Effectiveness of Artemether/Lumefantrine for the Treatment of Uncomplicated *Plasmodium vivax* and *P. falciparum* Malaria in Young Children in Papua New Guinea

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Background. Artemisinin combination therapy is recommended as treatment for uncomplicated *Plasmodium falciparum* (*Pf*) malaria, whereas chloroquine is still widely used for non-*Pf* infections. A common treatment for both vivax and falciparum malaria would be welcome.

Methods. A longitudinal prospective effectiveness study of 1682 children aged 3–27 months in outpatient clinics in Papua New Guinea. The main outcome was clinical treatment failure rate following treatment with artemether/lumefantrine (AL).

Results. Among 5670 febrile episodes, 1682 (28%) had positive rapid diagnostic test (RDT) results and were treated with AL. A total of 1261 (22%) had an infection confirmed by blood slide examination. Of these, 594 *Pv* and 332 *Pf* clinical malaria cases were included in the primary effectiveness analysis. Clinical treatment failure rates at 7, 28, and 42 days were 0.2%, 2.2%, and 12.0%, respectively, for *Pv* and 0.3%, 1.2%, and 3.6%, respectively, for *Pf*. A single malaria-unrelated death occurred within 42 days following treatment with AL, in a child who was aparasitemic by blood slide at reattendance.

Conclusions. AL provides a rapid clinical response against both *Pf* and *Pv* malaria, but is associated with a high rate of *Pv* recurrent clinical episodes between days 28 and 42. In order to prevent relapsing infections from long-lasting hypnozoites, AL should ideally be complemented with a course of primaquine. In the absence of better treatment and diagnostic options, the use of AL in young children in routine practice is an acceptable, interim option in coendemic areas where *Pv* is resistant to chloroquine and specific treatment for *Pv* hypnozoites not feasible.

Keywords. malaria; artemether/lumefantrine; vivax; effectiveness.

Whereas artemisinin combination therapies (ACTs) are now almost universally recommended as first-line treatment for uncomplicated *Plasmodium falciparum* (*Pf*) malaria [1], chloroquine (CQ) is still recommended for non-*Pf* infections in most countries. The differing recommendations for *Pf* and *Pv* malaria have several potential negative consequences in routine clinical practice. Most importantly, they require good-quality parasitological diagnosis in remote areas where most malaria cases are diagnosed and treated. Even where species diagnosis is performed, misdiagnoses occur, and minority species in a mixed infection can easily be missed. Given the almost universal presence of CQ-resistant *Pf* [2–4], such misdiagnosis can have serious consequences. Using rapid diagnostic tests

Received 20 September 2012; accepted 28 January 2013; electronically published 12 February 2013.

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Clinical Infectious Diseases 2013;56(10):1413–20

DOI: 10.1093/cid/cit068

(RDTs) based on *Pf* histidine-rich protein 2/pan–lactate dehydrogenase, or *Pf*-HRP2/aldolase, it is impossible to differentiate monospecies *Pf* infections from mixed infection with *Pf* and another species in the absence of microscopic confirmation. The resulting complex recommendations are likely to confuse health workers in coendemic areas. Finally, in areas with significant levels of CQ resistance such as Oceania and Indonesia, but also increasingly elsewhere [5], the World Health Organization now recommends the use of ACTs also for the treatment of *Pv* [1]. Thus, a common treatment approach for both vivax and falciparum malaria would be welcome.

Douglas and colleagues [6] reviewed the appropriateness of a single ACT-based strategy for both *Pf* and *Pv* in coendemic regions and concluded that it might be a reasonable option where *Pv* is resistant to chloroquine. However, the authors also pointed out that this recommendation is based on a small number of highly controlled efficacy trials and that data are lacking on the effectiveness of this strategy in routine settings [7–9].

