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**Impact of chemoprophylaxis on *Plasmodium vivax* and *Plasmodium ovale* infection among civilian travellers: a nested case-control study with a counterfactual approach on 862 patients**

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**Running title:** Prophylaxis on non-falciparum malaria.

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**Key points:** Among civilian travellers infected by the relapse-causing species *P. vivax* or *P. ovale*, chemoprophylaxis users had a greater risk to present late-onset illness, especially those who followed blood-stage agents only. This call for new chemoprophylaxis acting on liver stages.

## ABSTRACT

**Background.** The impact of malaria chemoprophylaxis targeting *Plasmodium falciparum* on *Plasmodium vivax* and *Plasmodium ovale*, which may remain quiescent as hypnozoites in the liver, is debated.

**Methods.** We conducted a nested case-control analysis of the outcomes of *P. vivax* and *P. ovale* infections in imported malaria cases in France among civilian travellers from January 1st, 2006, to December 31st, 2017. Using adjusted logistic regression, we assessed the effect of chemoprophylaxis on the incubation period, time from symptoms to diagnosis, management, blood results, symptoms, and hospitalization duration. We analysed the effect of blood-stage drugs (doxycycline, mefloquine, chloroquine, chloroquine-proguanil) or atovaquone-proguanil on the incubation period. We used a counterfactual approach to ascertain the causal effect of chemoprophylaxis on post-infection characteristics.

**Results.** Among 247 *P. vivax*- and 615 *P. ovale*-infected civilian travellers, respectively, 30% and 47% had used chemoprophylaxis, and seven (3%) and eight (1%) were severe cases. Chemoprophylaxis users had a greater risk of presenting symptoms more than two months after returning for both species (*P. vivax* odds ratio (OR), 2.91 [95% confidence interval (CI), 1.22–6.95],  $P = .02$ , *P. ovale* OR, 2.28 [95% CI, 1.47–3.53],  $P < .001$ ). Using drugs only acting on the blood stage was associated with delayed symptom onset after 60 days, while using atovaquone-proguanil was not.

**Conclusions.** Civilian travellers infected with *P. vivax* or *P. ovale* reporting chemoprophylaxis use, especially of blood-stage agents, had a greater risk of delayed onset of illness. The impact of chemoprophylaxis on the outcomes of infection with relapse-causing species calls for new chemoprophylaxis acting against erythrocytic and liver stages.

## INTRODUCTION

Malaria remains a global health problem, with 241 million cases and 627 000 deaths worldwide in 2020 [1]. It is also the most important cause of febrile illness among ill-returning travellers [2]. Even though most cases and fatalities worldwide are due to infection with *Plasmodium falciparum*, infections with *Plasmodium vivax* and *Plasmodium ovale* are responsible for significant morbidity, and for higher mortality than previously thought [3–5]. *Plasmodium vivax* is the most widespread malaria, responsible for 76% of cases in the World Health Organization (WHO) Region of the Americas [1,3–5]. This distribution is also seen in travellers: *P. vivax* is the dominant species in malaria acquired outside Africa [6].

Unlike *Plasmodium falciparum*, *P. ovale* and *P. vivax* can remain quiescent as hypnozoites in the liver and cause relapses after the initial infection. Consequently, the treatment of these species requires a ‘radical cure’ (i.e., hypnozoite therapy) [7,8]. Primaquine and, most recently, tafenoquine in the US are the only approved drugs for this indication [9]. To date, suppressive chemoprophylaxis applying blood schizontocidal drugs and targeting *P. falciparum* prevails in travel medicine in France [10] and most European countries. Although atovaquone-proguanil acts on liver stages of *Plasmodium* (schizonts), none of the currently recommended drugs affects hypnozoites of *P. ovale* and *P. vivax* [11,12]. Thus, patients who followed prophylaxis may present with a relapse occurring months to years later. This result explains the inadequacy of chemoprophylaxis to protect against all species of malaria.

