New Microbiologica, 43, 1, 28-33, 2020, ISN 1121-7138

FULL PAPER

Clinical management of imported malaria in Italy: results from a national cross-sectional survey in 2015

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SUMMARY

In Italy, malaria continues to be one of the most common imported parasitoses; therefore, continuous surveillance of epidemiological data and clinical management is needed. In 2016, the National Institute for Infectious Diseases 'Lazzaro Spallanzani' in Rome promoted a retrospective questionnaire-based survey to assess the clinical management of imported malaria cases in Italy in 2015. The questionnaire was sent to 104 Tropical and/or Infectious Diseases Units in the country, and 37 of them filled out and returned the questionnaires. A total of 399 malaria cases were reported in 2015, mostly caused by *Plasmodium falciparum* and imported from Africa. Malaria chemoprophylaxis was correctly used by a minority of patients. Most patients presented with uncomplicated malaria and were treated orally. In severe cases, intravenous artesunate or quinine alone or in combination were administered, although one third of these severe cases received oral treatment. This retrospective survey reveals a lack of homogeneity in management of malaria-imported cases in Italy. Improvement of malaria chemoprophylaxis, standardization of clinical management of malaria cases and harmonization of oral and intravenous drug availability are needed throughout the country.

Received December 03, 2019 *Accepted* February 14, 2020

INTRODUCTION

In 2015, the World Health Organization (WHO) European Region reported zero indigenous cases of malaria, reaching the Tashkent Declaration goal (WHO, 2016). A positive trend was also observed on a global scale, with an 18% reduction in estimated malaria cases and a 48% decline in the total number of deaths between 2000-2015 (WHO, 2015a).
Despite this encouraging scenario, and with an increasing number of countries moving toward malaria elimination, according to the latest WHO data from 2018, the number of malaria cases worldwide still amounts to more than 200 million, with a total of 405,000 deaths (WHO, 2019). Moreover, the reduction in global malaria incidence does not seem to result in a lower notification rate in the EU/EEA; 6199 confirmed malaria cases were reported in Europe in 2015 according to the European Centre for Diseases Control and Prevention (ECDC), of which 99.8% were travel-related (ECDC, 2018). In Italy, a slight and continuous increase in reported malaria cases has been observed, from 706 in 2015 to 830 in 2017 (ECDC, 2019).
In non-endemic countries, malaria is still the first cause of fever in travelers returning from endemic areas. Nevertheless, locally acquired malaria cases have been reported recently in European countries (particularly Greece, France, Spain, Lithuania and Italy), highlighting the need for a risk assessment for potential autochthonous malaria transmission (ECDC, 2017).
In this scenario, we conducted a retrospective survey to provide an up-to-date analysis on the clinical management of imported malaria cases treated in Italian Tropical and/or Infectious Diseases (ID) Units in 2015.

MATERIALS AND METHODS

From June to December 2016, a national cross-sectional survey was conducted by the Italian National Institute of Infectious Diseases 'Lazzaro Spallanzani' (INMI) with the sponsorship and endorsement of both the Italian Societies of Infectious and Tropical Diseases: SIMIT (Società Italiana di Malattie Infettive e Tropicali) and SIMET (Società Italiana di Medicina Tropicale e Salute Globale). A survey questionnaire was sent to all of the 104 Italian In-

Key words:
Imported Malaria, Italian National Survey, *Plasmodium falciparum*, Clinical Management.

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fectious and Tropical Diseases Units throughout the county, including the two main islands, Sardinia and Sicily, to collect data on the management of malaria cases observed from January to December 2015.

All centers were invited to voluntarily participate in this survey by filling out the questionnaire through an online platform, or by reporting back to INMI by email.

The questionnaire consisted of a few questions on easy-to-collect patient data in different sections:

1) *Demographic data*. Epidemiological information on malaria cases in each unit, with a focus on severe cases;
2) *Use of Malaria chemoprophylaxis*. Information on drug, timing, dose, duration and adverse events;
3) *Diagnosis*. Diagnostic methods available and in use in daily health care activities;
4) *Treatment*. Oral and/or intravenous drug used for the treatment of both uncomplicated and severe malaria;
5) *Clinical outcome*. Admission to critical care area and patient outcome.