Papua New Guinea (PNG), Solomon Islands, and Vanuatu have adopted artemether/lumefantrine (AL) as a common first-line antimalarial treatment. To date, 3 trials have investigated the in vivo efficacy of AL for *Pv* in endemic populations [4, 10, 11]. Despite good initial clearance of parasites, clinical recurrences occurred in >10% of recipients within 42 days. Karunajeewa et al [4] showed also in PNG that more than half of patients with *Pv* infections at enrollment had recurrent *Pv* parasitemia by day 42 following initial treatment with AL. All these trials were carried out in highly controlled settings with active case detection, and a recent review by Bassat [12] concluded, like Douglas [6], that a rigorous assessment of the use of AL in routine clinics to treat *Pv* infections is required.

Papua New Guinea is highly endemic for malaria in coastal areas, where malaria incidence rates in small children are approximately 1 episode per year per child [7, 9]. In children aged <2 years, *Pv* accounts for at least half of all malaria infections and clinical episodes [7, 9, 13]. As part of a large trial of intermittent preventive treatment in infancy (IPTi) [9], all malaria participants were treated with a 3-day course of AL irrespective of infecting species. This standardized treatment strategy offered a unique opportunity to assess the effectiveness of a common treatment with AL for malaria in young children based on RDT results in routine clinics.

METHODS

Context and Study Sites

This work was carried out from 2006 to 2010 alongside a 3-arm drug trial of IPTi including 1605 children aged 3–27 months (www.clinicaltrials.gov: NCT00285662) [9]. Children were randomly assigned to a treatment course of sulfadoxine/pyrimethamine (single dose, 25/1.25 mg/kg) combined with 3 days of either 10 mg/kg of amodiaquine or 4 mg/kg of artesunate, or to a placebo group. The treatments were given every 3 months during the first year of life. This trial took place in 2 different settings: Mugil (Madang province), the main study site, at which 1125 study participants were enrolled, is situated 60 km north of Madang town. It is a rural area with an incidence rate of clinical malaria of 0.94 episodes per child per year, with *Pv* accounting for two-thirds of all infections [9]. Maprik (East Sepik province), 400 km north of Madang, was a secondary study site where 480 study participants were enrolled. The incidence rate of malaria is 0.13 episodes/child/year, with *Pf* accounting for two-thirds of all episodes [9].

Data Collection (Passive Case Surveillance)

A passive case detection surveillance system was set up alongside the IPTi study to collect data on illness episodes as well as to monitor potential adverse events related to study drugs. A standard case report form was filled that included relevant signs and symptoms as well as details of the clinical management. When presenting with fever or history of fever in the past 48 hours, children were screened with an RDT for *Pf* and non-*Pf* malaria infections (ICT Combo, South Africa) and only treated with AL (Coartem, Novartis, Switzerland) if the test result was positive. Treatment doses of AL were adapted according to body weight of the children. The first dose was given directly by the nurses (squeezed with water) and the subsequent doses were provided to parents with instructions. At the time of the study, a course of primaquine for radical cure of *Pv* hypnozoites was not part of the PNG standard treatment guidelines. In case of symptoms or signs of severe disease, children were admitted to the nearest health facility. Two thick and thin blood slides (BSs) for malaria microscopy were collected. Parents could also present at mobile clinics that visited participating villages on a monthly basis to deliver the IPTi intervention.

Further details of the clinical trial and the morbidity surveillance used have been reported previously [9]. Ethical approval for the IPTi study was granted by the Medical Research Advisory Committee of PNG (MRAC number 05/20).

Study Design and Procedures

Febrile episodes were identified in the IPTi morbidity database according to the following criteria: illness episodes that occurred in children aged 3–27 months with history of fever and/or axillary temperature >37.5° without records of a positive RDT for malaria in the past 4 weeks, without fever in the past 2 weeks, and without a severe illness. A clinical malaria case was defined as a febrile episode with a positive RDT that

was treated with AL. An individual child could contribute 1 or more illness episodes to the analyses.

