



## Imported Malaria in Immigrants to Italy: A Changing Pattern Observed in North Eastern Italy

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**Background.** Seventy percent of imported malaria cases in Italy occur in immigrants, generally with milder clinical presentation due to premunition acquired through repeated infections. Nevertheless, premunition could be progressively lost after a long period of nonexposure. We investigated the changing pattern of malaria in immigrants in two definite 5-year periods one decade apart.

**Methods.** We retrospectively examined the main laboratory findings of all malaria cases observed in immigrants from 1990 to 1994 and from 2000 to 2004. We stratified patients by reason for traveling: subjects in Italy who traveled to visit friends and relatives (VFR) or new immigrants (NI).

**Results.** Forty-eight cases of malaria in immigrants occurred from 1990 to 1994, while 161 were observed from 2000 to 2004. Patients admitted in the latter period had a significantly higher parasitemia (median 6,298 vs 3,360 trophozoites/ $\mu$ L,  $p = 0.028$ ) and lower platelet count (median  $96.5$  vs  $132 \times 10^9$ /L,  $p = 0.012$ ) and hemoglobin (median  $12.6$  vs  $13.4$  g/dL,  $p = 0.049$ ). While NI did not show any significant difference in the two study periods, in the VFR subgroup a higher parasitemia (median 8,845 vs 2,690 trophozoites/ $\mu$ L,  $p = 0.003$ ) and lower platelet count (median  $96$  vs  $131 \times 10^9$ /L,  $p = 0.034$ ) were observed during the second period, during which three cases of severe malaria occurred in VFR. A longer stay in Italy was reported in VFR admitted during the second study period (median 8.3 vs 5.7 years).

**Conclusions.** We found a changing pattern of malaria presentation in immigrants over a decade. The most likely explanation is the longer average stay outside endemic countries and subsequent loss of premunition observed in the second cohort. Immigrants living in Italy for some time and traveling to VFR should no more be considered a low-risk group for severe malaria. Pretravel advice should be particularly targeted to this group.

In Italy, imported malaria cases in immigrants showed an increasing trend since 1990, reaching a peak in 1999,<sup>1</sup> subsequently declining. Nevertheless, this group still accounts for approximately 70% of reported cases.<sup>2</sup> Malaria cases are more frequently observed in immigrants settled in Italy and occasionally traveling to endemic areas to visit friends and relatives (VFR) than in those arriving for the first time [new immigrants (NI)].

Malaria in immigrants is characterized by a milder clinical presentation, lower parasitemic levels, and a shorter fever duration than malaria in nonimmune travelers.<sup>3,4</sup> These differences are explained by the persistence of premunition acquired through repeated infections. Premunition tends to disappear after several

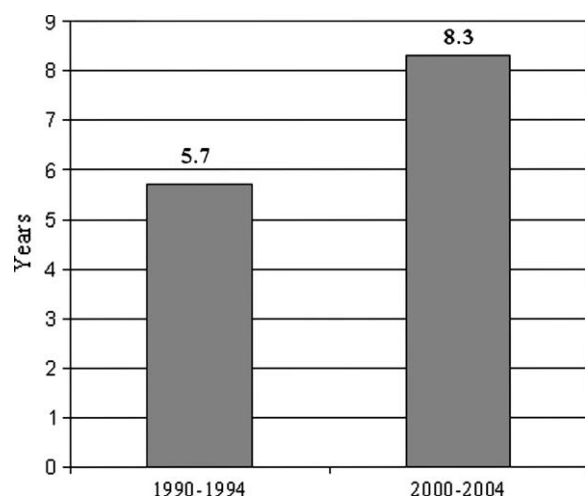
years of nonexposure. Nevertheless, the mean time required to lose semi-immunity has yet to be defined.<sup>5</sup>

We investigated the changing picture of malaria in immigrants over a decade, by analyzing the cases observed from 1990 to 1994 and from 2000 to 2004. Our working hypothesis was that cases observed during the second study period could be more severe on average in the VFR group, as they have lived for a longer period outside malaria endemic countries. Conversely, we did not expect to find any significant difference in the NI group.

### Methods

We retrospectively examined all falciparum malaria cases observed in immigrants from January 1, 1990 to December 31, 1994, and from January 1, 2000 to December 31, 2004, at the Centre for Tropical Diseases, S. Cuore Hospital of Negrar, Verona. The two cohorts were further grouped, and separately analyzed, by reason of travel: VFR or NI.

