

FAILURE OF NATIONAL GUIDELINES TO DIAGNOSE UNCOMPLICATED MALARIA IN BANGLADESH

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Abstract. During the mid 1990s, national guidelines were established in accordance with World Health Organization recommendations for the diagnosis of uncomplicated malaria in Bangladesh. Based on simple clinical and epidemiologic criteria these guidelines were designed to be applied outside of tertiary care centers where microscopy was not feasible. We evaluated the positive predictive value (PPV) of these criteria using microscopic slide examinations as the gold standard in 684 subjects diagnosed and treated for malaria, sampling from eight subdistrict centers. The PPV for malaria was 32% with 19% for falciparum and 14% for *Plasmodium vivax*. Medical officers assigned to the study also gave their own clinical impression of whether cases could have been malaria. With the additional criteria of a medical officers' diagnosis, the PPV increased negligibly to 37% with 23% and 14% for falciparum and vivax, respectively. Since the PPV of diagnosis is low and cannot be improved on clinical grounds alone, we recommend the incorporation of laboratory diagnosis. This is especially important as we detect resistance to the first-line therapy chloroquine and require more expensive, potentially more toxic, regimens.

INTRODUCTION

In many areas of the world where microscopy is unavailable, the diagnosis and treatment of malaria depends on clinical and epidemiologic criteria. Because severe consequences may exist if a falciparum case is not treated, the guidelines have been conservative, resulting in the overtreatment of many who do not have malaria. If first-line drugs, such as chloroquine, are effective its low-cost and low-toxicity compensate for overtreatment, making this still an efficient method of case management. However, as drug resistance develops and recommendations are made for alternate drugs that are more expensive and potentially more toxic and difficult to comply with, one must reassess the costs and benefits of current diagnostic guidelines, which lead to overtreatment.¹ In addition to these immediate effects, the need to limit drug use as a possible means of delaying the long-term development of resistance has now become an important consideration.

The malarious areas of Bangladesh are along its eastern border with about 35 million people at risk. There were about 378,000 reported clinical cases and about 60,000 laboratory-confirmed cases with 528 deaths in 1998.² During the peak transmission months, just prior to and after the rainy season, a 20% increase was present in the number of cases. Malaria is a known cause of febrile illness in this area of Bangladesh for a long period³. There were a few thousand malaria deaths per year reported from these areas during the mid 1990s.⁴ During this period, Bangladesh revised its malaria-control strategy in line with the World Health Organization (WHO) guidelines to emphasize early detection and prompt treatment of cases in more peripheral health facilities, many without the ability to support microscopy for the large number of cases.⁵ The new diagnostic criteria were: fever or history of fever within the last 48 h; residence in an endemic area, an absence of signs of other disease; and inadequate antimalarials (or none) during the 4 weeks prior to present illness. In conjunction with these diagnostic criteria, chloroquine was advocated as first-line treatment of uncomplicated malaria (UM). Unfortunately, neither the accuracy of diagnosis nor the efficacy of

chloroquine for falciparum malaria have been evaluated since these guidelines were made.

Recently we have reported *in vivo*, *Plasmodium falciparum* chloroquine resistance of 70% in this area.¹ This study also showed a much higher efficacy of alternate regimens (quinine for 3 days plus Fansidar, quinine for 7 days and mefloquine), which are much more costly and hard to administer. With the recommendation now being considered to change first-line therapy, we thought it important to evaluate the amount of overtreatment that would occur if one continues with the current diagnostic guidelines. In epidemiologic terms we were looking at the positive predictive value (PPV) of standard diagnosis (by National Guidelines and/or clinical impression). The PPV is defined as the proportion of those positive by standard diagnosis who had malaria according to a gold standard test (slide confirmation). In addition, we examined if a medical officer's diagnosis could improve the PPV of diagnosis and therefore reduce the amount of overtreatment.

METHODS

Design. The study was designed as a multicentered, cross-sectional study blocked by season and time of day when patients presented. Its principal purpose was to determine the PPV of subjects diagnosed and treated for uncomplicated malaria by the National Guidelines using microscopic diagnosis as the gold standard. The PPV of the doctors' diagnosis of malaria in addition to criteria of the national guidelines diagnosis will be evaluated. These doctors were assigned as part of the study and did not make the initial malaria diagnosis by National Guidelines. The study size (targeting 800 subjects) was calculated to be able to give a 95% confidence intervals of $\pm 4\%$ around a point estimate of PPV of 50%. In addition, with 400 in each group, we could detect a 10% difference from the point estimate of PPV of 50% ($\alpha = 0.05$; $\beta = 0.20$) for comparisons between seasons and between morning and afternoon patients. Statistical tests used were χ^2 and exact binomial determinations of confidence intervals. We performed a sensitivity analysis, which added the error/

uncertainty of our slide reading results, (compared with reference laboratory) to the statistical uncertainty.