The clinical effectiveness of treating young children for malaria with a common treatment of AL based on RDT results was investigated in the following way: Clinical treatment failures were defined as patients who spontaneously reattended the clinic with a febrile illness and a BS-confirmed infection with the same species within a maximum of 42 days. Only the clinical malaria episodes with an infection confirmed by both RDT and BS results at the initial visit were retained. Mixed infections (RDT and BS positive for *Pf* and *Pv*) were excluded from the analysis. Patients were censored when they reattended within the observation period with a heterologous recurrence (eg, *Pv* following a *Pf* infection) and received malaria treatment. For all analyses, children who had received an IPTi treatment dose within 42 days following the initial clinical episode were excluded.

All children with a positive RDT were included in an analysis investigating their clinical response within 28 days following routine management with AL of clinical malaria based, irrespective of the BS result. For this analysis, we excluded all episodes that received an IPTi dose before day 28. On reattendance, we looked whether they still had fever, and examined the clinical and parasitological outcomes (RDT and/or BS). These were classified as severe illness (including death) or nonsevere illness treated as ambulatory cases. Any illness episode was defined as severe if it resulted in hospital admission or was life-threatening.

Interpretation of BS and RDT Results

Thick films were examined by light microscopy for 200 fields, and parasite species and densities for positive cases were recorded as the number of parasites per 200 white blood cells. Densities were converted to the number of parasites per microliter of blood assuming 8 000 cells/μL. All slides were read independently by 2 experienced microscopists; in cases of discrepant readings, a third independent read was performed.

The interpretation of the combination of BS and RDT was done according to a matrix published elsewhere (Supplementary Table 1) [14]. The malaria status was defined as (1) negative = BS and RDT negative, BS or RDT negative, and corresponding BS or RDT absent; (2) definite malaria = BS and RDT positive; (3) probable malaria = BS positive and RDT negative or absent; or (4) possible malaria = RDT positive and BS negative or absent.

Data Analysis

All data management and analyses were performed using Stata software (versions 11.0 and 12.0). The analysis was stratified by species (*Pf* or *Pv*), excluding mixed infections. Survival analysis was performed using a Cox proportional hazards model to assess hazard ratios (HRs) for the difference in reattendance rates. Kaplan-Meier survival curves were calculated and displayed as time to first clinical infection with the same species over a 42-day observation period following an initial *Pf* or *Pv* infection. All rates are displayed with a confidence interval (CI) of 95%.

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 and Maprik = 480). The morbidity surveillance recorded a total of 8944 illness episodes (Madang = 5978 and Maprik = 2966), of which 7223 involved fever (Madang = 5249, Maprik = 1974); the study flowchart is shown in Figure 1. Thirteen deaths and 371 severe illnesses were reported during the observation period.

Of 5670 febrile episodes (Madang = 4103, Maprik = 1567), 1728 (30%, 95% CI: 29%–32%) had a positive RDT for any species and 1682 were treated with AL. Of these, 1261 were confirmed by BS, and 152 had no BS performed and 40 had a mixed infection with *Pf* and *Pv*. Table 1 displays the correlation between positive RDT results and BS results.

Clinical Treatment Failure Rates for *Pv* and *Pf* Malaria at Days 7, 28, and 42

After excluding episodes in children who received an IPTi dose within 42 days following treatment with AL and who had mixed infections, 594 *Pv* and 332 *Pf* clinical malaria episodes confirmed by BS and RDT were identified. Table 2 details the rates of reattendance following *Pv* and *Pf* malaria episodes treated with AL. Clinical treatment failure rates, defined as BS ± RDT positive for the same species upon reattendance within 7, 28, and 42 days, were 0.2%, 2.2%, and 12.0%, respectively for *Pv*. Comparatively, the rates for *Pf* were 0.3%, 1.2%, and 3.6%, respectively. Details of treatment failure rates for mixed infections and reinfection with heterologous species (*Pf* following a *Pv* infection and vice versa) are presented in Supplementary Table 2.

In the survival analysis, treatment failure rate was significantly higher for *Pv* compared to *Pf* (HR, 1.79 [95% CI, 1.15–2.76], $P = .009$). Kaplan-Meier survival curves with 95% CIs showing time to first clinical *Pv* and *Pf* clinical infections are shown in Figure 2.