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**Figure 1** Mean stay in Italy before traveling for visiting friends and relatives.

The diagnosis was based on microscopic examination of Giemsa stained thick and thin blood films. In accordance with some previous studies,<sup>3-5</sup> the following main laboratory findings were analyzed: parasitemia, hemoglobin, and platelet count.

Univariate analysis was used to describe the study sample. Laboratory results, which are continuous variables, were also categorized and results presented as percentages in addition to means and standard deviation (SD). Differences in laboratory findings according to reason of travel and patient classification were examined with Fisher's exact test for categorical variables and Kruskal-Wallis test for continuous variables.

## Results

### *Malaria in Immigrants*

#### 1990 to 1994

From 1990 to 1994, we observed 174 cases of imported falciparum malaria, 48 (27.5%) of which occurred in immigrant adult patients. Forty (83.3%) had traveled to VFR after an average stay in Italy of 5.7 years (median 5.5 years, SD 2.3 years, range 1–11 years), while 8 (16.7%) had come to Italy for immigration (NI) (Figure 1).

#### 2000 to 2004

From 2000 to 2004, 292 cases of falciparum malaria were admitted to our Centre, of which 161 were immigrant adult patients. A total of 128 (79.5%) had traveled for VFR after an average stay in Italy of 8.3 years (SD 4.6 years, range: 1–19.7 years), 27 (16.8%) were NI, and 6 (3.7%) had traveled for other reasons (Figure 1).

The main demographic characteristics of patients admitted during the two periods are reported in Table 1.

In both periods, patients mostly came from Nigeria and Ghana, although from 2000 to 2004, we observed some malaria cases imported from other countries as well (Table 2).

As is shown in Table 3, immigrants admitted from 2000 to 2004 (data available for 103 patients) had significantly higher parasitemic level on admission and showed (data available for 158 patients) significantly lower average platelet count and hemoglobin than those admitted from 1990 to 1994.

From 1990 to 1994, uncomplicated malaria was treated with different antimalarial drugs: halofantrine, mefloquine, sulphalene-pyrimethamine, or chloroquine.

During the second study period, according to the regimen adopted by our Centre, patients with uncomplicated malaria were treated with oral quinine plus sulphalene-pyrimethamine (Metakelfin®).<sup>6</sup>

In both periods, patients with severe malaria and those with vomiting were given intravenous quinine.

### *Malaria in VFR Travelers*

A separate analysis was carried out for the VFR and NI groups.

No significant differences in the mean values of platelets, hemoglobin, and parasitemia were detected in the latter group during the two periods (Table 4). Conversely, VFR immigrants with falciparum malaria during the period 2000 to 2004 were found to have significantly higher parasitemia and significantly lower platelet count than those observed from 1990 to 1994 (Table 4, Figure 2).

In VFR travelers, the average time elapsed between the onset of symptoms and the diagnosis was similar in both periods: 4.2 days (1990–1994) versus 4.7 days (2000–2004).

**Table 1** Main demographic characteristics of new immigrants (NI) and visiting friends and relatives (VFR) patients, 1990 to 1994 versus 2000 to 2004

	1990–1994		2000–2004		
Number of malaria cases	228		380		
Falciparum cases <i>n</i> (%)	174 (76.3)		292 (76.8)		
Falciparum malaria in adult immigrants <i>n</i> (%)	48 (27.5)		161 (42.4)		
Reason for travel in adult immigrants <i>n</i> (%)	NI	VFR	NI	VFR	Other reason
	8 (16.7)	40 (83.3)	27 (16.8)	128 (79.5)	6 (3.7)
Male <i>n</i> (%)	7 (87.5)	30 (75)	18 (66.7)	95 (74.2)	6
Female <i>n</i> (%)	1 (12.5)	10 (25)	9 (33.3)	33 (25.8)	0
Age mean (SD)	24.8 (7.3)	32.4 (5.1)	30.8 (11)	36.3 (7.1)	40.5 (5)

