

# Fourteen-year experience with imported malaria

## *Esperienza di quattordici anni con la malaria da importazione*

Alfredo Focà<sup>1</sup>, Giorgio S. Barreca<sup>1</sup>, Vincenzo Barbieri<sup>1</sup>, Giovanni Matera<sup>1</sup>, Maria Carla Liberto<sup>1</sup>, Marta De Rosa<sup>2</sup>

<sup>1</sup>Institute of Microbiology, Department of Medical Sciences, University of Catanzaro, Catanzaro, Italy;

<sup>2</sup>U.O. Virologia, A.O. B.M.M., Reggio Calabria, Italy

### ■ INTRODUCTION

**A**nually *Plasmodium* spp. cause 300-500 million of malaria cases around the world and one million fatalities [1]. Even if indigenous malaria has been eradicated in developed countries, today the problem appears to have shifted to a new malaria transmission pattern. In the last twenty years there has been an increase in imported malaria, defined as the illness developing in a non-endemic area, diagnosed by microscopy, but due to an infection acquired abroad, during a stay in an endemic region. This has become a source of concern [2, 3]. Political changes, economic difficulties, business and leisure travel [2], and military missions contribute significantly to the very sharp increase in imported malaria. In Italy the risk of acquiring malaria concerns non-immune international travellers and immigrants from nearby African and Asian countries, and depends on several factors such as travel pattern, destination, duration of the stay and prophylaxis used; plasmodium drug resistance may further increase the risk of the infection [3, 4].

Calabria is the southernmost region of continental Italy. The region not only shares with other western areas the factors contributing to an enhanced number of imported malaria cases, but also represents a natural point of arrival for immigrants coming to Europe from regions where malaria is endemic, such as most African countries, Turkey and many Central Asian countries [5].

Moreover, the increased incidence of reported

cases concerning resident foreigners on visits to their place of origin, produced a clear change in epidemiological aspects of this parasitic infection [5]. To verify this trend in our region we retrospectively analyzed data on imported malaria diagnosed from 1988 to 2001.

### ■ PATIENTS AND METHODS

We analyzed cases of imported malaria, both reported and unreported to the Italian Ministry of Health and confirmed by haemoscopic tests, in Calabria from 1988 to 2001. Such work was carried out by consultation with the Ministry of Health via ledgers of the Infectious Diseases Prophylaxis Office, by consultation with the Higher Institute of Health via computerized archives of parasitological laboratories, and with data from Regional Health Offices and from hospitals where patients had been admitted. For some clinical cases, data were collected or integrated by telephone interviews with patients. For each subject the following variables were considered: demographic data, time and place of malaria acquisition, travel purpose, clinical aspects of the disease and hospitalization, haemoscopic diagnosis, species of plasmodium observed, chemoprophylaxis and treatment used. Citizenship was based on the reported status at the time of diagnosis. Fisher's Exact Test was used to address statistical differences between percentages when variables were categorical in nature.

## RESULTS

From 1988 to 2001, 34 slide-confirmed malaria cases were reported; 33 (97.0%) fulfilled the definition criteria of imported malaria, whereas

one represented a relapse case. Based on citizenship, our cases are reported in two tables, for Italian subjects (Table 1) and for foreigners (Table 2). There were 25 male patients (75.7%) and 8 female (24.2%) with a male:female ratio

