Am. J. Trop. Med. Hyg., 66(5), 2002, pp. 481–486

CLINICAL AND LABORATORY PREDICTORS OF IMPORTED MALARIA IN AN OUTPATIENT SETTING: AN AID TO MEDICAL DECISION MAKING IN RETURNING TRAVELERS WITH FEVER

VALÉRIE D'ACREMONT, PIERRE LANDRY, IVO MUELLER, ALAIN PÉCOUD, AND BLAISE GENTON
Travel Clinic, Medical Outpatient Clinic, University of Lausanne, Lausanne, Switzerland; Swiss Tropical Institute, Basel, Switzerland

Abstract. No evidence-based information exists to guide clinicians for giving presumptive treatment to returning travelers when malaria is strongly suspected on clinical grounds but laboratory confirmation is not immediately available or is negative. A prospective study was conducted in travelers or migrants who sought care for fever to identify clinical and laboratory predictors of *Plasmodium* parasitemia. A total of 336 questionnaires were collected (97 malaria case patients and 239 controls). Multivariate regression analysis showed inadequate prophylaxis, sweating, no abdominal pain, temperature $\geq 38°C$, poor general health, enlarged spleen, leucocytes $\leq 10 \times 10^3$/L, platelets $< 150 \times 10^3$/L, hemoglobin < 12 g/dL, and eosinophils $\leq 5\%$ to be associated with parasitemia. Enlarged spleen had the highest positive likelihood ratio for a diagnosis of malaria (13.6), followed by thrombopenia (11.0). Posttest probabilities for malaria were 85% with enlarged spleen and 82% with thrombopenia. A rapid assessment can thus help to decide whether a presumptive treatment should be given or not, especially when the results of the parasitological examination are not immediately available or are uncertain.

INTRODUCTION

The diagnosis of malaria in nonendemic countries remains a challenge. Improving the awareness and ability of doctors to identify patients with a high probability of having malaria should reduce severe morbidity and case fatality.[1,2] Although access to microscopic examination is easy in developed countries, the failure of physicians to think of malaria in febrile patients and to recognize the necessity of a prompt diagnostic confirmation may lead to unacceptable delay in initiating treatment.[3] Also, microscopical diagnosis is often slow and inaccurate in nonspecialized laboratories.[4] Even in the setting of specialized centers, malaria cases can be missed as a result of the low sensitivity of microscopy,[5] especially in nonimmune travelers receiving chemoprophylaxis. Because of these limitations, after assessing blood for definite diagnosis, it is sometimes appropriate to administer a presumptive treatment in febrile patients who do not present obvious symptoms or signs specific for another disease. Unfortunately, there is no evidence-based information to guide clinicians in treating patients without laboratory confirmation.

Reports on imported malaria generally describe the clinical presentation of hospitalized patients in centers that specialized in tropical medicine,[6–15] although no study was specifically designed to estimate the predictive values of the different clinical characteristics. One study in Canada investigated retrospectively whether the clinical presentation or the laboratory parameters could be used for predicting malaria infection in febrile travelers. They found symptom duration, temperature, immune status, fever pattern, and presence of enlarged spleen to be significant variables.[16] A study in the United Kingdom that investigated the causes of imported fever found thrombopenia and hyperbilirubinemia to be useful markers of malaria.[17]

The aim of the present study was to identify useful criteria to improve the presumptive diagnosis of imported malaria. We prospectively investigated all patients presenting at a university outpatient clinic with a complaint of fever or malaise after returning from the tropics, and we used a case control approach to identify significant predictors. Likelihood ratios (LR) of the different clinical and laboratory parameters were calculated and posttest probabilities estimated in this population of travelers.

MATERIALS AND METHODS

Resident physicians of patients who attended the Medical Outpatient Clinic, University of Lausanne, Switzerland, with a complaint of fever or malaise and in whom a malaria test was performed (blood films for the whole period, plus Para-Sight-F test for the last 2 years) received a questionnaire to be filled during the patient follow-up. Because the physicians were responsible for patient management, they were aware of the diagnosis at the time the questionnaire was filled out. The questionnaire included the patient's demographical data, travel history, preventive measures against malaria, details on symptoms and signs at admission, laboratory results, final diagnosis, treatment, and outcome. The definition of fever included raised temperature or perceived fever malaise comprised feelings of cold/warmth, chills, headache, myalgia, or some combination of these. Entry criteria were based on the literature and on in-house experience of symptoms indicative of potential malaria. There was no prerequisite checklist for the patient's interview, clinical examination, and laboratory tests to be performed. However, the institution had informal guidelines for the diagnosis of fever in returning travelers including precise and specific questions on travel history and preventive measures used, detailed clinical examination, and full blood cell count, including distribution of white cells, hemoglobin concentration, and hematocrit. Erythrocyte sedimentation rate, creatinine and liver function tests were ordered at the discretion of the attending practitioner and were thus not recorded for all patients.