Study Site/Population. The study was conducted at eight health centers of five malaria endemic areas of Bangladesh. Two medical officers from each center were retrained regarding malaria symptoms and the national guidelines for diagnosis and treatment. Subjects were selected from patients attending the outpatient departments of the health center who were diagnosed and treated as uncomplicated malaria (not by the study doctors) according to national guidelines. Although a national policy exists to encourage taking malaria smears at these health centers, because of an overwhelming demand, the majority of patients are treated without slides. In addition, slides are often not read in time to affect individual patient's treatment but taken as an epidemiologic survey of malaria load presenting to the hospital. Patients with any signs or symptoms of severe malaria, gave a history compatible with malaria treatment failure or had evidence of a nonmalaria febrile illness were excluded from the study. After subjects were diagnosed as having malaria by national guidelines, the study's medical doctors were allowed to confer with each other before giving their own malaria diagnoses that were categorized as either very likely, maybe, or unlikely. We had planned to enter a total of 800 subject with 100 subjects from each health complex, with half of the subjects to be enrolled during peak transmission season and half during the period of lower transmission. In addition, half of the subjects were to be enrolled during the morning hours and half during the afternoon, since it was felt that sicker patients, possibly associated with malaria, may present more often during the morning clinic. Thick and thin blood films were made, but results were read later and not used in the management of cases. Standard blood slide examination was done by a medical officer trained in malaria microscopy, according to the WHO Guidelines⁶, and slide readers were blinded to the clinical diagnoses. Ten percent each of the positive and negative slides were reexamined blindly by the National Malaria Reference Laboratory to evaluate the accuracy of our study's slide examination results.

RESULTS

Verbal informed consent of the participants or from parents or legal guardians was obtained, and the study was approved by the Ethical Clearance Committee of Chittagong Medical College, Chittagong, Bangladesh.

During the 6-month study period, between May 1998 and October 1998, a total of 944 subjects were enrolled. The age distribution of patients were: under 9 years, 29.1%; between 10–19 years, 30%; between 20–29 years, 19.5%; between 30–39 years 11.9%; and 9.6% patients were above the age of 40, with a mean (\pm SD) of 18.2 (\pm 1.2) years. Fifty-two percent of subjects were female. Midway through the study, we examined the quality of slides and found that 37% of the 444 slides were unreadable due to preparation, storage, or staining problems. After retraining all technicians, the rate of unacceptable slides was reduced to 19% of 500 during the second half of the study. The unreadable slides were not associated with any particular health center, severity of illness, or doctors' opinion. Therefore, out of 944 slides collected, 260 slides were classified as unreadable and excluded from the analysis. Ten percent of the readable positive and negative slides were

sent for confirmatory reading at the National Reference Malaria Laboratory where of the 12 slides classified as *P. falciparum* by the investigators, only 11 were confirmed (one confirmed as negative), only five of the seven vivax slides were confirmed (two confirmed as negative) and 40 of the 41 negative slides were confirmed (one confirmed as *P. falciparum*). From the evaluations comparing field reading to those done by the reference laboratory, for both types of malaria the sensitivity was 94% (95% CI 71.3–99.9), and the specificity was 93% (95% CI 90.0–98.5). The patient profile of the 684 cases with readable slides were: fever at presentation 425 (62.1%), fever in preceding 48 hours 629 (91.9%), migrant 21 (3.1%), and history of antimalarials (inadequate doses) during preceding 4 weeks 53 (7.7%). Two hundred and eighty five patients (41.7%) were enrolled before noon, and 399(58.3%) were enrolled in the afternoon. Approximately, 457 patients (66.8%) were enrolled during peak transmission season (May, September, and October), and 227 patients (33.2%) were enrolled in off-peak months (June–August).

The category of diagnosis and parasitologic status of the patients enrolled in the study has been provided in the Table 1. For any type of malaria, the PPV of the national guidelines was 32.3% (95% CI, 28–36). The PPV of the peak transmission season was significantly lower (27.6%) than that of the off-peak season (40.8%), $P < .001$. There was no significant difference in the PPV ($P > .5$) of national guideline diagnosis between afternoon and before noon subjects. The overall (without stratification by season or time of day) PPV for *P. falciparum* was 19.4% (95% CI 16.5–22.6). For *Plasmodium vivax* the PPV was 12.7% (95% CI, 10.3–15.5). If one adds the uncertainty of slide reading to the statistical uncertainty, the uncertainty interval for any type of malaria increases to 23–37.6%, for *P. falciparum* it increases to 14.9–24.2%, and for vivax the combined uncertainty is 6.75–15.5%. According to the doctors' diagnosis subjects were categorized as: very likely 422 (61.7%), maybe 216 (31.6%), and unlikely 46 (6.7%). If one diagnoses malaria by the national guidelines and adds the criteria that a doctor's opinion would also be very likely, the PPV increases slightly to 37% (95% CI 32.4–41.7) for all malaria cases; for *P. falciparum* to 23.2% (95% CI 19.2–27.5); and for *P. vivax* to 13.7% (95% CI 10.7–17.4). We did not perform a sensitivity analysis of this latter set of results because we are more concerned with the point estimate values rather than the uncertainty intervals. Of those meeting National Guidelines criteria, for those diagnosed by the study doctors as negative, the proportion who were slide negative (with a negative predictive value, [NPV]) was 75% (95% CI 69.5–80.3) for all malaria; 86% (95% CI 81.5–

