

Chapter 10

Diagnosis of malaria disease

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Introduction

Confirming malaria infection does not automatically mean that the patient's symptoms are due to this infection. In non-immune patients, this is highly probable, but in endemic countries many otherwise healthy people can have parasites on their blood slides. In this setting, symptoms might be caused by another disease. How to distinguish then between "malaria infection" and "malaria disease" ?

This chapter will first describe a method to determine malaria morbidity in endemic settings, and discuss the diagnostic pitfalls related to the difference between "malaria disease" and "malaria infection". Based upon this difference clinical presumptive diagnosis will be put in perspective. In addition we discuss additional laboratory investigations, and we mention briefly the differential diagnosis starting from the key symptoms and signs.

What is malaria disease ?

The diagnosis of malaria disease can be difficult. Let's start with some examples where making the correct diagnosis was a problem in the authors' experience.

One day in Zaire in 1976, one of us was called to the 1-year-old daughter of a colleague, who had fever and a convulsion. She was on daily chloroquine malaria prophylaxis. She was brought to the clinic, where she had another convulsion that ended in unrousable coma. Respiratory arrest occurred. Mouth to mouth resuscitation was started, a thick film was taken, and IM quinine was immediately given. Shortly afterwards, cardiac arrest occurred, but with cardiorespiratory resuscitation cardiac rhythm was quickly restored and spontaneous respiration resumed after half an hour. The thick film was reported to be negative. For years we have discussed whether this was cerebral malaria or not.

A second case in the same region was a 32-year-old local chief, who presented one evening in 1984 with abnormal behaviour and a fever of 38.5°C. A thick film showed scanty parasites of P. falciparum, chloroquine was given. The next day the patient was well. The diagnosis of incipient cerebral malaria was made. Several months later, the patient presented again with extensive Kaposi lesions, and he died with the diagnosis of AIDS a short time later.

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*A third case was a 10-year-old child in Guinea-Conakry, who was seen with fever at the health centre. Chloroquine was given, but after three days the fever did not disappear, and the parents decided to go to the district hospital. The child was hospitalised, a thick film was taken, and chloroquine was again given. The next day, the result of the thick film arrived: it was scanty positive for *P. falciparum*. Chloroquine was stopped, and quinine was administered, supposing a chloroquine resistant strain. After three days, the fever did not resolve, the diagnosis of typhoid fever was made on clinical grounds and chloramphenicol was given. The next day the child complained of pain in the right subcostal region. An ultrasound showed a liver abscess, probably amoebic.*

Are the diagnoses and the decisions correct in all these cases ? Before we discuss the cases, some general notions have to be explained (or gone through again).

Malaria Disease versus Malaria Infection

What is malaria disease? We could state that “malaria disease” is the presence of symptoms and signs provoked by the parasite. The difference between malaria disease versus malaria infection is more than academic. Since parasites can be found in a high proportion of apparently healthy people in endemic regions, the mere presence of parasites is not a proof of a causal relationship between these parasites and the symptoms and signs. Moreover, symptoms and signs are not specific to malaria, we lack an unequivocal specific *indicator of morbidity* of malaria.

Thresholds

Parasitological threshold

The number of parasites present in a microlitre of blood, required for the technician to be able to detect them in a thick film or with the other diagnostic tools, (see chapter ##, diagnosis of malaria infection) is the *parasitological threshold*. (Figure 1) It depends on the type of laboratory technique, the time spent for searching parasites, the skill of the technician. For a thick film, it is generally accepted to be as low as 1 parasite per microlitre, but good laboratories go a lot further for suspected cases (T. Vervoort, personal communication). It should be stressed that this threshold does not depend on the patient.

Clinical threshold

The transition from the presence of parasites (triggering and sustaining immunity), to symptoms unequivocally attributable to malaria disease is the *clinical threshold*. It depends on the species and the strain of the parasite, and on the immunity of the patient. The number of infective bites, or the endemicity will play a role through the effect on the immunity. The drugs already taken and the relative resistance of the parasite against the drug have no influence. A “universal” clinical threshold does not exist: it will differ quite a lot between small children in hyperendemic (“malaria stable”) areas, adults in the same regions, people in hypo-endemic (“malaria unstable”) regions, displaced people, migrants, travellers and expatriate residents. In this respect, it is important to emphasise that immunity may fade temporarily in pregnancy, and temporarily or permanently in semi-immune people leaving the endemic region.