In France, a recent study found that nearly 44% of imported malaria cases took chemoprophylaxis [13]. It is important to understand whether the course of the disease caused by species causing relapses is altered by chemoprophylaxis. This question is subtle, as chemoprophylaxis may first change the occurrence of infection and lead to selection bias according to prophylaxis in those who are infected. However, using the statistical method of principal stratification allows for the analysis of ‘post-infection’ outcomes and overcomes selection bias [14].

In this study, we set out to describe clinical episodes of *P. vivax* and *P. ovale* malaria in civilian travellers returning from malaria-endemic areas and assess the effect of chemoprophylaxis on ~~infection~~ postinfection characteristics.

## **METHODS**

### **Participants and data sources**

We analysed all imported *P. vivax* and *P. ovale* malaria cases in travellers from endemic regions reported to the Malaria National Reference Centre (MNRC), a network of 110 French hospitals, in metropolitan France from January 2006 to December 31, 2017. At the time of consultation in a participating hospital, data were obtained on demographic characteristics, travel, illness, management, and use of chemoprophylaxis (Supplementary Text 1).

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

### **Diagnosis and case definition**

Cases of malaria were diagnosed according to the WHO recommendations [7] (for *P. vivax*, extended to *P. ovale*), following routine diagnostic procedures carried out by physicians and biologists in the participating hospitals. Biologists submitted a blood sample for polymerase chain reaction (PCR) and/or a blood smear control to the reference laboratory, leading to the final characterization of species. Criteria for severity at admission were taken from the 2015 WHO recommendations [7] (Supplementary Text 2).

After excluding mixed infections, we analysed only the first recorded episode for patients with repeated visits to the participating centres. We distinguished three groups: autochthonous, military, and civilian travellers, and retained only the latter (Supplementary Text 3).

### **Postinfection<sup>2</sup> characteristics and chemoprophylaxis analysed**

We analysed the association between chemoprophylaxis and several post-infection characteristics. First, we examined the time elapsed between the date of return considered as the last exposure and the onset of symptoms (this time defining the incubation period). A threshold of 60 days was chosen to consider a possible chemoprophylactic regimen followed for up to four weeks after return, as previously described [15]. Cases were divided into early (within two months of return) and late malaria. Then, the time between symptoms and diagnosis (more than three days), blood results at admission (haemoglobin  $\leq 12$  g/dL, platelet count  $\leq 150 \times 10^9/L$ , white blood cells count  $\leq 4 \times 10^9/L$ , parasitemia  $>0.5\%$ ), type of symptoms, defined as 'simple' (biological or

morphological symptoms of malaria only and nonsevere cases without vomiting) and ‘complicated’ (nonsevere case with vomiting and severe case), hospitalization rate, and duration of hospitalization (more than three days). We analysed atovaquone-proguanil and the other prophylaxis (doxycycline, mefloquine, chloroquine or chloroquine-proguanil) for their association with an incubation period longer than 60 days. We separated chemoprophylaxis into these two subgroups because of their particular mechanism of action, atovaquone-proguanil, which is effective in liver schizonts of *Plasmodium*.

### **Statistical analysis**

Patient characteristics were described using percentages or medians (interquartile ranges). Fisher’s exact tests and Wilcoxon-Mann-Whitney tests were used to compare patients following prophylaxis or not.

Multiple imputations using chained equations (MICE) were applied to fill in the missing data [16] (Supplementary Text 4).

We used univariable and multivariable logistic regression models to analyse the association between chemoprophylaxis and postinfection characteristics and the association between the different types of chemoprophylaxis and delay between return and symptoms. Variables for adjustment, ~~were~~ selected on *a priori* analysis using a directed acyclic graph-[17] (Supplementary Figure 1) were region of malaria acquisition, reason of travel, duration of stay, Personal Protection Against Vectors (PPAV), residence area, age, sex, ethnicity.

Statistical analyses were performed with R version 1.1.456 (R Foundation for Statistical Computing, Vienna, Austria).

