Imported Malaria: Prospective Analysis of Problems in Diagnosis and Management

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Imported malaria is an increasing problem in many countries. The objective of this study was to prospectively evaluate the diagnosis and treatment of imported malaria cases identified by active surveillance. Microscopic diagnosis at the community level was also compared to reference microscopic and blinded molecular diagnostic methods. Most travelers who acquired malaria had sought pretravel advice from a physician; however, only 11% used recommended chemoprophylaxis and only 17% used insect protection measures. The diagnosis of malaria was initially missed in 59% of cases. Community-based microscopic diagnosis provided incorrect species identification in 64% of cases. After presentation, the average delay before treatment was 7.6 days for falciparum malaria and 5.1 days for vivax malaria. Overall, 7.5% of *Plasmodium falciparum*–infected patients developed severe malaria, and in 11% of all cases therapy failed. Patients who present to a center without expertise in tropical medicine receive suboptimal treatment. Improvements in recognition, diagnosis, and treatment of malaria are essential to prevent morbidity and death among travelers.

Between 1980 and 1990 the number of Canadians and Americans traveling to the developing world doubled to >12 million annually [1, 2]. Current travel destinations and immigration policies, combined with the escalating incidence of drug-resistant malaria, have resulted in an increase in the number of cases of imported malaria [2, 3]. In 1996, 744 cases of malaria were reported in Canada, representing a 73% increase from the 432 cases recorded in 1994 [4]. The rate of imported malaria in Canada is now five to 10 times the per capita rate reported in the United States [5]. The rates in both countries are likely underestimates because of the prevalence of underreporting. It is estimated that 40%–70% of cases are not reported to health authorities [2, 3, 6].

The case fatality rate associated with imported *Plasmodium falciparum* malaria varies from 0.6% to 3.8% [7, 8], and that associated with severe malaria is ⩾20%, even when it is managed in modern intensive care unit (ICU) settings [9, 10]. Therefore, preventing fatal outcomes in cases of falciparum malaria requires early recognition of infection, accurate laboratory diagnosis, and prompt therapy. Delays in recognition and treatment of malaria are associated with increases in morbidity and mortality [7, 11, 12]. Since ~90% of travelers who contract malaria will not become ill until returning home, recognition of malaria, laboratory diagnosis, and treatment depend on the expertise of physicians and diagnostic laboratories in areas of nonendemicity [1, 2].

Retrospective case series have suggested that the recognition and management of imported malaria is problematic [11, 13–17]. However, the design of these studies did not permit an assessment of the individual components that account for the overall delays in diagnosis and treatment of malaria. Nor did they assess the problem from a community physician and laboratory perspective. Furthermore, data concerning malaria cases identified by passive reporting or hospital referral may be incomplete and biased [3].

The objectives of the present study were to (1) systematically investigate the temporal sequence of events leading to the diagnosis of imported malaria, (2) identify problems in the recognition and treatment of malaria by community physicians, and (3) evaluate the turnaround time and accuracy of microscopy for the diagnosis of malaria with use of molecular methods as reference standards.

Materials and Methods

Subjects

During 1994, an active surveillance system was established to identify malaria cases in the greater metropolitan Toronto area (GTA). Laboratory heads and chief technologists at five private companies, each with multiple regional laboratories, and 28 hospital-based laboratories in the GTA were contacted and requested to forward slides, whole blood samples, and patient data from all known or suspected cases of malaria to the Tropical Disease Unit (TDU) at the Toronto Hospital. A toll-free (1-800-) hotline was established to facilitate reporting and specimen transport. Periodic notices were circulated by electronic mail, facsimile, and mail to all GTA laboratories, reminding them of the ongoing study and requesting their participation.

Received 23 October 1997; revised 3 March 1998.

Financial support: This study was supported by a grant from the Physicians Services Incorporated. K.C.K. is supported by a Career Scientist Award from The Ontario Ministry of Health.

This project was reviewed and approved by the Ethical Review Committee of The Toronto Hospital.