Although the study was conducted prospectively, we used a case control approach. A case of malaria was defined as a patient with at least one of the tests positive for malaria, irrespective of any other incidental diagnosis. All blood slides were read by 2 microscopists trained in malaria identification. When discordant results or species uncertainty occurred, the slides were read at the reference laboratory in Switzerland (Swiss Tropical Institute) for confirmation. A control was de-

fined as a patient with negative tests for malaria on all occasions.

Each variable found to be significantly associated with diagnosed malaria in the univariate analysis was included in a stepwise backward model (significance level for exclusion of $P = 0.01$) to identify the most important predictors of malaria. The continuous variables, which had demonstrated an association with malaria in the univariate analysis, were recoded as binary variables by using accepted thresholds for normality. Accepted thresholds were preferred to "optimal" thresholds that is, thresholds with the best discriminant power—because the former are more standardized and easier to use for clinicians. These categorical variables were then included in the multivariate analysis. Logistic regression analysis was performed by Stata statistical software (Version 6.0, College Station, TX).

The significant variables associated with malaria in the multiple logistic regression model were retained and used for the estimation of the test performance. Likelihood ratios were calculated by the standard formulas for binary outcomes [LR+ = sensitivity/(1 – specificity); LR– = (1 – sensitivity)/specificity],[18] and 95% confidence intervals (CIs) were estimated by Confidence Interval Analysis,[19] version 2.0.0. The pretest probability (prevalence of disease in the sampled population) multiplied by the LR gave the posttest probability. The product of the individuals LR were used when a combination of 2 independent tests was considered. For continuous values, LR were modeled as an exponential result of the test result.[20]

RESULTS

A total of 336 questionnaires with complete information were collected from 1990 to 1998. Not all consecutive patients with fever or malaria were recruited because some doctors did not fill the questionnaire out adequately, despite repeated queries. A total of 97 patients (29%) were positive for any *Plasmodium* species (3 with the ParaSight-F test only). Among them, 64 harbored *Plasmodium falciparum,* including 7 mixed with *Plasmodium vivax* and 2 undetermined species considered as *falciparum* for management purposes; 19 had *P. vivax* alone, 9 had *Plasmodium ovale,* and 5 had *Plasmodium malariae.* Among the patients with malaria, 20 (20.6%) were hospitalized immediately. The rest were managed as outpatients.[21]

Nonmalaria cases consisted of the following: 21% flulike syndromes, 18% diarrhea, and 13% respiratory infections (Table 1). The median age of patients was 33.1 years (range, 16–76 years). A majority (62%) of the patients were men and had returned from travel to Africa. No children or pregnant women were included in the study. A total of 94 patients (28%) were of nonwhite origin; two-thirds were returning from visiting their home country, and one-third were arriving in Switzerland for the first time. A total of 89% of falciparum malaria cases were acquired in Africa, and 8% were acquired in Asia (32 and 47%, respectively, for cases of vivax malaria). Prevalence rates of demographic and clinical conditions in the overall sample of 336 patients are presented in Table 2. Table 3 shows the mean values of continuous variables in the same groups. The strength of association of each condition with a diagnosis of malaria and the level of confidence are also shown in Tables 2 and 3. Thirty of 49 variables tested were significantly associated with malaria in the univariate analysis.

