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Epidemiology and clinical features of vivax malaria imported to Europe: Sentinel surveillance data from TropNetEurop

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Abstract

Background: *Plasmodium vivax* is the second most common species among malaria patients diagnosed in Europe, but epidemiological and clinical data on imported *P. vivax* malaria are limited. The TropNetEurop surveillance network has monitored the importation of vivax malaria into Europe since 1999.

Objectives: To present epidemiological and clinical data on imported *P. vivax* malaria collected at European level.

Material and methods: Data of primary cases of *P. vivax* malaria reported between January 1999 and September 2003 were analysed, focusing on disease frequency, patient characteristics, place of infection, course of disease, treatment and differences between network-member countries.

Results: Within the surveillance period 4,801 cases of imported malaria were reported. 618 (12.9%) were attributed to *P. vivax*. European travellers and immigrants were the largest patient groups, but their proportion varied among the reporting countries. The main regions of infection in descending order were the Indian subcontinent, Indonesia, South America and Western and Eastern Africa, as a group accounting for more than 60% of the cases. Regular use of malaria chemoprophylaxis was reported by 118 patients. With 86 (inter-quartile range 41–158) versus 31 days (inter-quartile range 4–133) the median symptom onset was significantly delayed in patients with chemoprophylaxis ($p < 0.0001$). Common complaints were fever, headache, fatigue, and musculo-skeletal symptoms. All patients survived and severe clinical complications were rare. Hospitalization was provided for 60% and primaquine treatment administered to 83.8% of the patients, but frequencies varied strongly among reporting countries.

Conclusions: TropNetEurop data can contribute to the harmonization of European treatment policies.

Introduction

Plasmodium vivax, has a major adverse impact on global health [1], accounting for 70–80 million clinical cases annually. It is responsible for over 50% of malaria outside Africa, notably in Southeast Asia and Central and South America, and particularly on the Indian subcontinent. It also accounts for around 10% of cases in Eastern and Southern Africa but has only limited prevalence in West Africa, presumably due to the presence of Duffy-negative blood group variants that limit erythrocyte invasion by the parasite [2-5]. Similar to *Plasmodium falciparum*, *P. vivax* may cause severe anaemia, but major complications like cerebral malaria, hypoglycaemia, metabolic acidosis and respiratory distress observed in *P. falciparum* malaria, do not occur [3,6].

When imported to non-endemic areas, vivax malaria, despite its uncomplicated course, requires special attention for two reasons. First, diagnosis often is complicated by the late onset of symptoms which unlike those observed in falciparum malaria, may occur several months after arrival from endemic areas [7-10]. Second, case management is complicated by the fact that parasites can remain dormant in the liver as hypnozoites. Thus, even if blood stages of the parasite are cleared, reactivation of these liver forms may cause relapses within a few months [5,11].

Malaria is a notifiable disease in all European countries [12]. As shown by national surveillance reports [13-19], *P. vivax* is presently the second most frequent cause of imported malaria in most of Europe, except France [9,20], accounting for up to 40% of the annual cases in single countries. However, since *P. vivax* is less virulent than *P. falciparum* [3,6], surveillance reports primarily focus on *P. falciparum* infections. Epidemiological and clinical details of imported *P. vivax* malaria are, therefore, hardly described.

Since 1999, the importation of vivax malaria into Europe has also been systematically monitored by the TropNetEurop surveillance network. The present article summarises epidemiological and clinical data of the disease collected during the first 56 months of surveillance at European level, focusing on disease frequency, patient characteristics, place of infection, course of disease and treatment. Differences between network-member countries are highlighted.

Patients, materials and methods

The European network TropNetEurop was founded in 1999 to effectively detect emerging infections of potential regional, national or global impact at their point of entry into the domestic population, to link clinical and epidemiological knowledge and to serve as a platform for

multi-centre research. Sentinel surveillance reporting is carried out by participating sites by use of a standardised and computerised reporting system. Electronic transmission of anonymous case information, comprising standardised demographic, epidemiological and clinical data, to the central database assures rapid detection of sentinel events. Presently 46 clinical sites from 16 European countries are organised in the network. Additional information about TropNetEurop and the reporting instruments can be received from the internet at <http://www.tropnet.net>.