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Clinical Infectious Diseases 1998; 27:142–9

1058–4838/98/2701–0027$03.00

All diagnostic laboratories in the province are legally required to report positive malaria smears to the provincial laboratory and send smears or whole blood samples for confirmation. In order to identify cases that might have bypassed our surveillance system, we requested for review the smears and whole blood samples referred to the provincial laboratory from the GTA during the study period. Records of these samples were checked against those that were forwarded directly to the TDU.

Diagnosis of Malaria

All referred malaria slides were re-read by a single expert microscopist at the TDU, who was blinded to the results of diagnostic PCR [18, 19]. Blood smears were considered to be negative if no parasites were seen in 500 oil immersion fields (×1,000) on a thick film. Parasite density was calculated by determining the number of parasites per 200–500 WBCs on a thick smear. Baseline WBC counts were used to calculate parasitemia (parasites/μL). All patients whose malaria smears were read as positive at the TDU were eligible for inclusion in the present study.

Referred whole blood samples (pretreatment) and those collected at the TDU were subjected to PCR for malaria detection and species identification as previously described [18–20]. All amplification and detection steps were performed by technicians blinded to the microscopic results. In cases of discrepancy between reference microscopy and PCR, the species diagnosis was confirmed by amplification and detection of an additional plasmodial species-specific gene [21–25]. On the basis of previously demonstrated advantages, PCR was considered the reference standard [21–26].

Follow-up examinations, blood smears, and PCR for test of cure on day 7 and day 28 following initiation of therapy were arranged at the TDU for the majority of patients [23, 24]. Alternatively, clinical follow-up was organized and blood samples were sent to the TDU via the attending physician. Patients were encouraged to return to the TDU for assessment of fever recurring within the year following therapy.

Data Ascertainment and Analysis

Enrolled patients and/or their attending physicians were interviewed within 5 days of receipt of a positive smear at the TDU; the majority were interviewed within 24 hours. All available hospital and emergency department records, including pharmacy records and nurses' notes about drug administration, were reviewed. Laboratory records were examined to determine the types of malaria smear examinations performed, results generated, and turnaround times.

Information from patients, physicians, laboratory records, and hospital charts was abstracted on a standardized data-acquisition form. Information was collected on patient demographics, pretravel health advice, travel history, and use of and compliance with chemosuppressive regimens and personal protection measures against mosquito bites. In addition, the following specific time periods were identified: (1) duration (days) of travel in areas where malaria is endemic; (2) time (days) from departure from the last area of endemicity until the onset of symptoms; (3) time (days) from onset of symptoms until the first consultation with a health care professional; (4) time (days) from first seeking medical consultation until malaria smear analyses were ordered; (5) time (days) from when malaria smear analyses were ordered until a malaria diagnosis was reported to the physician; and (6) time (hours) from receipt of the malaria diagnosis by a physician until initiation of treatment.

In addition to determining the temporal relationship of events leading to the diagnosis and treatment of malaria, we evaluated the clinical management and laboratory specimen handling in each case with use of a predetermined scoring system. The scoring system consisted of a numeric sum of ''major'' errors occurring in the prevention, recognition, laboratory diagnosis, and treatment of malaria cases, on the basis of published and accepted recommendations for malaria management in areas of nonendemicity [27–29]. Major errors were those considered to be preventable and with the potential to have a measurable negative impact on outcome.

These parameters were based on published and accepted Canadian, American, and World Health Organization (WHO) guidelines [27–30] and included (1) an inappropriate chemosuppressive regimen prescribed by a health care provider (pretravel); (2) failure of a physician to consider the diagnosis of malaria at the time of the patient's presentation; (3) failure of a laboratory, when requested, to interpret a thick and thin smear to exclude malaria; (4) failure of a diagnostic laboratory to accurately identify malaria, i.e., by not providing a species identification or by identifying it incorrectly (compared with reference methods); (5) incorrect treatment (wrong drug regimen) given to individuals with laboratory-confirmed malaria; (6) errors in the initial management of severe malaria (e.g., failure to administer a parenteral drug in severe or complicated falciparum malaria); (7) failure to determine blood glucose level in cases of falciparum malaria; (8) delay in initiation of therapy (>6 hours) after laboratory confirmation of falciparum malaria was reported to physician; (9) failure to perform laboratory or clinical follow-up of falciparum malaria cases; (10) nonimmune individuals infected with *P. falciparum* not admitted to hospital; (11) failure to perform cardiac monitoring for patients receiving parenteral quinidine therapy; and (12) failure to check glucose-6-phosphate dehydrogenase (G6PD) level before prescribing primaquine to patients infected with *Plasmodium vivax* or *Plasmodium ovale* or failure to prescribe primaquine to such individuals with normal G6PD levels.