The complete questionnaire is available as Supplementary material.

Descriptive statistics (proportion, mean, median) were used to analyze and interpret the results.

RESULTS

Thirty-seven (37/104, 35.6%) centers filled out and returned the survey questionnaires. Centers from Northern Italy were represented more than centers from Central and Southern Italy, including islands (*Table 1*). A total of 399 malaria cases were managed in the year 2015, with only one center reporting zero cases of malaria. Most cases were hospitalized (369/399, 92.5%) while only a minority (30/399, 7.5%) were managed as outpatients.

Plasmodium falciparum was found to be the most common agent (301/399, 75.4%) followed by *P. vivax* (59/399, 14.8%), *P. ovale* (12/399, 3.0%) and *P. malariae* (7/399, 1.7%). No cases of malaria caused by *P. knowlesi* were reported. Mixed infections were identified in 12/399 patients (3.0%) but data on species were available in only three cases: one (1/399, 0.3%) mixed uncomplicated malaria caused by *P. falciparum/P. ovale* and two (2/399, 0.5%) mixed severe malaria by *P. falciparum/P. vivax*. In 18/399 (4.5%) cases, including nine mixed infections, no data about species identification were available.

Table 1 - *Distribution of participating Centers and reported malaria cases.*

Italian Regions	*ID Units*		*Malaria Cases*	
	N	*(%)*	*N*	*(%)*
Northern	21/37	56.8	314/399	78.7
Central	7/37	18.9	66/399	16.5
Southern/Islands	9/37	24.3	19/399	4.8

Legend: ID = infectious diseases.

Most infections were acquired on the African continent (343/399, 86.0%) with a predominance of infections from West Africa (291/399, 72.9%). Two cases out of 399 (2/399, 0.5%) were imported from Central/Southern America and 41/399 (10.3%) from Asia. *Figure 1* details countries of infection. This information was not available in 13 cases (3.3%).

Malaria diagnosis was performed in all participating centers by rapid diagnostic test (RDT) and/or optical microscopy. In 10/37 (27.0%) units, polymerase chain reaction (PCR) assay on whole blood was carried out to confirm the diagnosis.

Most cases were classified as uncomplicated malaria (347/399, 87.0%) and 47/399 (11.8%) as severe malaria, according to the 2010 WHO definition criteria (WHO, 2010). Five cases (5/399, 1.2%) were not classified. Malaria severity signs and symptoms are specified in *Table 2*.

Uncomplicated malaria cases were caused by *P. falciparum* (258/347, 74.3%), followed by *P. vivax* (58/347, 16.7%), *P. ovale* (12/347, 3.5%), *P. malariae* (6/347, 1.7%) and mixed infections with *P. falciparum* (10/347, 2.9%); the second reported agent was *P. ovale* in only one case. No data about species were available in 12 (12/347, 3.5%) cases, including nine mixed infections.

Severe malaria cases were caused mostly by *P. falciparum* (43/47, 91.5%), followed by *P. vivax* (1/47, 2.1%), *P. malariae* (1/47, 2.1%) and two mixed infections (2/47, 4.3%) by *P. falciparum/P. vivax*.