### **Causal effect of treatment on postinfection outcomes (Supplementary Text 5)**

As our data concern only infected travellers, the result of the regressions described above is subject to selection bias compromising the causal interpretation of the impact of chemoprophylaxis on manifestations of infection (‘post-infection’ outcomes). Indeed, suppose that chemoprophylaxis prevented infection only in those who would have experienced infection and early clinical manifestations without it. Then the “untreated infected” would report early and late manifestations but the “treated infected” would only report late manifestations. One would conclude that prophylaxis causes an increase in late manifestations when the right conclusion would be that it prevented infections with early manifestations. Using principal stratification analysis for postinfection outcomes [14], we designed a method to conclude with more certainty.

In this method, we compared latent groups of patients who would have been infected irrespective of prophylaxis

(a 'doomed' strata) for whom the causal effect of prophylaxis on the postinfection episode can be defined. It is impossible to assign a particular individual to this group. However, the principal stratification framework makes it possible to estimate the average effect of prophylaxis on the characteristics of episodes, depending on the frequency of chemoprophylaxis use among travellers.

### **Ethics statement**

Ethical considerations are described in Supplementary Text 6.

## RESULTS

### Selected malaria cases (Figure 1)

From January 2006 to December 31, 2017, a total of 711 *Plasmodium vivax* and 1232 *Plasmodium ovale* imported malaria cases were reported to the MNRC. The number of primary reports of civilian traveller monoinfection were 247 for *P. vivax* and 615 for *P. ovale*.

### Characteristics of *P. vivax* and *P. ovale* malaria episodes according to prophylaxis use (Table 1)

Young men were predominant. *Plasmodium ovale* patients had travelled to Africa, usually to visit friends and relatives, or were living in endemic areas as expatriates or for humanitarian work. Visits to the WHO African region were responsible for 27% of *P. vivax* cases, mainly in the Horn of Africa, Madagascar, and Comoros.

The malaria diagnosis occurred more than seven days after the onset of symptoms in 25% of cases. At admission, parasitemia was low; 41% of cases had anaemia and 81% thrombopenia. Cases were nonsevere without vomiting in 75% of *P. vivax* and 83% of *P. ovale* cases; hospitalization occurred in 58% and 57% of cases, respectively, and one-third of patients were hospitalized for at least three days. Seven (3%) and eight (1%) severe *P. vivax* and *P. ovale* cases, respectively, were recorded as having severe anaemia, neurological symptoms, jaundice, shock, and acidosis. All patients survived, except one with *P. ovale* infection.

The use of chemoprophylaxis was reported in 30% of *P. vivax* and 47% of *P. ovale* cases (mainly doxycycline, mefloquine, and atovaquone-proguanil), with poor compliance in 59% and 56% of users, respectively. Prophylaxis usage was higher for those having travelled to Africa and for those travelling for tourism. People using chemoprophylaxis also used PPAV, which was reported in 35% of patients.

### Infections among civilian travellers under chemoprophylaxis

Among 64 *P. vivax* and 227 *P. ovale* patients who had used chemoprophylaxis, 26 (41%) and 100 (44%), respectively, reported total adherence to treatment. Among them, eight (31%) and ten (10%) episodes of *P. vivax* and *P. ovale* infection, respectively, occurred while still under recommended prophylaxis.

### Association between chemoprophylaxis use and postinfection characteristics (Figure 2)



Chemoprophylaxis use was associated with delayed onset of symptoms after 60 days among civilian travellers infected by both species (adjusted *P. vivax* odds ratio (OR), 2.91 [95% confidence interval (CI), 1.22–6.95],  $P = .02$ , adjusted *P. ovale* OR, 2.28 [95% CI, 1.47–3.53],  $P < .001$ ).

The median incubation time for *P. vivax* and *P. ovale* cases was 12 days [2–123] and 15 days [3–78] in civilian travellers who did not use prophylaxis and 46 days [19–106] and 67 days [23–158] in those who used prophylaxis, respectively. The other outcomes of interest were not significantly affected by the use of chemoprophylaxis.