Results

Reference Laboratory Diagnosis and Parasite Characteristics

From 15 January 1994 to 1 December 1994, 100 consecutive cases of malaria were identified and prospectively followed.

The diagnostic findings in these 100 cases by the reference laboratory are shown in table 1. At the reference laboratory of the TDU, both microscopy and molecular methods were used in a blinded fashion to detect and identify parasites.

A microscopic diagnosis of malaria was made on analysis of the first smear in all cases except one (1%). This patient was taking chloroquine and proguanil for chemosuppression; smears were not positive until 48 hours after presentation. However, *P. falciparum* was detected by PCR at presentation. Overall, there was excellent agreement between reference laboratory microscopy and the PCR-based method used for species identification, with complete or partial concordance in 98% of cases. On the basis of PCR results, malaria was caused by *P. falciparum* alone in 40 individuals, *P. vivax* in 50, *P. ovale* in 5, *Plasmodium malariae* in 1, and mixed pathogens in 4 (table 1).

Overall, 78% of malarial infections were acquired in Africa or the Indian subcontinent. The majority of *P. falciparum* infections were acquired in Africa (95%), although two (5%), including a mixed *P. falciparum/vivax* infection, were identified in travelers from India. All cases due to *P. ovale* and *P. malariae* were acquired in Africa. On the other hand, *P. vivax* infections were acquired in a variety of regions; the majority (34%) originated in the Indian subcontinent. Although it has been previously reported that vivax malaria is rare in sub-Saharan Africa because the majority of the population is negative for the *P. vivax* erythrocyte receptor (the Duffy antigen) [31], 18% of the *P. vivax* infections in this study were identified in travelers returning from Africa, including 6% from West Africa.

Population Demographics and Epidemiological Data

The epidemiological characteristics of malaria-infected patients are shown in table 2. Of these 100 patients, 83% were residents of Canada (for >2 years) who had visited or traveled to an area where malaria is endemic and 17% were more recent immigrants.

Overall, 63% of travelers who acquired malaria had sought pretravel advice from a physician, including 70% of travelers to Africa. In spite of receiving this advice, only 17% used personal protection measures against insect bites, such as bed nets and insect repellents, and only 11% were compliant with recommended chemosuppressive regimens [27, 28]. Travelers to India who acquired malaria were less likely to use and adhere to chemoprophylactic regimens than were travelers to other destinations. In contrast, visitors to Southeast Asia and Oceania were more likely to use insect protection measures and chemosuppressive agents. While 57% of travelers to sub-Saharan Africa reported the use of chemoprophylaxis, only 29% used a recommended drug regimen and only 5% were compliant with it.

The majority of cases of falciparum malaria involved individuals using no chemosuppression (42%) or were breakthrough infections in travelers using chloroquine alone or chloroquine combined with proguanil (26%). Three travelers to Africa who developed malaria reported compliance with mefloquine. Two of these infections were relapses due to *P. ovale* or delayed primary infections occurring >2 months after departure from an area of malaria endemicity (which do not represent mefloquine failures), and one was due to *P. falciparum*.

Table 1. Microscopic and PCR-based diagnosis of malaria at the reference laboratory.

Plasmodium species identified	No. of cases diagnosed by	
	Microscopy*	PCR
P. vivax (PV)	45	44, 1 PV/PF†
P. falciparum (PF)	33	33
P. ovale (PO)	6	4, 2 PO/PM
P. malariae (PM)	2	1, 1 PO/PM
Unidentified species‡	8	6-PF†, 1 PV, 1 PO
PV/PF	2	2 PV†
PV/PO	1	1 PV
PF/PO	1	1 PF†
PV/PM	2	2 PV
Total	100	100

* Reference microscopic diagnosis and species identification at the Tropical Disease Unit at the Toronto Hospital.

