

When Is “Malaria” Malaria? The Different Burdens of Malaria Infection, Malaria Disease, and Malaria-Like Illnesses

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Abstract. In this review we discuss the different meanings of the term ‘malaria’ and urge writers and readers to distinguish accurately between them. The distinction is important in clinical practice, clinical trials, epidemiology, and the evaluation of control programs. Both over- and under-diagnosis of malaria as the cause of a disease episode are inevitable; over-diagnosis is common in high-transmission areas and underdiagnosis is common in areas with little or no transmission. Parasite density thresholds, attributable fractions, and clinical algorithms have played important but only partial roles in strengthening diagnosis. Methods by which malaria infection could be confidently identified as the cause, rather than an irrelevant accompaniment, of an illness, are important targets for research. One such ‘signature’ is a distinctive retinopathy that occurs in severe malaria and not in clinically similar diseases. Other indicators of a malarial etiology of clinical disease are needed to strengthen clinical and scientific approaches to the control of malaria.

DEFINITIONS

The word ‘malaria’ has varieties of meaning that can be misleading if not carefully distinguished:

1. *Malaria* in an individual is **an illness or disease** that is due to parasites of the genus *Plasmodium* in the blood or tissues
2. *Malaria* is a generic term often used for protozoa of the genus *Plasmodium*, usually as part of the compound term ‘malaria parasites’. *Malaria transmission* is a phrase utilizing this definition (malaria parasites are transmitted, malaria disease is not). The presence of parasites of any stage, in any part of the human body indicates the presence of malarial **infection**, which may or may not be causing disease.
3. *Malaria* is a **public health problem** afflicting a community, and consisting of the combined effects of the infection on the population as a whole.

Each of these can be measured or counted in various situations, when it is essential to be aware of what is being reported. The statement “> 50% of children in primary schools had malaria on the day of the survey” probably refers to definition 2 rather than definition 1, whereas “malaria diminishes productivity” refers to definition 3 and is a statement that cannot be quantified simply by measuring the sum of 1 and 2.

The measurement of each of these varieties of malaria is susceptible to error:

1. None of the many forms of illness that can result from plasmodial infection is distinctive: all can be accurately mimicked by other microbial or non-infectious diseases. The presence of parasites in the blood provides no proof of causality because people in high-transmission areas learn to tolerate parasitemia, many without illness are para-

sitemic, and parasites accompanying an illness may be passengers, not agents of the disease.

2. The sensitivity of common methods of detecting parasitemia is such that low but important densities of parasitemia can be missed, even by a competent microscopist, especially in the non-immune and in young children (who are at greatest risk of severe disease if infected).
3. Several studies suggest that public health consequences of plasmodial infections are greater than can be predicted by counting recognizable illnesses or parasitemias (i.e., that there are indirect consequences for health [anemia, malnutrition and the risk of other infections being fatal] that can be recognized only by the improvements that follow when the parasite life-cycle has been interrupted).^{1,2}

WHEN ACCURATE MEASUREMENT IS IMPORTANT

An erroneous identification of malaria illness or infection can have costly or dangerous consequences. Accurate recognition is particularly important:

1. In the management of an individual patient, when incorrect diagnosis can result either in failure to treat a potentially dangerous malarial illness, or failure to seek and treat an alternative cause of the illness
2. In enrolling “cases” to a study of pathogenesis or therapy, when false diagnoses may mask important results or bring up spurious ones
3. In identifying endpoints in preventive or therapeutic intervention trials
4. In documenting the extent of the public health problem (“the burden of malaria”) and how this changes over time, when properly identified trends may indicate the need for new efforts or the success of existing ones.

Misdiagnosis of malaria is common both in the identification of uncomplicated disease (the febrile illness) and in the diagnosis of severe or complicated malaria. Both underdiagnosis and over-diagnosis may occur. The implications of this inaccuracy depend upon whether diagnosis is being used for clinical or for research purposes.

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THE OVERDIAGNOSIS OF MALARIAL ILLNESS

Malaria as an illness may be overdiagnosed (a) when a disease episode is presumed to be due to plasmodial infection without any attempt to identify parasites in the individual's blood, (b) when parasites are looked for but not found, yet because of the possibility of an undetectable but dangerous infection being present, treatment is deemed to be advisable, and (c) when parasitemia is correctly identified but wrongly assumed to be the cause of the illness (Figure 1). Each of these may be unavoidable or even necessary strategies in many circumstances; however, when they are used, it is important for the implications to be recognized.