**Table 1 - Epidemiological and clinical features of imported malaria cases in Calabria. Italian subjects.**

No.	Year	Sex/Age (yrs)	Job	Countries visited	Length of stay	Travel purpose	Prophylaxis drugs/length	Diagnosis delay	Malaria species	Treatment	Outcome
1	2000	M/37	N.A.	Nigeria	N.A.	business	N.A.	6 days	Pf	quinine	N.A.
2	2000	M/27	N.A.	Tanzania	N.A.	business	N.A.	5 days	Pf	quinine/ tetracycline	N.A.
3	2000	F/26	student	Kenya	14 days	tourism	Chloroquine/ Full	1day	Pf	mefloquine	improved
4	1998	F/27	sociologist	Mali	9 months	business	Chloroquine +proguanil/ partial	1day	Pf	quinine	resolved
5	1998	M/42	sailor	Ivory Coast	N.A.	business	N.A.	4 days	Pf	mefloquine	N.A.
6	1998	M/34	engineer	Malawi	9 months	business	Mefloquine/ Partial	4 days	Pf	quinine	improved
7	1997	F/34	housewife	Ghana	8 months	visiting relatives	N.A.	30 days	Pf	mefloquine	resolved
8	1996	M/44	manual worker	Sierra Leone	N.A.	business	Chloroquine/ Full	10 days	Pf	N.A.	N.A.
9	1996	F/50	housewife	Nigeria	9 months	visiting relatives	N.D.	30 days	Pv/Pm	chloroquine	N.A.
10	1996	M/51	teacher	Mali	1 month	tourism	N.D.	6 days	Pf	quinine/ tetracycline	resolved
11	1995	M/3	unemployed	India	N.A.	visiting relatives	N.D.	41 days	Pv	chloroquine/ primaquine	resolved
12	1995	M/47	sailor	Ivory Coast	N.A.	business	N.A.	9 days	Pf	quinine	DEAD
13	1995	M/56	teacher	Mali	14 days	tourism	N.D.	5 days	Pf	quinine/ doxycycline	resolved
14	1994	F/29	office worker	Colombia	1 month	tourism	N.D.	7 days	Pv	chloroquine/ primaquine	resolved
15	1994	M/51	manager	Madagascar	N.A.	business	N.A.	N.A.	Pv	N.A.	N.A.
16	1994	M/21	soldier	Somalia	4 months	military mission	Chloroquine+ proguanil/ Full	6 days	Pv	chloroquine/ primaquine	resolved
17	1994	M/20	soldier	Somalia	3 months	military mission	Chloroquine+ proguanil/ Full	21 days	Pv	chloroquine	improved
18	1994	M/20	soldier	Somalia	3 months	military mission	Chloroquine+ proguanil/ Full	17 days	Pv	quinine/ primaquine/ tetracycline	resolved
19	1994	M/20	soldier	Somalia	3 months	military mission	Chloroquine+ proguanil/ Full	8 days	Pv	quinine/ primaquine/ tetracycline	resolved
20 bis1994	M/21	soldier	Somalia	5 months	military mission	Chloroquine+ proguanil/ Full	10 days	Pv	chloroquine/ primaquine relapse		
20	1993	M/20	soldier	Somalia	5 months	military mission	Chloroquine+ proguanil/ Full	11 days	Pv	Sulfametho- pyrazine/ pyrimethamine	improved
21	1992	M/59	pensioner	Sierra Leone	4 months	visiting relatives	Chloroquine/ Full	5 days	Pv	chloroquine/ primaquine	resolved

N.A. = information not available; N.D. = not done; Pf = P. falciparum; Pv = P. vivax; Pm = P. malariae.

**Table 2 - Epidemiological and clinical features of imported malaria cases in Calabria. Foreign subjects.**

No.	Year	Sex/Age (yrs)	Job	Countries visited	Length of stay	Travel purpose	Prophylaxis drugs/length	Diagnosis delay	Malaria species	Treatment	Outcome
22	2001	F/33	N.A.	Senegal	N.A.	N.A.	N.D.	5 days	Pf	quinine	N.A.
23	2001	M/44	priest	Congo 1	month	visiting relatives	Fansidar/full	7 days	Pf	mefloquine	resolved
24	2000	M/41	N.A.	Senegal	N.A.	visiting relatives	N.A.	N.A.	Pf	Quinine/ Tetracycline	N.A.
25	1998	F/28	volunteer	Thailand	4 months	business	N.D.	105 days	Pv	cloroquine	improved
26	1997	M/22	N.A.	Turkey	N.A.	refugee	N.A.	1 day	Pv	cloroquine/ primaquine	resolved
27	1996	M/27	N.A.	Senegal	N.A.	N.A.	N.D.	2 days	Pf	mefloquine/ tetracycline	improved
28	1995	F/1.5	unemployed	India	19 months	visiting relatives	N.D.	61 days	Pv	cloroquine/ primaquine	resolved
29	1995	M/52	sailor	Camerun	N.A.	business	N.A.	15 days	Pf	quinine	resolved
30	1993	M/19	trader	Nigeria	42 days	tourism	N.D.	15 days	Pf	mefloquine	resolved
31	1992	M/37	manual worker	Nigeria	N.A.	tourism	N.A.	N.A.	Pf	N.A.	N.A.
32	1989	M/30	trader	Senegal	N.A.	N.A.	N.A.	N.A.	Pf	N.A.	N.A.
33	1989	M/N.A.	N.A.	Niger	N.A.	tourism	N.A.	N.A.	Pf	N.A.	N.A.

N.A. = information not available; N.D. = not done; Pf = *P. falciparum*; Pv = *P. vivax*; Pm = *P. malariae*.

of about 3:1. The age distribution ranged between below 10 and over 50 years. During the year, morbidity rose from March to September. Among our studied cases, 21 were Italians and 12 were foreigners (63.6% vs. 36.3%).