† Clinically important problems in reference laboratory microscopic diagnosis.

‡ Level of parasitemia too low for accurate microscopic identification of species.

Physician Recognition and Non-Reference-Laboratory Diagnosis

The temporal sequence of events leading to the diagnosis and treatment of malaria is shown in figure 1 and table 3. The mean time from departure from the area of malaria endemicity until the onset of symptoms was significantly shorter for individuals infected with *P. falciparum* (mean, 10 days) than for those infected with *P. vivax* (mean, 134 days; $P < .0001$ per Mann-Whitney rank sum test, two-tailed). However, there was no significant difference in the duration of symptoms before patients sought medical attention (mean, 3.6 days), regardless of the type of malaria; where they presented for assessment; or whether they were residents or recent immigrants (table 3; data not shown).

After consultation of a physician, there were significant delays in the recognition, laboratory diagnosis, and initiation of treatment of malaria when patients presented to centers without expertise in tropical medicine (figure 1, table 3). For cases of falciparum malaria involving patients presenting to centers other than the TDU, the diagnosis of malaria was missed by the physician at initial presentation in 61% of cases; 16% of patients with a history of fever reported that they presented to ⩾3 physicians before malaria was suspected; 45% of the laboratories from which a diagnosis was requested provided either no parasite-species identification or a wrong one; and it

Table 2. Epidemiological and demographic characteristics of travelers with malaria.

Area of travel (*n*)	Age: mean y (range)	Sex ratio (M:F)	Duration of travel: mean no. of d (95% CI)	Percentage of travelers who: Sought pretravel advice from physician	Used PPM*	Used chemoprophylaxis: Any	Correct measure(s)	With compliance
All cases (100)	30.9 (0.5–67)	61:39	93 (66–119)	63	17	46	26	11
Africa (57)	29.1 (5–63)	33:24	89 (59–119)	70	11	57	29	5
Indian subcontinent (19)	32.7 (0.5–67)	12:7	103 (23–230)	58	0	16	0[†]	0
Central and South America (11)	32.8 (19–42)	7:4	102 (42–163)	27[‡]	18	27	27	18
Southeast Asia and New Guinea (13)	34.7 (19–59)	9:4	88 (20–156)	69	69[§]	58	58	50[§]

* Personal protection measures, including bed nets or insect repellents.
[†] $P = .004$, χ^2 for heterogeneity; $P = .009$, Indian subcontinent vs. other travel destinations (Yates's corrected χ^2).
[‡] $P = .06$, χ^2 for heterogeneity.
[§] $P < .001$, χ^2 for heterogeneity; $P < .001$, Southeast Asia/New Guinea vs. other travel destinations (Yates's corrected χ^2).

took a mean of 7.6 days after presentation to a physician before treatment was initiated.

For *P. vivax* malaria, the diagnosis was missed at presentation in 51% of cases; in only 26% of cases did laboratories correctly identify *P. vivax;* and a mean delay of 5.1 days occurred before treatment was initiated. Twenty percent of attending physicians in the community were pediatricians or internists, 5% were infectious disease physicians, and the remainder were family physicians.

In a follow-up phone survey of diagnostic laboratories in the GTA, 85% reported that they routinely use thick smears for malaria detection. However, in this study, thick-smear analyses were performed on only 59% of the specimens initially evaluated by these same laboratories.