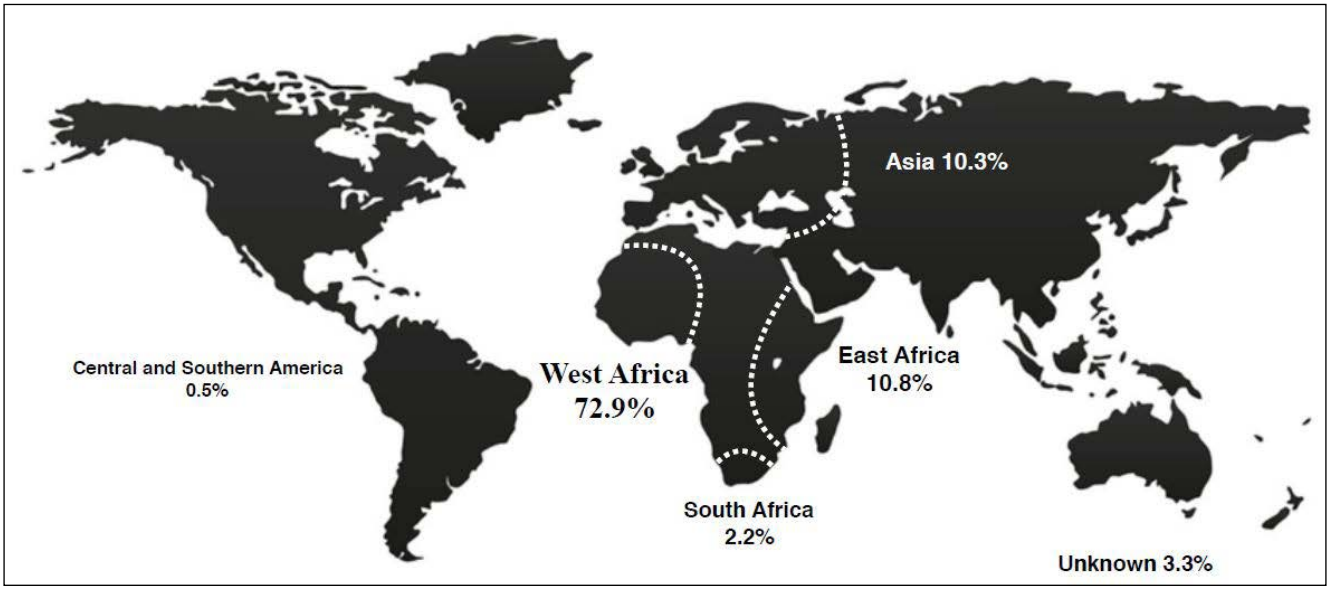


Figure 1 - *Percentages of reported malaria cases distributed by origin from endemic countries.*

Table 2 - *Signs and symptoms of severe malaria cases in Italy in 2015. N= 47.*

Signs or symptoms	*N*	*%*
Hyperparasitaemia	15	32
Jaundice and/or total bilirubin increase	10	21.3
Severe malarial anemia	7	14.9
Renal impairment	5	10.7
Impaired consciousness	3	6.4
Respiratory distress	2	4.2
Shock	2	4.2
Hypoglycemia	1	2.1
Metabolic acidosis	1	2.1
Abnormal bleeding/DIC	1	2.1

Legend: DIC = disseminated intravascular coagulation.

In the study population, 70/399 (17.5%) patients received pre-travel medical counseling and a prescription of malarial chemoprophylaxis. Nevertheless, only 9/399 (2.3%) subjects correctly took the drugs. Motivations for the incorrect use or no use of chemoprophylaxis were reported by 19 centers: forgetfulness or poor compliance in 9/21 (42.9%) cases, adverse events in 2/21 (9.5%) cases, and other reasons in 10/21 (47.6%) cases.

The most frequent antimalarial chemoprophylaxis drug was mefloquine (35/70, 50.0%) followed by atovaquone/proguanil (11/70, 15.7%) and doxycycline in 5/70 (7.2%) patients. Other drugs were prescribed in 7/70 (10.0%) cases while chemoprophylaxis was not specified in 12/70 (17.1%) cases.

For uncomplicated *P. falciparum* cases (258/347, 74.3%), the first therapeutic option was dihydroartemisinin/piperaquine (180/258, 70.0%) followed by quinine in association with doxycycline (31/258, 12.0%), mefloquine (17/258, 6.6%), atovaquone/proguanil (12/258, 4.6%), arthemeter/lumefantrine (12/258, 4.6%), quinine alone (5/258, 1.9%) and quinine/clindamycin (1/258, 0.3%).

