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Imported malaria in Slovenia, 2001-2011

Research Article

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Abstract: Background: A retrospective analysis was conducted to determine the epidemiological and clinical characteristics of imported malaria in Slovenia. Materials and methods: We analysed 73 malaria cases reported to the National Institute of Public Health of Slovenia from January 2001 to July 2011. Results: Patients were predominantly (71.2%) male and the majority (42.5%) were between 18 and 29 years of age. They mostly arrived from Ghana (17.8%) and India (15.1%), where they resided on average 89 days. 16 cases were considered to have been taking adequate malaria chemoprophylaxis. The dominant causative species were *Plasmodium falciparum* (31), *P. vivax* (28) and *P. ovale* (3). In 2 cases, a mixed infection of *P. vivax - P. ovale* and of *P. vivax - P. falciparum* was identified. Fifty-six cases were hospitalised for 1 to 21 days (median 3 days). Conclusions: Slovenian travellers to West Africa and India are at significant risk. Given the low compliance rate of chemoprophylaxis, the high percentage of malaria cases could have been avoided by an appropriate prophylaxis and better pre-travel counselling. Public health efforts are needed to improve awareness regarding malaria risks and the benefits of malaria prophylaxis.

Keywords: *Diagnosis • Epidemiology • Chemoprophylaxis • Slovenia*

1. Introduction

Malaria imposes an enormous burden of illness and substantial mortality on the tropical world and in many subtropical regions (109 countries) [1]. As international travel to tropical and subtropical destinations has become more frequent and migration from endemic regions more prominent, an increase in imported cases has been observed in recent years in non-endemic countries [2]. Sporadic cases of autochthonous malaria have recently been described in several European countries, which poses a concern about the possible resurgence of malaria in countries previously affected by this disease [3]. Today, therapeutic strategies are based on an "intercultural collaboration" that relies on the use of mosquito nets, DDT, and multi-drug combinations [1,4]. The constant threat of the parasite and vector mosquito developing resistance to medicines and insecticides, and the on-going climate change make the challenge of eradicating malaria extremely difficult [5].

Slovenia was officially declared malaria-free by the World Health Organisation (WHO) in 1975. Since then, only imported cases of malaria have occurred. During the nineties, due to the political conflicts and resulting economic slowdown in the region of the former Yugoslavia, the number of travellers was somewhat reduced, but in the last decade travel by Slovenian citizens to malaria-endemic regions has been continually increasing. The present study was conducted to optimize counselling concerning malaria, to obtain in-depth information about the travel destinations that represent the highest risk of acquisition of malaria for Slovenian travellers; we also investigate common clinical presentations and the use of prophylactic and therapeutic regimens. We wanted to determine data on preventive behaviour for imported malaria cases, especially with reference to appropriate chemoprophylaxis and screening of the specific groups of patients, such as travellers, immigrants, and refugees to/from endemic areas.

2. Materials and methods

2.1 Data collection

To identify the main characteristics of imported malaria in Slovenia, we retrospectively analysed the epidemiological data and clinical history of 73 confirmed malaria cases reported to the National Institute of Public Health

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of Slovenia (NIPH) between January 2001 and July 2011. In accordance with the law governing infectious diseases, notification of malaria to the NIPH is mandatory. Notifications collected regionally are sent to the NIPH on a weekly basis, and the data is merged at the national level. For enhanced surveillance purposes in addition to the standardized notification form, a standardized malaria case surveillance form is completed by the regional epidemiologist for every notified case, either in person or by telephone in consultation with the medical providers, laboratory staff, and the patient. The data collected on the surveillance form includes the notification date, gender, age, resident status, travel destination, travel and immigration history (work/business, tourism, visiting relatives and friends, other), history of prior infections, malaria prophylaxis, time of onset and description of the symptoms/signs, treatment efficacy, hospitalization, outcome data, species of *Plasmodium,* and information on whether or not the diagnosis was confirmed by microbiological tests.