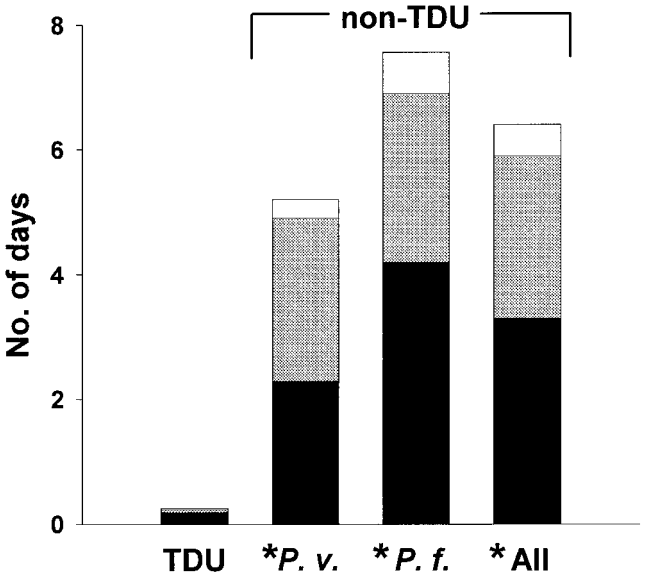

Figure 1. Bar graph showing time from presentation to a health care provider until initiation of treatment for malaria. *Black bars* = mean time from presentation to a physician until malaria smear analyses were ordered; *gray bars* = mean time from ordering of smear analyses until laboratory diagnosis of malaria; *white bars* = mean time from receipt of malaria diagnosis until treatment was initiated; TDU = patients presenting initially to the Tropical Disease Unit at Toronto Hospital; non-TDU = patients presenting elsewhere; All = all non-TDU; *P.v.* = non-TDU with *Plasmodium vivax* infection; *P.f.* = non-TDU with *Plasmodium falciparum* infection (*$P < .001$, Yates's corrected χ^2 for non-TDU vs. TDU).

Laboratory Features

Overall, 41% of patients were anemic at presentation and 3.5% had a hemoglobin level below 80 g/L. WBC counts were elevated above 9.8×10^9/L in only 2.5% of patients but were $<5.0 \times 10^9$/L in 47.5%. *P. vivax*–infected patients were more likely than *P. falciparum*–infected patients to be thrombocytopenic (82.5% vs. 61.1%) and had significantly lower mean platelet counts (102×10^9/L vs. 137×10^9/L; $P = .03$ per Mann-Whitney rank sum test, two-tailed). Elevated serum lactate dehydrogenase levels (>190 U/L) were observed in 64.3% of 55 cases, and in 17% of patients mild elevations in hepatic transaminase levels (aspartate aminotransferase, >40 U/L) were detected. None of 38 patients who had blood glucose levels randomly determined at presentation were hypoglycemic (mean, 5.8 mmol/L; 95% CI, 5.3–6.3).

Management and Course of Infection

An overall assessment of malaria management was performed with use of a predetermined scoring system based on a numeric sum of errors occurring in the recognition, laboratory diagnosis, and treatment of cases (table 4). Ninety-two percent of patients presenting to a center or physician without expertise

Table 3. Temporal sequence of events leading to the diagnosis and treatment of malaria.

Patients (*n*)	Mean no. of days (95% CI) until		Diagnosis missed at presentation (%)	Mean no. of days (95% CI) until		Percentage of cases		Mean no. of hours (95% CI) until initiation of treatment[#]
	Onset of symptoms*	Medical attention[†]		Malaria smear ordered[‡]	Malaria diagnosis[§]	Thin smears only	Species identification errors[‖]	
Non-TDU** (75)	91 (45–138)	3.6 (2.5–4.7)	59[††]	3.3[‡‡] (2.0–4.5)	2.6[‡‡] (1.4–3.8)	41[††]	64[††]	12[§§] (1.1–22.9)
TDU** (25)	95 (12–178)	3.8 (2.3–5.3)	0[††]	0.2[‡‡] (−0.1–0.54)	0.04[‡‡] (−0.1–0.12)	0[††]	12[††]	4[§§] (−1.8–9.8)

* Time from leaving area of endemic malaria until onset of malaria symptoms.
[†] Time from onset of symptoms until first medical consultation.
[‡] Time from medical attention until malaria smear analyses ordered.
[§] Time until malaria species identification (diagnosis) made.
[‖] Species either not identified or incorrectly identified, on basis of reference molecular methods.
[#] Time from malaria diagnosis until initiation of treatment.
** TDU = patients presenting initially to the Tropical Disease Unit of Toronto Hospital; non-TDU = patients presenting elsewhere.
[††] $P \leq .001$ (Yates's corrected χ^2).
[‡‡] $P = .000$ (Mann-Whitney rank sum test, two-tailed).
[§§] $P = .03$ (Mann-Whitney rank sum test, two-tailed).

in tropical medicine encountered at least two major errors in their care (mean, 3.5 errors per episode), including failure to consider the diagnosis when the patient presented, laboratory errors in recognition and species identification, and incorrect therapy (see Materials and Methods section).