The oral treatment for non-*P. falciparum* uncomplicated malaria (89/347, 25.6%) consisted of chloroquine/primaquine combination (44/89, 49.4%), followed by dihydroartemisinin/piperaquine (21/89, 23.6%), chloroquine alone (8/89, 9.0%), artemether/lumefantrine (4/89, 4.6%), atovaquone/proguanil (2/89, 2.2%) and quinine/ doxycycline plus primaquine (2/89, 2.2%). No data were available for eight cases out of the total (8/89, 9.0%). See *Figure 2*.

Of the 47 severe malaria cases, 33 patients (70.2%) were treated with regimens including intravenous artesunate alone (16/33, 48.5%) or quinine alone (10/33, 30.3%) or in combination with doxycycline (2/33, 6.1%) or clindamycin (2/33, 6.1%) or artesunate (3/33, 9.0%), while the remaining 14 patients (14/47, 29.8%) were treated with oral drugs only; 11 patients (11/14, 78.6%) received dihydroartemisinin/piperaquine, two patients (2/14, 14.3%) arthemeter/lumefantrine and one patient (1/14, 7.1%) was treated with atovaquone/proguanil. See *Figure 3*.

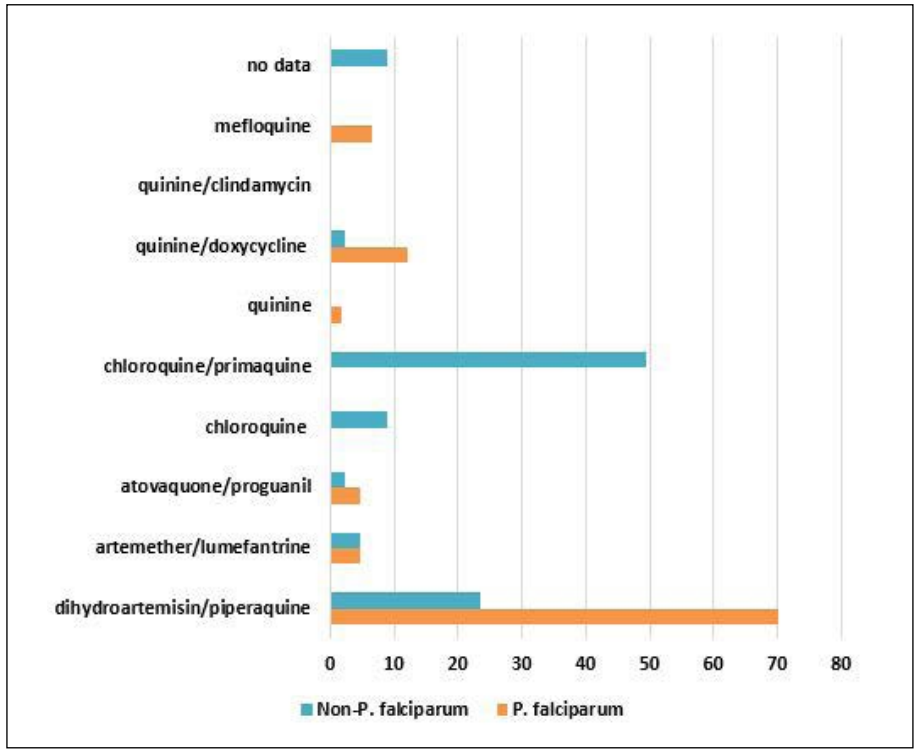
Finally, intravenous artesunate was available in 20/37 centers (54.0%), intravenous quinine in 29/37 (78.4%) centers, and no access to intravenous drugs was reported in 8/37 units (21.6%).

Two patients (2/399, 0.5%) needed intensive care unit (ICU) admission and no deaths related to malaria were reported.

