MAJOR ARTICLE

Rapid Diagnostic Test–Based Management of Malaria: An Effectiveness Study in Papua New Guinean Infants With *Plasmodium falciparum* and *Plasmodium vivax* Malaria

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Background. In malaria-endemic areas it is recommended that febrile children be tested for malaria by rapid diagnostic test (RDT) or blood slide (BS) and receive effective malaria treatment only if results are positive. However, RDTs are known to perform less well for *Plasmodium vivax*. We evaluated the safety of withholding antimalarial drugs from young Papua New Guinean children with negative RDT results in areas with high levels of both *Plasmodium falciparum* and *P. vivax* infections.

Methods. longitudinal prospective study of children aged 3–27 months visiting outpatient clinics for fever. RDT was administered at first visit. RDT and microscopy were performed if children returned because of persistent symptoms. Outcomes were rates of reattendance and occurrence of severe illnesses.

Results. Of 5670 febrile episodes, 3942 (70%) involved a negative RDT result. In 133 cases (3.4%), the children reattended the clinic within 7 days for fever, of whom 29 (0.7%) were parasitemic by RDT or microscopy. Of children who reattended, 24 (0.7%) presented with a severe illness: 2 had lower respiratory tract infections (LRTIs) with low-density *P. vivax* on BS; 2 received a diagnosis of *P. vivax* malaria on the basis of RDT but BSs were negative; 16 had LRTIs; 3 had alternative diagnoses. Of these 24, 22 were cured at day 28. Two children died of illnesses other than malaria and were RDT and BS negative at the initial and subsequent visits.

Conclusion. Treatment for malaria based on RDT results is safe and feasible even in infants living in areas with moderate to high endemicity for both *P. falciparum* and *P. vivax* infections.

In many countries, patients are treated presumptively for malaria when presenting with febrile illnesses. This is because (1) no diagnostic tools are available (microscopy or rapid diagnostic tests), (2) health workers do not trust the results of these tests [1, 2], or (3) there are scarce data on the safety of withholding antimalarial drugs in patients with a negative malaria test result. This is especially true in children aged <5 years, for whom presumptive antimalarial treatment was promoted by the World Health Organization (WHO) [3] for decades before a change of policy toward universal diagnosis beginning in 2010 [4].

The situation has evolved, and more tools and data are now available for the management of suspected malaria episodes, in particular in sub-Saharan Africa [5]. First, community awareness in endemic areas of the importance of early attendance at a health facility when a child is febrile has improved [6]. Second, reliable and affordable rapid diagnostic tests (RDTs) for malaria are now widely available [7, 8, 9, 10]. Third, safe and highly efficacious treatments for malaria (artemisinin-based combination therapies) are available in almost all endemic countries. Last, 2 recently published studies have demonstrated

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the safety of withholding antimalarial drugs in children aged <5 years and adults with negative malaria RDT results in Tanzania, where *Plasmodium falciparum* is the predominant species [11, 12].

The safety and effectiveness of microscopy or RDT-based malaria treatment have not been investigated in infants. Moreover, it is not clear whether withholding antimalarial treatment in young children with fever and negative RDT results is safe in different epidemiological contexts, especially in areas with a high prevalence of *Plasmodium vivax* infections. This is a concern, because it is now well established that untreated *P. vivax* infections might lead to severe diseases [13, 14]. Part of the uncertainty lies in the fact that many RDTs are less sensitive for the diagnosis of *P. vivax* infections than for *P. falciparum* [8, 15, 16, 17]. More data are thus needed to ensure that the new WHO policy of prescribing antimalarials only to children with confirmed parasitemia is safe in all settings [18]. It must be a priority in terms of clinical management of febrile illnesses, because it is well recognized that presumptive treatment for malaria may delay the management of other potentially life-threatening diseases and promote the development of resistance to antimalarial drugs [1].