TABLE 1
Diagnoses found in nonmalaria cases (n = 239)

Diagnosis	Proportion, n (%)
Flulike syndrome	50 (21)
Febrile or bacterial diarrhea	41 (17)
Upper respiratory tract infection	18 (8)
Pneumonia	7 (3)
Urinary tract infection	8 (3)
Angina	6 (3)
Acute hepatitis	5 (2)
Typhoid or paratyphoid fever	4 (2)
Intestinal amebiasis	3 (1)
Dengue fever	2 (1)
Rickettsiosis	2 (1)
Mononucleosis	2 (1)
Cytomegalovirus	2 (1)
Meningitis	1 (0)
Miscellaneous	62 (26)
Unknown	26 (11)

The backward logistic regression model, which included all significant variables by univariate analysis, showed that inadequate prophylaxis, sweating, no abdominal pain, temperature $\geq 38°C$, poor general health, enlarged spleen, hemoglobin < 12 g/dL, leucocytes $\leq 10 \times 10^3/\mu L$, platelets $< 150 \times 10^3/\mu L$, and eosinophiles $\leq 5\%$ remained significantly associated with malaria (Table 4).

The test performance of the variables found to be significantly associated with a diagnosis of malaria in the final model are presented in Table 5. The highest LR for a positive test was found for enlarged spleen (assessed clinically) (13.6), followed by thrombopenia, defined as platelet count $< 150 \times 10^3/\mu L$ (11.0); the lowest LR for a negative test was for leucocytes $\leq 10 \times 10^3/\mu L$ (0.11). When considering a threshold of platelets of $< 100 \times 10^3/\mu L$, the LR rose to 40.7 (95% CI, 11.1–151). The posttest probability for a diagnosis of malaria was 85% with enlarged spleen [$(97/239) \times 13.6 = 5.52$; $5.52/(1 + 5.52) = 84.7\%$] and 82% with thrombopenia ($< 150 \times 10^3/\mu L$). When both enlarged spleen and thrombopenia were combined, the posttest probability was 98%. Figure 1 illustrates the probability of malaria as a function of the temperature and of the platelet count.

DISCUSSION

This study represents what is to our knowledge the first attempt to prospectively identify the predictors of a diagnosis of malaria in returning travelers or migrants. Several studies have been conducted in semi-immune children in endemic areas to improve the diagnosis of malaria in the absence of microscopy,[22–27] but their conclusions are not readily applicable to nonimmune travelers returning from the tropics with fever. From the purely descriptive studies in nonimmune travelers or migrants,[6–15] we expected inadequate prophylaxis, measured fever, enlarged spleen, and thrombopenia to be important predictors of malaria. These parameters were confirmed in our study. The association of parasitemia and enlarged spleen or parasitemia and thrombopenia were strong, which is in agreement with previous findings.[16]

In addition, we found poor general health, absence of abdominal pain, sweating, absence of eosinophilia, anemia, and absence of leucocytosis to be significant predictors of malaria

TABLE 2

Prevalence rate of demographic, clinical, and laboratory conditions in sick patients and strength of association with malaria by univariate analysis

