Clinical Infectious Diseases

MAJOR ARTICLE

Relapse of *Plasmodium vivax* and *Plasmodium ovale* Malaria With and Without Primaquine Treatment in a Nonendemic Area

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Background. The effect of primaquine in preventing *Plasmodium vivax* relapses from dormant stages is well established. For *Plasmodium ovale*, the relapse characteristics and the use of primaquine is not as well studied. We set to evaluate the relapsing properties of these 2 species, in relation to primaquine use among imported malaria cases in a nonendemic setting.

Methods. We performed a nationwide retrospective study of malaria diagnosed in Sweden 1995–2019, by reviewing medical records of 3254 cases. All episodes of *P. vivax* (n = 972) and *P. ovale* (n = 251) were selected for analysis.

Results. First time relapses were reported in 80/857 (9.3%) *P. vivax* and 9/220 (4.1%) *P. ovale* episodes, respectively ($P < .01$). Without primaquine, the risk for relapse was higher in *P. vivax*, 20/60 (33.3%), compared to 3/30 (10.0%) in *P. ovale* (hazard ratio [HR] 3.5, 95% confidence interval [CI] 1.0–12.0). In *P. vivax*, patients prescribed primaquine had a reduced risk of relapse compared to episodes without relapse preventing treatment, 7.1% vs 33.3% (HR 0.2, 95% CI .1–.3). In *P. ovale*, the effect of primaquine on the risk of relapse did not reach statistical significance, with relapses seen in 2.8% of the episodes compared to 10.0% in patients not receiving relapse preventing treatment (HR 0.3, 95% CI .1–1.1).

Conclusions. The risk of relapse was considerably lower in *P. ovale* than in *P. vivax* infections indicating different relapsing features between the two species. Primaquine was effective in preventing *P. vivax* relapse. In *P. ovale*, relapse episodes were few, and the supportive evidence for primaquine remains limited.

Keywords. malaria; *P. ovale*; *P. vivax*; primaquine; relapse.

Malaria is a major threat to human health in the countries endemic for malaria as well as for visitors to these countries [1]. Although malaria control efforts have resulted in reduced number of clinical cases and deaths due to *Plasmodium falciparum* malaria in many areas, the other species causing malaria have not been affected to the same extent [1–3], partly explained by the relapsing features of *Plasmodium vivax* and *Plasmodium ovale* [4, 5].

In *P. vivax*, the hibernating liver stages, that is, hypnozoites, may cause relapse infections over the course of weeks to years after clearance of the blood stage infection [6–8]. Geographical differences in relapse frequencies and latency periods are well established for *P. vivax* and explained by differences between temperate and tropical parasite strains and patient immunity [9–11]. In contrast, the data on relapse caused by *P. ovale* are sparse and the actual presence of hypnozoites in *P. ovale* infection is not as clear [5, 12].

For the treatment of *P. vivax* and *P. ovale*, chloroquine is recommended as first line therapy for the acute symptomatic infection, except for infections from Southeast Asia and Oceania where artemisinin-based combination therapy (ACT) is preferred [11, 13]. After the blood stage treatment, radical treatment of *P. vivax* and *P. ovale*, that is, for clearance of the hypnozoite stage parasites, relies on the 8-aminoquinoline drug primaquine, and more recently tafenoquine as an alternative [14–16]. In the World Health Organization (WHO) guidelines for the treatment of malaria, primaquine is recommended to prevent relapse for both *P. vivax* and *P. ovale*, and the evidence is stated to be strong [13, 17]. The use of the 8-aminoquinolines is limited by the risk of hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD)-deficiency, which requires testing before treatment [10]. In cases when primaquine is unsuitable, long-term chemoprophylaxis with chloroquine may be considered, especially during pregnancy [13].

Received 7 May 2021; editorial decision 27 June 2021; published online 3 July 2021.

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Clinical Infectious Diseases® 2022;74(7):1199–207

https://doi.org/10.1093/cid/ciab610

Assessment of relapses and primaquine efficacy in endemic areas is often disturbed by reinfections. In Sweden, malaria occurs only in migrants or travelers returning from endemic countries, with approximately 150 diagnosed cases annually [18]. Here we assessed relapse frequencies and the effectiveness of primaquine in preventing relapse of *P. vivax* and *P. ovale* in a retrospective nationwide study over 2 decades in Sweden.

