Symptomatic identification of malaria in the home and in the primary health care clinic

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In endemic areas in the absence of microscopy, the WHO case definition of malaria is the presence or a history of fever without other obvious cause. Yet there is little empirical evidence on the accuracy, predictability and reliability of clinical signs and symptoms for diagnosing malaria within different endemic settings. Studying patients in endemic communities in the Philippines, we found that fever alone did not discriminate well for malaria. In contrast, a sequential occurrence of fever, chills and/or sweating, or a combination of all three symptoms was a good general predictor of the disease. However, the place of diagnosis and observation (home or clinic), age, and season affected the positive predictive values obtained. Specificities and positive predictive values were greatest (over 80%) for those at most risk—children under 9 years of age in highly endemic communities—and were most reliable when the diagnosis was made at home. Predictive values were also greatest during the season when childhood acute lower respiratory infections in the study area increase. The good predictability of clinical signs and symptoms for high-risk groups suggests that simple protocols can be developed for the management of malaria in endemic areas of the Philippines.

Introduction

Malaria is one of the most important parasitic infections affecting man because, of the estimated 270 million who get infected each year, approximately 110 million manifest clinical symptoms. Some 500 000 children are estimated to die from malaria each year, primarily in Africa. The present aim of control is to prevent malaria-related deaths and to diagnose and alleviate clinical symptoms of the disease as quickly as possible (1). Yet there are surprisingly scanty data on the clinical symptoms, whether they are predictable, and whether they are reliable enough to be used to identify malaria cases and accelerate their treatment. Considering WHO’s focus on clinical disease rather than the infection in its malaria control efforts, there is an urgent need for such data to guide diagnostic efforts in the absence of effective microscopy in highly endemic areas.

One of the reasons for poor information on the value of clinical predictors has been a historical reliance upon microscopic diagnosis to achieve the goal of eradication and an assumption that a better field-based diagnostic tool would eventually be developed. Although it is preferable to identify cases with the aid of microscopy, effective laboratory support is often absent in endemic areas, particularly in the high transmission season. Even then, parasitaemia does not automatically result in clinical malaria, nor does a negative slide mean absence of parasitaemia. Thus malaria diagnosis and treatment at the periphery invariably depend on the clinical picture.

How useful and efficient is the clinical picture in detecting malaria morbidity? What clinical criteria can best predict the disease? How does disease presentation vary with different exposures? In Africa, one of the earliest studies of clinical symptoms for malaria is a 1966 study of patients self-reporting for malaria treatment within forest areas of rural Nigeria, which showed a positive relationship between recorded body temperature and parasite density (2). This relationship was confirmed in a study of schoolchildren in urban clinics in Nigeria and by a more recent study of young children observed at home in Benin (3, 4), but not by a recent study in urban and rural Nigeria which showed that nearly half the schoolchildren (47.1%) in the study had acute malaria with a very low parasitaemia (5).

Within the same ecological zone of Africa, Rougemont et al. examined a sample of children below the age of 10 who presented with and without fever at a rural dispensary in Niger, and showed the relative risk of having a malaria-related fever in the high-transmission season to be 27.5 when the fever was high (>39 °C), had no other obvious cause and
been however, Trape et al. found clinical criteria for malaria to be non-specific and the parasite density to be the only criterion which distinguished suspected malaria cases from unsuspected malaria (9). In Zimbabwe, only 26% and 28% of diagnosed malaria cases (using unspecified clinical criteria) in urban and rural clinics, respectively, were found to be parasite positive, whereas in Tanzania the clinical diagnoses of children by physicians were 84–99% predictive of malaria compared with 66–74% when diagnosed by rural medical aids; all misclassified patients were seen on the first day of illness (10, 12).

In Asia, a retrospective examination of Malaysian clinic records showed that 60% of parasite-positive cases from an uncharacterized reference population (all ages combined) had fever with or without associated signs, whereas in India fever had a high positive association (75%) with falciparum infections. Age-specific exposure rates were not given (13, 14).

It is difficult to draw conclusions from the above findings for several reasons, not least because of differences in study design, populations, and epidemiological settings. Malaria prevalence was largely unreported. Predictive values of any screen, as with sensitivity and specificity, are influenced by prevalence. As prevalence can vary considerably within and between geographical areas, statements about the predictive values, sensitivity or specificity (posterior probability) of clinical diagnosis are misleading if the prevalence (prior probability) is not defined (15, 16). Indeed, prevalence is probably the most important, but least understood, factor affecting the usefulness of a test result. Without information on prevalence, no judgement can be made on the extent to which the screening method contributes to further identifying an infected population, beyond that which could have been identified by chance.