Condition	Overall prevalence (336 patients), n (%)	Prevalence in malaria cases (97 patients), n (%)	Prevalence in nonmalaria cases (239 patients) n (%)	Odds ratio	95% confidence interval	P value
Demographic and travel characteristics						
Nonwhite origin	94 (28)	39 (40)	55 (23)	2.25	1.36–3.73	0.002
Male sex	207 (62)	74 (76)	133 (56)	2.56	1.50–4.37	0.001
Africa as travel destination	217 (65)	75 (77)	142 (59)	2.33	1.36–4.00	0.002
Travel duration (d)						0.073
1–14	52 (16)	9 (9)	43 (18)	Ref	–	–
15–31	126 (38)	31 (32)	95 (40)	0.64	0.28–1.46	0.29
32–93	59 (18)	23 (24)	36 (15)	0.33	0.14–0.78	0.014
94–365	34 (10)	14 (14)	20 (8)	0.3	0.11–0.81	0.017
> 365	19 (6)	6 (6)	13 (5)	0.45	0.14–1.51	0.2
Immigrants*	46 (14)	14 (14)	32 (13)	0.48	0.18–1.24	0.13
No insectifuge	296 (88)	87 (90)	209 (87)	1.25	0.59–1.50	0.63
No bed nets	252 (75)	71 (73)	181 (76)	0.88	0.51–1.56	0.73
No protective clothing	242 (72)	83 (86)	159 (67)	2.98	1.59–5.58	0.001
No repellent use	221 (66)	75 (77)	146 (61)	2.17	1.26–3.73	0.005
Inadequate prophylaxis	207 (62)	81 (84)	126 (53)	4.54	2.51–8.22	< 0.001
Symptoms						
Fever	293 (87)	93 (96)	200 (84)	4.53	1.57–13.1	0.005
Chills	196 (58)	75 (77)	121 (51)	3.32	1.94–5.70	< 0.001
Sweating	177 (53)	66 (68)	111 (46)	2.46	1.49–4.03	< 0.001
Malaise	124 (37)	42 (43)	82 (34)	1.46	0.90–2.37	0.12
Headache	225 (67)	78 (80)	147 (62)	2.57	1.46–4.52	0.001
Myalgia	182 (54)	67 (69)	115 (48)	2.41	1.46–3.97	0.001
Nausea	108 (32)	37 (38)	71 (30)	1.46	0.89–2.39	0.13
Vomiting	56 (17)	21 (22)	35 (15)	1.61	0.88–2.94	0.12
Diarrhea	113 (34)	24 (25)	89 (37)	0.55	0.33–0.94	0.029
Bloody stools	14 (4)	4 (4)	10 (4)	0.98	0.30–3.22	0.98
Abdominal pain	95 (28)	18 (19)	77 (32)	0.48	0.27–0.86	0.013
Signs						
Temperature ≥ 38°C	114 (34)	55 (57)	59 (25)	4.00	2.43–6.57	< 0.001
Poor general health	49 (15)	29 (30)	20 (8)	4.67	2.48–8.78	< 0.001
Pallor	51 (15)	27 (28)	24 (10)	3.46	1.87–6.37	< 0.001
Jaundice	17 (5)	11 (11)	6 (3)	4.97	1.78–13.8	0.002
Dehydration	35 (10)	17 (18)	18 (8)	2.61	1.28–5.31	0.008
Enlarged liver	9 (3)	3 (3)	6 (3)	1.24	0.30–5.06	0.77
Enlarged spleen	26 (8)	22 (23)	4 (2)	17.2	5.76–51.6	< 0.001

* Immigrants are defined as migrants living in Switzerland without a recent visit to an endemic area.

TABLE 3

Means of demographic, clinical, and laboratory values (continuous variables) in sick patients and strength of association with malaria by univariate analysis

Condition	Available data no.	Overall mean	Malaria cases (mean ± SD)	Nonmalaria cases (mean ± SD)	Odds ratio	95% Confidence interval	P value
Age (y)	336	33.1	33.1 ± 10.2	33.1 ± 11.0	0.99	0.98–1.02	0.95
Duration of symptoms (d)	336	15.4	8.0 ± 12.8	19.1 ± 82.9	0.99	0.97–1.00	0.12
Signs							
Temperature	336	37.6	38.2 ± 1.3	37.4 ± 1.0	1.96	1.57–2.44	< 0.001
Pulse	336	84.4	90 ± 16.5	82 ± 15.5	1.03	1.02–1.05	< 0.001
Systolic pressure	336	125	123 ± 16.1	126 ± 15.4	0.99	0.97–1.00	0.16
Diastolic pressure	336	80	76 ± 11.1	81 ± 9.7	0.95	0.93–0.98	< 0.001
Laboratory findings							
Hemoglobin	336	141	136 ± 18.7	143 ± 14.5	0.97	0.96–0.99	0.001
Hematocrit	336	42.7	41.0 ± 5.5	43.4 ± 4.2	0.90	0.85–0.95	< 0.001
Erythrocytes	336	4.81	4.65 ± 0.7	4.88 ± 0.5	0.48	0.31–0.75	0.001
Platelets	336	215	142 ± 82.2	244 ± 75.4	0.98	0.98–0.99	< 0.001
Leucocytes	336	7.88	5.96 ± 2.2	8.66 ± 4.6	0.73	0.65–0.81	< 0.001
SR	147	18	25 ± 20.9	15 ± 20.9	1.02	1.00–1.04	0.014
Creatinine	184	92	95 ± 17.1	90 ± 24.4	1.01	0.99–1.02	0.16
Bilirubin	72	19.4	24.5 ± 13.4	14.5 ± 17.8	1.05	1.01–1.09	0.017
Gamma-Glutamyl Transpepridase	138	46.0	45.7 ± 42.8	46.2 ± 69.4	0.99	0.99–1.01	0.96
Glutamic Oxaloacetic Transaminase	180	58.1	31.9 ± 15.3	72.2 ± 274	0.99	0.99–1.00	0.40
Glutamic Pyruvic Transaminase	180	70.7	35.0 ± 27.7	89.9 ± 419	0.99	0.99–1.00	0.41