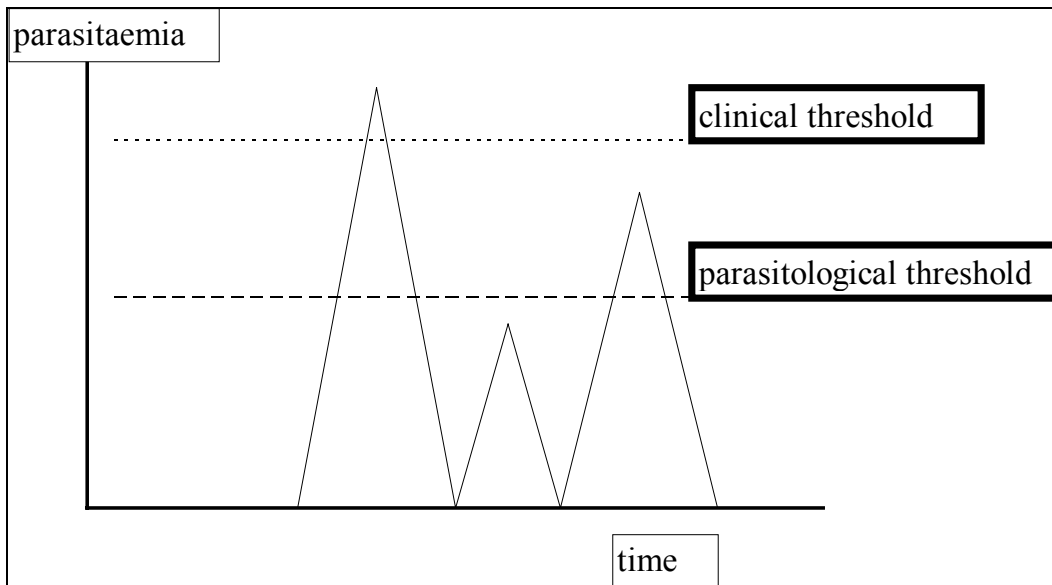


Figure 1 **parasitological (lower) and clinical (upper) threshold.**

Some spikes of parasitaemia cause clinical symptoms (the first), some are detectable but do not cause symptoms (the last) and some are not detectable by routine laboratory techniques (the middle).

In holo-endemic regions, the clinical threshold is mostly several orders of magnitude higher than the parasitological threshold.

In travel medicine however, it is extremely rare to find parasites in the blood of an otherwise healthy traveller (that would mean that the clinical threshold would be higher than the parasitological threshold, as is the case in endemic regions). For *P. falciparum* infections the clinical threshold is mostly equal to the parasitological threshold. For *P. ovale* infections it may be lower than the parasitological threshold (cf. chapter ##, clinical features). Of course these statements hold true only for a highly skilled laboratory, where (in suspected cases) parasites are sought for at least 15 minutes in a thick film.

There are similar threshold examples in medicine, although there are some fundamental differences. The interpretation of the presence of microbes in the culture of midstream urine e.g. also requires the notion of a “clinical threshold” (more than 100.000 colonies per millilitre). The difference is that in this case an unequivocal indicator of morbidity is generally accepted: the presence of microbes in urine obtained by sterile puncture of the bladder. All tests will be evaluated against this “gold standard”. In contrast to this, in malaria the clinical threshold has to be deduced from statistical analysis.

Test-Treatment threshold

These two thresholds should not be confused with the *test-treatment threshold*, which defines the level of evidence or disease probability at which one decides to forgo further testing and to start treatment. This decision can be made on a personal basis, in a clinical situation, or on a population basis, in the form of algorithms or strategies.

The determination of the test-treatment threshold depends on the benefit of the treatment, the risk and the cost of the treatment, the characteristics and the risk of additional tests. (Pauker 1980) (Figure 2)