TABLE 1
Category of doctors' opinion and parasitologic status in 944 cases of uncomplicated malaria

	Very likely	Maybe	Unlikely	Total
<i>Plasmodium falciparum</i>	98	29	6	133
Mixed	0	1	0	1
<i>Plasmodium vivax</i>	58	25	4	87
Negative	266	161	36	463
Not Readable	202	55	3	260
Total	624	271	49	944

90.2) for *P. falciparum*; and 89% (95% CI 84.5–92.5) for *P. vivax*.

DISCUSSION

This study revealed that malaria is responsible for febrile illness in only one third (PPV) of patients who received treatment in outpatient departments of hospitals in high-risk areas according to national guidelines of Bangladesh. Furthermore, there was little improvement of diagnostic accuracy when physicians' clinical diagnosis was added. These findings apply to both *P. falciparum* and *P. vivax* malaria considered together and separately. There was no difference in diagnostic accuracy by time of day at which patients presented to the clinic. However, there was a significant increase in the PPV during the lower malaria transmission season. This latter finding is somewhat difficult to explain because the PPV should increase with a higher prevalence of a disease (during the peak transmission season). It is possible that during the low transmission season there is a reduction in the absolute number of malaria cases but an even greater reduction in the incidence of illnesses whose symptoms mimic malaria. Alternatively, the lower PPV during the high malaria transmission season might mean that the clinics were anticipating, and diagnosing, much more malaria than what actually occurs. We did not attempt to determine the etiology of illnesses, which were clinically misdiagnosed as malaria, nor did we try to determine the outcome of mistreatment with antimalarial drugs.

With the centers performing so few slides routinely, the number of poorly prepared slides for the study was high and could have been the cause of inaccurate readings. The sample of slides sent for confirmatory reading should have been larger to better estimate the magnitude of error in slide reading. Nevertheless, we performed a sensitivity analysis to adjust for the slide reading errors and found that the additional uncertainty did not change our conclusion of low PPV values of diagnosis, resulting in significant overtreatment and little improvement with a doctor's clinical diagnosis.

Our finding of poor clinical diagnosis is compatible with results of others^{7,8,9} but incompatible with a 70% PPV previously found in a nearby study area¹⁰. In this latter study conducted in a new settlers' camp of high-risk areas, all the febrile cases were included from one community over a period of 1 year. The category of uncomplicated malaria was not made in that study.

In a situation of low PPV, the resulting overtreatment of patients who do not have malaria would be acceptable if the drug is cheap and with few side effects. In this era of drug resistance another important consideration must be to limit the widespread administration of antimalarials which results in higher drug pressure and more rapid development of resistance. For those with malaria when the first-line therapy has low efficacy, we must change to more expensive, potentially more toxic, alternatives; this is sometimes difficult to comply with. This decision that improves the cure rate for malaria patients is unnecessarily costly for the majority who do not have malaria. When one considers changes in first-line drugs, one first wonders how much overtreatment is occurring under the standard diagnostic guidelines. The PPV reflects (its compliment) this amount of overtreatment. Conversely, the negative predictive value, NPV (proportion of those diagnosed as negative who are truly negative by gold standard

test), reflects (its compliment) the proportion of malaria patients who do not receive treatment. To some extent under-treatment is independent of what first-line drug is used and the NPV is considered only when diagnostic criteria change (perhaps as a consequence of changing drugs). Thus, this study focused on the PPV rather than the NPV, because we were initially concerned with only a drug change. With our findings of inaccurate diagnosis, we are forced to consider diagnostic changes and consequently an evaluation of both PPV and NPV.

Our recent finding of poor chloroquine efficacy will force us to recommend such costly alternatives,¹ coupled with this will be a recommendation to improve the PPV of current diagnosis. From our study, it seems obvious that this improvement can neither be achieved by better clinical judgment nor by stratifying patients according to simple epidemiologic factors (time of day of presentation, season). It is time to consider incorporating laboratory diagnosis such as microscopy and dipstick methods at this level of patient care. The only other alternative would be to make clinical diagnosis so restrictive that a high PPV will be achieved. But in this case, one would need to evaluate the number of malaria cases who would be untreated and the NPV of diagnosis.

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