#### **Association between type of chemoprophylaxis and delayed onset of symptoms (Figures 3 and 4)**

Among civilian travellers infected by *P. vivax* or *P. ovale*, the use of blood-stage agents only (doxycycline, mefloquine, chloroquine or chloroquine-proguanil) was associated with delayed onset of symptoms after 60 days (adjusted *P. vivax* OR, 3.54 [95% CI, 1.27–9.86],  $P = .02$ , adjusted *P. ovale* OR, 2.98 [95% CI, 1.85–4.80],  $P < .001$ ). The use of atovaquone-proguanil was not significantly associated with delayed onset of symptoms after 60 days for either species (adjusted *P. vivax* OR, 2.14 [95% CI, .53–8.62],  $P = .3$ , adjusted *P. ovale* OR, 1.13 [95% CI, .55–2.29],  $P = .7$ ). The median incubation time for *P. vivax* and *P. ovale* was 38 days [28–77] and 45 days [21–86] in infected travellers who followed an atovaquone-proguanil regimen and 54 days [15–134] and 79 days [24–170] in infected travellers who followed one of the four other chemoprophylaxis regimens, respectively.

## DISCUSSION

The relatively high rate of chemoprophylaxis use among travellers infected by *P. vivax* and *P. ovale* called attention to the impact of chemoprophylaxis on the clinical and biological manifestations of infection. In this study, 30% and 47% of *P. vivax* and *P. ovale* patients, respectively, used chemoprophylaxis. We found that they were at greater risk of disease onset after 60 days, especially those on doxycycline, mefloquine, chloroquine or chloroquine-proguanil. We did not find a major impact of chemoprophylaxis on other postinfection characteristics, including the time between symptoms and diagnosis, biological and clinical features, malaria-related hospitalization rate and duration of hospitalization.

Delayed onset of *P. vivax* and *P. ovale* malaria under recommended chemoprophylaxis has been reported previously. Schwartz *et al.* [15] observed that 50–70% of US and Israeli travellers infected by these species had used chemoprophylaxis, with disease onset occurring after 60 days in 75% of them. More recently, Meltzer *et al.* [18] observed that 57%, 49%, and 44% of patients under atovaquone-proguanil, mefloquine, and doxycycline regimens, respectively, developed *P. vivax* malaria two to nine months after return. However, two points need to be emphasised: first, data were limited to cases only. Second, these are postinfection outcomes, and chemoprophylaxis may have already changed the risk of infection. This leads to selection bias that can distort associations, and thus conclusions regarding the causal effects of chemoprophylaxis on these outcomes. Here, we assessed the potential difference between the raw odds ratio for the association of chemoprophylaxis with postinfection characteristics and the corresponding causal odds ratio using a counterfactual approach. We found that the magnitude of the causal odds ratio would change depending on the percentage of prophylactic use in all travellers. It will likely remain in the same direction as the raw estimate if chemoprophylaxis is used by less than 50% of all travellers (Supplementary Figure 2). This rate varies widely in the literature, from 23% to 35% in European travellers [19,20] and 26% to 46% among American travellers [21]. As this percentage is less than 50%, it confirms the existence of a causal role of chemoprophylaxis in the delayed symptom onset in civilian travellers infected by relapsing species.

Consequently, *P. vivax* and *P. ovale* malaria should be considered among infections with long incubation periods, especially in patients who take suppressive chemoprophylaxis. Delayed onset of symptoms outside the expected incubation period may delay health care presentation, diagnosis, and treatment and therefore worsen clinical outcomes [22]. In our study, three and one percent of *P. vivax* and *P. ovale* infections, respectively, were severe, and all patients, except one *P. ovale* case, survived. These results are expected for these species [22] and

remind us that infection with *P. vivax* and *P. ovale* can be associated with serious illness and death. Furthermore, 58% of patients were hospitalized, and 30% were hospitalized for more than three days, which incurs significant costs: the average hospital cost for non-severe malaria in France is 1300 Euros per day [23].