DISCUSSION

This questionnaire-based survey summarized the management of imported malaria cases in Italy in 2015. Although only a third of the invited centers participated in the study (37/104), the total number of 399 reported malaria cases represented more than half of the overall number of 706 malaria cases confirmed in Italy in 2015 (Italian Health Ministry, 2016).-

Figure 2 - *Treatment of uncomplicated malaria cases (%) N=347.*



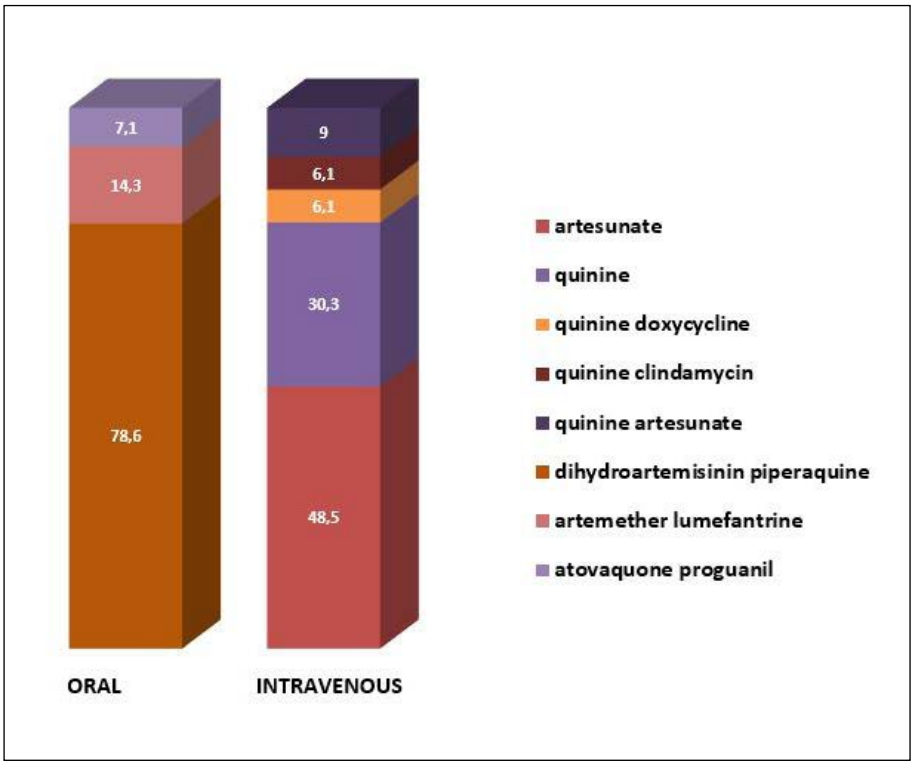


Figure 3 - *Treatment of severe malaria cases (%) N=47.*

The highest number of malaria cases was observed in Northern Italy ID Units and was confirmed by official data from the National Reporting System: 82% of malaria cases were reported in northern Italian regions in the period 2011-2015 (Ministero della Salute Italia, 2016). A 5-year malaria surveillance in Italy in 2002-2006 showed a similar case distribution among Northern and Southern regions (Lombardia *vs* Calabria, 30% *vs* 0.2% respectively) (Boccolini *et al*., 2007).

In our survey, West African countries contributed to the vast majority of imported cases, mostly due to *P. falciparum*: this region has the highest burden of disease despite a significant reduction in the total number of estimated cases and deaths occurred in the period 2010-2018 (WHO, 2019).

The prevalence of *Plasmodium spp* in our survey is in line with data from the largest analysis of malaria cases in travelers in Italy: *P. falciparum* accounted for an 82.5% prevalence rate, followed by *P. vivax* (11.7%), *P. ovale* (3.8%) and *P. malariae* (1.8%) (Zanotti *et al*., 2017). Consistent data were also described by the GeoSentinel group for imported severe cases: *P. falciparum* followed by *P. vivax* (Angelo *et al*., 2017). In particular, the role of *P. vivax* in severe malaria was recently highlighted by an increasing number of studies arguing the role of severe thrombocytopenia in spite of low parasitemia (Naing *et al*., 2014, Antinori *et al*., 2016). Likewise, severe malaria cases caused by *P. malariae* have been described in the literature in association with rosetting mechanisms in peripheral blood, acute renal failure and increased sepsis susceptibility (Neri *et al*., 2008, Rahman *et al*., 2009, Bellanger *et al*., 2010, Badiane *et al*., 2014). Anemia, hypotension and, as expected, renal injury complicated the *P. malariae* case reported in this survey.

