or from rapid demographic techniques, aerial surveys, etc.) and a record of place of origin of in-patient malarial cases, it should be possible to define the geographical limits for a population within which the utilization of the hospital for severe disease is reasonably constant. Hospital based morbidity and mortality records would then be collected for this population and rates derived.

Such data would have two main uses; (1) within year and between year comparisons, to provide information on the seasonality of severe disease and to act as an indicator of worsening in the malaria situation, or of the effect of changes in control measures in the area; (2) to provide 'minimum' rates for the population. The usefulness of minimal malaria-specific mortality rates for comparison with other areas will be enhanced if in addition one can estimate the proportions of deaths occurring outside hospital. It may be possible to do this by interviewing a random sample of mothers from the monitored population and determining the place of death for all deceased children.

Although not all causes of death necessarily have the same community/hospital distribution, it may even be possible to estimate this factor specifically for malaria if a question is asked concerning deaths in which convulsions were a feature of the final disease. Such estimates could be used to correct the 'minimal' rates obtained from hospital based monitoring.

## (2) Improving accuracy of data collection

At present the usual source of diagnoses is hospital record books. Any attempt to collect more information must be designed to impose minimal requirements on busy health care personnel, therefore any data collection must concentrate on essential information. This might include (1) age, (2) sex, (3) results of blood slide, (4) main clinical features (fitting/severe anaemia/other), (5) was the child transfused?, (6) drug and route used for hospital treatment, (7) outcome (died or discharged).

If, in addition, a single blood sample was taken at the time of admission, techniques now exist which would allow retrospective quality control with acceptable accuracy for semi-quantitative detection of malaria parasites and, in addition, the measurement of levels of antimalarial drugs on samples stored on filter paper (these could be performed in large batches at a centralized facility).

Issues which need to be addressed include who would collect the information and the actual format (e.g. record books, special case notes, direct recording on hand held computers). Such issues are probably best tackled in the context of operational research into the broader issue of improving health facility information systems for all disease. Even such a relatively simple set of investigations as described above would require a considerable input to maintain the accuracy of data collection. However, if such a system proved feasible it would provide information on:

- a) the pattern (age, sex, clinical features, seasonal variation and outcome) of severe malaria from a defined population
- b) the calculation of minimal rates for severe disease and malarial death in that population and relative changes in these rates with time (and therefore an assessment of any antimalarial interventions applied in the population)
- c) with a limited demographic extra input (estimation of proportions of deaths occurring at home and in hospital), corrected rates for severe disease and mortality
- d) with the extra input of a single blood sample, checking of diagnosis and information on usage and changes in usage of antimalarial drugs and relationship to clinical outcome.

Clearly there would be many inaccuracies and uncertainties in the approaches outlined, nonetheless for large areas of the world cases reaching health centres are the only possible source of information on severe disease and thus attempts to develop even crude monitoring systems should be supported. There will be areas where the approach could not work, but in other areas it is possible to imagine that from a network of selected health centres producing approximate rates for known population denominators it would be possible to derive estimates which would be of acceptable accuracy for planning purposes.

### 3. FACTORS DETERMINING THE SEVERITY OF OUTCOME OF INFECTION

Within malaria endemic areas at any one time the majority of non immune subjects (young children) are parasitized asymptotically. Even in less stable areas, such as large parts of South-East Asia, only a minority of clinical cases in children and adults develop severe and complicated malaria. There must therefore be factors connected with the circumstances of a particular infective episode that influence the progression from parasitization to severe, life-threatening disease. Such factors may be host, parasite or vector-related and their identification and means of interaction are relevant to both immediate control strategies and the development of new methods for treatment and prevention of severe disease (Greenwood, Marsh and Snow, 1991).

#### Study Designs

These questions could be approached using a number of study designs, all of which have advantages and disadvantages. Longitudinal cohort studies in most areas would need to be extremely large in order to generate enough cases of severe malaria and the monitoring of a cohort should in itself reduce the chances of severe malaria and death. However, there may be a role for such prospective studies to test particular hypotheses generated in other studies (for instance, if there is evidence that a particular host characteristic is important, it may be possible to screen a large population and to form cohorts of individuals with that characteristic and ones without it). Case-control studies of severe malaria provide a means of generating large numbers of cases and avoid some of the ethical problems of cohort studies but they have limitations, they are unsuitable for examining the effects of certain factors (for instance, immune status or factors which in themselves are changed by the episode of illness, or short acting effects preceding entry to hospital). They are best regarded as a means of generating hypotheses to be tested in other studies.