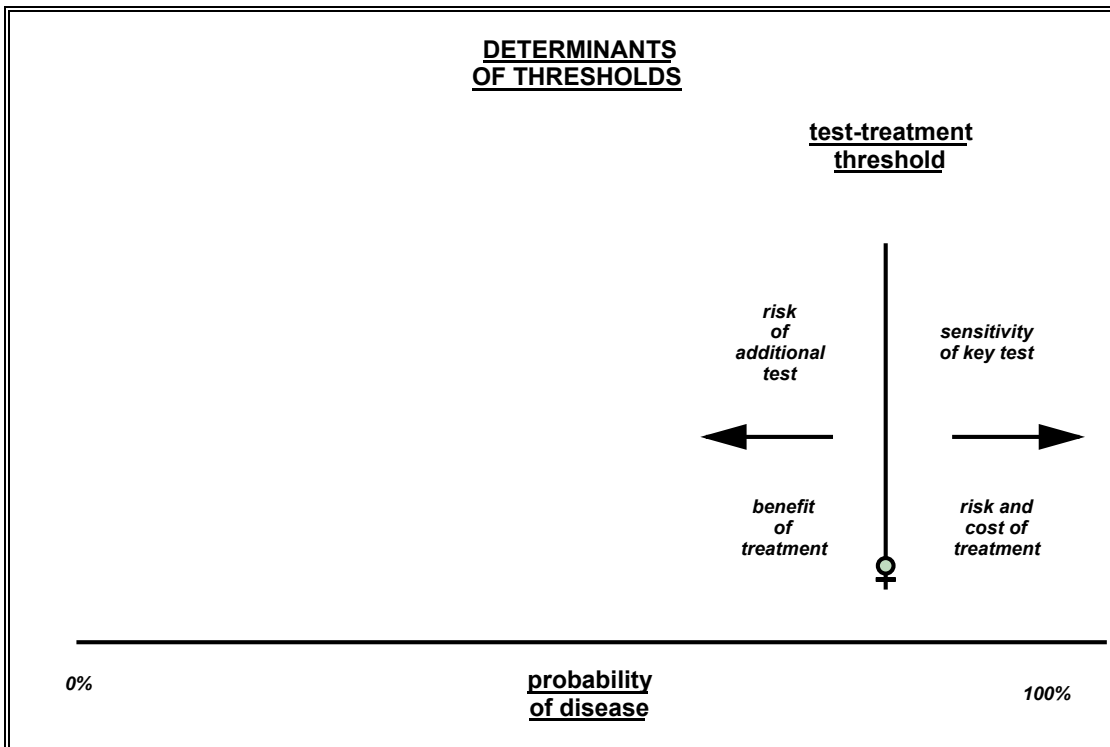


Figure 2 Representation of the most important factors that influence the test-treatment threshold.

The threshold for treating without further testing is shifted to the right in case of expensive or dangerous treatment and in case of a test that has few false negatives (highly sensitive). It is shifted to the left if further testing confers some risks or if the treatment is highly beneficial.

For any disease, we do not need to be so certain of the diagnosis if it is a life-threatening disease, with a highly beneficial treatment. We would easily agree to treat some patients who do not have the disease. An example is meningitis caused by meningococci: fever, nuchal rigidity and petechiae are sufficient to start treatment immediately, without lumbar puncture if this can not be performed within minutes.

We must be more certain of the diagnosis if the treatment is dangerous, or expensive. Example: African trypanosomiasis. Except for some rare cases, a parasitological diagnosis in blood, lymph nodes or spinal fluid is required before treatment is started.

We should test further, and hence obtain a higher level of certainty if the next test has few false negatives. If the next test could miss a lot of cases however, we would prefer to treat immediately, without ordering the test. Example: if ultrasound is available, we should order it before starting treatment for amoebic abscess.

We should treat at a lower level of certainty, and not order a test if it is expensive or dangerous (especially if the sensitivity or specificity are not very high). Example: X-ray of the chest for bronchitis.

For malaria,

- it is a life-threatening disease, with a highly beneficial treatment. It is acceptable to treat some patients who do not have the disease.
- the treatment is not dangerous, or expensive. This lowers our threshold.
- the thick film has few false negatives. It will miss almost no cases. This is an argument for doing the test, and treating at a higher level of certainty.
- the thick film is not dangerous, but it is expensive in field conditions. This brings the threshold down.
- how to determine the clinical threshold ?
- For different settings, one could define a clinical threshold as a level of parasitaemia above which the likelihood that the symptoms are caused by malaria is higher than the likelihood that the symptoms are provoked by another disease.

In recent years, a lot of work has been done in this field. Since there is no unequivocal specific indicator of morbidity, no gold standard for “malaria disease”, one has to rely on statistical methods, which try to distinguish between fever attributable to malaria and other fevers. The best method is the “attributable fraction” that calculates the number of fevers due to malaria for different levels of parasitaemia. (Smith 1994)

Attributable Fraction

Taking all cases of fever, the proportion due to malaria is the attributable fraction (AF). In patients who present with fever and whose thick film is positive for malaria parasites, only some are due to malaria, the remainder of the fevers being caused by other diseases. In patients with fever but with a negative smear, it is unlikely that the fever is caused by malaria. (if not a P. ovale infection). So we presume that there is no malaria attributable disease in this group. (Figure 3)