2.2 Case definition

A confirmed case of malaria was defined as:

1. an individual with fever or a history of fever and
2. *Plasmodium* observed on microscopic examinations of Giemsa-stained thick and thin blood smears.

If the initial blood smear was negative, the examination was repeated using at least three additional smears within 48 hours. A result was considered negative if no parasites were observed in at least 500 oil immersion visual fields at a magnification of 1000x.

2.3 Data analysis

The following statistics were calculated and expressed as absolute numbers and percentages: the annual number of cases, yearly incidence rate, age (age groups, median age, standard deviation), gender, country and/or region of permanent residence, duration of exposure in the country of infection and parasite identified, clinical signs and symptoms, time elapsed before diagnosis of malaria was established, treatment outcomes, and chemoprophylaxis used during travel to the risky areas.

3. Results

3.1 Demographic characteristics

From January 1, 2001, to July 31, 2011, 73 cases of laboratory-confirmed diagnoses of malaria were reported to the Institute of Public Health of Slovenia. The number of cases per year ranged from a low of 3 cases in 2006 to 10 cases in 2003, on average 3.5 cases per 100,000 (Figure 1).

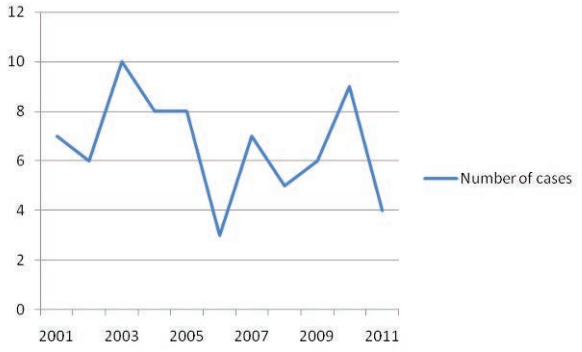

Figure 1. Reported cases of malaria by year in Slovenia, January 2001-July 2011.

The median age of patients with reported malaria was 38 years (range 6-81 years, standard deviation 15.1) (Figure 2). Fifty-two (71.2%) were men and 21 (28.8%) were women, thus the overall male to female ratio was 2.5:1. Fifty-seven (78.1%) cases were travellers from Slovenia, 10 (13.7%) were persons with Slovenian citizenship who temporarily worked in the malaria endemic countries, 5 (6.8%) were immigrants to Slovenia, and 1 (1.4%) was a refugee from Iran (Table 1).

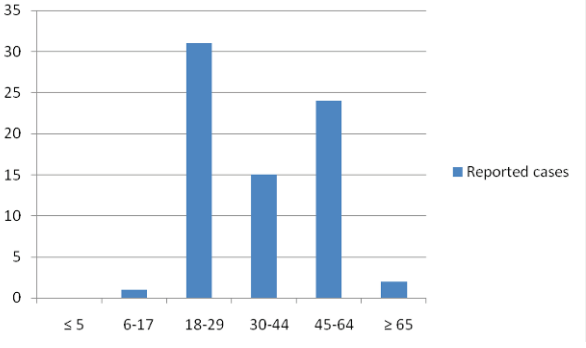

Figure 2. Age distribution of malaria cases in Slovenia, January 2001-July 2011.

3.2 Microbiological data and country of infection

Plasmodium falciparum was identified in 31 (42.5%) cases, *P. vivax* in 28 (38.4%) cases, and *P. ovale* in 3 (4.1%) cases. The laboratory results of 2 (2.7%) cases showed a mixed infection of *vivax* and *ovale* malaria (imported from Mauritania and Mali), and of *vivax* and *falciparum* malaria (imported from India). *Plasmodium* was identified, but no species was determined for 9 cases (12.3%). Figure 3 shows the geographical origin of *Plasmodium* species identified in Slovenia from January 2001 to July 2011.

In the observed period, reported malaria cases originated from 40 endemic countries where infected persons resided from 5 to more than 365 days (on average 89 days). Investigation of the countries of acquisition

Table 1. Demographic characteristics of malaria cases in Slovenia, January 2001-July 2011 (n=73).