METHODS

Study Population

Malaria is a notifiable disease in Sweden, according to Swedish Communicable Diseases Act. This includes mandatory reporting by both the treating physician and the diagnostic laboratory. All notified cases of malaria identified in the national surveillance database between 1 January 1995 until 30 June 2019 were extracted and medical records were acquired from the treating hospitals using the unique personal number carried by all residents in Sweden, or the temporary identification number given to visitors and newly arrived migrants [19, 20].

The first episodes of *P. vivax* or *P. ovale* detected in Sweden were regarded as the first diagnosed episodes of the patient. Relapse was defined as recurrence of malaria parasites of the same species ≥ 21 days following acute phase treatment [13, 21], without any other time limit in patients denying new travel to a malaria endemic country. Recurrent parasitemia before 21 days after treatment was considered as a failure of blood stage treatment and was not regarded as a relapse infection.

In the analyses, first diagnosed episodes were restricted to those diagnosed until 30 June 2018, to allow for at least 12 months of follow -up time to capture potential relapses.

Data Collection

Data were extracted from medical records regarding demographic and epidemiological factors, clinical presentation, laboratory parameters including *Plasmodium* species, as well as treatment and outcome. Origin of infection and also patient country of origin were categorized into regions according to UN Geoscheme [22] and into nonendemic and endemic country, according to WHO [23].

Malaria Diagnosis

Malaria diagnosis was made by microscopy of Giemsa or Field stained blood films in all included cases by the regional microbiology department or the on-call infectious disease specialist. Species specific real-time polymerase chain reaction (PCR) was occasionally used when microscopy was inconclusive regarding species identification. Data from all positive malaria PCR tests since October 2009 were acquired from the Department of Clinical Microbiology at Karolinska University Hospital, the only center offering PCR diagnostics for malaria in Sweden. PCR analysis was based on the species specific 18rRNA gene, detecting *P. falciparum, P. vivax, P. ovale* (including the 2 subspecies, but without distinction), *Plasmodium malariae* and *Plasmodium knowlesi* [24].

Statistical Analyses

Stata v 14.2 (StataCorp, College Station, Texas, USA) was used for statistical analyses. Numerical variables were summarized as medians and interquartile range (IQR) and categorical variables as total number and percentages. For non-normally distributed continuous variables the Wilcoxon Mann-Whitney *U* test was used to compare medians. Categorical variables were analyzed using χ^2 or Fisher exact test when appropriate, in the comparative analyses. *P*-values <.05 was regarded as statistically significant.

The hazard rate for relapse was estimated using Cox proportional hazard regression. The final adjusted model included origin of infection and relapse preventing treatment. Schoenfeld residuals test was used to assess the proportional hazards assumption. Kaplan-Meier estimate was used to assess time to relapse in *P. vivax* and *P. ovale.* Smoothed hazard function was calculated to visualize the risk and timing of relapse.

Ethical Considerations

The study was approved by the Ethical Review Board in Stockholm, Sweden (2009/1328-31/5, 2010/1080-32, 2012/1155-32 and 2017/383-32).

RESULTS

Medical records were retrieved for 3069/3499 (88.4%) of all notified malaria episodes. In addition, medical records from 161 unnotified episodes were identified through hospital data, rendering in total 3254 episodes in 2973 unique individuals. *P. vivax* and *P. ovale* were diagnosed in 972 and 251 episodes, respectively, including 26 *P. vivax* and 17 *P. ovale* episodes in mixed infections with *P. falciparum* (Figure 1). Among all episodes, 857 *P. vivax* and 220 *P. ovale* were the first diagnosed episodes in Sweden, that is, not including relapse episodes, occurring between 1 January 1995 and 30 June 2018, allowing for at least 12 months of follow-up time in all episodes. Species identification relied on light microscopy, although 40/857 (4.7%) *P. vivax* and 31/220 (14.1%) *P. ovale* episodes were confirmed by PCR.

In total, 9 *P. vivax* episodes and 12 *P. ovale* episodes presented for the first time at 31-487 and 27-653 days, respectively, after treatment of *P. falciparum* or *P. malariae*, in patients denying any new travel to a malaria endemic country. These cases were regarded as first diagnosed episodes, although a missed mixed infection at the time of *P. falciparum* infection could not be excluded.