Regarding the distribution of imported malaria related to nationality, place of residence and year of acquisition, during the first seven-year period (1988-1994) 12 cases were registered: eight were Italians resident in Italy, one was a non-resident foreigner and three were of un-

**Table 3 - Signs and symptoms in 21 patients with imported malaria.**

Sign or symptom	No. patients	%
Fever	20	95.2
Chill	14	66.6
Fatigue	6	28.5
Myalgia, arthralgia	6	28.5
Sweats	5	23.8
Vomiting	5	23.8
Nausea	4	19.0
Pale skin and mucous membranes	3	14.3
Headache	3	14.3
Dry cough	2	9.5
Other	2	9.5

Data are numbers and percentages (n = 21) for which such information is available.

known origin. A different situation appeared in the last seven-year period (1995-2001), with an increased number of cases (n=21), represented by 12 Italian residents and 7 foreigners living in Italy.

The remaining two subjects were an Italian woman, who regularly spent 8 months a year in Ghana visiting her husband, and a male foreign patient not resident in Italy.

Most of the infections were acquired in West Africa (51.5%, n=17) followed by East Africa (27.3%, n=9), Central Africa (6%, n=2), Asia (9.1%, n=3), South America and Europe (6%, n=2).

The infection risk did not increase with length of stay. Although for 15 subjects included in our study the length of stay was unknown, 27.8% of the remaining cases (n = 18) were in endemic areas for less than 1 month, 5.5% for 2 months, 33.3% for 2-4 months and 33.3% for more than 4 months.

Information on trip purpose revealed that 15 patients (13 Italians, including 5 members of the armed forces, and 2 foreigners) went to endemic areas for work, 7 for travel, 6 to see relatives.

One Indian child arrived in Italy for adoption. Data regarding four patients were not available. Clinical features of our patients are reported in Table 3. As can be seen, fever and chill are the most frequently observed clinical features, although other non-specific signs and

**Table 4 - Distribution of Plasmodium species.**

Species	No. of patients (%)	Geographical area where infection occurred
<i>P. falciparum</i>	20 (60.6)	Africa
<i>P. vivax</i>	7 (21.2)	Africa
<i>P. vivax</i>	3 (9.1)	Asia
<i>P. vivax</i>	1 (3)	South America
<i>P. vivax</i>	1 (3)	Europe
<i>P. vivax/P. malariae</i>	1 (3)	Africa
Total	33 (100)	
Data are numbers and percentages of patients.		

symptoms (fatigue, myalgia/arthralgia, sweats, vomiting, nausea) showed fairly high percentages. The remaining non-specific clinical features highlight the need to obtain a thorough clinical and travel history from all febrile patients who had been in a malaria-endemic area.

Prophylaxis aspects, which are substantially known for most Italian cases, are reported in Tables 1 and 2. Information on chemoprophylaxis were classified into 4 categories: adequate chemoprophylaxis, partial chemoprophylaxis, no chemoprophylaxis and unknown chemoprophylaxis. Only 9 subjects (27.3%) received correct anti-malarial preventive treatment, 2 subjects (6%) partial chemoprophylaxis, 10 subjects (30.3%) received no treatment, whereas data were not available for 12 subjects (36.3%).

*Plasmodium falciparum* and *Plasmodium vivax* were the most common infecting parasites, together being responsible for 97.0% of the cases (Table 4). In particular *P. falciparum* was found only in patients coming from Africa, while *P. vivax* infected patients came from all areas considered. Only one mixed infection by *P. vivax/Plasmodium malariae* was recorded.

Data on treatment of malarial cases were available only for 29 patients. Among these subjects, the drugs most frequently used, alone or in combination, were mefloquine (17.2%, n=5), quinine (20.7%, n=6), chloroquine (10.3%, n=3), chloroquine/primaquine (24.1%, n=7), quinine/tetracycline (13.8%, n=4), quinine/primaquine/tetracycline (6.9%, n=2), mefloquine/tetracycline (3.4%, n=1), and sulfamethopyrazine plus pyrimethamine (3.4%, n=1).

A case of death was recorded and concerned an Italian sailor coming from West Africa (Ivory Coast).