In a minority of cases only, *Plasmodium* species were not identified. For centers where malaria diagnosis relied on RDT or microscopy only (Tatem *et al*., 2017), a possible explanation for the missed identification could be the lack of expertise and trained technicians involved in the correct staining and interpretation of blood film. This is common especially for imported malaria infections with low-level parasitemia. However, we cannot rule out the hypothesis that a misinterpretation of the questionnaire format might be responsible for this lack of information: in particular, the etiology was not reported in nine out of 12 mixed infections. According to our data, RDTs and PCR were commonly used, representing an important step forward in malaria diagnosis.

Our data confirmed a very limited use of anti-malarial chemoprophylaxis and a low adherence to drugs, as previously reported in the literature (Troiano *et al*., 2017, Stoney *et al*., 2016, Romi *et al*., 2010). Conversely to other studies in which atovaquone/proguanil was the most used drug (Troiano *et al*., 2017, Stoney *et al*., 2016), in our case series mefloquine was more frequently prescribed. This difference could be related both to the low rate of mefloquine-resistant strains present worldwide (CDC, 2019) and to a difference in costs between mefloquine and atovaquone/proguanil. Indeed, costs have already been identified as a cause of chemoprophylaxis refusal in the United States (Stoney *et al*., 2016) and a similar behavior could be hypothesized in Italy, as chemoprophylaxis drugs are not reimbursable by the National Health System.

Reasons for low compliance were poorly investigated in our study; nevertheless, patients reported forgetfulness by than adverse events, revealing a possible low perception of the risk of malaria infection among travelers, as previously reported by Stoney et al. (Stoney *et al*., 2016). Moreover, a recent investigation conducted in Italy reported that more of 90% of persons interviewed showed no concern about the risk of contracting an infectious disease while travelling, referred no recommendations on preventable

diseases received before departure, and gave travel agencies as the preferred means of updating travelers' knowledge on prophylaxis (Ali Adou *et al.*, 2019). Considering that behavioral factors play a crucial role in individual compliance, targeted and clinically oriented public health interventions should be used to increase knowledge and use of pharmacological and non-pharmacological malaria prophylaxis measures.

Our data suggest that the treatment of malaria cases in Italy was not homogeneous for both uncomplicated and severe malaria. Uncomplicated *falciparum* and non-*falciparum* malaria cases received one of the WHO-recommended regimens in approximately three quarters of cases (WHO, 2010): 74.6% and 77.6%, respectively. According to our data, a discrepancy between the total number of uncomplicated *P. vivax* and P. *ovale* malaria cases (71) and the total number of treatments with primaquine (46) was observed due to a possible underestimation of primaquine use. This could be attributed to several reasons, including the questionnaire format, the lack of specification by the reporting centers, the use of primaquine after patient discharge, the availability of this drug only in hospitals, in Italy, and finally, lack of patient follow-up.

Based on our survey, the use of intravenous quinine (alone or in combination) was the first-line regimen chosen in severe malaria cases. WHO guidelines recommend the use of intravenous artesunate for at least the first 24 hours (WHO, 2015b) based on the results of two large trials carried out in malaria-endemic countries that showed artesunate to be superior to quinine in terms of efficacy (rapid decay of parasitemia), safety (no major adverse events) and better survival (Dondorp *et al.*, 2005, Dondorp *et al.*, 2010, Kurth *et al.*, 2015, Roussel *et al.*, 2017).