TABLE 4
Strength of association with malaria of the significant variables by multivariate analysis

Condition	Odds ratio	95% Confidence interval	P value
Inadequate prophylaxis	4.65	1.96–11.1	0.001
Sweating	2.13	1.03–4.44	0.042
No abdominal pain	4.05	1.50–10.9	0.006
Temperature ≥ 38°C	3.45	1.57–7.60	0.002
Poor general health	4.41	1.34–14.5	0.015
Enlarged spleen	7.71	1.87–31.8	0.005
Hemoglobin < 12 g/dL	6.92	1.80–26.5	0.005
Leucocytes ≤ $10 \times 10^3/\mu L$	19.1	4.15–87.5	< 0.001
Platelets < $150 \times 10^3/\mu L$	12.4	5.45–28.2	< 0.001
Eosinophils ≤ 5%	4.68	1.18–18.5	0.028

in the final multivariate model. One may argue that poor general health is subjective and thus is of little clinical value. Complementary analysis (data not shown) showed, however, that this criterion was associated with several more objective clinical signs (temperature, diastolic pressure); it may thus still be of some help in diagnosis establishment and management. Elevated white blood cell count is usually considered to be an indication of bacterial infection; it is also a criterion for severe malaria[28] and is even a prognostic factor for fatal outcome.[29] We infer from our data that it is rarely found in mild or moderate malaria, a condition that is usually encountered in the general practice of an outpatient clinic.[21] Even if enlarged spleen, thrombopenia, and normal white blood cell count were strong predictors of malaria in our sample, they are also characteristic of a number of other diagnoses of fever in returning travelers, especially typhoid fever.

One limitation of the study is that the history-taking and the clinical examination may have not been performed the same way in the patients with malaria and in controls without malaria because the clinician may have searched for symptoms and signs specific to the diagnosis he or she thought was the most probable. Because the doctors knew that the study was focused on malaria, they might have placed more emphasis on cases of malaria. But although this criticism may be true for the analysis of symptoms and signs, it is certainly irrelevant for laboratory values. The selection bias, which is reflected by the high prevalence of malaria (29%) in our sample, is, however, unlikely to have led to a bias in the estimation of the LRs, the key information provided by the present study, because the latter is based on sensitivity and specificity rates that are independent of the prevalence.

The study is not observational and therefore provides no indication on the respective incidence of diseases in returning travelers. However, we believe that the type of patients recruited is representative of the traveling population who attends a nonspecialized outpatient clinic. This sample is close to the one that visits general practitioners for fever upon return from the tropics. We are therefore confident that the results of the LRs (and not of the test probabilities) can be generalized to adults belonging to this entire population. The LR estimated from our study can also be used for the calculation of test probabilities in an emergency department of a hospital, as long as the prevalence of malaria, available from the hospital statistics, is known in each setting. On the other hand, caution should be taken when applying these results to other populations, especially children, in whom malaria often presents with gastrointestinal symptoms or signs.[30]

In developed countries, the recommendations—to perform a parasitological examination in all febrile patients returning from a malaria-endemic area and to initiate a specific treatment as soon as the diagnosis of malaria is confirmed—are not always followed. Parasitology results are often delayed or equivocal, especially in nonspecialized centers. Also, because of the low pyrogenic threshold in nonimmune patients and the frequent use of chemoprophylaxis, parasite densities are often low; because the sensitivity of microscopy is low in these conditions, the confirmation of the diagnosis cannot be made early in the course of the disease. In the meantime, the patient can develop complications that may be fatal.

The estimation of the test's performance outside a blood slide examination to diagnose malaria can be seen as an aid for the practitioner, allowing him/her to decide on the relevance of providing presumptive malaria treatment. Given a particular combination of test results (presence or absence of symptoms or signs, laboratory values) in a patient, how likely is the result to be malaria compared with nonmalaria? A LR of 14 for enlarged spleen tells us that this sign is 14 times more likely in patients with malaria than in the patients without malaria; the constellation of enlarged spleen plus thrombopenia is 154 (14 × 11) more likely in patients with malaria than in patients without malaria. More interesting is the estimation of the posttest probabilities (positive predictive values using Bayes' theorem), which are 85% for enlarged spleen, 82% for thrombopenia, and 98% for the combination of both.