There was one episode of early (before 21 days after completion of blood stage treatment) recurrent parasitemia of *P. vivax*, on day 12 after treatment with atovaquone/proguanil in a traveler returning from India, and this was regarded as treatment

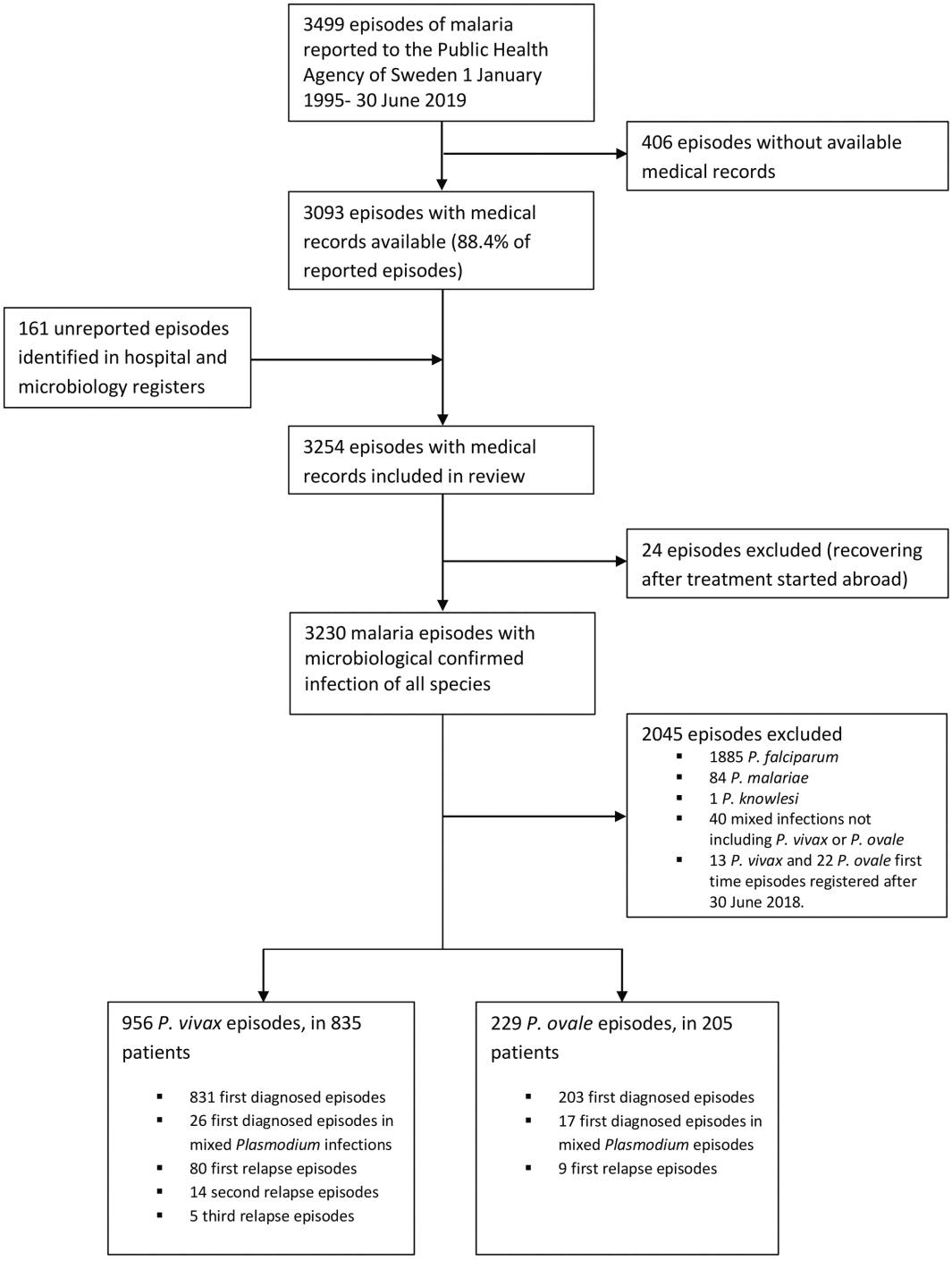

Figure 1. Chart of study population.

failure rather than a relapse. No early recurrent infections, indicating treatment failure, were seen in *P. ovale*.