Clinical Outcome of Children Treated With AL Based on RDT Results Within 28 Days

The outcomes up to day 28 for all children who were treated for clinical malaria with AL based on RDT results in the outpatient clinics are displayed in Figure 3. We observed that 178

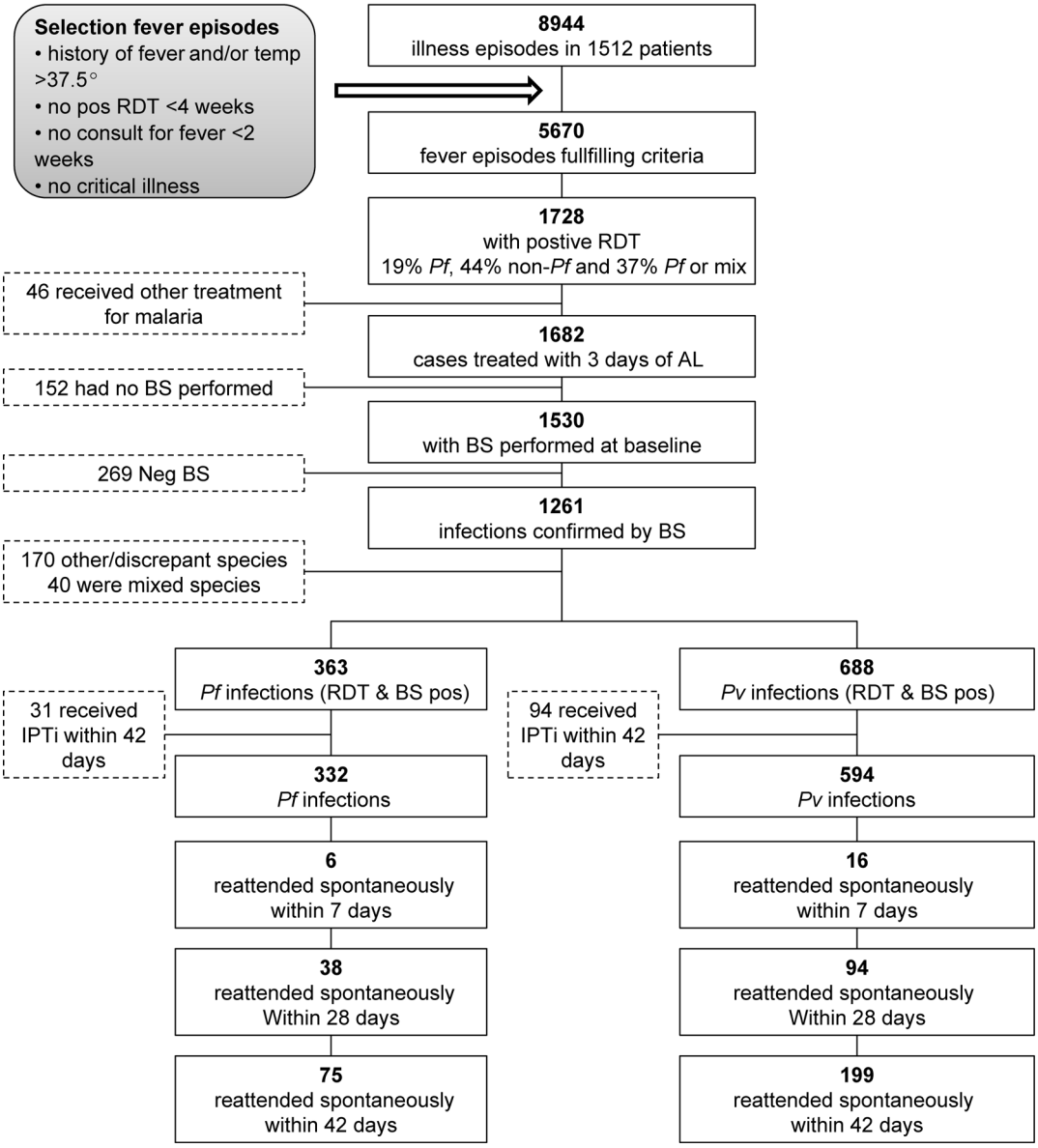

Figure 1. Study flowchart. Abbreviations: AL, artemether/lumefantrine; BS, blood slide; IPTi, intermittent preventive treatment in infancy; mix, mixed infection; *Pf*, *Plasmodium falciparum*; *Pv*, *Plasmodium vivax*; RDT, rapid diagnostic text.