Our results are consistent with the current understanding of *P. vivax* and *P. ovale* pathophysiology. The life cycles of these species include first a liver stage (formation of schizonts and hypnozoites) and then an erythrocytic stage, which is responsible for symptoms, after an incubation period of approximately 14 days. Relapses caused by the reactivation of the quiescent hepatic forms particular to *P. vivax* and *P. ovale* species can occur months to years after exposure [7]. In our population of patients who followed prophylaxis, we observed early and late malaria. Atovaquone-proguanil has the unique ability of inhibiting both liver schizonts and blood-stage of *Plasmodium falciparum*, allowing its use for only one week of therapy postexposure [11,12]. The four other chemoprophylaxis agents act exclusively against the blood-stage of *Plasmodium* and are prescribed for 21 to 28 days after exposure. We speculate that the molecular mechanisms of the different drugs, their half-lives, and the duration of prescription explain the association observed. Because the postexposure duration of therapy is shorter for atovaquone-proguanil than other drugs, symptoms may appear earlier, and both early and late malaria are observed. Its use is therefore not associated with delayed-onset illness. For those who followed one of the four other chemoprophylaxis regimens, malaria symptoms arising during the first erythrocytic stage were masked by the use of these drugs, and their use was therefore associated with delayed-onset illness. Symptoms arising 60 days after exposure (late malaria) are mainly relapses.

We observed 27% of *P. vivax* cases travelling to Africa and 8% in West and Central Africa. Due to the high prevalence of Duffy-negative individuals in this subcontinent, the population is considered refractory to *P. vivax* infection. However, recent studies using sensitive diagnostic tools (PCR) [24] challenge this notion. Our study highlights the underestimation of non-falciparum malaria in sub-Saharan Africa. Thus, once travellers are deemed to need malaria chemoprophylaxis based on their risk of exposure, most will be at risk of *P. vivax* or *P. ovale* infections. To date, liver-acting prophylaxis for people travelling to any malaria-endemic area has been overlooked. However, it offers complete protection, as it prevents primary attack by all species as well as late relapses. Moreover, these regimens enable travellers to discontinue prophylaxis soon after their departure from endemic areas, increasing regimen adherence. Unfortunately, the number of available liver-acting drugs is limited. Primaquine, used for radical cure of relapsing malaria, is currently not recommended for prophylaxis, although it has been effective and well tolerated [25]. Tafenoquine, recently approved in Australia and US [9] for the prophylaxis of any malaria species in adults has the potential to improve adherence, with a long half-life

allowing weekly administration [26,27]. The main disadvantage of 8-aminoquinolines is the risk of haemolysis in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency, requiring a preliminary quantitative G6PD test [28,29].

Our study has several limitations. The malaria surveillance system in metropolitan France is thought to capture one case out of two, and it is considered representative of the burden of imported malaria in France [13]. A computerized form was used to standardize data input, but numerous data items were missing (Table 1). The completeness of reporting depends on the involvement of the participating centre and should not introduce selection biases. However, the typical biases of retrospective evaluation and declarative reporting may have been present. Focusing on civilian travellers and their first occurrence in the database was a means towards reducing such biases. This is a population for whom chemoprophylaxis use is variable and who are likely to consult in the participating hospitals. In our study, some were humanitarian or expatriate workers and had a unique exposure due to their long stays in exposed areas. However, they account for 11% and 6% of *P. ovale* and *P. vivax* cases, respectively, and this has no impact on our results (data not shown). We observed symptomatic patients while declaring concomitant prophylaxis, possibly due to drug malabsorption, interaction or bioavailability. Because drug blood levels were not available, we did not consider this factor, nor did we consider low compliance with prophylaxis, which was reported for more than half of the patients. However, this means that the strength of the effect could be even larger, given that noncompliance is likely to reduce the differences between treated and untreated cases. Finally, while we could identify and adjust for some possible confounders, we could not adjust for comorbidities limiting the use of chemoprophylaxis. However, as our population is composed of travellers, mostly young, this probably does not affect our results.

In conclusion, this work suggests that using chemoprophylaxis, especially doxycycline, mefloquine, chloroquine or chloroquine-proguanil, may delay the onset of symptoms of *P. vivax* and *P. ovale* malaria cases. As relapse-causing species require alternative approaches to chemoprevention, antimalarial chemoprophylaxis should be changed, including in areas where cocirculation of *P. falciparum* and *vivax* or *ovale* species occurs. Once individuals are deemed to need chemoprevention against any species, they should benefit from hypnozoitocidal chemoprophylactic alternatives acting against both erythrocytic and liver stages. Further studies evaluating 8-aminoquinolines among travellers living in nonendemic areas are needed to define new recommendations for travellers, considering tolerability, dosing frequency, and cost.