In coastal Papua New Guinea, malaria is highly endemic and *P. vivax* accounts for at least one-half of all infections in children aged <5 years [19, 20, 21]. As part of a large trial of intermittent preventive treatment in infants (IPTi) (Senn N et al, submitted, September 2011), a passive case detection surveillance system was implemented. All sick study participants presenting spontaneously at the study clinics with fever or history of fever were screened with an RDT for *P. falciparum* and non–*P. falciparum* malaria infections and treated with artemether-lumefantrine only when the test was positive for one or the other species. The standardized approach to case management used thus offered an excellent opportunity to investigate the safety of withholding antimalarial drugs in febrile patients with a negative RDT result in a situation where *P. vivax* infections are very common.

METHODS

Background and Study Sites

This work was carried out alongside an IPTi trial that included 1605 children aged 3 months old at enrollement and followed-up until 27 months between 2006 and 2010 (www.ClinicalTrials.gov: NCT00285662). Children were randomly assigned to a treatment course of a single dose of sulfadoxine/pyrimethamine (SP) with either 3 days of amodiaquine (SP-3AQ) or 3 days of artesunate (SP-3AT), or to a placebo group. The doses were given every 3 months during the first year of life, along the immunization schedule.

This trial took place in 2 locations: (1) Mugil (Madang province): the main study site where an average of 0.94 episodes per child per year was observed and *P. vivax* accounted for more than two-thirds of all infections; and (2) Maprik (East Sepik province): a secondary study site where the incidence of malaria was significantly lower (0.13 episodes per child per year; $P < .001$).

Data Collection

A passive case detection surveillance system had been established for 16 years in Maprik [14] and 3 years in Mugil [22] prior to the present study. The same infrastructure was used for IPTi. A standard case report form was completed for each illness episode that included all relevant signs and symptoms, as well as the clinical management. When presenting with fever/history of fever during the past 48 hours, children were screened with an RDT for *P. falciparum* and non–*P. falciparum* malaria infections (ICT Combo, South Africa) and treated with

Table 1. Matrix of Interpretation of Blood Slides and Rapid Diagnostic Test Results Upon Reattendance at Clinic

	RDT Results				
BS Results	Neg	Pf	Pv	Possibly Mixed Pf and Pv	No RDT
Neg	Def neg[a]	Poss Pf[b]	Poss Pv[b]	Poss Pf and poss Pv[b]	Prob neg[a]
Pf	Prob Pf[c]	Def Pf[d]	Prob Pf and poss Pv[d]	Def Pf and poss Pv[d]	Prob Pf[c]
Pv	Prob Pv[c]	Prob Pv and poss Pf[d]	Def Pv[d]	Def Pv and poss Pf[d]	Prob Pv[c]
Pm	Prob Pm[c]	Prob Pm and poss Pf[d]	Def Pm[d]	Def Pm and poss Pf[d]	Prob Pm[c]
Mix	Prob Pf and prob Pv[c]	Def Pf and prob Pv[d]	Def Pv and prob Pf[d]	Def Pf and def Pv[d]	Prob Pf and prob Pv[c]
No BS	Poss neg[a]	Poss Pf[b]	Poss Pv[b]	Poss Pf and poss Pv[b]	No results[e]

Abbreviations: BS, blood slide; Def, definite; neg, negative; Pf, *Plasmodium falciparum;* Pm, *Plasmodium malariae;* poss, possible; prob, probable; Pv, *Plasmodium vivax;* RDT, rapid diagnostic test.

[a] Negative malaria.

[b] Possible malaria.

[c] Probable malaria.

[d] Definite malaria.

[e] No results.