of 1566 infants (11.4%) reattended the clinic for an ongoing or new fever episode; 162 were nonsevere cases. In total, 29 (1.9%) children reattended the clinic with a malaria episode confirmed by BS. Among the 16 who experienced a severe illness, up to 3 different "on-site" diagnoses were recorded per child. Seven were diagnosed with clinical malaria and 9 with a lower respiratory tract infection, 8 had neurological syndromes (such as febrile fits or meningitis), 3 had anemia, and 3 had other diagnoses. One child with a severe illness died the day after admission, with the dual diagnosis of lower respiratory tract infection and possible severe malaria. This child had a severe respiratory distress syndrome on admission, and a positive RDT result but negative BS. No adverse event related to AL was reported. About 20% of children did not undergo blood collection while presenting with a severe illness. Reasons included that the admission occurred after hours when no study staff was present, the severe illness occurred at home (particularly in cases of death), or the parents refused the bleeding. If the observation period is extended to 42 days, the clinical outcomes are not different.

Table 1. Corresponding Blood Slide Results for All Children With Positive Rapid Diagnostic Test Results Treated With Artemether/Lumefantrine at First Attendance (N = 1682)

	Non-*Pf*	*Pf* ± Mixed Infection[a]	Total
BS results (research read)			
Negative	110	159	269
Plasmodium falciparum	10	357	367
Plasmodium vivax	570	267	837
Pm	8	0	8
Mixed infection (*P. falciparum* & *P. vivax*)	3	46	49
No BS	41	111	152
Total	742	940	1682

Abbreviations: BS, blood slide; *Pf*, *Plasmodium falciparum*; *Pm*, *Plasmodium malariae*.

[a] Rapid diagnostic tests have one strip common to all 4 species (phosphatase Lactate Dehydrogenase antigen) and one specific for *Pf* (histidine-rich protein II antigen). If both are positive, it is impossible to differentiate a single *Pf* infection from a mixed infection (*Pf* ± another species).

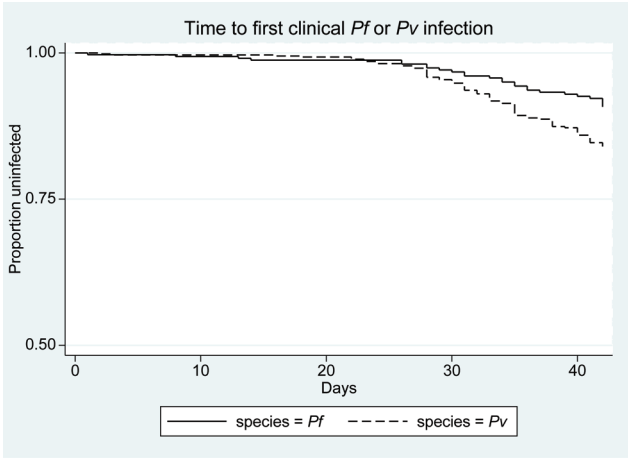

Figure 2. Kaplan–Meier estimates of the proportion of patients remaining free of clinical infection following an initial treatment with artemether/lumefantrine. Children who underwent an intermittent preventive treatment in infancy visit between day 0 and day 42 were censored at the time they received the treatment. Abbreviations: *Pf*, *Plasmodium falciparum*; *Pv*, *Plasmodium vivax*.