Previous antimalarial treatment initiated abroad within 6 months were reported in 191 *P. vivax* and 43 *P. ovale* episodes, respectively. Due to the unreliability of data on malaria diagnosed abroad, including species and treatment, the first diagnosed episode was defined as the first episode diagnosed in Sweden, if blood stage asexual *Plasmodium* parasites were detected and there was no ongoing treatment initiated abroad.

A description of the study population is presented in Table 1. The distribution of diagnosed episodes of *P. vivax* and *P. ovale* varied over time, with a peak of episodes, especially in *P. vivax*, seen in 2014–2015 following a large number of clinical malaria in recently arrived migrants from Eritrea, described elsewhere

Table 1. Characteristics of the Study Population at the First Diagnosed Episode in Sweden

	P. vivax	*P. ovale*
Number of Patients (%)	n = 857	n = 220
Patients with first time relapse	80 (9.3)	9 (4.1)
Number of relapse episodes diagnosed in Sweden		
1 relapse	66 (7.7)	9 (4.1)
2 relapses	9 (1.1)	0
3 relapses	5 (0.6)	0
Age, years, median, IQR	26 (19–39)	28 (21–39)
Age group, years		
≤5	15 (1.7)	6 (2.7)
6–17	172 (20.1)	33 (15.0)
18–59	627 (46.6)	174 (79.1)
≥60	42 (4.9)	7 (3.2)
Female sex	258 (30.1)	73 (33.2)
Pregnancy	10 (1.2)	2 (0.9)
Region of birth		
Nonendemic country	363 (42.4)	112 (50.9)
Endemic country[a]	494 (57.6)	108 (49.1)
Origin of infection		
Africa	475 (55.4)	208 (94.5)
South Asia	155 (18.1)	7 (3.2)
Southeast Asia	97 (11.3)	0
Americas	59 (6.9)	1 (0.5)
Oceania	56 (6.5)	1 (0.5)
Other/unknown	15 (1.8)[b]	3 (1.3)[c]
Relapse preventing treatment after first diagnosed episode		
Primaquine[d], all	756 (88.2)	179 (81.4)
Standard dose[e]	701 (81.2)	178 (80.9)
Double dose	55 (6.4)	1 (0.5)
Long-term chloroquine[f]	23 (2.7)	6 (2.7)
No treatment	60 (7.0)	30 (13.6)
Missing data	18 (2.1)	5 (2.3)
Prescription of primaquine according to gender and age group		
Adult female	176 (91.2)	50 (92.6)
Adult male	407 (92.5)	96 (85.0)
Children	173 (94.5)	33 (80.5)
Time to relapse after completion of blood stage treatment, days, median (IQR)	82 (60–144)	59 (37–221)
In episodes prescribed primaquine	79 (61–130)	210 (120–221)
In episodes prescribed long-term chloroquine	178 (61–212)	…
In episodes with no relapse preventing treatment	92 (54–127)	59 (45–1893)

Abbreviation: IQR, interquartile range.

[a]Countries with indigenous spread of malaria, according to World Malaria Report [1].

[b]Western Asia (n = 11), Unknown (n = 4).

[c]Unknown (n = 3).

[d]Recommended length of treatment 14 days.

[e]Standard dose was defined as primaquine 0.25 mg base/kg bodyweight per day.

[f]≥3 months.

[20, 25]. The clinical presentation, and severity of disease in all species, including *P. vivax* and *P. ovale* in this cohort, has been previously reported [20].

Relapses of *P. vivax* and *P. ovale*

Overall, relapses were recorded in 80/857 (9.3%) *P. vivax* and 9/220 (4.1%) *P. ovale* episodes ($P = .01$) (Figure 2). In episodes not prescribed relapse preventing treatment, the proportion of relapses was significantly different in *P. vivax* and *P. ovale*, 20/60 (33.3%) compared to 3/30 (10.0%) ($P = .02$), corresponding to a higher risk of relapse in *P. vivax* infections (hazard ratio [HR] 3.5, 95% confidence interval [CI] 1.0–12.0).