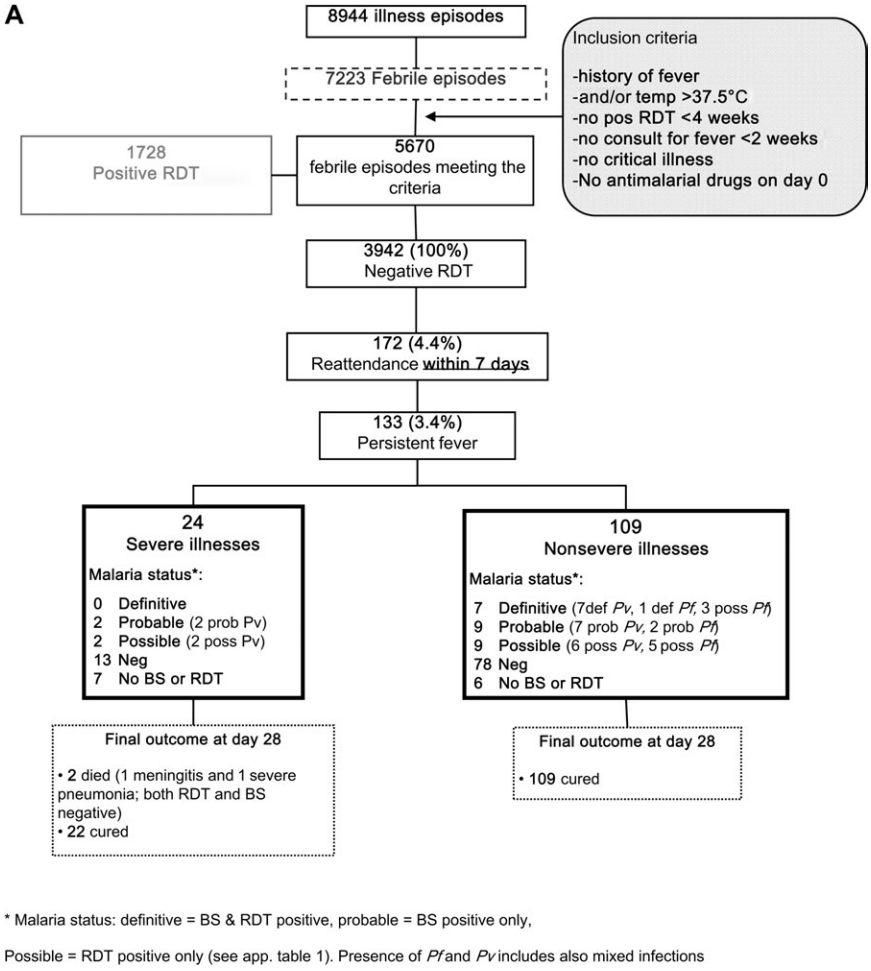

Figure 1. *A* and *B,* Flowcharts showing the clinical and parasitological outcomes upon reattendance within 7 and 28 days following a negative rapid diagnostic test (RDT) result. Abbreviations: *Pf, Plasmodium falciparum; Pv, Plasmodium vivax.*

artemether-lumefantrine (Coartem, Novartis) only if the test result was positive for any species.

Two thick and thin blood slides (BSs) for malaria microscopy were also collected. On the rare occasions when infants visited a health facility after hours (when the study clinics were closed), they were managed according to the national guidelines by the staff on duty. A review was made by study nurses on the following day. If a child died at home, a verbal autopsy was performed (assessing the possible cause of death on the basis of information provided by parents through a standardized questionnaire).

All procedures followed the Good Clinical Practice guidelines, and all parents signed an informed consent form when enrolling their child in the IPTi study. The IPTi protocol was approved by the Medical Research Advisory Committee of Papua New Guinea (MRAC no. 05/20).

Study Design and Procedures

The present work makes use of morbidity data of the IPTi trial cohort to perform a safety assessment of children for whom an RDT was performed as part of a passive case detection visit. The inclusion criteria were as follows: RDT performed, children aged 3–27 months enrolled in the IPTi study, history of fever during the previous 48 hours and/or temperature >37.5°C, no positive RDT result during the previous 4 weeks, no consultation for history of fever/elevated temperature during the past 2 weeks, no antimalarial drugs prescribed on the day of consultation if RDT negative, and no severe illness on the day of consultation. One or more illness episodes could occur for each child enrolled in the study.