**Table 2** New Immigrants (NI) or visited (VFR), 1990 to 1994 versus 2000 to 2004

Countries	1990–1994		2000–2004	
	NI	VFR	NI	VFR
Ghana <i>n</i> (%)	6 (75)	32 (80)	7 (25.9)	64 (50)
Nigeria <i>n</i> (%)	1 (12.5)	4 (10)	7 (25.9)	34 (26.6)
Ivory Coast <i>n</i> (%)	0	0	3 (11.1)	5 (4)
Senegal <i>n</i> (%)	0	0	2 (7.5)	12 (9.3)
India <i>n</i> (%)	0	0	1 (3.7)	4 (3.1)
Congo <i>n</i> (%)	0	0	3 (11.1)	0
Other West Africa Countries <i>n</i> (%)	1 (12.5)	2 (5)	3 (11.1)	8 (6.2)
Other East, Central or Southern African Countries <i>n</i> (%)	0	2 (5)	1 (3.7)	1 (0.8)

NI = new immigrants; VFR = visit friends and relatives.

In the first study period (1990–1994), nobody had followed any chemoprophylaxis. From 2000 to 2004, 15 (11.7%) VFR followed a chemoprophylactic regimen, albeit inadequate.

We found that 35% (30/86) of VFR immigrants admitted from 2000 to 2004 had a length of stay in Italy longer than 10 years, in comparison with 5.3% (2/38) VFR immigrants admitted during the first study period (Table 5).

#### Severe Malaria

From 2000 to 2004, three malaria cases in adult immigrants responded to World Health Organization criteria for severe malaria.<sup>7</sup> They had traveled for VFR after a stay in Italy of 13.6, 13.8, and 19.5 years, respectively. All required intensive care and survived with no major sequelae.

Conversely, from 1990 to 1994, no severe malaria case was observed in immigrants.

#### Discussion

An increasing proportion of malaria cases in immigrants was observed by *TropNetEurop* in several European countries during the past decade.<sup>8</sup> A similar tendency had occurred in Italy in the 1990s, while the incidence in Italian travelers had remained quite stable.<sup>9</sup> Since the year 2000, a decreasing number of cases in immigrants was reported in our country. Nevertheless, immigrants still account for about 70% of reported cases in Italy.<sup>2</sup>

Most malaria cases were observed in immigrants who traveled to VFR.<sup>10</sup>

In comparison with Italian travelers, VFR immigrants are more likely to visit rural locations and tend to stay longer in endemic areas.<sup>11</sup> Furthermore, they have a lower perception of malaria risk, and they make less frequent use of adequate protective measures (chemoprophylaxis, repellents, bed nets, and air conditioning).<sup>12</sup>

While the total number of adult immigrants admitted to our hospital for malaria increased more than three times from 1990 to 1994 to 2000 to 2004, the proportion of VFR travelers remained similar in both periods (Table 1).

We have recently described the clinical and parasitological findings of falciparum malaria in nonimmune, Italian travelers versus semi-immune immigrants.<sup>13</sup> Our data confirm the significant clinical and parasitological differences between semi-immune and nonimmune patients investigated in two previous studies conducted in Italy.<sup>3,4</sup>

In a recent French study, falciparum malaria in African VFR patients who had lived in France for more than 4 years, in comparison with European nonimmune patients, showed a lower parasite density, a less frequent severe presentation, and a faster parasite and fever clearance.<sup>5</sup>

The so called semiimmunity, or premunition, seems then to last for years, despite the notion that a frequent exposure to malaria is required to maintain it.<sup>14</sup>

Our main study purpose was to investigate if the pattern of malaria presentation in immigrants showed any change in two definite 5-year study periods one decade apart: from 1990 to 1994 and from 2000 to 2004. We found that immigrants admitted during the second study period had on average a significantly higher parasitemia and lower platelet count and hemoglobin. When we carried out a further analysis, stratified by reason for traveling, we found that the observed differences only concerned the VFR group. We suggest that the most likely explanation is a longer average stay outside malaria endemic countries for the second cohort.