Nevertheless, data from our survey are in line with an 8-year multicenter observational study of severe malaria in Europe in which intravenous quinine was the first-line regimen in half of cases and a heterogeneous scenario was shown (Kurth *et al.*, 2017). In Europe, intravenous artesunate availability has been unsatisfactory because it does not respect good manufacturing practice (GMP)-standard quality, causing a lack of harmonization in the application of guidelines for severe malaria treatment across Europe and Italy (Askling *et al.*, 2012). Moreover, in a previous Italian experience, 9% of severe malaria cases were treated with a combination of quinine and artesunate. This combination allowed the use of the most effective drug (artesunate) in combination with the only approved and GMP drug available in Italy (quinine) (Bartoloni *et al.*, 2010).

Furthermore, in almost 30% of severe malaria cases, oral treatment options were prescribed. These data are not surprising since 8/37 (21.6%) units have no access to any intravenous antimalarial drug and nearly half of them had no access to intravenous artesunate. However, data are increasing on the use of oral treatment for severe malaria cases classified by the presence of one single WHO criterion in the absence of any comorbidity or organ failure (Kurth *et al.*, 2017).

As opposed to a previous study on Italian travelers to malaria endemic countries, which showed an average case fatality rate of 0.5% in patients with *P. falciparum* infection (Romi *et al.*, 2010), no death cases and very low rates of admission to ICU were reported in our survey. This could be ascribed to the highly qualified management of infectious emergencies in the surveyed clinical centers.

Our study has some limitations: first, the analysis includes only 37 out of the 104 Italian ID centers with a predominance of Northern regions, and these data may only partially reflect the management of malaria in Italy; nevertheless, more than half of malaria cases detected in Italy in 2015 were identified. Second, information concerning the reason for traveling, the distinction between adult and pediatric cases, and the occurrence of relapses were not investigated in the questionnaire, thereby limiting our analysis. Finally, the modality of our survey administration was not optimal: for example, a more advanced and interactive questionnaire (i.e., designing a specific computer application) could facilitate the collection of data.

In the era of "moving towards malaria elimination," WHO encourages countries to develop national strategic plans, taking into account the particular aspects of malaria epidemiology and heterogeneity that can vary from one country to another (WHO, 2015b). In conclusion, the implementation of malaria chemoprophylaxis, the availability of treatment options, and the standardization of clinical practice are needed to eliminate the differences highlighted in our study in order to improve the management of imported malaria cases.

Acknowledgements

This work was supported by *Ricerca Corrente and Ricerca finalizzata* WFR PE-2013-02357936, funded by the Italian Ministry of Health.

We thank Società italiana Malattie Infettive e Tropicali (SIMIT) and Società Italiana di Medicina Tropicale (SIMET) for actively contributing to the survey promotion, Mirella Biava for the English revision, and all participating centers for their essential contributions.

We would also like to thank the Italian Survey Working Group on Clinical Management of Imported Malaria Cases: M. Andreoni, G. Angarano, M. Anselmo, T. Ascoli Bartoli, A. Bartoloni, P. Bassi, N. Bevilacqua, Z. Bisoffi, B. Cacopardo, S. Caligaris, C. Calzetti, S. Casolari, G. Cassola, L. Chianura, A. Chiodera, M. Conforto, N. Coppola, A. De Luca, M. Feasi, C. Ferrari, P. Filippini, G. Foti, E. Francavilla, F.M. Fusco, S. Gebremeskel Tekle, M.L. Giancola, A. Giammario, M. Giobbia, M.T. Giordani, F. Gobbi, A. Gori, P. Grossi, C. Iacobello, M. Iannetta, M. Libanore, R. Luzzati, G. Magnani, V. Manfrin, A. Mariano, C. Mastroianni, F. Mazzotta, L. Mecocci, V. Mondardini, A. Montineri, L.A. Nicolini, A. Oliva, C. Palazzolo, G. Pasquale, V. Portelli, M. Puoti, T. Quirino, T.A. Santantonio, L. Sarmati, M.P. Sciotti, P. Scotton, L.R. Tomasoni, F. Toscanini, S. Tunesi, E. Vanino, P. Viale, P. Viganò, C. Viscoli, V. Vullo.

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