One may argue that such an estimation is of little value because of its dependence on the prevalence of the disease in the sampled population (pretest probability). This is true for

TABLE 5
Test performance of the predictors of malaria*

Condition	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Likelihood ratio for positive test (95% CI)	Likelihood ratio for negative test (95% CI)
Inadequate prophylaxis	84 (74–90)	47 (41–54)	1.6 (1.4–1.8)	0.35 (0.22–0.54)
Sweating	68 (58–77)	54 (47–60)	1.5 (1.2–1.8)	0.60 (0.43–0.80)
No abdominal pain	81 (72–88)	32 (26–39)	1.2 (1.0–1.4)	0.58 (0.36–0.89)
Temperature ≥ 38°C	57 (46–67)	75 (69–81)	2.3 (1.7–3.0)	0.58 (0.45–0.72)
Poor general health	30 (21–40)	92 (87–95)	3.6 (2.1–6.0)	0.77 (0.66–0.86)
Enlarged spleen	23 (15–33)	98 (96–99.5)	13.6 (5.0–36.8)	0.79 (0.69–0.86)
Hemoglobin < 12 g/dL	16 (9–25)	97 (93–98)	4.6 (2.1–10.3)	0.88 (0.79–0.94)
Leucocytes ≤ $10 \times 10^3/\mu L$	97 (91–99)	27 (22–33)	1.3 (1.2–1.5)	0.11 (0.04–0.33)
Platelets < $150 \times 10^3/\mu L$	60 (49–70)	95 (91–97)	11.0 (6.4–19.1)	0.43 (0.33–0.53)
Eosinophils < 5%	95 (88–98)	12 (8–17)	1.1 (1.0–1.2)	0.43 (0.17–1.02)

* 95% CI = 95% confidence interval.

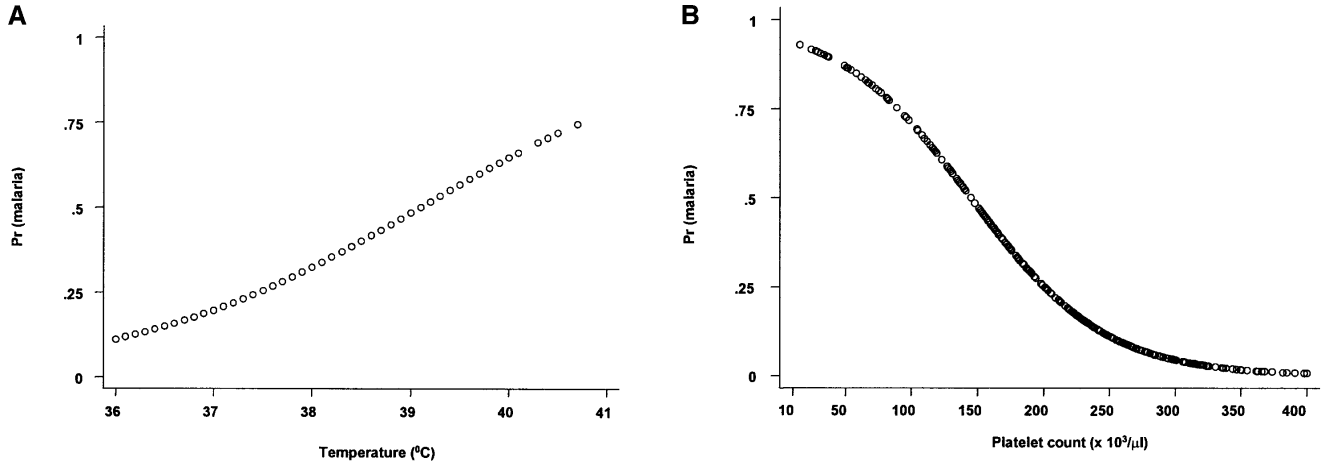

FIGURE 1. Likelihood ratio as a function of **(A)** axillary temperature and **(B)** platelet count. These functions were derived from logistic regression analysis.

predictive values calculated from 2 × 2 contingency tables. The use of LRs allows to estimate predictive values in populations of patients with different prevalence rates of disease. For example, a patient returning from the tropics with fever or malaise (as defined in the present study) had a pretest probability of 29% (97 of 336); adding an enlarged spleen allowed us to estimate a posttest probability of 85%. If this patient had been selected from a sample of patients drawn from a general practice with a prevalence of 10%, the posttest probability would have been 60%. The LRs available from our analysis thus provide the clinician with some evidence-based information that allows him/her to estimate the probability of a certain patient having malaria.