If the prevalence of disease is very low, indiscriminate use of screening tests on subjects selected at random is likely to fail; even with very accurate screening there will be a relatively small number of true positives in relation to the number of false positives, and this reduces the predictive value of the screen. Therefore, if missing a single case does not have serious public health implications (as in HIV [human immunodeficiency virus] screening), attempts at clinical or laboratory precision usually cannot justify the extra effort. If the prevalence of the infection is very high, a high correlation with any clinical symptom is possible even if the symptom is unrelated because, by definition, the majority of the population will have the infection. It is where the prevalence is a moderate 20–50% that clinical and laboratory screens are most useful because they can increase the probability of detecting disease (posterior probability) far beyond that expected by chance (i.e., prevalence or prior probability), and the increase in predictive power through a diagnostic screen becomes very important in selecting patients who will respond to treatment. None of the above-mentioned studies established the additional contribution of the clinical screen.

Moreover, with two exceptions (in Benin and India) (4, 14), the research has been based on populations selected from uncharacterized outpatient and school settings. It is obviously easier to recruit patients from such settings. However, outpatients constitute a self-selected population drawn from different transmission sites. In malaria, selection of a well-characterized reference population for assessment of morbidity is critical as the acquisition of immunity and the severity of symptoms is known to vary with prior exposure; indeed small variations in transmission intensity within the catchment area from which a clinic recruits patients will affect the exposure and subsequent clinical response leading to unspecified distortion in estimates of pyrogenic thresholds or the measurement of clinical response to infection, even with controls for age and transmission season.

Finally, the home is the setting for clinical symptoms to appear and for malaria management; if the symptoms are severe enough, the patient will seek treatment. There is some evidence to suggest that patients with malaria and other diseases come to clinics for acute episodes when they are further away from the clinic, and have no other diagnostic and treatment alternative. Some patients appear to visit clinics more frequently when living closer to it. Antipyretics or antimalarials may have been taken prior to a clinic visit to bring an elevated temperature down. However, a variation of body temperature can also be expected as part of the disease process, and clinic patients are obviously seen at different points in the progression of a disease episode. Thus the constellation of symptoms and their predictive values for disease, as observed in the clinic, can be influenced by a variety of factors related to the location and use of the clinic and the point in the episode at which the patient is seen. This makes it necessary to examine the range and predictive values of signs and symptoms accompanying a malaria attack as soon as symptoms occur (i.e., at home) and to compare the results observed at the clinic. Such a comparison has an important bearing on malaria control: in areas where malaria can rapidly result in death, early identification of the signs and symptoms of malaria and provision of support to seek rapid and appropri-
ate care and treatment affect the progress and outcome of the disease. In sum, to establish whether or not there is a significant, predictable human response to a given level of parasite challenge it is important to be able to separate errors due to variance in exposure from the other factors which affect clinical response, such as prior administration of chemotherapy and the presence of other concurrent infections. Although well-validated diagnostic criteria for malaria may ultimately have greater application in outpatient clinics, such uncharacterized reference populations incorporate an unknown bias. It is first necessary to establish and validate algorithms for malaria within well-defined communities, and to compare the bias inherent in outpatient presentation where differential exposure, distance, and ability to pay tend to confound interpretation. To accomplish both these objectives, the present study was undertaken in an endemic area of the Philippines.

Materials and methods

Study area and population

Surveillance was conducted in the mountainous area of Kalinga Apayao Province on Luzon island in the Philippines, over a 3-year period on the entire population of 600 in a small group of villages. Some 32 years ago, thick, virgin tropical rain forest blanketed this area, which is now extensively degraded, and dominated by slash and burn farming. The inhabitants are entirely Isneg, a subgroup of the Igorot ethnic group who rarely travel far from their ancestral lands. The district hospital and outpatient health clinic are located half-a-day’s journey away and can only be reached by hiking across the mountains or by riverboat along the Apayao river. The average rainfall in this area ranges from 2000 to 5000 mm per year; maximum precipitation occurs in August–September when riverboat transportation becomes impossible.

Malaria in this area, as in the rest of south-east Asia, is rural, stable and most dangerous in scrub or partially forested foothills. Indeed, the reduction of malaria risk in the Philippines is now regarded as having been as much a result of extensive deforestation in these areas as of vector control, because the principal vector of the Philippines archipelago, Anopheles flavirostris, breeds in shady, slow-flowing, clear mountain streams.