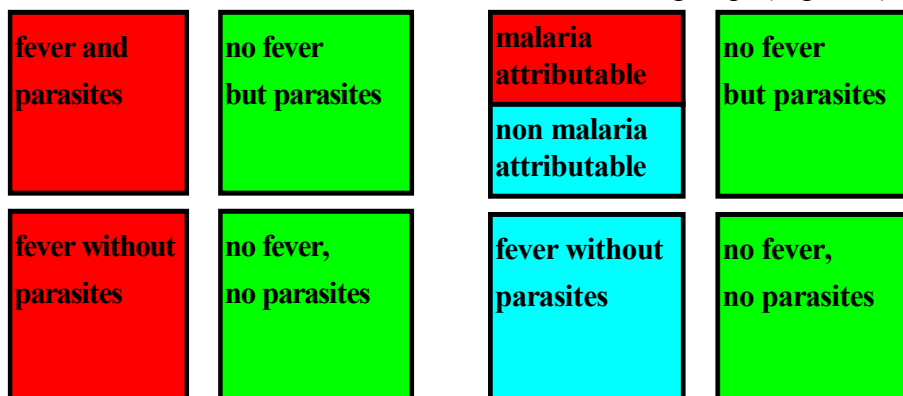


Figure 3 Attributable fraction.

On the left we see the four groups of patients, or categories of combinations of fever and parasites. On the right we see that only some of the fevers with parasites are malaria attributable. Fevers without parasitaemia are not malaria attributable.

How do we calculate the malaria attributable disease ? First, let us assume that the proportion of febrile children amongst parasitemic children is called f_p , and the proportion of febrile children amongst aparasitaemic children is called f_{p0} .

Among the children with parasites and fever, the proportion of fevers due to malaria, is³:

$$(f_p - f_{p0})/f_p$$

Further, if we call “p” the proportion of cases of fever with parasites, then the fevers due to malaria in all children with fever, or the attributable fraction⁴ is

$$AF=p(f_p - f_{p0})/f_p$$

Let us have a look at an example, drawn from a population study in children in the Gambia. (Alonso 1993)

Table 1 Presence of fever depending on parasitaemia in a population study.

	fever	no fever	total
any parasite	41	86	127
no parasite	33	247	280
total	74	333	407

Intuitively, we would state that the presence of parasites is suggestive of malaria disease: more parasitaemic children have fever (41/127, 32%) than aparasitaemic children (33/280, 11%).

These numbers give f_p and f_{p0} :

$$f_p = 0.32 \text{ or } 32\%$$

$$f_{p0} = 0.11 \text{ or } 11\%.$$

Among the children with parasites and fever, the proportion of fevers due to malaria ($(f_p - f_{p0})/f_p$) is:
 $(0.32 - 0.11)/0.32 = 0.63.$

In normal language this means that 63% of children with fever and parasites are presumed to be ill with malaria, in the other 27% the fever is probably caused by another disease.

Among cases with fever, 41/74 or 0.55 are parasitemic, thus

$$p = 0.55.$$

The overall probability that the fever is caused by malaria (or the attributable fraction) will be:

$$AF = 0.55 \times 0.63 = 0.35$$

In normal language, this means that only 35 percent of all fevers are probably due to malaria.

Attributable fraction for different levels of parasitaemia

Let us look at another study of cases with and without fever, and with and without parasitaemia seen in a setting in Mali. (Rougemont 1991)(Table 2) This is a study starting from patients with fever, for whom an equal number of adequate controls were subsequently found.

Table 2 Parasite density (in parasites/microlitre) and probability of fever in Mali.

Parasite density	cases	controls
	(fever)	(no fever)
<hr/>		

³This proportion often is referred to as attributable risk.

⁴There is a lot of confusion about definitions: for some authors, the attributable fraction is the proportion of fevers due to malaria, $(f_p - f_{p0})/f_p$.

>100000	43	7
25000-99999	61	15
10000-24999	19	10
1-9999	40	67
no parasites	122	186
total	285	285

It is intuitively clear that of all cases with fever, some will have other diseases than malaria, since controls also have parasitaemias that may rise as high as > 100 000 per microlitre. On the other hand, it is intuitively clear that from 10 000 parasites on, people are more likely to be suffering from malaria. Finally, it is strange that we see more low parasitaemia in controls without fever than in cases !

The AF can be calculated for different levels of parasitaemia. The method faces a pitfall, also made clear in Table 2: in a hyperendemic region, a smaller number of children with low parasitaemias are febrile than children without parasites. Patients with non malaria-attributable fever have a lower parasite density because fever or other physiopathological mechanisms reduce the parasite density. Mathematical corrections allow for a normalised model. (fig 4) (Smith 1994)

The proportion of patients presenting with fever is shown for a range of parasitaemias. From a certain point on, malaria enters the scene, once the attributable fraction exceeds 0.