It is obvious that the concept of "therapeutic threshold" must be assessed at this stage. Deciding at what level of probability a presumptive treatment should be envisaged, or even strongly advised, is arbitrary. We believe that a posttest probability of > 80% should lead to the administration of presumptive treatment against malaria. Some may argue that it would be wiser to wait for another 12 hours and then repeat a parasitologic examination. Besides helping the clinician decide whether or not to provide treatment, the estimation of posttest probabilities also allows the clinician to decide on the relevance of performing additional investigations to identify the cause of the disease. If the clinician is reluctant to provide antimalarial treatment in the absence of documented *Plasmodium* parasites even though the posttest probability is > 90%, he/she should at least refrain from performing expensive serologies. Rather, the clinician should wait for the results of an additional blood slide examination performed some hours later.

Acknowledgments: We thank R. Darioli, who initiated collection of data in returning travelers, the resident physicians who conscientiously filled in the questionnaires, and the microscopists at the Medical Outpatient Clinic, University of Lausanne. We also thank C. Hatz for comments on the article in manuscript and Elisabeth Escher for quality-control reading of the blood films.

Authors' addresses: Valérie D'Acremont, Pierre Landry, Alain Pécoud, and Blaise Genton, Travel Clinic, Medical Outpatient Clinic, University of Lausanne, Rue César-Roux 19, 1005 Lausanne, Switzerland; Telephone: 41-21-345-22-22, Fax: 41-21-345-23-23. Ivo Mueller and Blaise Genton, Swiss Tropical Institute, Socinstrasse 57, 4002 Basel, Switzerland.

Reprint requests: Blaise Genton, Medical Outpatient Clinic, University of Lausanne, Rue César-Roux 19, 1005 Lausanne, Switzerland, Telephone: 41-21-345-22-22, Fax: 41-21-345-23-23; E-mail: Blaise.genton@hospvd.ch.

REFERENCES

1. Jensenius M, Ronning EJ, Blystad H, Bjorneklett A, Hellum KB, Bucher A, Haheim LL, Myrvang B, 1999. Low frequency of complications in imported falciparum malaria: a review of 222 cases in south-eastern Norway. *Scand J Infect Dis 31:* 73–78.
2. Greenberg AE, Lobel HO, 1990. Mortality from *Plasmodium falciparum* malaria in travelers from the United States, 1959 to 1987. *Ann Intern Med 113:* 326–327.
3. Winters RA, Murray HW, 1992. Malaria—the mime revisited: fifteen more years of experience at a New York City teaching hospital (see comments). *Am J Med 93:* 243–246.
4. Kain KC, Harrington MA, Tennyson S, Keystone JS, 1998. Imported malaria: prospective analysis of problems in diagnosis and management. *Clin Infect Dis 27:* 142–149.
5. Makler MT, Palmer CJ, Ager AL, 1998. A review of practical techniques for the diagnosis of malaria. *Ann Trop Med Parasitol 92:* 419–433.
6. Wiselka MJ, Kent J, Nicholson KG, 1990. Malaria in Leicester 1983–1988: a review of 114 cases. *J Infect 20:* 103–110.
7. Raglio A, Parea M, Lorenzi N, Avogadri M, Grigis A, Goglio A, 1994. Ten-year experience with imported malaria in Bergamo, Italy. *J Travel Med 1:* 152–155.
8. Jelinek T, Nothdurft HD, Loscher T, 1994. Malaria in nonimmune travelers: a synopsis of history, symptoms, and treatment in 160 patients. *J Travel Med 1:* 199–202.
9. Svenson JE, MacLean JD, Gyorkos TW, Keystone J, 1995. Imported malaria: clinical presentation and examination of symptomatic travelers. *Arch Intern Med 155:* 861–868.
10. Hansmann Y, Staub-Schmidt T, Christmann D, 1997. Malaria brought into Strasbourg: an epidemiological, clinical, biological and therapeutic study. *Trop Med Int Health 2:* 941–952 (published erratum appears in *Trop Med Int Health* 1997;2: 1110).
11. Wetsteyn JC, de Geus A, 1995. Falciparum malaria, imported into the Netherlands, 1979–1988. II. Clinical features. *Trop Geogr Med 47:* 97–102.
12. Matteelli A, Colombini P, Gulletta M, Castelli F, Carosi G, 1999. Epidemiological features and case management practices of imported malaria in northern Italy 1991–1995. *Trop Med Int Health 4:* 653–657.
13. Oh HM, Kong PM, Snodgrass I, 1999. Imported malaria in a Singapore hospital: clinical presentation and outcome. *Int J Infect Dis 3:* 136–139.
14. Lopez-Velez R, Viana A, Perez-Casas C, Martin-Aresti J, Turri-