For all children with the above-mentioned inclusion criteria, we determined whether they reattended any of the study clinics during the following 7 and 28 days. Upon reattendance, we investigated whether they still had fever and examined the clinical and laboratory outcomes. Each child's reattendance was classified as death, severe illness, or nonsevere illness managed as an ambulatory case. The result of the new RDT performed upon reattendance was confirmed by BS for all illness episodes and deaths. For the children who had died or had been admitted elsewhere or after hours, we recorded the diagnosis, management,

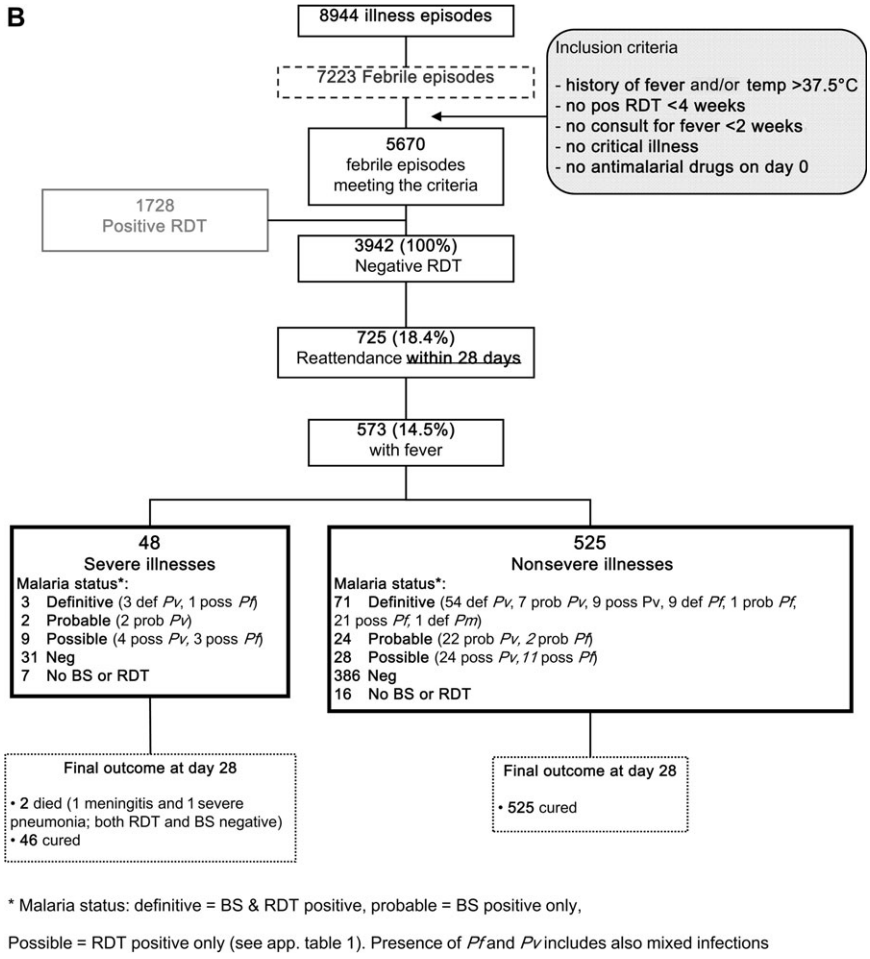

Figure 1. Continued.

and treatment from the health book or records from the health center. A severe illness was defined as an illness episode that resulted in hospital admission or was life-threatening (see Supplementary Table 1 for criteria).

Interpretation of Blood Slide and RDT Results

Study participants who experienced a febrile episode underwent RDT so that a course of treatment could be determined. A BS was also collected for research purposes but was read months after the episode. Thick films were examined by light microscopy for 200 fields before being declared infection negative. Parasite species in positive films were identified and densities recorded as the number of parasites per 200 white blood cells (WBCs). Densities were converted to the number of parasites per microliter of blood assuming 8000 WBCs per μL (population average WBC count [3]). All slides were read independently by 2 experienced microscopists, and in cases of discrepant readings a third independent reading was performed.

It is well known that discrepancies between BS readings and RDT results can be important because of the fact that the 2 tests detect different components (antigens for RDT and whole parasites for microscopy). Therefore, we designed a matrix to interpret the combination of BS and RDT upon reattendance using conservative criteria to define malaria (see Table 1). According to this matrix, we defined 4 categories of malaria status upon reattendance: (1) negative = BS negative and RDT negative, or BS or RDT negative and corresponding BS or RDT absent; (2) definite malaria = BS positive and RDT positive; (3) probable malaria = BS positive and RDT negative or absent; (4) possible malaria = RDT positive and BS negative or absent.