Relapse episodes were identified at similar frequency in patients of Sub-Saharan African origin with temporary or permanent personal number, for *P. vivax* 20/314 (6.4%) and *P. ovale* vs 11/168 (6.6%), respectively ($P = .9$).

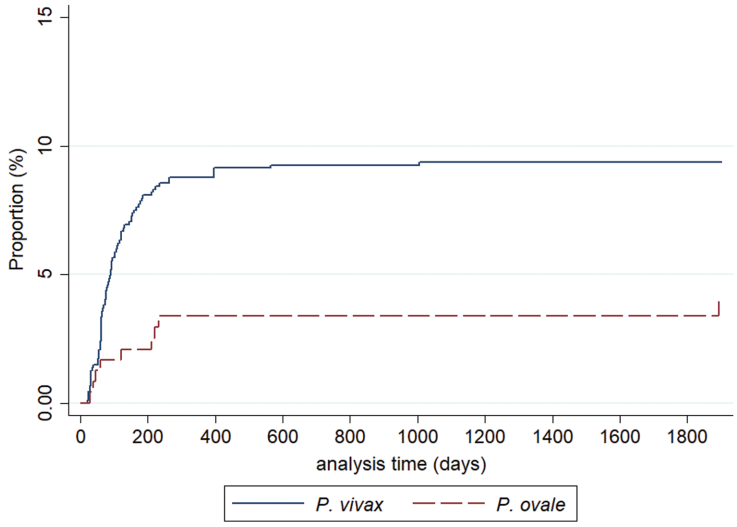

Figure 2. Kaplan-Meier analysis comparing the occurrence of relapse in all first diagnosed *P. vivax* (*blue solid line*) and *P. ovale* (*red dashed line*).

In episodes with relapse, PCR was used for species confirmation in 7/80 (8.8%) of the *P. vivax* episodes, either at the first diagnosed episode or at the time of the relapse, while for *P. ovale,* PCR was used in 5/9 (55.5%) of the relapsing episodes.

Prescription and Effectiveness of Relapse Preventing Treatment

Radical 14-day treatment with primaquine was prescribed in 756/857 (88.2%) first diagnosed *P. vivax* episodes and in 179/220 (81.4%) of the *P. ovale* episodes. The standard dose (adult dose 2 tablets, approximately 0.25 mg base/kg bodyweight/day) was given in 701/756 (92.7%) *P. vivax* episodes and double dose in the remaining 55 (7.3%) episodes. Double dose primaquine were more often prescribed in cases of *P. vivax* returning from Oceania (18/56, 32.1%), and Southeast Asia (21/97, 21.7%), compared to *P. vivax* infections from other areas (16/704, 2.3%) ($P < .001$). Prescription of primaquine was similar in males and females, and similar between children and adults (Table 1).

In *P. vivax* episodes with available data on hypnozoite treatment and dosing, first time relapses were detected in 54/756 (7.1%) of the episodes prescribed primaquine, compared to 20/60 (33.3%) in episodes not receiving any relapse preventing treatment ($P < .001$), corresponding to an over 80% risk reduction by primaquine (HR 0.2, 95% CI .1–.3) (Table 2). Age group, sex, and region of birth was individually included in the model adjusted for relapse preventing treatment and origin of infection, but these factors did not reach statistical significance.

Comparing dosing of primaquine, first time *P. vivax* relapses after standard dose primaquine was detected in 46/701 (6.6%) compared to 8/55 (14.6%) episodes prescribed double dose ($P = .05$). Long-term (≥3 months) chloroquine prophylaxis was prescribed after initial treatment of 23/857 (2.6%) *P. vivax* episodes, and in this group, 5/23 (21.7%) relapsed. In *P. ovale*, 6/220 (2.7%) received long-term chloroquine; none relapsed.

In patients with *P. ovale*, 5/179 (2.8%) relapsed despite prescription of primaquine compared to 3/30 (10.0%) in patients not prescribed relapse preventing treatment ($P = .09$); this difference remained nonsignificant in the regression analysis (HR 0.3, 95% CI .1–1.1) (Table 2).

Among patients with a first time *P. vivax* relapse, a second relapse episode was seen in 14 (21.2%) patients, and 5 of them had a third relapse (Supplementary Table 1). In *P. ovale*, no infection relapsed more than once.