DISCUSSION

We investigated in a large cohort of young children the effectiveness in routine practice of a common treatment with artemether/lumefantrine for clinical malaria due to *Pf* or *Pv* diagnosed by RDT. We compared the rate of reattendance in children with *Pv* and *Pf* clinical infections. The clinical response to treatment was very good for both species, as only 1.2% and 2.2% of children who were initially diagnosed with *Pf* and *Pv*, respectively, reattended with a BS positive for the same species within 28 days. However, by day 42, the clinical treatment failure rate was significantly higher for *Pv* (12%) compared to *Pf* (3.6%). The difference is most likely due to relapsing *Pv* infections originating from hepatic hypnozoites, which do not occur in *Pf*.

It should be noted that these figures do not take into consideration illness episodes where only the RDT was positive upon reattendance, as RDT results can remain positive for several weeks after a treatment [15–17]. These data indicate clearly that a common antimalarial treatment of AL for both *Pf* and *Pv* provides an excellent early clinical response [2, 6]. However, while the overall effectiveness for the treatment of *Pf*

Table 2. Crude Rates of Reattendance for Children Having a Clinical Malaria Episode Confirmed by Rapid Diagnostic Test and Blood Slide and Treated With Artemether/Lumefantrine Presenting With a New Clinical Malaria Due to the Same Species (Polymerase Chain Reaction Uncorrected)

			Reattendance 0–7 d With Same Species				Reattendance 0–28 d With Same Species				Reattendance 0–42 d With Same Species			
No. of Malaria Episodes			BS^+/RDT^+ or $^-$	BS^-/RDT^+	BS^-/RDT^-	No BS/RDT	BS^+/RDT^+ or $^-$	BS^-/RDT^+	BS^-/RDT^-	No BS/RDT	BS^+/RDT^+ or $^-$	BS^-/RDT^+	BS^-/RDT^-	No BS/RDT
Pv	597	No.	1	2	7	10	13	3	65	15	71	14	92	22
		%	0.2	0.3	1.2	1.7	2.2	0.5	10.9	2.5	12.0	2.4	15.5	3.7
Pf	332	No.	1	3	0	2	4	26	6	2	12	38	18	7
		%	0.3	0.9	0.0	0.6	1.2	7.8	1.8	0.6	3.6	11.4	5.4	2.1

Included are malaria cases (defined as fever episode with positive RDT plus treatment with AL plus no positive RDT in the past 2 weeks, no fever episode in the past 4 weeks, and no critical illness) that were confirmed by BS and did not receive any intermittent preventive treatment in the next 42 days following the initial diagnosis of malaria. Mixed infections confirmed by both RDT and BS were excluded.

Abbreviations: BS^+/RDT^+ or $^-$, definite or clinical malaria; BS^-/RDT^+, possible clinical malaria; BS^-/RDT^-, negative malaria or non-*Pf*/non-*Pv* malaria; BS, blood slide; *Pf*, *Plasmodium falciparum*; *Pv*, *Plasmodium vivax*; RDT, rapid diagnostic test.