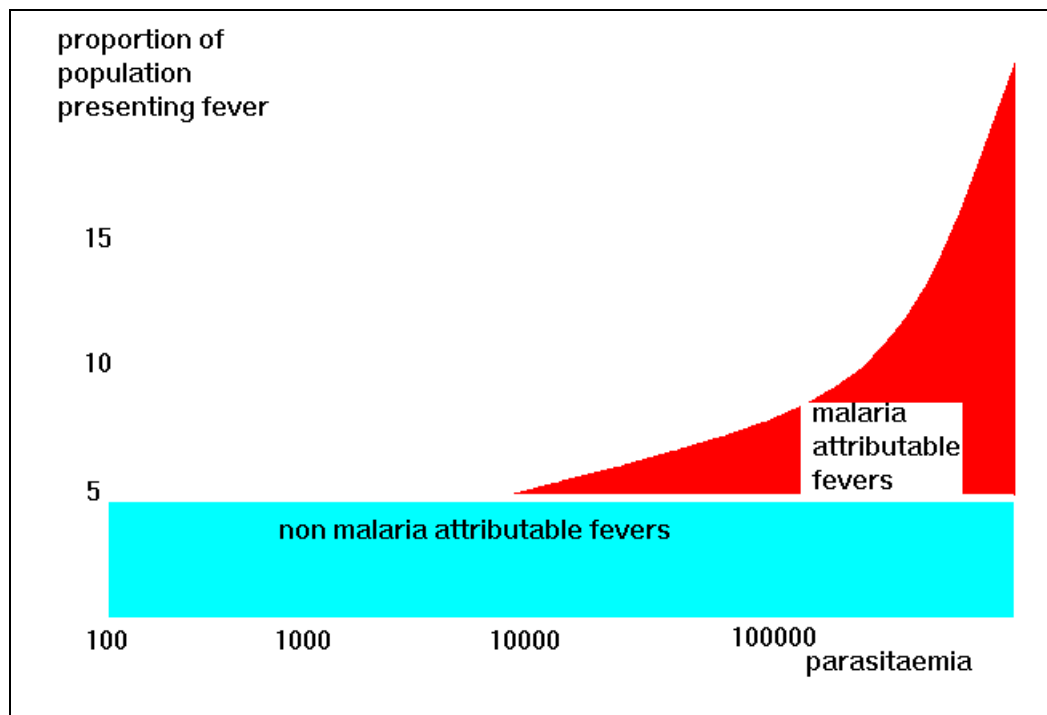


Figure 4 attributable fraction as a function of parasitaemia level.

From a certain level of parasitaemia on, malaria attributable fevers appear, and become even predominant. Background non-malaria attributable fevers persist over the whole range of parasitaemia. [adapted from Smith, (Smith 1994)]

In holoendemic areas, attributable fraction studies often put the mean clinical threshold at 10.000 parasites per microlitre. (Baudon, 1988; Genton, 1994) In meso-endemic or oligo-endemic regions this can be lower: e.g. in Thailand it was 1460/ μ L for P. falciparum and 181/ μ L for P.vivax. (Luxemburger 1996)

The question whether the risk of malaria morbidity increases with age for any parasite density studied, in other words if the clinical threshold lowers with age, has not yet been answered. In recent studies, this thesis has been challenged. (Petersen 1991) There is certainly a decrease in mean body temperature with age for a given level of parasitaemia, but for adults in a holoendemic region, there is no attributable morbidity at all ! (Smith, 1995) This corresponds with the finding in another study, that it was impossible to define a clinical case of malaria for adults. (Petersen 1991)

Diagnostic Pitfalls

In hyperendemic areas, we could incorporate the threshold logic. This should be done with caution, since there are some pitfalls:

- Combining a positive slide with fever, whatever the parasitaemia, is not absolute proof of the diagnosis “clinical malaria”. It might be that the parasites are not the cause of the fever, that an innocent viral disease or another condition is in fact the diagnosis. Combining a positive slide with fever for the diagnosis of malaria can therefore be dangerous. If the diagnosis of malaria is accepted, and if further clinical history taking and physical examination is careless, one could miss the diagnosis of pneumonia, infectious diarrhoea, meningitis ...
- For a high parasitaemia, statistically it will be more probable that malaria is involved, but it is not an absolute proof, since high parasitaemias can be found in “healthy” children.
- Not to take into account a positive thick film in a patient might be dangerous too: even if he presents symptoms or signs that suggest another diagnosis such as pneumonia or dysentery, the symptoms could in fact be due to malaria, or he could have two diseases at the same time.