## DISCUSSION

Retrospective analysis on data concerning cases of malaria in Calabria shows a well-defined epidemiological situation. There is currently no risk of an indigenous infection, as demonstrated by the lack of cases of endemic malaria: the last case reported in Calabria of locally acquired malaria occurred in 1955 [6]. Therefore in this paper only imported malaria cases are discussed. However, the presence of three busy airports and many harbours, the frequent landing of illegal refugees and a number of seasonal workers from endemic areas, might change the complex, multifactorial pattern of imported malaria in this region.

First, we may observe a considerable difference between the two seven-year periods considered; during 1995-2001 an increased number of cases (21 vs 12) was found over the previous seven years.

The population group with a high risk of infection is represented by Italians residing in Italy travelling on business to endemic areas (n=13). Of these subjects, five (23.8% of all Italian cases) were returning from a military mission in East Africa (Somalia); these five infected soldiers represented almost 4.5% of the whole Italian military personnel who became malaria-infected during the mission [7]. Mention should be made of a female Italian sociologist who went to Mali for research purposes and became infected with *P. falciparum* at the beginning of her pregnancy [8]. A different group is represented by tourists who included 7 subjects without significant differences between 1988-1994 period (4 people) and 1995-2001 period (3 people).

Another population group with a high risk of infection consists of people who return to endemic areas to visit relatives for a short time.

This group appears to be increasingly infected (5 cases) during the last seven-year period, which agrees with the nationwide trend [9]. The delay in malaria diagnosis was very frequent, from 4-6 days until 1 month and more. This gives cause for concern about the ability to make a rapid diagnosis both clinically and based on laboratory tests such as haemoscopic identification and about the availability of PCR methods in many hospitals [10]. As regards the aetiology of malaria, *P. falciparum* was found in patients coming from Africa (60.6%), while *P. vivax*, alone or associated with *P. malariae*, was isolated from 24.2% of patients coming from African areas and 9.1% of patients from Asia. Infections occurring in Africa are more likely due to *P. falciparum* rather than to other plasmodium species (60.6% vs. 24.2%), while infections occurring in non-African areas were more likely due to non-falciparum species (15.15% vs. 0.0%) ( $p < 0.005$  by Fisher's exact test). Percentage of cases of *P. falciparum* infections increased from the period 1988-1994 (15%) to the next seven years (45%), while *P. vivax* (or *P. vivax/P. malariae*) diagnosed cases decreased from 24% observed in 1988-1994 to 15% found in the 1995-2001 period ( $p = 0.04$  by Fisher's exact test). The age distribution ranged between below 10 years and more than 50 years. The percentage of patients diagnosed with *P. falciparum* was lower (18.7%) among subjects younger than 31 years old and higher (40.6%) among older ones with a probability of 0.014 at Fisher's exact test. Morbidity was highest in March through September. In our study, one patient died of malaria due to *P. falciparum*. Other authors have reported fatal imported malaria in Italy [11]. More effective control of the risk of malaria requires on-going education for health-care providers and more detailed information in terms of pharmacology and prophylaxis, together with sound behaviour during business or tourism travel in endemic areas [12]. Calabria's hydrogeological and environmental features, residual anophelism and the continuous increase in illegal refugees should prompt strict epidemiological surveillance. According to Italian government data, the number of illegal immigrants rose from 848 in 1998 to over 6000 in 2001, the majority coming from countries where malaria is endemic, hence potential carriers of malarial gametocytes. Moreover peak arrivals of refugees falls in the summer/autumn period which corresponds to peak activity of the potential vectors of plasmodial species (*Anopheles*

*labranchiae* and *Anopheles superpictus*). Although *A. labranchiae* seems quite resistant to infection with *P. falciparum*, this does not hold for *P. vivax* infection. Indeed a local *A. labranchiae* was reported to be the vector of a case of *P. vivax* malaria in an Italian woman with no history of travel to malaria endemic areas (13). However the susceptibility of *A. superpictus* to *P. falciparum* of African origin is probably significant, because this mosquito belongs to the subgenus *Cellia*, like the major African vectors [6, 14]. Also we observed a delay in reporting cases from the hospitals to the Ministry of Health (e.g.: during the year 2000 only 3 cases were reported vs 4 cases we observed and in 2001 the 2 cases we found were still unreported to the Ministry of Health). This delay combined with severe underestimation of cases is observed particularly among refugees and immigrants, thus suggesting a great increase in potential gametocyte carriers. This feature deserves additional clinical and epidemiological studies. Moreover, the increasing number of Italian and foreign malaria patients, the delay in the diagnosis and the mild and unspecific clinical presentation of some cases might suggest an increasing source of infection by unusual transmission (e.g. parenteral route). This type of spread of malaria infection includes needle sharing between drug-abusers, as well as blood transfusion, since the appropriate test for malaria is rarely used in blood banks either in Italy or in other non-endemic areas [15, 16]. Unapparent or hard-to-track parenteral transmission has been recently reported in Italy (17). Moreover in foreigners residing in Italy and in other non-endemic areas, the infection can be less obvious (e.g. without fever) and may continue for many months [18]. Therefore the patient will not seek a physician's advice and may represent a source of malaria being spread by either more evident or unapparent ways, including shared razors or toothbrushes, dental surgery, or unprotected sexual activity among persons with minimal mucosal bleeding. Based on the above reported data, regional laboratories and health offices should be more committed to strict epidemiological surveillance concerning potential gametocyte carriers and the distribution of the vectors, besides undertaking further studies of new malaria cases due to unusual transmission mechanisms.