Presumptive diagnosis of uncomplicated malaria. The World Health Organization (WHO) advises presumptive diagnosis as the basis for first-line treatment of uncomplicated malaria in places where a parasitological test is not possible. This policy allows uncomplicated malarial illnesses to be treated by village health workers, shopkeepers, or relatives in the home, and thus minimizes delays in treatment, especially for those living a long way from formal health facilities. Several investigators have measured the extent to which this policy leads to overdiagnosis of malaria as the cause of illness. Amexo and colleagues collected 24 such studies; among subjects with clinically diagnosed malarial illness, the percentage with a negative blood film ranged from 32–93%. The mean in 24 studies was 61%.³

To conclude that the film-negative patients with febrile illness in these studies were misdiagnosed as malaria involves several assumptions: (1) that a negative blood film excludes malaria as a cause of illness—in populations living in areas of intense transmission, this assumption will nearly always be correct; (2) that the blood film has been competently made, stained and interpreted—27% of negative malaria films in one hospital study in Tanzania were judged on subsequent quality-checking to have actually been positive⁴; and (3) that some subjects had not been rendered aparasitemic by an antimalarial drug a day or two before the blood sample was taken. Despite these caveats, it is undoubtedly the case that a large proportion of individuals presumptively diagnosed and treated as malaria are not suffering from malaria.

Where many in the population are parasitemic, overdiagnosis of malarial illness may be considerably greater than indicated by the proportion of clinically diagnosed subjects who are film-negative, because many of those who are film-positive may also have another cause of illness, their parasitemia being “incidental” (Figure 1).

Does presumptive treatment and overdiagnosis of uncomplicated malaria matter? The WHO recommendation is based on the balance of benefit over hazard. The benefits of basing treatment on presumptive diagnosis include promptness of therapy (and therefore hopefully reduced risk of progression to severe malaria); reduced cost in time and money for the patient or guardian/s to attend a formal health outlet; lack of expenditure on diagnostic facilities and on the maintenance of reagents and skilled staff to provide these; and equity in the availability of treatment of all levels of society. The drawbacks include costs of supplying more drugs than are actually needed for the management of malaria; over-exposure of the population to risks of drug toxicity; likelihood of inaccurate dosing, including the use of sub-therapeutic treatments that may favor the evolution or spread of drug resistance; neglect

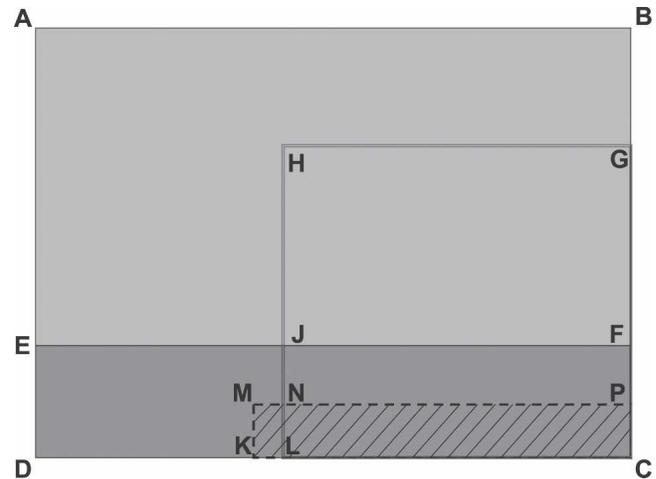


FIGURE 1. The whole box ABCD represents the population living in a malaria-endemic area. The hatched area MPCK represents people who are suffering from illness due to malaria. EFCD (darker gray area) = people with febrile illness. These will be treated for malaria on the basis of a ‘presumptive diagnosis’ policy, whether applied at home or at a health facility HGCL (square box) = people who are *P. falciparum* parasitemic—these have *P. falciparum* infection but only some (NPCL) are ill because of it. JFCL = people with fever and parasitaemia—these will be treated as malaria if laboratory diagnosis is available, although not all are sick because of malaria. HGFJ = asymptomatic parasitaemia—these will be included (with JFCL) in the count of malaria infections in cross-sectional surveys. JFPN = parasitaemic and febrile, but fever has another cause. MNLK = malarial illness with negative blood film—uncommon, may be due to very low parasite density (likeliest in the non-immune) or to incorrect laboratory technique

of alternative diagnoses; distrust of antimalarial drugs if incorrect diagnosis commonly leads to apparent treatment failure; inaccurate or absent documentation for clinical or epidemiologic monitoring purposes. The balance of benefit versus hazard for presumptive diagnosis may shift if first-line drugs become more expensive or toxic, if their availability is limited, or if their regimen is too complex for likely adherence.