The present work summarises data of primary cases of *P. vivax* malaria reported within the network between January 1999 and September 2003. Relapse notifications were excluded from the database to avoid multiple-counting of importation events. Mixed-infections with *P. vivax* and other Plasmodium species were included. However, while analyses focusing on disease frequency, patient characteristics and place of infection were based on all observations, analyses with clinical end point were restricted to mono-infections elicited microscopically (confirmed cases) or by antibody detection (probable cases) in order to reduce bias. Patients with mixed plasmodial or other concomitant infections, cases diagnosed by clinical reasoning (suspected cases) and cases reported without specification of the underlying diagnostic proof (unclassified cases) were excluded from those analyses.

All analyses were done with the SAS software (release 8.01 by SAS Institute Inc., Cary, NC, USA). Missing values were

assumed to be non-systematic. Incomplete cases were therefore disregarded in single calculations. However, sample size or missing data information is given with each result.

Results

Between January 1999 and September 2003, a total of 4,801 patients with travel-related malaria were reported within the TropNetEurop network. *P. vivax* was involved in 618 (12.9%) cases, either as sole pathogen (n = 585) or in mixed-infections with other species (n = 33), thus accounting for the second highest number of cases after *P. falciparum*. The reported proportion of *P. vivax* was rather steady with 10.9% in 1999, 12.6% in 2000, 15.1% in 2001, 12.3% in 2002 and 12.9% in 2003. All 16 TropNetEurop countries reported *P. vivax* malaria. However, as shown in table 1, the number of cases varied strongly between countries. Germany (24.3%), Spain (15.5%) and the UK (12.0%) reported most cases, whereas reports from Switzerland (1.8%), Poland (1.6%), Finland (1.0%), Ireland (1.0%) and Portugal (0.3%) were scarce. According to diagnostic information 557 (90.1%) of the 618 infections were confirmed, two (0.3%) were probable and eight (1.3%) were suspected cases. The remaining 51 (8.3%) could not be classified, due to missing information on the underlying diagnostic procedure. Those and the suspected cases were excluded from analyses with clinical endpoints in the latter.

Table 1: Frequency of *P. vivax* malaria by year and reporting country

Country	1999 n (%)	2000 n (%)	2001 n (%)	2002 n (%)	2003* n (%)	Total n (%)
Austria	2 (2.1)	8 (4.9)	5 (2.7)	5 (3.9)	3 (6.3)	23 (3.7)
Belgium		17 (10.4)	8 (4.3)	7 (5.5)	2 (4.2)	34 (5.5)
Czech Rep.	9 (9.6)	13 (7.9)	20 (10.8)	5 (3.9)	3 (6.3)	50 (8.1)
Denmark	14 (14.9)	16 (9.8)	12 (6.5)	5 (3.9)	1 (2.1)	48 (7.8)
Finland		1 (0.6)		6 (4.7)		6 (1.0)
France	1 (1.1)	1 (0.6)	4 (2.2)	7 (5.5)	2 (4.2)	15 (2.4)
Germany	31 (33.0)	35 (21.3)	51 (27.6)	22 (17.3)	11 (22.9)	150 (24.3)
Ireland		2 (1.2)	1 (0.5)	1 (0.8)	2 (4.2)	6 (1.0)
Italy	8 (8.5)	10 (6.1)	16 (8.6)	3 (2.4)		37 (6.0)
Norway			4 (2.2)	8 (6.3)	1 (2.1)	13 (2.1)
Poland	3 (3.2)		4 (2.2)	3 (2.4)		10 (1.6)
Portugal				1 (0.8)	1 (2.1)	2 (0.3)
Spain	15 (16.0)	31 (18.9)	23 (12.4)	23 (18.1)	4 (8.3)	96 (15.5)
Sweden	4 (4.3)	8 (4.9)	15 (8.1)	8 (6.3)	8 (16.7)	43 (7.0)
Switzerland	4 (4.3)	1 (0.6)		5 (3.9)	1 (2.1)	11 (1.8)
UK	3 (3.2)	22 (13.4)	22 (11.9)	18 (14.2)	9 (18.8)	74 (12.0)
Total	94 (100)	164 (100)	185 (100)	127 (100)	48 (100)	616 (100)