Surveillance for morbidity

From January 1990 onwards, following an initial demographic survey, monthly malariometric, morbidity, and nutrition surveys have been conducted. The research team stayed at the study sites for approximately 8 days for this purpose. All individuals resident within the study villages were routinely examined for infection. Following slide examination by the project technician, symptomatic cases were treated and asymptomatic cases referred for treatment with drugs provided by the project team.

Prior analysis of longitudinal data from the study villages had established that there was no clear relationship between parasite density and acute disease. Thus entry into the nested symptomatic study population was made on the basis of observed elevated temperature (>37.6 °C), a history of fever, or a history of “chilly rigors” during the week of the study team’s residence. “Chilly rigors” in the Isneg vernacular is a synonym for malaria. The latter group were included for two reasons: to establish the accuracy of self-diagnosis and because there is some evidence to suggest that symptomatic patients know when they have a repeated infection and are accurate in giving clinical histories (17–20).

Each person selected into the symptomatic study population was clinically examined by two project physicians. Temperature, spleen size and liver size were established, as was the presence or absence of rapid, wheezy or noisy breathing. A clinical history of symptoms was taken, including length of illness, fever, chills, sweating, loss of appetite, cough, colds, headache, abdominal pain, vomiting, diarrhea, urine changes, and jaundice. The duration, combination, and sequence of symptoms were noted. The patient was asked for details of any treatment which had been taken, and any health services consulted (traditional or modern). Additional information was elicited on past history of other diseases (measles, pneumonia, diarrhoea, hepatitis, pertussis). Patients themselves were interviewed, except for children under 10 years old, where the person who was normally looking after the child—not always the mother—was interviewed together with the child. Interviews were jointly conducted without information about the results of microscopic diagnosis. Each case was recruited only once into the nested study on symptoms and recruitment ceased when there were no new individuals to be recruited within the communities studied, 18 months later.

Concurrent with the population-based survey of morbidity, a second group of cases attending the only rural health clinic for the province were simultaneously recruited into the symptoms study, and identical clinical examinations and interviews were conducted.

Of a total of 614 cases examined and interviewed, 58% of cases were observed at home, and the rest clinically examined and interviewed on an outpatient basis.
Laboratory examinations

Numbered thick and thin films from fingerprick blood were made at the time of the consultation for each patient and stained with Giemsa. Each slide was examined by the same project technician on site, and slides were subsequently re-read by the same senior microscopist of the malaria control services in Manila using a standard procedure to examine the slides before declaring it negative (21). Parasite counts were estimated against leukocytes assuming 8000 white blood cells per μl.

Statistical methods

The results are presented below in the form of predictive values. A positive predictive value is the percentage of parasite positive results in patients where the clinical sign or cluster of symptoms is present. A negative predictive value is the percentage of parasite negative slide results when the clinical finding or cluster is absent. Positive and negative predictive values bear directly on the clinical situation in which the diagnostician does not know if the target disease is present or absent; in fact this is precisely what (s)he wishes to know. Faced with a patient complaining of a group of symptoms in a malaria endemic area, the important question is: what is the likelihood that the infection is present? In the absence of the same symptoms, what is the likelihood that the infection is absent? The approach is useful not only because it models what some clinicians do, but importantly, it sheds light on issues which are not clear to competent diagnosticians.

Results

Epidemiology of the area

Age-specific incidences of infection and disease (fever, parasitaemia and splenomegaly) within the study villages over a period of 3 years are given in Fig. 1. The study area was clearly hyperendemic, with no discernible seasons for infection or disease. Period prevalence of infection was clearly much higher (average, 47%) for children under 6 years and up to 10 years (51.5%), compared with the group over 10 years of age (19.7%). Patients with an elevated temperature (>37.5 °C) constituted 11.3% of malarial infections for children below 6 years, 9.0% for 6–10-year-olds, and 4.9% for the group aged over 10 years. Corresponding figures for splenomegaly were 51.4% for children under 6 years, 71.9% for 6–10-year-olds, and 32.6% for persons over 10 years of age.

The predominant species of infection was Plasmodium falciparum (66.9%); 22.2% of all infections were P. vivax, 5.1% were mixed infections (P. falciparum and P. vivax) and 6.6% were P. malariae infections, a species long assumed to have been eradicated from the Philippines.

Some 60–63% of infections in children below the age of 10 and 73% of infections in adults were P. falciparum; adults were almost as often infected with P. vivax as with P. malariae. Trends of age-specific infection by species are provided in Fig. 2.