It is difficult to explain these warnings to health care workers in the field or to nurse practitioners, and even to medical doctors not trained in decision analysis. This is probably the reason why the results of so many malaria laboratory tests are not taken into account, even if they are available. Too often also, these results arrive too late to be useful in clinical decisions.

It is time to comment on the three cases we presented in the beginning of this chapter.

...One day in Zaire in 1976, one of us was called to the daughter of a colleague, who had fever and a convulsion. She was on daily chloroquine malaria prophylaxis...

For some cases, it has been shown in post-mortem slides that malaria was the cause of death, despite a negative thick film. (Wolf-Gould, 1992) Most authors believe that this is the exception, rather than the rule. (White, 1992) Normally, no fever is attributed to malaria if the thick film is negative (with the exception of P. ovale infections)

Could the thick film have been negative because of the chloroquine prophylaxis ? The assumption that antimalarials bring parasitaemia down under the detection threshold, and provoke a false negative slide is not correct: if patients still have fever, the thick film will be positive. Neither the intake of antimalarials, nor chloroquine resistance have an influence on the clinical threshold (which is -for P. falciparum- always equal to or higher than the parasitological threshold).

...A second case in the same region was a 32-year-old local chief, who presented one evening in 1984 with abnormal behaviour and fever of 38.5°C. A thick film showed scanty parasites of P. falciparum....

Was this fever and this abnormal behaviour attributable to the scanty parasites they found in the thick film ? It is improbable. Petersen did not find malaria attributable disease in adults in a holo-endemic situation (AF=0). Moreover, the low level of parasitaemia makes a relationship still less probable.

...A third case is a 10-year-old child in Guinea-Conakry, that was seen with fever at the health centre. Chloroquine was given, but after three days....the thick film was scanty positive.... the diagnosis of typhoid fever was made on clinical grounds and chloramphenicol was given...an ultrasound showed a liver abscess, probably amoebic.

This case shows that some fevers with positive slides are due to other causes, in this case an amoebic liver abscess. It was not very intelligent to go on with chloroquine the third day: if a patient is referred after two days, chloroquine resistance should be suspected, and a second line drug should be instituted. The presence of parasites after three days of treatment indeed suggests chloroquine resistance, even if this case was probably not malaria attributed. Furthermore, the result of the thick film should be obtained immediately, not the following day, in order to adjust decisions immediately.

Presumptive Diagnosis versus Confirmed Diagnosis

Presumptive Diagnosis

Introduction

In malaria endemic countries economic and logistic reasons force entire populations to rely on clinical diagnosis. This is not the only reason for presumptive diagnosis: when we take the difference between parasitological and clinical threshold, and the pitfalls of interpretation into account, the often heard statement “*it is mandatory to obtain the laboratory confirmation of the presence of malaria parasites in the patients body, whenever possible*” becomes debatable. If one cannot correctly interpret the presence of parasites in the blood of the patient, parasitological diagnosis of malaria is not useful, and might be dangerous. Even if all laboratory tools are available, in most hyperendemic regions the laboratory confirmation of malaria is not useful at all levels. Presumptive diagnosis is thus not only a strategy of poverty, but can be defended scientifically.

rationale

What defines a presumptive diagnosis is the decision to forgo further testing and to start treatment. As we explained earlier, this decision is made at the *test-treatment threshold*, the required level of certainty or probability that the patient has malaria. As was also explained, this involves the probability that the patient has malaria-disease and not only malaria infection.

The determination of the test-treatment threshold depends on several factors: the benefit of the treatment, the risk and the cost of the treatment, and the characteristics and the risk of an additional test. (Figure 2)

As already explained, the benefit of treatment for malaria is high, and withholding a treatment from someone really suffering from malaria can have serious consequences. The risk of withholding treatment is dependent on the false negative rate of the case definition. If the case definition is based on fever, patients with malaria-attributable symptoms but without fever will not be treated. Some of them may have severe malaria.

The risk for serious side-effects of most first-line malaria treatments is low: even for sulfadoxine-pyrimethamine this risk is considered to be between 1 in 10^4 and 1 in 10^7 . (Stürchler, 1995) Except for some countries with high level multiresistance, the cost of first-line treatment is also low.

The risk of additional testing is non-existent. The cost, however, is considerable, since microscopes have to be purchased, an unaffordable expense in most rural settings.