Characteristic	n	%
Sex		
Male	52	71.2
Female	21	28.8
Age		
≤ 5	0	0
6-17	1	1.4
18-29	31	42.5
30-44	15	20.5
45-64	24	32.9
≥ 65	2	2.7
Race		
White	68	93.1
Black	3	4.1
Asian	1	1.4
Indian	1	1.4
Travellers from Slovenia	57	78.1
Slovenian residents abroad	10	13.7
Angola	2	2.7
Sudan	1	1.4
Cameroon, Gabon	1	1.4
Madagascar	2	2.7
India	1	1.4
Central African Republic	1	1.4
Congo	1	1.4
Nigeria	1	1.4
Immigrated to Slovenia	5	6.8
India	1	1.4
Burkina Faso	1	1.4
Ghana	**3**	4.1
Refugee	1	1.4
Iran	1	1.4

revealed an obvious predominance of Ghana (n=13, 17.8%), India (n=11, 15.1%), Indonesia (n=7, 9.6%), Kenya (n=5, 6.8%), and Burkina Faso (n=5, 6.8%). Africa, Asia, and the Americas contributed 48 (65.8%), 23 (31.5%), and 2 (2.7%) of all the malaria patients (Figure 4). No *falciparum* malaria was acquired in the Middle East and South America, whereas 45 (61.6%) malaria cases from West Africa were infected with *Plasmodium falciparum*. None of the patients were potentially exposed in more than one continent.

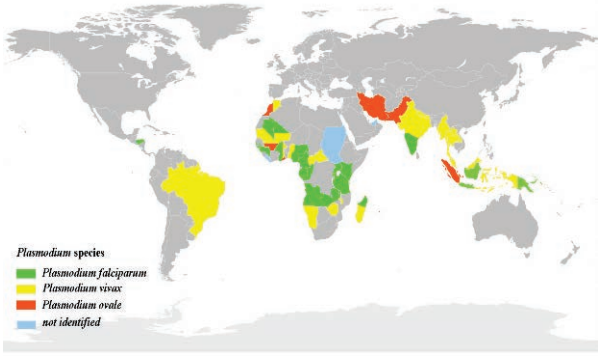

Figure 3. Geographical origin of description of plasmodium species identified in Slovenia, January 2001-July 2011.

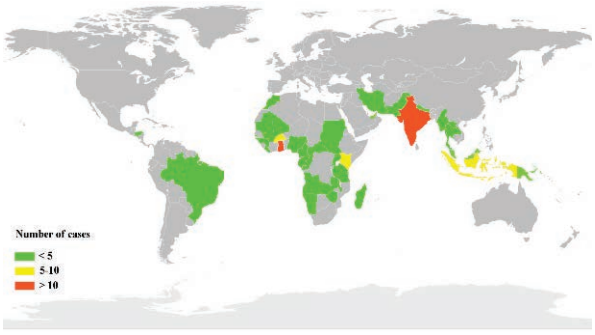

Figure 4. Geographical distribution of malaria cases in Slovenia, January 2001-July 2011.

3.3 Clinical presentation

Symptoms consisted of fever and headache in all patients, and in some cases were accompanied by arthralgias and/or myalgias (6.8%), and diarrhoea and/or abdominal cramps (2.7%). The duration of symptoms before diagnosis ranged from 1 to 136 days (on average 24 days, median 18) and were particularly dependent on the form of malaria acquired. In *falciparum* malaria, 19 (26.0%) patients were diagnosed in the first week and 4 (5.5%) within 2 weeks after the onset of symptoms (data was not available on 8 cases). In *vivax* malaria, diagnosis was established in 18 (24.7%) patients within 2 weeks. In 3 patients (4.1%), it took from 116 to 136 days before the diagnosis of *vivax* malaria was confirmed (data was not available on 7 cases). The duration of symptoms before the diagnosis of *ovale* malaria was established was known only for one patient, who was diagnosed on the 18th day of illness. No patient was diagnosed with cerebral malaria, and only 3 patients received blood transfusion because of haemolysis or anaemia. Seventeen (23.3%) cases were treated entirely as outpatients, 56 (76.7%) cases were hospitalized for 1 to 21 days (median 3 days), and for 5 patients, the duration of hospitalization was unknown.