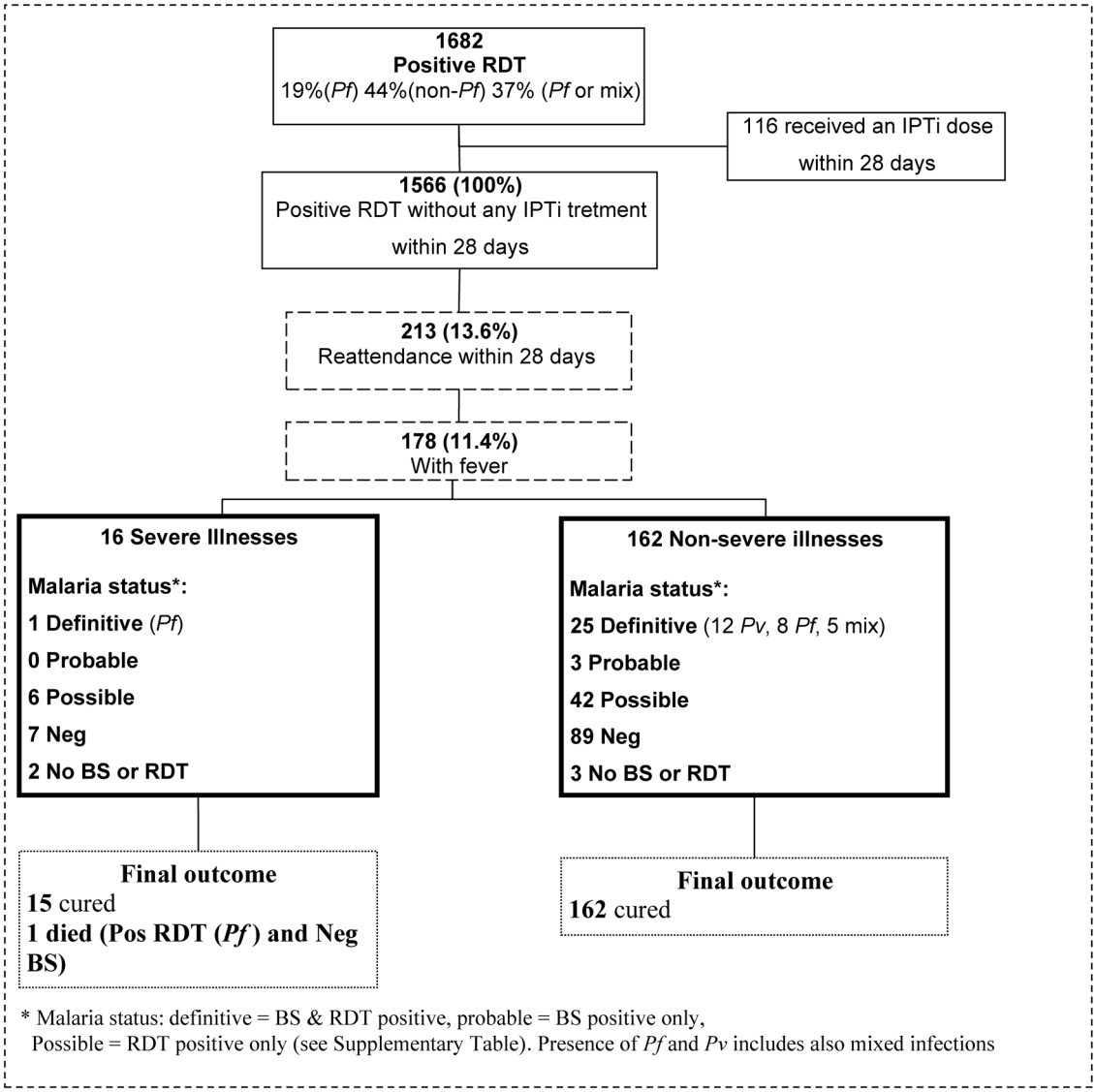

Figure 3. Reattendance and outcomes within 28 days of children treated with artemether/lumefantrine for a clinical malaria episode based on a positive rapid diagnostic text result. Abbreviations: BS, blood slide; IPTi, intermittent preventive treatment in infancy; mix, mixed infection; *Pf*, *Plasmodium falciparum*; *Pv*, *Plasmodium vivax*; RDT, rapid diagnostic text.

is excellent, a high rate of late clinical failure was observed for *Pv* if AL was used without an antirelapse therapy.

The reattendance rates appear to be comparable than those previously reported in PNG, Indonesia, or Africa [4, 11, 18–20]. In a study performed in PNG, a late clinical failure rate by day 42 of 15.2% was reported compared to 12% in the present study. This small difference was expected, as the previous in vivo efficacy studies included systematic screening for both parasitemia and signs and symptoms of febrile illness on defined days rather than spontaneous attendance such as the present study. Passive case detection may better identify illness episodes of significant importance and real health-seeking behavior, but is bound to detect fewer failures. Despite these methodological differences, our findings confirm the previously reported high late clinical failures rates with AL for *Pv*.