The equivalent of “presumptive diagnosis” may occur in hospitals admitting patients with suspected severe malaria, if the results of blood films are ignored. In a hospital study in Tanzania, Makani and colleagues reported that of 76 adults admitted with a diagnosis of “cerebral malaria,” 70 (92%) had a negative blood film.⁵ Because this is an endemic area, it is likely that few, if any, of these individuals were suffering from malaria (with a parasitemia density too low to be detected by microscopy—or low enough to be missed by a hurried microscopist). It is also possible that some of the patients in this study who were parasitemic were also suffering from non-malarial diseases because the prevalence of parasitemia among the patients was no different from that among local healthy controls.

Autopsy studies have demonstrated that, even when existing WHO criteria of severe malaria, including parasitemia, are fulfilled, a proportion of patients (7/28 in a study in Malawian children) actually have an alternative explanation of their disease.⁶ In a study of Malawian children with clinically diagnosed cerebral malaria, a number of patients had evidence of a viral encephalopathy when this was extensively sought [Mallewa, personal communication].

THE UNDERDIAGNOSIS OF MALARIAL ILLNESS

Underdiagnosis of malarial illness in an endemic area is more commonly the result of failure on the part of the patient to reach a health facility than the result of clinical assessment when at a health facility. In some communities a large majority of those suffering from malarial infection and disease do not come to formal health facilities and are therefore not counted.⁷ The size of this hidden burden of both uncomplicated and severe malaria is unknown.

Underdiagnosis is also a problem in non-malarious countries, when either the individual or the health professional may fail to consider the possibility of malaria.⁸ Occasionally a non-immune adult may present with a complication (e.g., acute renal failure, severe anemia, coma), and the malarial etiology may not be suspected.

MALARIA-ATTRIBUTABLE FRACTIONS AND THRESHOLD PARASITE DENSITIES

In a population of whom a large proportion are parasitemic but not ill, it is usually found that the likelihood of being ill increases with the density of parasitemia. This observation has led to many attempts to identify a threshold level of density of peripheral parasitemia that makes it likely that malaria is the cause of a fever. This figure is usually arrived at by cross-sectional population studies documenting fever and parasitemia in large numbers of people. Individuals are then stratified by their parasite density. The percentage of febrile individuals within each stratum of parasite density allows calculation of the sensitivity and specificity of each parasite density range as a predictor of fever. The malaria attributable fraction (MAF) is then the proportion of fevers in a particular group of people that are associated with a parasite density above the threshold (or the excess risk of fever associated with a parasite density above that level). The calculations can be refined by use of logistic regression, which may be modified to allow for non-continuity between negative and positive blood films.^{9,10}

Threshold density and MAF differ according to the prevalence of parasitemia in a population and with the associated degree of immunity in that population, factors that are affected by transmission intensity therefore varying with location,^{11,12} season,^{13,14} and altitude,¹⁵ by age (both immunity to parasites and tolerance of parasites increase with age)^{16,17} and by numerous behavioral factors including the use of drugs, bed nets, and environmental control. This diversity has led investigators to emphasize that threshold parasite densities and MAF for any population must be calculated on locally and currently derived data.¹¹ Others have challenged the use of a single blood film for calculating threshold density or MAF; in a single untreated individual, the density of peripheral parasitemia may vary by up to 100-fold within 6 h, and may fluctuate widely between times of the day and between days.¹⁸ These investigators questioned the value of estimating thresholds and MAF at all, and emphasized the need to combine many other elements in attempting to arrive at a diagnosis of malarial illness. This is particularly true for the diagnosis and clinical management of individuals, but threshold densities and MAF remain important tools for epidemiologic studies, provided that their limitations are recognized.

CLINICAL ALGORITHMS

Numerous attempts have been made to characterize both uncomplicated and complicated malaria disease by clinical features, to permit syndromic diagnosis. Most such attempts have arrived at algorithms that are poor in sensitivity, specificity, or both. This is presumably because many components of the malarial illness are mediated by host mechanisms that are common to diverse infections. The periodicity of fever that is used to characterize malaria in classic descriptions is inconspicuous early in the disease, especially in the case of *P. falciparum* infections. Malaria and acute respiratory infections are particularly difficult to distinguish by clinical features,^{19,20} and up to 30% of febrile children fulfill IMCI diagnostic criteria for both malaria and ARI.²¹ Algorithms have performed poorly in both high- and low-transmission areas.^{22–24}