Data Analysis

Data were double-entered using FoxPro software. Data management and analyses were performed using STATA software, version 10.0 (StataCorp). Reattendance rates within 7 and 28 days for the different outcomes were obtained for children fulfilling inclusion criteria.

RESULTS

General Description of the Cohort

Between June 2006 and May 2010, 1605 children aged 3–27 months were enrolled and followed up in the IPTi randomized controlled trial (Madang, 1125; Maprik, 480). A total of 1512 children (94%) experienced at least 1 illness episode (Madang, 1053; Maprik, 459). The morbidity surveillance reported a total of 8944 illness episodes (Madang, 5978; Maprik, 2966), of which 7223 were febrile (Madang, 5249; Maprik, 1974). The average number of febrile episodes per child was 4.8. Thirteen deaths and 371 severe illnesses were reported during the observation period. The mean duration of symptoms before attendance was 2.7 days (95% confidence interval [CI], 2.6–2.8 days) in febrile children.

A total of 5670 febrile episodes (Madang, 4103; Maprik, 1567) fulfilled the inclusion criteria and were included in the analysis; 1899 occurred in children enrolled in the SP-3AQ group, 1888 in the SP-3AT group, and 1883 in the placebo group. A total of 3942 (70%) of the episodes occurred in infants who had a negative RDT result at inclusion; 2512 (61% [95% CI, 60%–63%]) were negative in Madang (high endemicity) and 1430 (91% [95% CI, 90%–93%]) in Maprik (low endemicity). There was a positive RDT result at inclusion for 1728 (30% [95% CI, 29%–32%]) febrile episodes. According to RDT results, 19% (95% CI, 17%–21%) were positive for *P. falciparum* only, 37% (95% CI, 35%–39%) were possibly mixed infections (*P. falciparum* single or mixed with *P. vivax, Plasmodium ovale,* or *Plasmodium malariae*), and 44% (95% CI, 42%–46%) were non–*P. falciparum* infections. The median duration of symptoms was similar for children with negative and positive RDT results (2 days [interquartile ranges {IQRs} of 1–3 and 1–4, respectively]).

Clinical and Parasitological Outcomes Upon Reattendance Within 7 and 28 Days Following a Negative RDT Result

Figure 1*A* displays the outcome within 7 days of febrile episodes for children with a negative RDT result. Among the 3942 febrile episodes associated with a negative RDT result, 172 (4.4%) occurred in children who reattended the clinic within 7 days, of whom 133 (3.4%) had a history of fever and/or temperature >37.5°C. Twenty-nine (0.7%) of 3942 children with negative RDT result at day 0 reattended the clinic with a parasitemia identified by means of RDT and/or BS. Among the 133 children who reattended with fever, 24 children (0.7%) presented with a severe illness, the median duration between initial negative RDT result and severe illness being 2 days (IQR, 1–4 days). Table 2 describes these severe illnesses in detail. Six children with a severe illness had neither an RDT nor a BS performed. This was usually because they were admitted during the night at the health facility when no study staff were present. For these children, the likely diagnosis was made on the basis of clinical records matched with treatment records. Of the 24 patients reattending with a severe illness, 2 children died, one upon admission of probable severe respiratory infection (as per clinical assessment), the other a week after admission probably of meningitis while being treated for a lower tract respiratory infection (LRTI); for both children RDT and BS were negative at initial and subsequent visit(s). Among the other 22 patients, 2 infants merited antimalarial treatment, because they received a clinical diagnosis of LRTI simultaneous with low-density *P. vivax* parasitemia (<1000 parasites/μL), but neither received treatment. Two other children had an RDT positive for *P. vivax* with negative BS result.

Considering the cumulative reattendance pattern from 0 to 28 days (Figure 1*B*), 725 infants visited the clinic, 573 had fever, 48 had a severe illness, and 2 died within 7 days (those already described above). For the 48 severe illnesses, up to 3 different diagnoses per child were recorded. The recorded clinical diagnoses included 32 LRTIs, 10 malaria infections (according to BS and/or RDT results: 3 definite malaria, 5 possible, and 2 negative; detailed species results are displayed in Figure 1*B*), 8 neurological syndromes (febrile fits and/or meningitis), 4 gastrointestinal diseases, 5 cases of anemia, 2 cases of otitis, 2 upper respiratory tract infections, 1 skin infection, and 5 other diagnoses.