* Data reported between January and September 2003

Table 2: Characteristics of patients with *P. vivax* malaria

	N	%
Sex (n = 615)		
Male	422	68.6
Female	193	31.4
Pre-travel advice (n = 387)		
Yes	208	53.7
No	179	46.3
Prophylaxis (n = 554)		
None	320	57.8
Chloroquine	39	7.0
Proguanil	6	1.1
Proguanil + Chloroquine	45	8.1
Mefloquine	123	22.2
Doxycycline	12	2.2
Proguanil + Atovaquone	3	0.5
Other	6	1.1
Compliance (n = 190)		
Yes	118	62.1
No	72	37.9
Patient classification (n = 615)		
Immigrants/Refugees	121	19.7
Foreign visitors	36	5.8
Europeans living in EC	406	66.0
European expatriates	52	8.5
	Median	IQ-Range
Age (n = 606)	32	26–43

IQ-Range = Inter-quartile range

Table 2 describes characteristics of the 618 patients. About 2/3 were male. The median age was 32 years (inter-quartile range 26–43). About 50% reported reception of pre-travel advice, 42.2% stated use of anti-malarial chemoprophylaxis. Among those with prophylaxis, 62.1% stated compliance with the recommended regimen.

The majority of patients who imported vivax malaria into Europe were Europeans living and working in Europe (66.0%). Immigrants and refugees, summarising both those of overseas origin who may have lived in the reporting country for many years and very recent immigrants, made up the second largest group (19.7%), followed by European expatriates (8.5%) and foreign visitors (5.8%). Analysing patient classifications by reporting country revealed that immigrants and refugees accounted for distinctly more than the overall 20% proportion in Norway (61.5%), Italy (45.9%), France (40.0%), Spain (31.3%) and Denmark (25.0%).

Reasons for travel differed for Europeans and immigrants. While Europeans living in Europe mainly travelled for tourism (71.4%), followed by business (7.8%), mission-

ary work (7.0%), research (6.3%), visits to relatives or friends (6.0%), military missions (0.8%) or other reasons (0.8%). The main reasons for travel in the immigrant group were immigration to Europe (47.0%) or visits to relatives or friends in the former home country (44.4%).

Figure 1 marks 16 geographical regions from which *P. vivax* malaria was imported from during the 56 month surveillance period. The main regions of infection were the Indian subcontinent (17.0%), Indonesia (12.1%), South America (11.4%) and Western Africa (11.4%), as a group accounting for 52% of the cases. However, while the Indian subcontinent was the main region of infection each year, the others switched places in the annual ranking order. Further regions of importance were Eastern Africa (10.0%), Southeast Asia (8.6%), and Oceania (8.5%), contributing another 27% of the cases. Main countries of infection were Indonesia (12.1%), India (8.7%), Papua New Guinea (8.0%), Pakistan (7.8%) and Ecuador (5.7%).

Exclusion of patients with concomitant plasmodial or other infections and cases with suspected or unknown diagnostic status left 526 patients for the analysis of clinical endpoints. Symptom information was given for 487 of those. The most frequent complaints were fever, headache, fatigue and musculo-skeletal symptoms, affecting 95.5%, 51.3%, 32.6% and 29.6% of the patients, respectively. However, a variety of other symptoms was noted, too. Further information on the course of the disease is summarised in table 3. The median time from end of journey to symptom onset was 60 days (inter-quartile range 8–149). However, with 86 versus 31 days the median onset of symptoms was significantly delayed in patients with chemoprophylaxis ($p < 0.0001$ Wilcoxon rank test). More than half of the patients (60.1%) were hospitalised, although in-patient treatment was distinctly less common in Ireland (0%), Switzerland (9.1%), Belgium (15.6%) and Spain (26.1%). The median length of hospitalization was four days (inter-quartile range 2–5). Information whether complications occurred during the course of the disease, was given for 270 of the 526 patients. Complications were reported in 30 of them, 22 mentioning recrudescence or relapse, one G6PD-deficiency and seven indicating severe disease. Specific complications in the latter group were serious spleno- or hepatomegaly (3 patients), spleen-rupture (1 patient), pancytopenia (1 patient), macrohaematuria (1 patient) and psychosis (1 patient). All 618 patients survived.