During the 10-year observation period, no deaths and no blood transfusion–associated malaria was reported to the NIPH. Thirteen (17.8%) patients had a previous history of malaria, and 3 cases of relapse were recorded (one in *ovale* malaria and two in *vivax* malaria).

3.4 Treatment and chemoprophylaxis

Patients with malaria were treated with mefloquine in 9 cases, atovaquone/proguanil in 8 cases, chloroquine and primaquine in 5 cases, primaquine in 4 cases, quinine and doxycycline in 2 cases, artemisinin-based combination treatment in 2 cases, doxycycline in 1 case, sulfadosine-pyrimethamine in 1 case, and dihydroartemisinin in 1 case. Data was not available for 40 cases.

Investigation of the type of chemoprophylaxis revealed that 15 (20.5%) patients used incomplete or insufficient regimens, mainly because of the side effects. Thirty-seven (50.7%) patients used no prophylactic regimen at all. Two travellers stated that they did not take any antimalarial drugs because of a physician's instructions that no prophylactic was needed in the destination country, and 2 carried a standby medication only. Of the 16 (21.9%) patients considered to have been taking adequate chemoprophylaxis, 13 used mefloquine (visited Ghana – 3, Papua New Guinea – 2, Tanzania – 2, Guinea Bissau – 1, Honduras – 1, Indonesia – 1, Liberia – 1, Madagascar – 1, Malawi – 1), 2 (visited Ghana) used doxycycline, 1 (visited Uganda) used atovaquone/proguanil, whereas per the medical history data, the remaining 5 patients did not specify the drug.

4. Discussion

In 2007, 3836 cases of malaria were reported by 26 European Union (EU) and European Economic Area/European Free Trade Association (EEA/EFTA) countries; among them, 70% of the cases were reported by Germany, Italy, and the United Kingdom. In the 10-year observational period, 73 imported malaria cases were reported to the NIPH. Thus, the overall European notification rate was lower than the notification rate in Slovenia (0.91 and 3.5 per 100,000, respectively) [6]. In Slovenia, malaria was predominantly reported in tourists from Ghana and India, which differs from reports from Serbia, the largest republic of the former Yugoslavia, where most patients arrived from Equatorial Guinea and Nigeria, and the reason for travel was almost exclusively work/business [7]. The notification rate of malaria was disproportionately higher in males than in females, with the age group of 18 to 24 years having the highest rates; this presumably reflects population travel patterns rather than other risk factors. The number of reported cases in the European Centre for Disease Prevention and Control (ECDC) monthly reports increased during the summer holiday months and in the winter holiday period, whereas in our analysis there was no evident seasonal trend as the reported yearly numbers were low [6].

A few cases of autochthonous transmission of malaria in Europe have been reported over the last 10 years. Although no sustained local transmission has been identified to date, this poses a concern about the plausible reoccurrence of malaria in Europe [8]. In Slovenia, data on autochthonous malaria cases is incomplete because of the sporadic and benign course of the disease. Lipić reported on the tertiary type of imported and autochthonous malaria in Ljubljana in the 19th century, when 718 patients were recorded (2 of them died) from the year 1828 to the year 1832, and on average 94 cases per year were hospitalized [9]. Schiavuzzi reported on autochthonous malaria cases in Istria in the year 1889 [10]. Pirc reported on sporadic endemic and imported malaria cases from the 19th century up to the year 1937, which occurred in the southern and eastern part of Slovenia (e.g. Črnomelj, Kostanjevica na Krki, Prekmurje, Podravje, Ljubljana district, Dravsko polje, Lendava and Murska Sobota) [11]. In the 10-year observation period in Slovenia, there have been no reported cases of autochthonous malaria.