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**Potential conflicts of interest**

All the authors declare no conflict of interest.

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**Table 1.** Detailed features of the 225 *P. vivax* and 568 *P. ovale* civilian traveller cases, according to the use of chemoprophylaxis during travel.

	<i>P. vivax</i>				<i>P. ovale</i>			
	n	No prophylaxis 158 (70%)	Prophylaxis 67 (30%)	<i>P</i> Value	n	No prophylaxis 303 (53%)	Prophylaxis 265 (47%)	<i>P</i> Value
Demographic characteristics								
Gender (male)	225	116 (73.4)	49 (73.1)	1	568	195 (64.4)	145 (54.7)	.02
Age, median (IQR), y	225	29 [17–43]	31 [23–43]	.5	568	38 [28–52]	28 [16–47]	<.001
Pregnancy	225	0	0		568	4 (1.3)	6 (2.3)	.06
Immunodepression	211	1 (0.7)	1 (1.6)	.5	509	8 (3.0)	9 (3.8)	.6
Ethnicity	212			<.001	551			.7
Caucasian		69 (45.7)	47 (77.0)			76 (25.9)	74 (28.8)	
African		29 (19.2)	13 (21.3)			215 (73.1)	181 (70.4)	
Other ethnicities <sup>a</sup>		53 (35.1)	1 (1.7)			3 (1.0)	2 (0.8)	
Residence area	221			.4	560			<.001
Europe and North America		141 (90.4)	63 (97.0)			265 (88.6)	256 (98.1)	
Africa and Mediterranean		8 (5.1)	1 (1.5)			34 (11.4)	4 (1.5)	
South and central America, Caribbean, Asia and Pacific		7 (4.5)	1 (1.5)			0	1 (0.4)	
Travel characteristics								
Purpose of travel	225			.001	568			.02
Business		25 (15.8)	15 (22.4)			42 (13.9)	21 (7.9)	
Tourism		46 (29.1)	34 (50.7)			27 (8.9)	41 (15.5)	
Expatriate/Humanitarian/ Other <sup>b</sup>		11 (7.0)	3 (4.5)			36 (11.9)	26 (9.8)	
VFR		76 (48.1)	15 (22.4)			198 (65.3)	177 (66.8)	
WHO Region of malaria acquisition <sup>c</sup>	225			<.001	568			.04
African Region: West and Central part		14 (8.9)	5 (7.5)			288 (95.0)	247 (93.2)	
African Region: Southern and East part		24 (15.2)	17 (25.4)			10 (3.3)	18 (6.8)	
Region of the Americas		31 (19.6)	20 (29.8)			2 (0.7)	0	
South-East Asia Region and Western Pacific Region		38 (24.0)	25 (37.3)			2 (0.7)	0	
Eastern Mediterranean Region		51 (32.3)	0			1 (0.3)	0	
Length of stay, wk	218			.2	518			.001
0–4		46 (30.3)	20 (30.3)			79 (29.3)	75 (30.3)	
5–12		59 (38.8)	33 (50.0)			116 (42.9)	137 (55.2)	
>12		47 (30.9)	13 (19.7)			75 (27.8)	36 (14.5)	
PPAV during travel	176	25 (19.2)	39 (84.8)	<.001	417	43 (18.1)	98 (54.4)	<.001
Chemoprophylaxis used	64				228			
Atovaquone–proguanil			18 (28.1)				66 (28.9)	
Chloroquine			5 (7.8)				12 (5.3)	
Chloroquine–proguanil			12 (18.8)				20 (8.8)	
Doxycycline			17 (26.5)				63 (27.6)	
Mefloquine			12 (18.8)				67 (29.4)	
Chemoprophylaxis adherence	64				227			