Timing of Relapse of *P. vivax* and *P. ovale*

Relapses of *P. vivax* presented after median 82 days (IQR 60–144; range 22–1006) compared to 59 days for *P. ovale* relapses (IQR 37–221; range 28–1893) ($P = .8$). Time to the first *P. vivax* relapse from primary infection in episodes prescribed primaquine treatment was median 79 days (IQR 61–130) compared to 92 days (IQR 54–127) in episodes not prescribed relapse preventive treatment ($P = 1.0$). In *P. ovale,* time to first relapse from primary infection in episodes prescribed primaquine treatment was median 210 days (IQR 120–221) compared to 59 days (IQR 45–1893) in episodes not prescribed relapse preventive treatment ($P = .9$). The risk and timing of a first relapse was evaluated using the smoothed hazard function, showing a rapidly declining risk for relapse over the first 10 months from the first diagnosed episode, with a maximum hazard function of just over 0.08 cases per month at 2.5 months after the first diagnosed episode in *P. vivax* without prescribed relapse preventive treatment (Figure 3). The corresponding analysis of *P. ovale* revealed a modest risk reaching a maximum hazard function of 0.01 cases per month at 5 months following the first diagnosed episode (Figure 3).

Table 2. Hazard Ratios for Relapse After First Diagnosed Episode of *P. vivax* and *P. ovale*, Respectively

Number of Patients (%)	*P. vivax* Without Relapse, n (%) n = 777 (90.7)	*P. vivax* With Relapse, n (%) n = 80 (9.3)	*P* Value[a]	HR (95% CI)	Adjusted HR (95% CI)[b]	*P. ovale* Without Relapse, n (%) n = 211 (95.9)	*P. ovale* With Relapse, n (%) n = 9 (4.1)	*P* Value[a]	HR (95% CI)[c]
Relapse preventing treatment			<.01					.09	
Primaquine	702 (92.9)	54 (7.1)		0.2 (.1–.3)	0.2 (.1–.3)	174 (97.2)	5 (2.8)		0.3 (.1–1.1)
No treatment	40 (66.7)	20 (33.3)		1.0 (ref)	1.0 (ref)	27 (90.0)	3 (10.0)		1 (ref)
Other/missing data[d]	35 (85.4)	6 (14.6)				10 (90.9)	1 (9.1)		
Region of birth			<.01					.3	
Endemic country	462 (93.5)	32 (6.5)		1.0 (ref)	1.0 (ref)	102 (94.4)	6 (5.6)		
Nonendemic country	315 (86.8)	48 (13.2)		1.6 (1.0–2.6)	1.2 (.6–2.2)	109 (97.3)	3 (2.7)		
Origin of infection			<.01					.4	
Africa	442 (93.1)	33 (6.9)		1.0 (ref)	1.0 (ref)	200 (96.2)	8 (3.8)		…
Southern Asia	114 (92.9)	11 (7.1)		1.1 (.6–2.2)	0.8 (.4–1.8)	6 (85.7)	1 (14.3)		
Southeast Asia	80 (82.5)	17 (17.5)		3.0 (1.7–5.3)	3.5 (1.9–6.5)	0	0 (0)		
Americas	51 (86.4)	8 (13.6)		2.3 (1.1–4.9)	2.6 (1.2—5.8)	1 (100)	0 (0)		
Oceania	46 (82.1)	10 (17.9)		3.1 (1.6–6.3)	3.6 (1.7–7.4)	1 (100)	0 (0)		
Other[e]	14 (93.3)	1 (6.7)[f]		0.9 (.1–6.6)	1.4 (.2–10.4)	3 (100)	0 (0)		

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]Fisher exact test.

[b]Adjusted for relapse preventing treatment and origin of infection. Region of birth were added separately to this model for adjusted analysis.

[c]Calculation of hazard ratio in *P. ovale,* including adjusted modeling, was not feasible due to the limited sample size, with exception made regarding relapse preventing treatment.

[d]Long-term chloroquine (22), unknown (15), long-term mefloquine (1).

[e]Western Asia (11), unknown (4).

[f]Patient returning from Yemen.