entes MC, Garcia-Camacho A, 1999. Clinicoepidemiological study of imported malaria in travelers and immigrants to Madrid. *J Travel Med 6:* 81–86.
15. Nuesch R, Scheller M, Gyr N, 2000. Hospital admissions for malaria in Basel, Switzerland: an epidemiological review of 150 cases. *J Travel Med 7:* 95–97.
16. Svenson JE, Gyorkos TW, MacLean JD, 1995. Diagnosis of malaria in the febrile traveler. *Am J Trop Med Hyg 53:* 518–521.
17. Doherty JF, Grant AD, Bryceson AD, 1995. Fever as the presenting complaint of travellers returning from the tropics. *QJM 88:* 277–281.
18. Sox HC, Blatt MA, Higgins MC, Marton KI, 1988. *Medical Decision-Making.* Butterworth Publishers, MA.
19. Altman DG, Machin D, Bryant TN, Gardner MJ, 2000. *Statistics with Confidence.* BMJ Books. 2nd Edition. London, UK.
20. Giard RW, Hermans J, 1996. The diagnostic information of tests for the detection of cancer: the usefulness of the likelihood ratio concept. *Eur J Cancer 32A:* 2042–2048.
21. D'Acremont V, Landry P, Darioli R, Stuerchler D, Pecoud A, Genton B, 2002. The treatment of imported malaria in an ambulatory setting: a prospective study. *BMJ. 324:* 875–877.
22. Bassett MT, Taylor P, Bvirakare J, Chiteka F, Govere E, 1991. Clinical diagnosis of malaria: can we improve? *J Trop Med Hyg 94:* 65–69.
23. Olivar M, Develoux M, Chegou AA, Loutan L, 1991. Presumptive diagnosis of malaria results in a significant risk of mistreatment of children in urban Sahel. *Trans R Soc Trop Med Hyg 85:* 729–730.
24. Smith T, Hurt N, Teuscher T, Tanner M, 1995. Is fever a good sign for clinical malaria in surveys of endemic communities? *Am J Trop Med Hyg 52:* 306–310.
25. Redd SC, Kazembe PN, Luby SP, Nwanyanwu O, Hightower AW, Ziba C, Wirima JJ, Chitsulo L, Franco C, Olivar M, 1996. Clinical algorithm for treatment of *Plasmodium falciparum* malaria in children. *Lancet 347:* 223–227.
26. Luxemburger C, Nosten F, Kyle DE, Kiricharoen L, Chongsuphajaisiddhi T, White NJ, 1998. Clinical features cannot predict a diagnosis of malaria or differentiate the infecting species in children living in an area of low transmission. *Trans R Soc Trop Med Hyg 92:* 45–49.
27. Genton B, Smith T, Baea K, Narara A, al Yaman F, Beck HP, Hii J, Alpers M, 1994. Malaria: how useful are clinical criteria for improving the diagnosis in a highly endemic area? *Trans R Soc Trop Med Hyg 88:* 537–541.
28. World Health Organization, 2000. Severe falciparum malaria. *Trans R Soc Trop Med Hyg 94 (Suppl 1):* 1–31.
29. Genton B, al Yaman F, Alpers MP, Mokela D, 1997. Indicators of fatal outcome in paediatric cerebral malaria: a study of 134 comatose Papua New Guinean children. *Int J Epidemiol 26:* 670–676.
30. Genton B, D'Acremont V, 2001. Clinical features of malaria in returning travelers and migrants. Schlagenhauf P, ed. *Travelers' Malaria.* BC Decker Inc. Hamilton, Ontario, 371–392.