Morbidity

In the morbidity study, 503 (89%) individuals reported a febrile episode, but only 178 (35.4%) had a temperature >37.6 °C at interview. Similar proportions (39.5%) of febrile parasitaemic patients were observed in the home as in the outpatient clinic. However, 77% of the febrile patients observed at the clinic reported intermittent fever, compared with 46% of febrile patients observed at home (Table 1).

Overall, 166 individuals (33%) had a palpable spleen edge, 256 (50.9%) had episodes of chilling, 287 (57.1%) had bouts of sweating, 174 (34.6%)
reported loss of appetite, 281 (55.9%) had cough, 247 (49.1%) had colds, 351 (69.8%) reported having headache, and 149 (29.6%) reported abdominal pain. There was remarkably little age-specific variation in these frequencies except for children under 6 years who presented more frequently with coughs (66.4%) and less frequently with a watery nasal discharge (61.7%).

The WHO-recommended case definition of malaria—presence or history of fever—did not discriminate well. Overall, just over half of the fever cases (270 or 51.8%) were parasitaemic; the percentage was slightly higher within the community-based sample (55.6%) than the clinic sample (47%). Clinical silence was not systematically related to parasite density or prior history of infection; irrespective of species, parasite density was not significantly correlated with temperature among children below 10 years of age.

However, logistic regression analysis identified three symptoms, in combination or sequence, to be excellent predictors of disease: fever, chills and sweating. A history of fever rigors and/or sweating greatly increased the probabilities based on the prevalence of the disease (Fig. 3). Over 84% and 92% of under-6-year-olds presenting with fever followed by rigors or sweating (paroxysms) were microscopically positive when observed at home and at the clinic, respectively; 90% of older children (i.e., 6–10-year-olds) presenting with these symptoms were parasite-positive when observed at home. However, after the age of 10, there was a reduced likelihood for presentation with these symptoms, whether observed at home (59%) or in the clinic (62%). During the winter (November to January) when the prevalence of acute lower respiratory infections increased, the positive predictive values for paroxysms were 100% (Table 2).

Clinical silence, i.e., the absence of a symptom (or group of symptoms), did not necessarily indicate absence of infection; negative predictive values were therefore not high (41–57%). Only 11 (2%) of our sample had taken chemotherapy prior to interview.

**Discussion**

Clinical case definitions are often the most widely used therapeutic guide at the periphery because other diagnostic methods are not rapid enough or available. If we wish to reduce morbidity and prevent death, we need to develop and validate simple diagnostic criteria for case management so that more rational therapeutic, investigative and referral procedures develop. The goal is to allow early detection

| Table 1: Percentage of reported fever cases at home and in the clinic, by observed temperatures |
|------------------------------------------|---------------|-------------|---------------|-----------|
| Observed temperature | Reported fever (%) |             |              |           |
|                        | Reported fever (%) |             |              |           |
| At home:               | None | Continuous | Intermittent | Total (%) |
| >37.6 °C               | 8.6  | 44         | 46           | 100 (99)* |
| <37.6 °C               | 23.8 | 33.6       | 42           | 100 (113) |
| In the clinic:         |               |             |              |           |
| >37.6 °C               | 23           | 77          | 100          |
| <37.6 °C               | 2.3          | 73.8        | 100          |

* Figures in parentheses are the number of cases.
and therapeutic response of potentially severe or fatal conditions, to minimize unnecessary referrals and negative results of investigations, to improve case management, and to promote better compliance with treatment. For maximum impact the diagnostic criteria should be clear and precise enough to be understood and applicable by non-experts.

An essential requirement of a good diagnostic screen is that it should greatly increase the probability that the patient has the disease, compared with a guess based on the prevalence of the disease. Our data collected in a hyperendemic area of the Philippines where approximately half of all children were infected (prior probabilities), but only 11.3% had symptomatic infections, suggest that a fever case-definition/screen would not yield the desired improvement in diagnosis. We found the classical clinical picture of malaria was that of a patient complaining of fever. This was followed by a chilly sensation accompanied by shivering, rigor or seizures. Body temperature subsequently returned to normal with or without a bout of profuse sweating. An algorithm identifying patients who had two of these three classical symptoms of malaria (one of which was fever), in a combination or in a sequence, was a good discriminator for the disease.

The post-screen predictive values were extremely high in the endemic communities (84%) and acceptably high (77%) at the outpatient clinic—the only one in the province. The simplicity of the formula, the higher predictive value in the community compared to the clinic, and the poor access to outpatient care were sufficient criteria to warrant case-management within the community.