As far as clinical presentation is concerned, no severe malaria case in immigrants occurred in the first study period. Similarly, in a previous study in a referral hospital in Turin, no severe malaria cases were observed in immigrants from 1980 to 1994.<sup>15</sup>

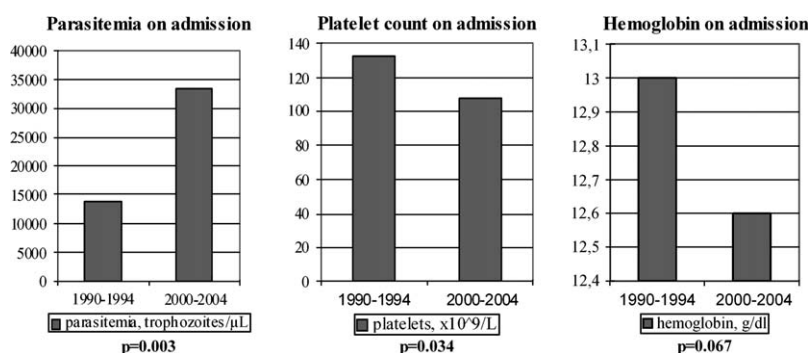
This pattern is susceptible to change. We have begun to observe severe malaria cases in immigrants during the

**Table 3** Main findings on admission in immigrant adult patients, 1990 to 1994 versus 2000 to 2004

Main findings	1990–1994		2000–2004		Kruskal–Wallis test
	<i>M</i> (SD), median (range)	No. of cases	<i>M</i> (SD), median (range)	No. of cases	
Platelets, × 10 <sup>9</sup> /L	137.7 (69.0), 132 (10–337)	48	112 (57.3), 96.5 (19–324)	158	<i>p</i> = 0.012
Hemoglobin, g/dL	13.0 (1.6), 13.4 (8.1–15.7)	48	12.5 (1.9), 12.6 (6.9–17.2)	158	<i>p</i> = 0.049
Parasitemia, trophozoites/μL	21288 (43207), 3,360 (15–230,400)	48	31251 (50501), 6,298 (15–258,050)	103	<i>p</i> = 0.028

**Table 4** Main findings on admission in immigrant adult patients separately analyzed by reason of travel: NI and VFR, 1990 to 1994 versus 2000 to 2004

Main findings	1990–1994		2000–2004		Kruskal–Wallis test
	<i>M</i> (SD), median (range)	No. of cases	<i>M</i> (SD), median (range)	No. of cases	
New immigrants (NI)					
Platelets, $\times 10^9/L$	159 (49.1), 165 (78–220)	8	130.5 (56), 118 (50–253)	27	$p = 0.16$
Hemoglobin, g/dL	12.5 (2.3), 12.4 (9.4–15.7)	8	11.6 (2.4), 11.8 (7.4–17.2)	27	$p = 0.38$
Parasitemia, trophozoites/ $\mu L$	58304.5 (76936.4), 33858.5 (150–230,400)	8	26476.4 (58477.8), 1109 (170–222,320)	15	$p = 0.22$
Visiting friends and relatives (VFR)					
Platelets, $\times 10^9/L$	133.4 (72.0), 131 (10–337)	40	108.3 (57.4), 95 (19–324)	126	$p = 0.034$
Hemoglobin, g/dL	13.0 (1.5), 13.5 (8.1–15.1)	40	12.6 (1.7), 12.6 (6.9–17.1)	126	$p = 0.067$
Parasitemia, trophozoites/ $\mu L$	13,885 (29155.6), 2,690 (15–130,126)	40	33,424 (50,459), 8,845 (15–258,050)	83	$p = 0.003$

**Figure 2** Visit friends and relatives: main findings on admission, 1990 to 1994 versus 2000 to 2004.

past period, and we suggest that VFR travelers should no more be considered a low-risk group for severe malaria.

More than one third of the patients of the second study period had stayed in Italy for longer than 10 years versus only 5% during the first period. The three clinically severe cases (all in the second period) reported staying in Italy for over 13 years before acquiring malaria.

## Conclusion

Our study raises concern on a seemingly increasing risk of severe malaria in immigrants due to a longer residence outside endemic areas and subsequent loss of premunition. Considering that immigrants still account for most imported malaria cases, we conclude that pretravel advice should be particularly targeted to this group, once considered at low risk for severe malaria.

**Table 5** Length of stay in Italy for visiting friends and relatives, 1990 to 1994 versus 2000 to 2004

Years	1990–1994 (data available for 38 patients), <i>n</i> (%)	2000–2004 (data available for 86 patients), <i>n</i> (%)
1–3	7 (18.4)	16 (18.6)
4–6	16 (42.1)	21 (24.4)
7–9	13 (34.2)	19 (22.1)
>10	2 (5.3)	30 (34.9)

## Declaration of Interests

The authors state that they have no conflicts of interest.

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