DISCUSSION

In this study, we show that managing febrile infants with antimalarials solely on the basis of results of RDT was safe and effective in areas with a high endemicity for both *P. falciparum* and *P. vivax* in Papua New Guinea. These findings provide solid evidence of the safety of withholding antimalarial drugs in infants in an area highly endemic for *P. vivax* on the basis of the results of RDT only. They also confirm those of 2 other studies performed in older children and adults in Africa where *P. falciparum* was the predominant species [11, 12].

Although this study was conducted alongside a randomized controlled trial, no active follow-up of study participants was performed. Such passive case detection may reflect health-seeking behavior in routine practice in a location such as Papua New Guinea.

Almost 6000 febrile episodes were included in our analysis, and one-third of them were associated with malaria parasitemia according to the RDT results. No child died or had a severe illness because he/she was not treated with an antimalarial drug when the RDT result was negative. Among the patients with a negative RDT result, <4% reattended one of the study clinics within 7 days with persistent fever and only 0.7% (24) presented with a severe illness. About 0.1% of children with an initial negative RDT result reattended within 7 days with parasitemia identified by RDT or BS (none had definite malaria on the basis of a positive RDT result and BS). This represents the most conservative estimate of possibly missed malaria cases. Indeed,

Table 2. Details of Severe Illnesses at Reattendance Within 7 Days After a Negative Rapid Diagnostic Test for Malaria

Case No.	RDTm at Reattendance	Blood Slide at Reattendance	Antibiotics Received[a]	Antimalarial Received	Likely Diagnosis[b]	Outcome	Comments
1	Neg	Neg	Yes	No	LRTI	Died	Died on day of reattendance
2	Neg	Neg	Yes	No	LRTI	Died	Died 7 days later of meningitis
3	Neg	Neg	Yes	No	LRTI	Cured	
4	Neg	Neg	Yes	No	LRTI	Cured	
5	Neg	Neg	Yes	No	Malnutrition + LRTI	Cured	
6	Neg	Neg	Yes	No	LRTI	Cured	
7	Neg	Neg	Yes	No	Gastroenteritis	Cured	
8	Neg	Neg	Yes	No	LRTI + febrile fits	Cured	
9	Neg	Neg	Yes	No	LRTI	Cured	
10	Neg	Neg	Yes	No	LRTI	Cured	
11	Neg	Neg	Yes	No	LRTI	Cured	
12	Neg	Neg	Yes	No	LRTI	Cured	
13	Neg	Neg	Yes	No	LRTI	Cured	
14	Pos	Neg	No	Yes	LRTI	Cured	
15	Pos	Neg	Yes	Yes	LRTI + gastroenteritis	Cured	
16	Not done	Neg	Yes	Yes	LRTI	Cured	
17	Neg	Pos (Pv 960/μL)	Yes	No	LRTI + anemia + parasitemia (Pv)	Cured	Received co-trimoxazole
18	Not done	Pos (Pv 360/μL)	Yes	No	LRTI + parasitemia (Pv)	Cured	
19	Not done	Not done	Yes	Yes	Skin abscess at injection site	Cured	
20	Not done	Not done	Yes	No	LRTI + febrile fits	Cured	
21	Not done	Not done	Yes	No	LRTI	Cured	
22	Not done	Not done	Yes	No	LRTI	Cured	
23	Not done	Not done	Yes	No	Tuberculosis	Cured	Received antituberculosis treatment
24	Not done	Not done	Yes	No	LRTI	Cured	

Abbreviations: LRTI, lower respiratory tract infection; neg, negative; pos, positive; Pv, *Plasmodium vivax;* RDTm, rapid diagnostic test for malaria.

[a] Received penicillin or erythromycin unless specified in the comment column.