MALARIA “SIGNATURES”

In view of the difficulty of knowing whether a parasitemia is indicative of the malarial etiology of an illness (Figure 2), and in view of the non-specificity of clinical syndromes, other indicators that an illness is due to malaria would be helpful both to clinicians and to epidemiologists. However, it has not been possible to establish conclusively which indicators are predictive of malaria illness both at the individual and the population levels. Studies examining the association of acute phase proteins and the presence of malaria have yielded inconclusive evidence. For example, the prevalence of ahaptoglobinemia was initially proposed as an index of malaria endemicity but the influence of haptoglobin genotypes on severe malaria has been equivocal.^{25–31}

Associations have been found between the severity of malaria and plasma concentrations of TNF- α ,^{32,33} and (inversely) of TGF- β .³⁴ Could the same host responses be used

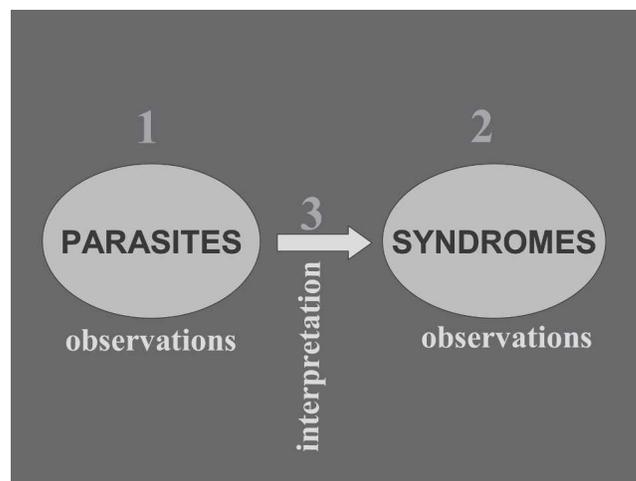


FIGURE 2. Both parasites and clinical syndromes can be documented objectively. Many studies are devoted to improving the accuracy of each of these. The relationship between them requires judgment incorporating evidence on multiple levels—parasite density, location, season, age, or other clinical findings. Causality is much more likely in non-immune than in semi-immune individuals. Clinical or laboratory ‘signatures’ that distinguish malarial disease from other (mainly infectious) syndromes are needed to improve diagnosis both for clinical, epidemiologic, and research purposes.

as a signature of malaria disease? This seems unlikely because of the non-specificity of these host responses. Plasma concentrations of cytokines such as interferon (IFN)-gamma and tumor necrosis factor (TNF)-alpha correlated inversely with the risk of fever and clinical malaria in a study in southern Ghana.³⁵

In encephalopathy associated with *P. falciparum* parasitaemia, a clinical sign that has been identified in recent years appears to be specifically associated with a malarial etiology. This is the retinopathy identifiable at the bedside by ophthalmoscopy, consisting of small patches of retinal whitening and a characteristic white or orange coloration of vessels.^{36,37} (White-centered hemorrhages and papilloedema may also be seen, but these are not malaria-specific). In an autopsy study, the ante-mortem presence of retinopathy was the best available clinical predictor of a post-mortem diagnosis of malaria as the cause of death (i.e., presence of sequestered *P. falciparum* and no alternative explanation of death in a detailed autopsy).⁷ Retinopathy is best identified by a skilled observer using an indirect ophthalmoscope with the patient's pupil dilated with reversible mydriatic drops. It remains to be seen how useful this "signature" will prove to be for clinical and research purposes.

Malaria-specific mortality is difficult to measure correctly because the disease is most common in remote areas without the resources necessary to make definitive diagnoses. However, the impact of malaria on all-cause mortality has been shown to be more than that usually attributed to malaria alone. This has been shown by the marked reduction in mortality rates that accompany successful malaria control programs.^{2,38,39} Recently, Snow and colleagues, on reviewing the available data, estimated that eliminating the risk of *P. falciparum* infection might lead to more than a 2-fold reduction in the under-5 mortality rates in sub Saharan Africa.⁴⁰

CONCLUSIONS

Measurement of the malaria burden (i.e., of the adverse effects of malaria on the health of people) requires careful distinction between different meanings of the term "malaria" and recognition of the difficulties of measuring both the presence and the effects of parasites. More "signatures," either clinical or laboratory-based, are needed by which clinical events and parasites can be more confidently linked. These will lead to improvements in our capacity to treat patients, our ability to define the burden of ill health due to malaria, and our confidence in monitoring the impact of control measures.

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