With all these elements an estimate can be made as of how many patients we accept to treat unnecessarily. With the attributable fraction methodology, we can determine which clinical case definition is acceptable for the test-treatment threshold already set.

If in the example of the Gambia we determine a clinical case definition as “fever”, we will treat 65% of fevers that are not malaria attributable with chloroquine. Is this acceptable ? When the resistance to chloroquine is high and the first line drug is sulfadoxin-pyrimetamin, one might prefer a higher threshold.

Algorithms

Substantial efforts have been made to refine presumptive diagnosis. A comparison between the clinical threshold (defined by the attributable fraction) and clinical symptoms and signs can result in a better case-definition. However, we should not forget that relying on concomitant symptoms and signs will result in a higher specificity (fewer false positives), with a loss in sensitivity (more false negatives, some patients with malaria disease will not be treated). (Rougemont 1991, Baudon 1988, Redd 1996, Genton 1994, Schellenberg 1994, Van den Ende 1996) Some authors suggest including measured temperature, nailbed pallor, and splenomegaly in the case definition (Redd, 1996); others suggest more complicated algorithms, at the cost of more false negatives. (Rougemont, 1991) Still others find that no algorithms can do better than the health workers' intuitive estimation. (Bassett 1991)

Generally, fever is considered to be the key symptom of malaria, and a presumptive diagnosis of malaria is made starting from fever. However, in a holoendemic setting in Tanzania, Smith et al.

found that for infants, a large proportion (66.5%) of malaria-attributable disease presents without fever. For older children, this is less than 40%, but is still considerable.

In holoendemic settings, fever is indeed a frequent complaint and a reason for consultation. Moreover, it might be that patients have such a high likelihood of malaria disease that further laboratory testing is senseless. In a holoendemic setting, the definition of malaria as “fever plus parasites” can be almost as non-specific as fever alone. (Schellenberg 1994) Of all children consulting for any illness in two settings in Malawi, 983/1124 had a history of fever, 672/1124 had parasites, and 285 had a parasitaemia > 10.000 per microlitre (malaria attributable). Of those with fever, 624/983 had parasites and 272/983 had a parasitaemia > 10.000 per microlitre. (Redd 1996) In Papua New Guinea, 32% of children < 10 years with fever had more than 10.000 parasites per microlitre. (Genton, 1994) In Burkina Faso, more than half of fever cases (> 38°) in children 5-14 years had more than 10.000 parasites per microlitre. (Coulibaly 1991) In the Gambia a community survey showed that 44% of febrile children had malaria attributable disease. (Schellenberg 1994) However, in the already mentioned study in Tanzania by Smith et al., lower figures of malaria attributable disease were found: for all episodes of whatever reported illness, 9.8% was malaria attributable in infants, 1.3% in children 1-4 years-old, 0.6% in children 5-9 years-old. No malaria attributable disease was found in adolescents and adults. (Smith, 1995)

The assumption that fever equals malaria may be wrong and dangerous in a hypo-endemic setting or during the low transmission period. In Zimbabwe, only 28% of patients with “clinical malaria” had any parasites in their blood. (Basset 1991) Only 10 of 277 patients with fever had a real malaria attack during the dry season in Niger, whereas the personnel made the diagnosis of “clinical malaria” in 270 of them ! (Olivar, 1991) If the probability of malaria drops below a certain level, presumptive diagnosis has no sense, and should be replaced by a parasitological diagnosis.

As a conclusion for algorithms we could state that:

“fever does not equal malaria”

but, after application of decision analysis

“fever equals malaria treatment in holoendemic areas, in the first line”

Confirmed Diagnosis: some additional remarks

Holo-endemic areas

If we incorporate the threshold logic in holo-endemic areas, we should be aware of the fact that a thick film showing fewer parasites than the presumed clinical threshold does not exclude malaria but that it makes malaria disease as the cause of the patient’s current clinical condition less probable. A thick film above the threshold is also not absolute, it does not give a verdict, but it shifts the emphasis in the differential diagnostic process towards malaria, not excluding other diseases.

Offering laboratory facilities to health centres should always be combined with a training in interpretation of results. This is difficult especially for malaria, and it is rarely done.

Too often, presumptive diagnosis creeps into second and third line medicine. Since other differential diagnoses are much more frequent at this level, and since treatment is more complicated, the medical decision logic for presumptive diagnosis is absent, and it should be

abandoned. A parasitological diagnosis at the hospital level is mandatory. Threshold logic is also useful here: negative slides and strongly positive slides will be of more interest than moderately positives.