[b] Likely diagnosis is based on the review of clinical records matched with RDTm and blood slide results and the treatment received.

this includes not only recrudescence and relapses, but also new infections, coincidental parasitemia (most of them had a clear alternative diagnosis), and persisting antigenemia detected by means of RDT. Two children were admitted with a possibly missed diagnosis of malaria 1 day after the initial visit (2 with low-density *P. vivax* on BS, 1 with RDT-negative result and 1 without RDT result). These 2 severe illness episodes were treated appropriately, and the patients recovered without sequelae. It is however not possible to tell whether these cases were truly missed, or if they involved a new occurrence of malaria, or whether it was coincidental infection not responsible for the febrile episode.

These data are especially reassuring, because the RDTs used are known to have a limited sensitivity for the detection of low-density *P. vivax* infections. Indeed, as shown in the WHO's report on the performances of RDTs (round 2), the test used (ICT Combo) performed well at high densities of *P. vivax* (2000 parasites/μL) with a detection score of >90%, but poorly with 200 parasites/μL (detection score close to 0%) [8, 23]. The sensitivity of BS is greatly dependent on an individual microscopist's skills. Although highly trained and experienced microscopists, such as those who participated in this study, are able to readily identify parasitemia at concentrations of as low as 40 parasites/μL, the sensitivity of routine field microscopy is often substantially lower [24] and may not be superior to RDT-based diagnosis [25]. Nevertheless, this study highlights that appropriate use of even an imperfect tool can result in a very high overall clinical effectiveness. Because a new generation of tests with sensitivities for *P. vivax* as high as those for *P. falciparum* [26] are now available, the effectiveness of RDT-based diagnosis and treatment should increase even further.

This good clinical performance of RDTs calls into question the benefits of using more sensitive diagnostic tools, such as

polymerase chain reaction (PCR), for the management of clinical cases in rural health centers. Although PCR may be useful to confirm the species or to identify cryptic infections in nonimmune patients, it requires substantial resources and, even if point-of-care PCR systems become available, is unlikely to be cost-effective in most settings.

Previous studies in Africa showed that clinicians did not always treat children on the basis of malaria test results and tended to give antimalarials even to children with negative results [1, 27]. More recent pilot programs of RDT implementation in Zanzibar and Tanzania showed an excellent adherence to a policy of prescription based on positive test results. This strategy led to a dramatic reduction in consumption of antimalarial agents [12, 28, 29, 30]. One of the main contributors to the success of the most recent studies was a comprehensive training program, which led to a true change in clinicians' behavior. Unfortunately, the guidelines for management of nonmalaria fever episodes are often based only on syndromic management. On the basis of the experience with malaria and RDT, there is thus a need to develop new strategies that include easy-to-use tools able to investigate objectively the etiologies of nonmalaria fever episodes, especially in remote areas with limited facilities.

One of the limitations of our study is the use of a passive case detection system, which leaves patients free to visit or not visit the health facilities when sick. This type of surveillance may miss some malaria episodes. In addition, patients may visit a different health facility than that of the study when sick. Because the study clinics were the most easily accessible health facilities and care was free of charge for the study children, such events should have been rare. Some children may also occasionally receive so-called over-the-counter medication in case of fever. However, treatments delivered outside the health system are not widely available in the study areas. Despite these issues, it is certain that none of the children died from or was disabled by malaria, because all children were followed up after their illness episode.

In conclusion, this study provides solid evidence that the management strategy for febrile infants in rural outpatient clinics including a screening for malaria using RDT is feasible and safe even in infants in a setting of high and moderate endemicity for both *P. falciparum* and *P. vivax* malaria infections. The national policy in Papua New Guinea has been recently amended to reflect the new WHO recommendation of laboratory-based diagnosis and treatment upon result, and our findings provide evidence for its relevance and safety.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Authors' contribution. N. S., B. G., and I. M. designed the study. N. S., P. R., D. M., and M. S. led the project in the field. N. S. analyzed the data and wrote the manuscript. L. J. R. led the microscopy readings, quality control, and compilation of microscopy results. P. S. facilitated the laboratory and field work at PNG IMR. S. R. and J. R. contributed to the manuscript. All authors commented on the paper and agreed on the content.

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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