In the highly endemic communities we studied, the predominant parasite was *P. falciparum* and age-specific rates of infection and disease were highest in the youngest age groups. If the children presenting with a sequence of the classical symptoms of malaria had been given radical treatment at home, 84–100% would have been correctly treated, 0–16% may have been false positives and unnecessarily treated (although it must be remembered that negative microscopic diagnosis does not necessarily mean absence of infection), and some 10% of infected

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<th>Table 2: Variations in predictive values of symptoms, by age, place of presentation and season</th>
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<td>Paroxysms: fever, chills and/or sweating</td>
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<tr>
<td>Age:</td>
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<td>&lt;5.9 years</td>
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<td>Place of observation:</td>
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children only reporting fever would have been falsely declared negative. During the winter season when respiratory infections among children increased, delivery of radical treatment to all children reporting a sequence of the classical symptoms would correctly include 94–100% of children with malaria. Radiographic evidence was not available to measure the co-existence of malaria and acute lower respiratory tract infection.

The present protocol for the malaria-endemic areas of the Philippines is derived from the eradication phase and requires that all suspect malaria cases should be declared slide-positive prior to delivery of chemotherapy. Reading of the blood slide, which takes from 9 days to 4 weeks at a peripheral health clinic in a low-level endemic area (22), takes much longer in an area where the case load is continuously high. Thus, radical treatment is given only if the patient makes a second visit to the clinic for this purpose.

Speed and reduced uncertainty in identification of mild and severely diseased patients who will respond to and comply with malaria treatment are critical. Fever alone oversimplifies the case definition for malaria. However, a relatively simple protocol in which fever is only one of the components can be developed to identify the disease clinically, especially among children within highly endemic communities (Fig. 4). Used correctly by mothers and community health-workers or in clinics, this protocol can lead to faster case management, thereby reducing morbidity at an earlier stage.

The goal of killing the parasite has no value unless the sick patient becomes better. It is therefore more important to improve our understanding of the possibilities and limits of clinical predictors and use them to target the treatment than to validate the one-to-one relationship between a given clinical predictor and a specific disease. What matters is to recognize which patients respond to different forms of treatment rather than argue over the truth of the diagnosis with which their syndromes are labelled.

Résumé
Identification symptomatique du paludisme au domicile du patient ou au centre de soins de santé primaires

Les définitions de cas cliniques constituent souvent le guide thérapeutique le plus utilisé dans les régions reculées, car les autres méthodes de diagnostic prennent trop de temps ou ne sont pas disponibles. Dans les zones d’endémie palustre où il est impossible de procéder à un examen microscopique, la définition du cas de paludisme adoptée par l’OMS est la présence ou un antécédent de fièvre sans autre cause évidente. Les recherches effectuées jusqu’ici sur cette question ont été menées sur des populations de patients ambulatoires mal caractérisées, et il est difficile d’en tirer des conclusions en raison de la nature variable des études, des populations étudiées et du risque épidémiologique. Il est donc difficile de se prononcer sur l’exactitude, la prédicibilité et la fiabilité des symptômes cliniques retenus pour poser le diagnostic de paludisme.

Aux Philippines, dans un environnement épidémiologique bien caractérisé, nous avons constaté que la température corporelle ou un antécédent de fièvre n’étaient pas de bons critères de diagnostic. Par contre, la survenue successive de la fièvre, de frissons et/ou de sueurs, ou une combinaison de ces trois symptômes, ont une bonne valeur prédictive. Etant donné que l’on peut s’attendre à ce que la température corporelle varie au cours de la maladie et que les patients se présentent à la clinique à différents stades de celle-ci, il n’est pas surprenant que la prédicibilité du diagnostic varie de façon significative selon le lieu où il est posé. La spécificité et la valeur prédictive positive étaient maximales pour les groupes d’âge particulièrement à risque (enfants de moins de neuf ans), et c’est au domicile du patient que le diagnostic était le plus fiable. La bonne prédicibilité des symptômes cliniques pour les groupes à haut risque permet de penser que des protocoles simples pourraient être mis au point pour la prise en charge du paludisme dans les zones d’endémie des Philippines.

Fig. 4. Simple protocol for case management of malaria.

Temperature > 37.6°C or history of fever

| Yes | Chills or shivering after fever
| Yes | Sweating

No

Probably not malaria

Probably malaria Treat with full course and observe

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References