Hypo or non-endemic regions

In hypoendemic regions the presence of parasites in the blood of healthy people is less frequent or rare. In these situations a confirmation by laboratory tests is strongly advocated, if economic and logistic constraints permit it. (Olivar, 1991; Jonkman 1995) In non-endemic regions (travel medicine, migrants, displaced people ...) the confirmation of suspicion is mandatory.

Clinicians in non-endemic countries need to be well aware of the possibility of imported malaria cases. Diagnosis in these cases may be difficult since the exposure to the infective bite may date back to a long time before clinical symptoms appear, especially in the case of P. vivax, P. ovale or P. malariae infections. The accurate geographical history (unde venis ?) should be a routine in every history taking of cases of fever even in the malaria-free world. Finally, it has to be stressed once more that P. falciparum infections in non immune subjects (travellers from non endemic western countries, migrants visiting their home country, ...) may be extremely severe, with high case-fatality rates if correct diagnosis and treatment are not carried out promptly.

It is clear that in imported malaria, in low endemicity settings, in research and epidemiology, the more sensitive tools like PCR, antigen detection and the like can be of value, but rarely in clinical medicine in holoendemic regions. In most malarious regions, we should look for less sensitive diagnostic tools. In a holoendemic setting, this could be solved by making a diagnosis with a thin smear instead of a thick film. The thin smear is less sensitive, but it is more specific and the technique is easy and the drying time much shorter.

Additional laboratory tests

For a classical malaria attack, a simple panel of haematological examinations (haemoglobin level, red blood cell count, hematocrit, white blood cell count, thrombocytes) are recommended.

The finding of marked anaemia, contrary to what was stated in older handbooks, is not a feature of classical malaria: marked anaemia is never the result of a simple infection, it is the hallmark of (an incipient) severe malaria, in its acute or subacute form.

The thrombocyte count is rarely normal in malaria infection by all species, it often falls below 50×10^9 /lit in falciparum malaria. In imported malaria, the positive predictive value of the triad fever, history of a recent stay in endemic areas and thrombocytopenia below 100×10^9 /lit has been found to be as high as 97% (Castelli, 1995). It is of course clear that a laboratory that reaches the level of sophistication of a thrombocyte count, should be able to interpret a thick film correctly !

No specific diagnostic indications are given by the white blood cell count, since the result may be normal, low or high. In severe malaria however, a high leucocyte count indicates a poor prognosis. (see chapter ##, clinical features)

Haptoglobin level, total cholesterol and HDL cholesterol are all very low in malaria, and could be of help in a situation where malaria should be ruled out and a reliable parasitological diagnosis can not be performed. However, we refer to the same remark as for the thrombocyte count.

As pointed out in chapter ## (clinical features), other laboratory tests can be of help in the diagnosis and the management of severe and complicated malaria: glycaemia, liver and kidney function tests, electrolytes, blood gas analysis, serum lactate, fibrin split products. These tests have no place in uncomplicated malaria: as said before, finding one of these tests to be significantly abnormal shifts the diagnosis from classical to severe malaria, with important consequences for treatment and management.

The utility of lumbar puncture in cerebral malaria has been questioned. The distinction between cerebral malaria and meningitis can be difficult, as cerebral malaria can present with nuchal rigidity, and meningitis can present without. Wright et al. found 7.2% of cerebral malaria with, and 36% of meningitis without nuchal rigidity in comatose Liberian children. They strongly advocate a lumbar puncture for every comatose child in malarious regions, since the clinical distinction between both diseases is not reliable. (Wright 1993)

Differential Diagnosis

The extremely wide spectrum of clinical symptoms and signs occurring during malaria disease is covered in chapter ##(Clinical aspects of malaria), and exceeds the purpose of this chapter. A brief and nonexhaustive list of possible differential diagnoses of falciparum malaria key symptoms and signs is nevertheless given in

Table 3.

Table 3 **Differential diagnosis of malaria.** (adapted from Gilles)

Conclusion

The diagnosis of malaria disease differs substantially in holo- and hypoendemic regions. Where in hypoendemic regions it equals parasitological diagnosis, in holoendemic regions the diagnosis depends on the clinical threshold, which can be found on a population basis by defining the attributable fraction for different levels of parasitaemia.

A presumptive diagnosis of malaria is not a strategy of poverty: it has formal scientific grounds, that rely on the theory of the test-treatment threshold. It should be restricted to holo-endemic malarious regions, and to the first line. Parasitological diagnosis remains mandatory in district hospitals and reference hospitals.

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