Treatment information was given for 518 confirmed and probable mono-infections. Table 4 presents frequencies of drugs used in the treatment of *P. vivax* malaria. Although primaquine and chloroquine was the most frequently used drug combination, 84 (16.2%) patients,

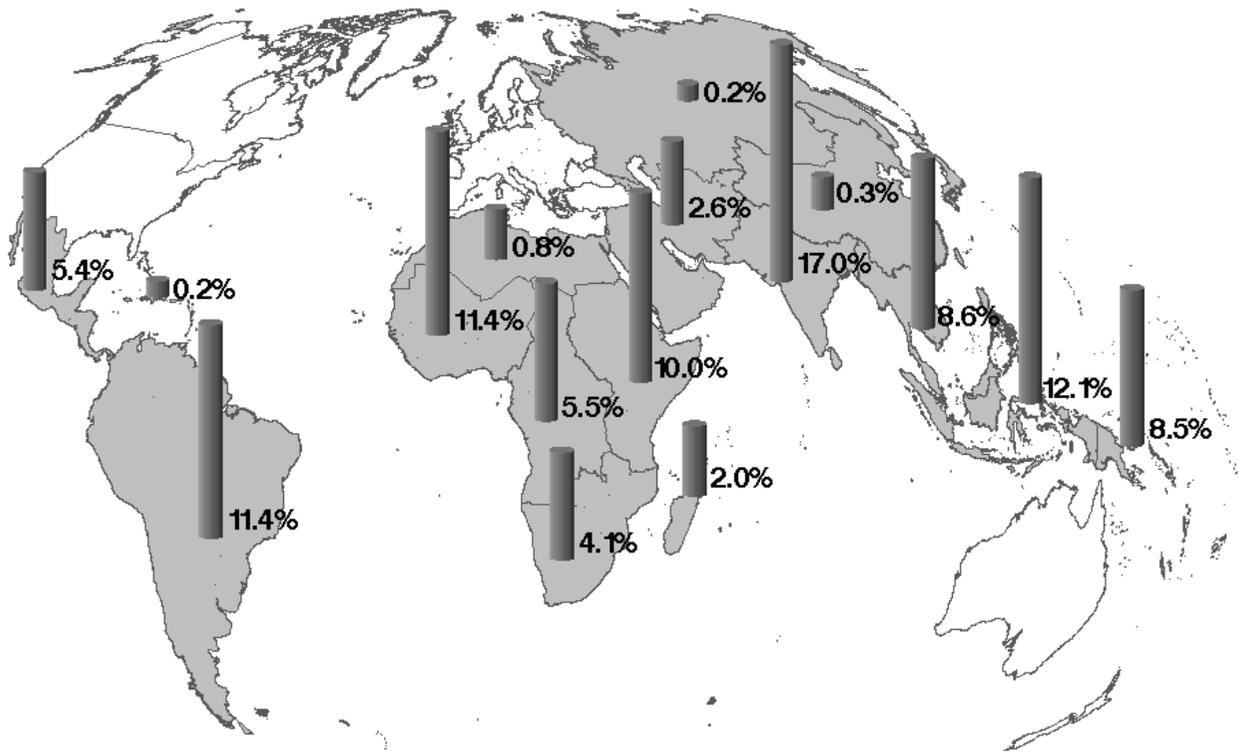


Figure 1
Geographical origin of *P. vivax* malaria imported to Europe between January 1999 and September 2003 (n = 618)

Table 3: Course of disease in 526 patients with confirmed or probable *P. vivax* mono-infection

	Median	IQ-Range
Days from end of journey to onset (nmiss = 80)	60	8–149
with chemoprophylaxis	86	41–158
without chemoprophylaxis	31	4–133
Days in hospital (nmiss = 400)	4	2–5
	N	% of non missing
In-patients (nmiss = 7)	312	60.1
Complications (nmiss = 256)	30	11.1
indicating treatment failure	23	8.5
indicating severe disease	7	2.6
Fatalities (nmiss = 0)	0	0.0

Nmiss= Number of cases disregarded due to missing data; IQ-Range = Inter-quartile range

including 61 males older than four, were not treated with primaquine. Least frequent use of primaquine was reported from France (0.0%), Ireland (20%), Poland (40.0%) and Finland (50.0%).

Table 4: Drugs used in the treatment of 518 patients with *P. vivax* malaria

Drugs	No. of patients	%
Primaquine	434	83.8
Chloroquine	426	82.2
Quinine	48	9.3
Mefloquine	36	6.9
Atovaquone/Proguanil	12	2.3
Artemether/Lumefantrine	4	0.8
Proguanil	3	0.6
Artemisinin-derivates	2	0.4
Pyrimethamine/Sulfadoxine	1	0.2

Note. Multiple entries per patient were possible

Discussion

Since network membership is self-selected, TropNetEurop surveillance data may not be representative for the whole of Europe. However, since most major referral centres of the continent are represented in the network and the number of patients treated within the network is large (~62,000 patients/year), approximate representativeness can be assumed. One objective of the present work was to look at differences between TropNetEurop-member countries. However, since some countries contributed only small numbers of cases to our database (see table 1) differences found in between country comparisons should rather be understood as hints than taken for proof.