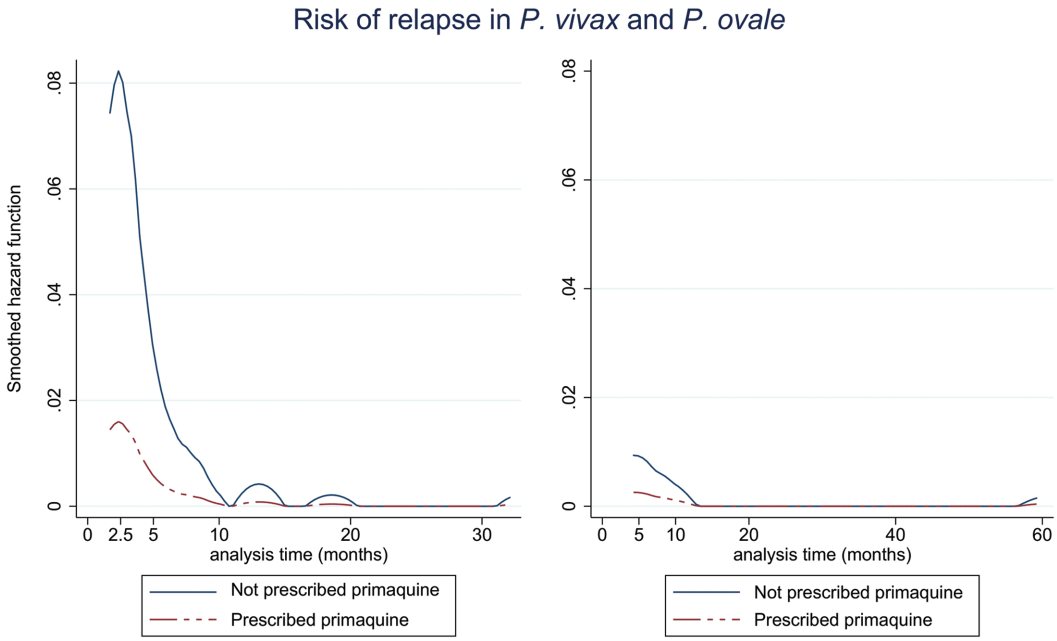

Figure 3. Plot visualizing the smoothed hazard function for relapse in *P. vivax* (*left*) and *P. ovale* (*right*) in episodes with (*red dashed line*) and without primaquine prescription (*blue solid line*). Long-term chloroquine is not included in the graph.

DISCUSSION

In this retrospective nationwide study, we assessed risk of relapse of *P. vivax* and *P. ovale* and the effectiveness of primaquine in preventing relapse of the respective species. In our cohort, the overall proportion of first time relapses, without primaquine or chloroquine prophylaxis, was more than 3 times higher for *P. vivax* than for *P. ovale*. Primaquine had a marked effect preventing *P. vivax* relapses, with an 80% reduction in risk of relapse. In *P. ovale,* relapses were rare, and there was only a nonsignificant tendency toward benefit from primaquine.

Although relapsing *P. vivax* is a clinical problem, causing a substantial, or even a dominant, part of all *P. vivax* episodes globally [4, 26], much less is known about relapsing feature of *P. ovale* [5, 12]. It has been estimated that *P. ovale* relapses cause as many as 60% of the *P. ovale* infections in a region in Papua New Guinea [27]. Nonetheless, the evidence for relapsing *P. ovale* infection remains very limited, where a systematic search identified just over 30 relapsing episodes in different settings described in the literature [5, 12, 28–30]. Here we report 9 episodes of *P. ovale* relapses in a non-endemic setting, corresponding to about 4% of all first diagnosed *P. ovale* episodes in Sweden, and 10% without primaquine, indicating a different relapse feature of *P. ovale* compared to *P. vivax*.

In previous studies on the effectiveness of primaquine in preventing *P. vivax* relapse, a 14-day course of primaquine reduced relapses from 18% to 9% [31], comparable with 33% to 7% in our study. Primaquine treatment is well established and supported by high quality evidence in *P. vivax* [31]; however, the role of primaquine to prevent relapse of *P. ovale* remains uncertain as clinical trials are lacking [5, 12]. Despite this, the WHO treatment guidelines recommend primaquine treatment in both species, stating strong evidence, but providing references for *P. vivax* only [17].