Forty-eight percent of these patients received inappropriate initial treatment, including those whose *P. vivax* infections ($n = 35$) were treated with chloroquine alone (23%), quinine plus doxycycline (23%), quinine plus clindamycin and primaquine (6%), or chloroquine plus doxycycline (3%). *P. falciparum* infections ($n = 33$) were incorrectly treated with quinine or sulfadoxine/pyrimethamine monotherapy (9%), chloroquine alone or combined with primaquine (18%), and mefloquine combined with quinine plus doxycycline (3%). Twenty-three percent of patients had delays of >6 hours after the attending physician received a laboratory-confirmed diagnosis of malaria until antimalarial therapy was initiated, and 36% of *P. falciparum*–infected patients had no follow-up within the first 4 days to ensure tolerance of oral antimalarials or to exclude complications and early treatment failure.

Of those patients with falciparum malaria, 54% were hospitalized (86% of cases presenting to the TDU, compared with 43% at other institutions). Three patients (7.5%) fulfilled the WHO criteria for severe or complicated malaria [30]. None were pregnant. One developed adult respiratory distress syndrome requiring ventilation, and two presented with hyperparasitemia (>5% parasitemia); all three patients survived.

Overall, 11 patients' therapy failed. A 5-year-old boy with falciparum malaria acquired in West Africa failed directly observed therapy with quinine plus clindamycin. A mother and her two daughters who visited Ghana developed falciparum malaria and were treated with chloroquine by their family doctor. For all three, treatment failed by days 24–28 because of RI resistant infections (RI level = recurrence of parasites between 7 and 28 days after initiation of therapy) [30–33]. Another male with falciparum malaria, acquired in Nigeria, was treated with sulfadoxine/pyrimethamine monotherapy by his physician and failed on day 5 because of an RII resistant infection (RII level = recurrence of parasites within 7 days after initiation of therapy) [31–33]. For three patients infected with

Table 4. Problems encountered in the management of 100 consecutive cases of malaria (15 Jaunary 1994 to 1 December 1994).

Patients (*n*)	Major errors*		Inappropriate initial therapy*	Delay in therapy (>6 h)	Inadequate follow-up	No G6PD level determination (for *P. vivax* and *P. ovale* infection)	No primaquine given[†] (for *P. vivax* and *P. ovale* infection)
	≥2 Errors	Mean no. of errors (95% CI)					
Non-TDU[‡] (75)	92[§]	3.5[‖] (3.1–3.9)	48[§]	23	27[§]	44[§]	22
TDU[‡] (25)	0[§]	0.2[‖]	8[§]	4	0[§]	0[§]	0

NOTE. Data are percentages of patients, except as otherwise indicated. G6PD = glucose-6-phosphate dehydrogenase.
* As defined in Materials and Methods section.
[†] For patients with normal G6PD levels.
[‡] TDU = patients presenting initially to the Tropical Disease Unit of Toronto Hospital; non-TDU = patients presenting elsewhere.
[§] $P \leq .009$ per Yates's corrected χ^2.
[‖] $P = .001$ per Mann-Whitney rank sum test, two-tailed.

P. vivax in Oceania, therapy with chloroquine or quinine plus doxycycline failed by day 28. Treatment with primaquine (15–22.5 mg base/d for 14 days) failed for three other patients, who had relapses of *P. vivax* infection 2–12 months after initial therapy was completed.

Discussion

This report is the first to systematically evaluate how malaria is recognized and managed in an area of nonendemicity and to compare diagnosis of malaria in the community setting to that with reference laboratory microscopy and molecular detection methods.