Twelve percent of the 73 imported cases did not have malarial species identification from the Giemsa-stained thick and thin blood smears, 77% were hospitalized, and almost 21% got sick despite claiming to have taken chemoprophylaxis. Similar to reports from other countries, including neighbouring countries Croatia [12] and Serbia [7], the most commonly isolated species was *P. falciparum*, which may cause a fatal infection in the previously unexposed. The second most frequent species in this study was *P. vivax*, which is observed by many authors as the most common species in travellers returning from Asia [13-15]. These findings have an influence on the current recommendations for provider and patient education, and on appropriate laboratory capacity to determine malarial species. Permanent clinical laboratory training and the availability of tests to identify *Plasmodium* at the species level are important. Species identification has an influence on treatment recommendations because treatment and drug resistance are not only dependent on the country of acquisition, but also on the species of *Plasmodium*. Diagnosis of malaria is most frequently done by parasite identification using peripheral blood smears [16]. In the case of an inability to diagnose malaria at the species level, Slovenian laboratory diagnosticians should regularly perform molecular diagnostic methods. One-fifth of the travellers became sick despite chemoprophylaxis, which indicates that one of the greatest current medical emergencies is the ever-increasing resistance to drugs, which has been caused by the large-scale and often incongruous use of various anti-microbial drugs [17]. This fact also poses concerns about adequate pre-travel counselling in Slovenia. Permanent education for health-care providers is needed to provide relevant pre-travel advice for those planning return visits to their country of origin [18]. A profound knowledge of malarial areas, the frequency of infection acquired by non-immune travellers, and possible parasite and vector mosquito resistance to medicines and insecticides are essential when advice about prophylaxis is given by a physician [19]. Since travel destination has been identified as the most important risk factor for ac-

quiring malaria, Slovene travellers should be better informed about the malaria epidemiological situation, particularly in the case of travelling to West Africa and India.

In the observed period, 5 cases of malaria were diagnosed in immigrants and 1 in a refugee. In Slovenia, there is no initial health screening for infectious diseases in immigrants and refugees. To prevent possible future health problems in immigrant/refugee populations and to reduce the risk of autochthonous malaria transmission, we propose that all primary refugees or immigrants from malaria-endemic areas should be screened for malaria whether or not the person is symptomatic. National efforts are inevitably needed to support refugee and immigrant health programs to improve access to health care for these vulnerable populations. This presents unique challenges since the diversity of the populations resettling in Europe will continue to change, depending on the current political and social unrest. The public health authorities need to consider these issues and recommendations as we continue to monitor the influence of immigration on the changing epidemiology of malaria [20].

5. Conclusion

The present results show that young people who travel to endemic countries, especially to West Africa and India, have a higher risk of acquiring malaria. In almost half of the imported cases, *falciparum* malaria was identified, and the leading health problems in our series of travellers were fever and headache. Results show that a high percentage of imported malaria in Slovenia could have been avoided by optimal pre-travel counselling and an appropriate prophylaxis regimen. Because of the favourable climatic and vector conditions for the development of the parasite, there is a potential risk of incidental malaria transmission by the indigenous Anopheles mosquitoes, which calls for continued malaria surveillance and the rapid identification and treatment of *Plasmodium* carriers in Europe. In the future in Slovenia, it is essential to electronically link clinical, epidemiologic, and laboratory data to improve the surveillance system's applicability and to contribute to the efficacy of prophylactics and treatment. Further collaborative studies are required to define the implications of our findings and to guide effective prevention and control measures of imported cases of malaria in Slovenia. It is necessary to provide additional education for physicians, particularly regarding appropriate chemoprophylaxis and adequate diagnostic protocols for imported malaria. Since all patients showed fever symptoms, screening all travellers with febrile illness returning from endemic regions, and all immigrants or primary refugees from malaria-endemic countries, whether or not the person is symptomatic, should be obligatory. In all cases of negative thick smears, a molecular test for *Plasmodium* should be performed.