**Keywords:** Imported malaria, epidemiological surveillance, immigrants, Calabria.

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### SUMMARY

Geographical position, an increasing flow of immigrants and refugees coming from regions where malaria is endemic might further increase those cases of malaria imported to Calabria due to travel on military missions, visiting relatives, business and leisure. However, few reports have been published regarding malaria imported into the southern Italian region of Calabria. Based on data from our laboratory, official reports received from the Italian Ministry of Health and Regional Health Offices, an epidemiological analysis of malaria cases registered in Calabria from January 1988 to December 2001 is reported. The epidemiological and clinical features concerning the cases are discussed.

A total of 34 slide-confirmed malaria cases were observed in Calabria during the period in question. Infections were mostly acquired in Africa (84.8%), while remaining infections came from Asia (9.1%) and South America

and Europe (6.0%). Length of stay in the endemic area did not increase the infection risk. Etiological diagnosis indicated *Plasmodium falciparum* as the species most often involved (60.6%), followed by *Plasmodium vivax* (36.3%) and *P. vivax/Plasmodium malariae* mixed infection (3.0%). The mortality rate was about 3.0%. The number of cases during the second seven-year period of this study was almost double that of the first seven-year period. Correct chemoprophylaxis was performed by only 27.3% of our studied subjects. Delay of malaria diagnosis ranged between 4 days and 1 month.

In conclusion, increases in malaria cases, mostly due to *P. falciparum*, delay in diagnosis and reporting to the Regional Health Office, as well as the increasing arrival of refugees from endemic areas, are epidemiological concerns in Calabria, the southernmost region of continental Italy.

### RIASSUNTO

La posizione geografica, il crescente flusso di immigrati e rifugiati provenienti da regioni dove la malaria è endemica potrebbero incrementare quei casi di malaria importata in Calabria in seguito a viaggi per missioni militari, visite ai parenti, affari e turismo. In letteratura è tuttavia presente solo un esiguo numero di rapporti concernenti la malaria da importazione in Calabria. Nel presente lavoro è riportata l'analisi epidemiologica dei casi di malaria registrati in Calabria dal 1988 al 2001, basata sui dati provenienti dal nostro laboratorio e sui rapporti ufficiali del Ministero della Salute e dell'Assessorato Regionale alla Sanità. Sono discusse anche le caratteristiche cliniche ed epidemiologiche concernenti i casi esaminati.

Durante il periodo Gennaio 1988 - Dicembre 2001 in Calabria sono stati osservati 34 casi di malaria confermati emoscopicamente. Le infezioni erano più frequentemente acquisite in Africa (84.8%), mentre le rimanenti provenivano dall'Asia (9.1%) e dal Sud-America ed Europa (6.0%). La durata del soggiorno in area endemica non aumentava il rischio di infezione. *Plasmodium falciparum* era la specie diagnosticata con maggiore frequenza (60.6%), seguita da *Plasmodium vivax* (36.3%) e da infezione mista *P. vivax/Plasmodium malariae* (3.0%). Il tasso di mortalità era di circa il 3.0%. Il numero di casi durante i sette anni successivi dello studio era quasi raddoppiato rispetto al primo periodo di

sette anni. Una corretta chemioprolifassi veniva fatta solo dal 27.3% dei soggetti studiati. Il tempo intercorso tra inizio della sintomatologia e diagnosi variava da 4 giorni ad 1 mese. L'aumento dei casi di malaria attribuibili per la maggior parte a *P. falciparum*, il ritardo nella

diagnosi e nella notifica all'Assessorato Regionale alla Sanità, così come l'aumento degli sbarchi di rifugiati provenienti da aree endemiche rappresentano una causa di preoccupazione sia in Calabria, la regione italiana più meridionale, che in Europa.

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