In 1994, 430 cases of malaria were reported to the Laboratory Center for Disease Control in Ottawa (1.5 cases/100,000 population), of which 220 cases were reported from Ontario (2.0 cases/100,000) [4]. We identified 100 cases of malaria in the GTA during a 10.5-month period (2.9 cases/100,000), indicating that imported malaria is neither rare nor exotic in this community. Despite this, the current study identified important problems at all stages of malaria diagnosis and treatment.

As reported in previous retrospective studies [14–16], the majority of patients in this study who acquired malaria were taking no chemosuppressive drugs, were using an inappropriate regimen, or were noncompliant. However, in past studies it has not been possible to determine whether this was a consequence of travelers' failure to seek pretravel advice or because of the inability of physicians to prescribe appropriate prophylaxis. In the present study, the majority of travelers had sought pretravel advice from a physician (63% overall and 70% of travelers to Africa). However, this pretravel consultation most often did not translate into the use of personal protection measures to prevent insect bites (17% overall) or the use of appropriate chemosuppression (11% overall).

Travelers to Southeast Asia were more likely to use insect protection measures and the recommended chemosuppressive drugs (46%) than those traveling to Africa (5%) and India (0%), despite their low risk for malaria [34]. These observations suggest that failure of travelers to use effective antimalarial chemoprophylaxis and insect protection measures may be attributable, in large part, to misconceptions about malaria risk and inappropriate advice provided by physicians, rather than to a lack of pretravel advice.

There was remarkable consistency in the duration of illness before patients sought medical attention, regardless of the malarial species or whether they were recent immigrants or long-term residents. This may be attributable, in part, to the health care system in Canada, in which there is little financial disincentive for patients to seek medical care. However, after presentation, patients who were first assessed in a center with clinical and laboratory expertise in tropical diseases were diagnosed more rapidly and treated more effectively than patients who presented elsewhere.

Overall, 59% of patients who presented elsewhere were not discovered to have malaria during their initial contact with a physician, and 16% required ⩾3 physician contacts before malaria smears were ordered. Previous studies based on retrospective chart reviews may have underestimated the frequency of missed diagnoses since information regarding preceding physician contact, such as visits to walk-in clinics and emergency departments of other hospitals, were infrequently recorded on patients' charts. Interviews of patients with use of direct questions to identify previous physician contacts were highly revealing in this study.

Microscopy has been the reference standard for malaria detection and species identification for decades [32]. To our knowledge, this is the first study to use molecular methods to assess the accuracy of community and reference microscopy for the diagnosis of malaria. The turnaround time and accuracy of microscopic diagnosis performed in centers other than the TDU were below the acceptable standard [35]. The majority of laboratories did not perform malaria smears on an urgent basis, nor did they routinely report species identification or levels of parasitemia. When species identification was provided, there was a tendency to overestimate *P. falciparum* infections, leading to the unnecessary use of second- and third-line antimalarials for *P. vivax* infections and to the failure to use primaquine to prevent relapses.

While expert microscopy at the TDU was far superior to that in community laboratories, it too had its limitations. Discrepancies between reference microscopy and PCR that were likely to have a clinical impact were primarily those of mixed infections and those where only a few ring forms were observed on thick smears, making microscopic species identification problematic. The only reference laboratory microscopic diagnosis likely to have resulted in a major treatment error (i.e., nontreatment of falciparum malaria) was in a case of a mixed infection with *P. vivax* and *P. falciparum,* interpreted as an infection with *P. vivax* only.

Although less important clinically, based on the reference microscopic diagnosis, a total of 3 *P. vivax* or *P. ovale*–infected patients would not have received primaquine, 4 patients would have unnecessarily received second- or third-line agents, and 1 patient would have received primaquine without justification. Therefore, while expertise in microscopy is adequate for clinical purposes, careful clinical and laboratory follow-up is still necessary in order to identify mixed infections and microscopic misdiagnoses.

Previous retrospective data from the Centers for Disease Control and Prevention indicate that ~30% of *P. falciparum*–infected travelers in the United States received therapy inconsistent with current recommendations [36]. In the present study, 48% of patients presenting to peripheral or referral hospitals other than the TDU received inappropriate therapy, on the basis of published Canadian or WHO guidelines [27, 29, 30]. Several patients received inappropriate drug combinations that provided partial treatment for both *P. vivax* and *P. falciparum* malaria. Whether this practice was a consequence of delays or uncertainties in laboratory diagnosis is unknown.