High adherence			26 (40.6)				100 (44.1)	
Low adherence			38 (59.4)				127 (55.9)	
Clinical characteristics of episode								
Delay between return and onset of symptoms, median (IQR), d	195	12 [2–123]	46 [19–106]	<.01	478	15 [3–78]	67 [23–158]	<.001
Before to 60 d after return		95 (69.3)	33 (56.9)			172 (70.2)	111 (47.6)	
61 d–6 mo after return		16 (11.7)	16 (27.6)			49 (20.0)	78 (33.5)	
>6 mo after return		26 (19.0)	9 (15.5)			24 (9.8)	44 (18.9)	
Delay between return and diagnosis, median (IQR), d	202	17 [9–126]	61 [28–138]	<.01	513	24 [11–90]	71 [29–166]	<.001
0–60 d		93 (65.9)	29 (47.5)			179 (66.1)	107 (44.2)	
61 d–6 mo		20 (14.2)	21 (34.5)			63 (23.2)	85 (35.1)	
>6 mo		28 (19.9)	11 (18.0)			29 (10.7)	50 (20.7)	
Delay between symptoms and diagnosis, median (IQR), d	214	5 [2–8]	5 [2–8]	.9	524	4 [2–7]	5 [3–8]	.04
Symptoms	224			.5	564			.01
Simple case <sup>d</sup>		114 (72.6)	53 (79.1)			261 (86.7)	208 (79.0)	
Nonsevere case with vomiting		37 (23.6)	13 (19.4)			35 (11.6)	53 (20.2)	
Severe malaria cases		6 (3.8)	1 (1.5)			5 (1.7)	2 (0.8)	
Severity criteria at diagnosis <sup>ee</sup>	224			.4	564			.02
Neurological symptoms <sup>ef</sup>		2 (1.3)	0			2 (0.7)	1 (0.4)	
Severe malaria anemia <sup>fg</sup>		2 (1.3)	0			0	2 (0.8)	
Jaundice <sup>gh</sup>		1 (0.6)	0			3 (1.0)	1 (0.4)	
Shock <sup>hi</sup>		2 (1.3)	1 (1.5)			1 (0.3)	0	
Acidosis <sup>ji</sup>		0	0			1 (0.3)	1 (0.4)	
No criteria of severity		151 (96.2)	66 (98.5)			296 (98.3)	261 (99.2)	
Biological characteristics of episode at diagnosis								
Leukocyte count, median (IQR), $\times 10^9/L$	206	5.2 [3.9–6.7]	4.8 [4.0–6.2]	.5	539	5.2 [4.2–6.8]	5.1 [4.0–6.3]	.1
Hemoglobin, median (IQR), g/dL	208	12.6 [11.1–14.0]	12.8 [11.9–14.4]	.3	538	12.9 [11.5–14.1]	12.0 [10.8–13.3]	<.001
Platelet count, median (IQR), $\times 10^9/L$	207	82 [60–124]	95 [60–121]	.9	532	96 [73–134]	103 [75–144]	.2
Parasitemia, median (IQR), %	165	0.3 [0.1–0.7]	0.3 [0.1–0.6]	.4	435	0.1 [0.04–0.3]	0.10 [0.04–0.3]	.8
Management and outcomes								
Treatment first line	208			.24	530			.05
Chloroquine		75 (51.4)	33 (53.2)			132 (47.1)	128 (51.2)	
Atovaquone-proguanil		36 (24.7)	10 (16.1)			85 (30.4)	54 (21.6)	
Quinine		17 (11.6)	13 (21.0)			24 (8.6)	18 (7.2)	
Artesunate		0	0			4 (1.4)	1 (0.4)	
ACT		7 (4.8)	4 (6.5)			25 (8.9)	30 (12.0)	
Other <sup>kk</sup>		11 (7.5)	2 (3.2)			10 (3.6)	19 (7.6)	
Inpatients	214	87 (58.4)	38 (58.5)	1	536	167 (59.0)	141 (55.7)	.5
Duration of hospitalization, median (IQR), d	72	3 [2–4]	3 [2–5]	.6	188	3 [2–4]	3 [1–4]	.4
>3 days		15 (36.6)	9 (29.0)	.7		29 (30.2)	26 (28.3)	.9
Cure rate	82	48 (100)	34 (100)	1	264	134 (100)	129 (99.2)	.5

Only available data are presented in descriptive Table 1 (8.9% and 7.6% of data, for *P. vivax* and *P. ovale*, respectively, were missing for the use of chemoprophylaxis). Data are presented as n (%) for categorical variables. P values are shown for the comparison between patients who followed prophylaxis or not, based on Wilcoxon-Mann-Whitney test for continuous variables, and Fisher's exact test for categorical variables.