According to TropNetEurop data, *P. vivax* is the second most frequent cause of malaria importation, accounting for 12.9% of the case imports into Europe since 1999. Analysis of data from 612 patients treated for *P. vivax* malaria in Europe between January 1999 and September 2003 yielded that 118 patients had contracted the disease despite compliant chemoprophylaxis. However, since standard chemoprophylactics do not act against hypnozoites [11,21-23], this does not indicate drug failure. Primaquine, which acts against hypnozoites [11,21-24] and was shown to be effective in the prevention of falciparum and vivax malaria [25-27] has been proposed in North America as an optional agent for regular or terminal prophylaxis in certain travellers [23,28-30]. The fact that primaquine prophylaxis was not reported in any of the TropNetEurop cases reflects the fact that it is either very effective, or uncommonly used in Europe. Most likely the latter is true, since primaquine is presently not licensed for prophylactic use. About half of the patients treated for vivax malaria in Europe were Europeans, who contracted the disease on holiday. Immigrants and refugees made up the second largest patient group, with an overall proportion of about 20%. In Norway, Italy, France, Spain and Denmark they accounted for even more of the cases. The fact that more than 40% of the immigrants had contracted

the disease on a visit to their former home country reveals that even those who may have lived in Europe for many still contribute considerably to malaria importation.

It seems peculiar that Western Africa was found to be a major region of infection, accounting for more cases than Eastern Africa. *P. vivax* prevalence was reported to be very limited in Western Africa, due to the presence of Duffy-negative blood-group variants [2-5]. Because our surveillance data lack a true denominator it cannot be excluded, that the larger number of patients returning from Western Africa with vivax malaria results from higher travel activity to that region. However, since international tourist arrivals counted by the world tourist organisation in 1999 and 2000 <http://www.world-tourism.org> were twice as high in Eastern Africa, this appears to be an unlikely explanation. Another hypothetical explanation would be that a major part of the vivax cases reported from Western Africa might be misclassified infections with *Plasmodium ovale*, which is more common in that region and difficult to distinguish from *P. vivax* microscopically.

Analysis of the course of the disease revealed that half of the patients fell ill later than 60 days after arrival from an endemic area. The most common complaints were fever, headache, fatigue, and musculo-skeletal symptoms. The finding that symptom onset was significantly delayed in patients with chemoprophylaxis is consistent with recently published findings [10]. This can be explained by the activity of standard prophylactics against blood stages but not against hypnozoites. No fatalities and only few severe clinical complications were reported, which emphasises *P. vivax*'s limited virulence as compared to *P. falciparum* [3,6]. More than half of the patients received inpatient treatment, indicating differences in national treatment policies rather than severe disease, since hospitalization rates varied greatly among TropNetEurop member countries.

None of the blood schizonticides used in the treatment of malaria affects hypnozoites of *P. vivax*, thus radical cure without relapses can only be achieved by additional administration of primaquine [11,21,23,31]. However, since *P. vivax* strains differ in their innate sensitivity to primaquine, anti-relapse treatment may fail, especially when underdosed [21,32-34]. On the other hand, omission of antirelapse treatment does not necessarily lead to relapses [35]. Both uncertainties might be used as an argument to restrict primaquine use to the treatment of recurrent episodes of the disease, even in patients without G6PD-deficiency [36]. Still, relapses may seriously threaten patients' health, whereas primaquine, which is highly effective in relapse prevention [31,32], is well tolerated [25-28]. This indicates that unrestricted use of primaquine in patients without G6PD-deficiency might offer additional health

benefits. However, this has not been evaluated in systematic risk benefit analyses. Our data on complications support the finding that primaquine treatment is well tolerated but not perfectly preventive. Within the network, 16.2% of the patients did not receive primary anti-relapse treatment with primaquine. Contraindications like G6PD-deficiency, young age or pregnancy could be ruled out as an explanation in most of these cases [21]. Primaquine relapse prevention was found to be common in most TropNetEurop member countries, with France, Ireland, Poland, and Finland showing clearly lower utilization of the drug. This indicates heterogeneity of national or site-specific treatment policies. An inquiry among members of TropNetEurop confirmed that some sites actually do limit primaquine to the treatment of recurrent episodes.

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