Although a reduced risk of *P. ovale* reinfection after primaquine has been shown in Papua New Guinea [27], this does not necessarily translate into a treatment indication for relapse prevention in a nonendemic setting. In our assessment, relapses of *P. ovale* were rare and although relapse episodes were 2.8% in the group prescribed primaquine compared to 10% in the group not receiving relapse preventive treatment, this difference was not statistically significant.

In *P. ovale*, studies suggest different relapse and latency patterns in the 2 sympatric subspecies, with longer latency in *P. ovale curtisi* compared to *P. ovale wallikeri* [29, 32]. Interestingly, Figure 2 reveals 2 bursts of *P. ovale* relapses, possibly indicating the presence of the two subspecies, although this remain speculatively as subspecies identification by PCR was not available.

The use of primaquine is limited by the risk of hemolysis in individuals with G6PD-deficiency, which requires testing of G6PD-activity prior to treatment [16, 33]. The WHO recommended adult standard dose of primaquine for the radical treatment of *P. vivax* and *P. ovale* is (approximately 0.25 mg base/kg/day) for 14 days, with double dose recommended for Oceania and Southeast Asia [13]. Some authors argue that double dose of primaquine should be considered to all episodes in settings

where G6PD-testing is readily available [34]. Moreover, there is support for shorter course of primaquine with remaining efficacy [35, 36] as well as use of single dose tafenoquine [14, 15], which would increase compliance compared to the 14-day course of primaquine. At this point, tafenoquine is not available in Sweden; like primaquine, tafenoquine is an 8-aminoquinoline with risk of hemolysis in G6PD-deficient recipients [12, 13]. The Swedish national treatment recommendations follow the WHO guidelines, and due to the small number of prescriptions of double dose in our study population, and confounding by origin of infection and parasite strain, the treatment effect depending on dosing could not be properly evaluated.

Strengths and Limitations

There are several limitations in this study, one that is inherent to the study design based on retrospective assessment of medical records. A strength of the study is, however, the nationwide coverage and mandatory reporting system, with medical records retrieved for nearly 90% of all notified malaria episodes in the national registry for over 2 decades. The personal identification number carried by all residents in Sweden, or the temporary number given to visitors or newly arrived migrants, allowed for a reliable identification of relapsing cases not limited to certain hospitals or regions in Sweden. However, in patients without permanent residency, a new temporary number is generated upon presentation to health care in another region. Thus, in this particular group of newly arrived migrants, relapse episodes could have been missed if previous malaria episodes were not mentioned in the medical record.

Primaquine therapy was given unsupervised, and compliance could be a bias in our study, possibly underestimating the effect of primaquine if taken according to the prescription. Microscopy was the most common method for species identification, and the use of PCR was limited and very rarely used in both the first diagnosed and the relapse episode. Microscopy in malaria diagnostics is challenging, especially in distinguishing between *P. vivax* and *P. ovale* [37]; thus, species misidentification cannot be excluded. However, in this study, at least half of the *P. ovale* infections in patients with relapse were confirmed by PCR. Another limitation is that PCR data were only available from 2009.

Nonetheless, the nonendemic setting, where there is no risk of reinfections distorting the analysis of relapse episodes, is a major strength of our study.

CONCLUSION

In this nonendemic setting, the risk of relapse episodes of *P. ovale* was lower compared to *P. vivax*, indicating different relapsing features between the two species. Primaquine was effective in preventing relapse of *P. vivax* infections and should be recommended to patients after ruling out G6PD-deficiency. In *P. ovale*, there were few and only single relapses and a nonsignificant tendency toward a benefit of primaquine. The scientific support for primaquine treatment in *P. ovale* remains limited.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.
Supplementary Table 1. Characteristics of episodes with second and third *P. vivax* relapses

Notes

Acknowledgments. The authors thank all Departments of Infectious Diseases, Departments of Paediatrics, Departments of Microbiology, and other departments for contributing with medical records. They also thank Linnea Widman at the unit for Biostatistics at Karolinska Institute for the statistical advice.

Financial support. This work was supported by Swedish Research Council (grant number 2018-04468), Stockholm County Council (grant numbers ALF SLL20150135 and FoUI-953118).

Potential conflicts of interest. H. H. A. reports serving as Chair SG NECTM8 (no payment, no direct sponsor contact), Co-Chair SC NECTM8 (Northern European Conference on Travel Medicine), and NECTM8 Rotterdam 2022, outside the submitted work. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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