Given the low effectiveness of AL against late *Pv* clinical treatment failures (>28 days), the addition of a treatment course of an efficient drug against liver stage parasites is required to improve treatment outcomes. Primaquine is currently the only licensed drug for the radical cure of hypnozoites and, given its activity against gametocytes, it would also aid in reducing transmission [21]. Although very well tolerated in G6PD-normal children in PNG [22], there are safety concerns regarding routine use of primaquine because of the risk of

hemolysis in G6PD-deficient patients [23]. Consequently, experts recommend systematic testing for enzyme deficiency to be performed prior to treatment or, where this is not logistically feasible, careful monitoring of patients and immediate cessation of primaquine treatment at the first sign of hemolysis. Given the absence of a reliable, easy-to-use point-of-care G6PD test, both strategies are logistically difficult to implement in many countries with significant burden of non-*Pf* malaria. In the interim, an alternative may be the use of a common treatment such as dihydroartemisinin/piperaquine (DHA/PPQ), which provides a longer posttreatment prophylactic effect for *Pv* infections and thus may suppress the first *Pv* relapse [24]. The standard treatment guideline in PNG, which includes AL as common first-line treatment for *Pf* and *Pv* together with primaquine treatment in parasitologically confirmed *Pv* cases and DHA/PPQ as second-line treatment, is therefore a rational short-term strategy.

The present work explores also the clinical outcome of feverish children managed according to RDT's results and treated with AL when positive in a routine setting. The majority of children initially diagnosed with malaria reattending the clinic with fever within 28 days had an alternative diagnosis to malaria and only 1.9% of all children treated with AL based on positive RDT came back within 1 month with a BS-confirmed parasitemia. The only death that occurred following a treatment with AL was probably related to a cause other than malaria. Finally, no serious adverse event related to AL was reported. These data complement previous work on RDT-based management of malaria that showed, in the same cohort, that withholding antimalarial drugs from children with a negative RDT was safe in a country with a high burden of non-*Pf* malaria [14].

This study was carried out alongside a passive case detection system, which leaves patients free to decide if they want to visit a health facility when sick (or go elsewhere) and which facility they wish to visit. A few malaria cases may have been missed. This, however, reflects routine practice, as fever episodes of minor importance often cure spontaneously. Some children may have also received over-the-counter medication, but this is rather uncommon in PNG. Also, AL was not available in the country at the time of the study. Finally, because of the nature of the study, adherence to treatment was not monitored by the study team, except for the first dose that was administered by the nurse. It is therefore reassuring to observe that even if adherence might have been suboptimal, the treatment was effective enough to achieve a good initial clinical response. This contradicts a previous report arguing that a poor adherence to AL might challenge its effectiveness [20].

In conclusion, this study shows that a common treatment with AL used on its own provides a good initial clinical response but is insufficient to prevent late clinical treatment failures of *Pv*. Primaquine should always complement AL when feasible, even if the effectiveness of this combination is not yet entirely known. Therefore, new strategies that efficiently prevent relapses of *Pv* hypnozoites need to be investigated. In the absence of better treatment and diagnostic options, the use of AL in young children in routine practice is an acceptable, interim option in areas highly endemic for *Pf* and *Pv* and with a high level of parasites resistant to chloroquine. Ideally, second-line treatment should be a long-acting ACT, combined with rational use of primaquine.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org/). 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

Acknowledgments. We thank all study participants and their parents; the study nurses who reviewed all sick study participants, performed the RDT, and collected the blood slides in the field; all staff members from the health facilities in Mugil and Wosera areas where the study was performed; Nandao Tarongka, Lina Lorry, and the Malaria Microscopy section at the PNG Institute of Medical Research (IMR), who read so many blood slides; and the data management staff who entered all questionnaires on the database.

Author contributions. 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. 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.

Financial support. The data used in this work were collected through an IPTi randomized controlled trial funded by a grant from the Bill & Melinda Gates Foundation to the PNG IMR.

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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