Conflict of interest

The authors declare no conflict of interest.

References

[1] Buonsenso D, Cataldi L. Watch out for malaria: still a leading cause of child death worldwide, Ital J Pediatr 2010; 36: 58

[2] Jelinek T, Nothdurft HD, Löscher T. Malaria in non-immune travellers: a synopsis of history, symptoms, and treatment in 160 patients, J Travel Med 1994; 1(4): 199-202

[3] Danis K, Baka A, Lenglet A et al. Autochthonous Plasmodium vivax malaria in Greece, 2011, Euro Surveill 2011; 16(42): pii=19993

[4] Shah NK. Assessing strategy and equity in the elimination of malaria, PLoS Med 2010; 7(8): e1000312

[5] Manigat R, Wallet F, Andre JC. From the past to a better public health programme planning for possible future global threats: case studies applied to infection control, Ann Ist Super Sanita 2010; 46(3): 228-235, DOI: 10.4415/ANN_10_03_02

[6] ECDC, Surveillance Report. Annual epidemiological report on communicable diseases in Europe, 2009

[7] Dakić Z, Pelemiš M, Djurković-Djaković O et al. Imported malaria in Belgrade, Serbia, between 2001 and 2009, Wien Klin Wochenschr 2011; 123(1): 15-19

[8] Kruger A, Rech A, Su XZ, Tannich E. Two cases of autochthonous Plasmodium falciparum malaria in Germany with evidence for local transmission by the indigenous Anopheles plumbeus, Trop Med Int Health 2001; 6(12): 983-985

[9] Lipić FV. Topographie der k. k. Provinzialhauptstadt Laibach, im Bezug auf Natur- u. Heilkunde, Medizinalordnung und Biostatik, 1834

[10] Schiavuzzi B. La malaria in Istria. Ricerche sulle cause che l'hanno prodotta e che la mantengono, u »Atti e Memorie della Societa Istriana di Archeologia e Storia Patria«1889; 5: 319-472

[11] Pirc I. Zdravje v Sloveniji. Zdravstvene prilike in delo higijenske organizacije v Sloveniji 1922-1936, Spomenica ob petnajstletnici higijenskega zavoda v Ljubljani
[12] Perić D, Skrobonja I, Skrobonja A. Malaria in Croatia in the period between 1987 to 2006, Lijec Vjesn 2009; 131(7-8): 192-195
[13] Miranda IB, Weber C, Fleischmann E, Bretzel G, Loscher T. Validity of malaria diagnosis in nonimmune travelers in endemic areas, J Travel Med 2008; 15(6): 426-431
[14] Smith AD, Bradley DJ, Smith V et al. Imported malaria and high risk groups: observational study using UK surveillance data 1987-2006, BMJ 2008; 337(7661): 103-106, DOI: 10.1136/bmj.a120
[15] Schmid S, Chiodini P, Legros F et al. The risk of malaria in travelers to India, J Travel Med 2009; 16(3): 194-199
[16] Najera JA, Gonzalez-Silva M, Alonso PL. Some lessons for the future from the global malaria eradication programme (1955-1969), PLoS Med 2011; 8(1): e1000412
[17] Antibiotic Resistance: Implication for Global Health and Novel Intervention Strategies: Workshop Summary, Institute of Medicine (US), Forum on Microbial Threats, Washington (DC): National Academies Press (US), 2010
[18] Franco-Paredes C, Santos-Preciado JI. Problem pathogens: prevention of malaria in travellers, Lancet Infect Dis 2006; 6(3): 139-149
[19] Nzila A, Ma Z, Chibale K. Drug repositioning in the treatment of malaria and TB, Future Med Chem 2011; 3(11): 1413-1426
[20] Seys SA, Bender JB. The changing epidemiology of malaria in Minnesota, Emerg Infect Dis 2001; 7(6): 993-995