Currently comprehensive case-control approaches are being taken in two centres in Africa. It is important that these studies should be linked up as soon as possible in order that data collection be standardized to increase the power of the studies. Given the unavoidable shortcomings of the method and the expense of case studies, it should not be a high priority to commission further large scale comprehensive case-control studies until initial analysis is carried out on those already running. However, it is appropriate to support attempts to apply a case-control approach (or other approaches) to specific hypotheses, especially those with direct relevance to control, most importantly hypotheses regarding behaviour such as the effect of drug usage in the community prior to becoming ill.

#### Hypotheses which could be tested in Field Studies

An understanding of why a minority of individuals suffer from severe disease is important not only for immediate planning of control, but to guide the application of basic science approaches to the development of new drugs and of vaccines. In addition to important behavioural factors such as drug usage and other treatment seeking behaviour, there are a limited number of possible mechanisms for which there is sufficient theoretical or experimental evidence to allow the construction of testable hypotheses.

a) The dose of sporozoite delivered may be important in determining the severity of infection. This hypothesis would place importance on the total body load of parasites and the speed at which it builds up. It requires that the load of parasites inoculated per unit time vary over an appreciable range under natural conditions. This idea is attractive on theoretical grounds and has some support from experimental evidence and important implications for control. Developing methods to test this hypothesis in the field is likely to be extremely difficult, but well thought out attempts to assess the contribution of vectorial factors to disease severity (as distinct from parasite transmission) deserve support.

b) Cytoadherence of infected erythrocytes. The sequestration of infected erythrocytes by means of attachment to the endothelium of deep vascular beds appears to be a central pathogenic event in severe malaria. There is now evidence that *P. falciparum* may use a range of possible endothelial receptors (thrombospondin, CD36, intracellular adhesion molecule I-ICAM I) and that parasites exhibit marked diversity in their ability to attach to different receptors. It is thus possible that clinical outcome of infection depends on particular combinations of characteristics which are polymorphic in both host and parasite. It is not known how widely humans vary in the expression of the different putative receptors on endothelium at different sites, including the brain, and attempts to explore this in post-mortem studies should be carried out in areas where this is culturally acceptable.

c) The role of cytokines induced by malaria infection. There is increasing evidence that the release of cytokines mediators, particularly Tumor Necrosis Factor (TNF) may play an important role in the pathogenesis of severe disease. High levels of TNF have been strongly associated with death in studies at several different sites. Such mediators may act directly but could also be implicated in infected erythrocyte cytoadherence as they have been shown to up-regulate expression of at least one of the putative endothelial receptor molecules.

An important area of research will be to determine whether and how individuals vary in their tendency to produce cytokines in response to malaria infectious and in their susceptibility to released cytokines.

In the case of the hypotheses outlined above (and of others which may arise) it is not considered appropriate to go further into methodological issues in this document, but it is important to recognize that in many instances the generation and testing of hypotheses concerning susceptibility, protection from and mechanisms of severe malaria requires the interaction between workers applying basic science approaches to cell biology, genetics, etc., and groups capable of testing hypotheses in the field.

An important component of such interactions will be the development of methodologies from a stage suitable for experimental use to the point where they can be applied to larger numbers of samples under field laboratory conditions. The difficulties in making this transition are often underestimated, leading to inappropriate study design.

## Summary of Recommendations

In this discussion document we have considered epidemiological aspects of severe malaria with an emphasis on identifying gaps in our knowledge which should be addressed in field based research. We consider that the following points deserve emphasis.

- (1) The major gap in our knowledge is the almost complete absence of accurate data on malarial morbidity and mortality for large areas of the endemic world. A necessary consequence is that the relationship between the level of transmission and the resulting health burden of malaria is not known. Emphasis must be placed on the development of appropriate methods to collect and use such information and their application in a variety of 'ecological' settings.
- (2) Definition of malarial morbidity and mortality are required for epidemiological studies. These should be based on the clinical picture of malaria in the setting where the study takes place and should be appropriate to the resources available. Whenever possible, data should be collected in a form which will allow comparison with other studies.
- (3) Further research is required on the use of verbal autopsy techniques in measuring malarial mortality in different settings. Investigators using these techniques should be aware of their inherent limitations.
- (4) Research into means of improving and using data available from existing health facilities should have a high priority.
- (5) It needs to be recognized that the quantification of malarial impact, (3) and (4) above, will usually best be done in the context of broader cross disease approaches and the implications for funding such research should be considered.
- (6) Further support for epidemiological studies to determine risk factors for severe malaria are justified, but an emphasis should be placed on those who have implications for manipulation and are thus relevant to the development of new therapeutics or control strategies.

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## MEETING ON SEVERE AND COMPLICATED MALARIA

1-4 July 1991

Kilifi, Kenya

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