Given that increasing numbers of imported cases of falciparum malaria are caused by drug-resistant strains, it is notewor-

thy that 36% of patients had inadequate follow-up in the first week after initiation of therapy. Close follow-up is important to ensure tolerance of antimalarials and to detect complications and early treatment failure. For patients with *P. vivax* or *P. ovale* infection, failure to exclude G6PD deficiency and to prescribe primaquine to prevent relapses were common problems. The reported rates are likely underestimates, since in the course of interaction with physicians during this study these endpoints may have been influenced.

In this study therapy failed for only one patient with falciparum malaria who was optimally treated, suggesting that current treatment recommendations are still effective [27, 29, 30]. Other falciparum malaria treatment failures involved patients who were treated with inappropriate drug regimens. Strains of *P. vivax* with decreased susceptibility to chloroquine and primaquine appear to be spreading [37, 38]. Infections with them can be difficult to cure with traditional treatment regimens based on chloroquine, quinine, and primaquine [37, 38].

Collectively, the failure of physicians to recognize malaria, slow and inaccurate laboratory diagnosis, and failure to initiate prompt and appropriate therapy resulted in unacceptable management errors in the treatment of malaria. After presentation, delays averaging 7.6 days for cases of falciparum malaria and 5.1 days for cases of vivax malaria were noted prior to treatment. For infections caused by *P. falciparum,* which can be rapidly fatal, such delays in recognition and initiation of therapy are clinically important and are directly related to increases in malaria-associated morbidity and mortality [7, 8, 12].

In fatal cases of falciparum malaria reported in the United States, 40% of patients were not recognized as having malaria during their initial contact with a physician [7]. While there were no fatalities during the present study, three *P. falciparum*–infected patients (7.5%) developed severe malaria, and two required admission to an ICU and subsequent prolonged hospitalization. Furthermore, in the year following this study, two fatal cases of falciparum malaria occurred in travelers returning to Ontario [39].

In summary, this study suggests that the diagnosis and treatment of imported malaria outside of tropical disease reference centers is suboptimal. It also identifies problem areas that should be targeted with educational and other interventions in order to improve the management of malaria. First, there is a need to educate travelers about the potential seriousness of malaria, the importance of measures to prevent insect bites and appropriate chemoprophylaxis, the need for prompt evaluation of fever during or after travel, the need to inform health care providers of their travel history, and the need for malaria smear evaluations.

Second, the limited knowledge of North American physicians about tropical medicine affects the health of not only business and pleasure travelers but also the large numbers of refugees and immigrants who now reside in these areas [40]. There is a real need to increase awareness amongst physicians about the risk of malaria in travelers. It is imperative that a travel history be obtained from all patients with a history of fever and that thick and thin smear evaluations be requested on an urgent basis for all individuals with fever who have traveled to an area where malaria is endemic. There is also a need to make widely available to physicians ''user-friendly'' treatment guidelines and therapies for severe malaria [39, 41].

Finally, microscopic diagnosis of malaria is problematic in areas of nonendemicity. In follow-up interviews with peripheral hospital and private laboratories, technologists expressed an almost universal apprehension about making and interpreting thick smears, largely attributed to a lack of appropriate training. These deficiencies need to be addressed through concerted efforts to train technologists to prepare and read thick smears, to require rapid turnaround times, and to monitor performance with proficiency testing [35].

With the current international travel patterns and immigration policies and with escalating drug resistance, imported drug-resistant malaria will be an increasing problem. Improvements in recognition, laboratory diagnosis, and treatment of malaria in areas of nonendemicity will be essential to prevent malaria-associated morbidity and death of travelers.

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This stamp was issued on 7 April 1962 to publicize the World Health Organization's drive to eradicate malaria. It illustrates an anopheles mosquito in the biting position. (From the medical philately collection of Dr. J. N. Shanberge, University of Michigan.)