Abbreviations: IQR, interquartile range; VFR, Visit Friends and Relatives; ACT, Artemisinin-based Combination Therapy.

<sup>a</sup> Asian, other.

<sup>b</sup> Other: students, travel for medical reasons.

<sup>c</sup> Patients visited the following countries, in Southern and East part of the WHO African Region: Botswana, Comoros, Eritrea, Ethiopia, Kenya, Malawi, Mozambique, Uganda, Madagascar, Tanzania, Zimbabwe. In West and Central part of the WHO African Region: Cameroon, Central African Republic, Congo, Gabon, Ivory Coast, Democratic Republic of Congo – Zaire, Guinea, Ghana, Guinea-Bissau, Mali, Mauritania, Niger, Angola, Benin, Burkina Faso, Liberia, Nigeria, Senegal, Sierra Leone, Chad, Togo. In the WHO South-East Asia Region and Western Pacific Region: Bangladesh, Cambodia, China, South Korea, India, Indonesia, Myanmar-Burma, Nepal, Papua New Guinea, Thailand, Philippines, Solomon Islands, Viet Nam, Vanuatu. In the WHO Region of the Americas: Bolivia, Brazil, Colombia, Costa Rica, Guyana, Honduras, French Guiana, Nicaragua, Peru, Venezuela. In the WHO Eastern Mediterranean Region: Afghanistan, Djibouti, Iran, Pakistan, Sudan.

<sup>d</sup> 'Simple' cases were defined as biological or morphological symptoms of malaria only and nonsevere cases without vomiting

<sup>d e</sup> None of severe *P. vivax* or *P. ovale* malaria cases had hypoglycemia, renal impairment, pulmonary oedema, significant bleeding.

<sup>e f</sup> Impaired consciousness (Glasgow coma score <11 in adults, or a Blantyre coma score <3 in children), and/or prostration, and/or multiple convulsions (more than two episodes within 24 hours).

<sup>f g</sup> Hemoglobin concentration <7 g/dL, or a haematocrit of <20% in adults (≤5 g/dL and ≤15%, respectively, in children <12 years of age).

<sup>g h</sup> Plasma or serum bilirubin >50 μmol/L (3 mg/dL).

<sup>h i</sup> Compensated shock is defined as capillary refill ≥3 second or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as systolic blood pressure <70 mm Hg in children or <80 mm Hg in adults, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill).

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<sup>†j</sup> A base deficit of >8 mEq/L or, if not available, a plasma bicarbonate level of <15 mmol/L or venous plasma lactate  $\geq$ 5 mmol/L.

<sup>†k</sup> Other: halofantrine, mefloquine, other.

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**Figure 1.** Flow Chart of *Plasmodium vivax* (*P. vivax*) and *Plasmodium ovale* (*P. ovale*) imported malaria cases diagnosed in Metropolitan France, 2006–2017<sup>\*</sup>.

Data on the reason of travel were missing for 19.7% (117/593) and 19.7% (204/1033) of *P. vivax* and *P. ovale* cases, respectively.

Species were confirmed by Polymerase Chain Reaction and/or a blood smear control by the Malaria National Reference Centre (MNRC) expert laboratory.

<sup>\*</sup> For patients with repeated visits, the first recorded episode was the only studied.

**Figure 2.** Association between the use of chemoprophylaxis and characteristics of civilian traveller malaria episodes, for (A) *P. vivax*, and (B) *P. ovale*.

Abbreviations: OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval.

Multivariable analyses were made on imputed data with only those having non-missing outcome data.

\* Adjusted OR: variables for adjustment were region of malaria acquisition, reason of travel, duration of stay, Personal Protection Against Vectors (PPAV), residence area, age, sex, ethnicity.

The Forest plot displays the association between the use of chemoprophylaxis and characteristics of episodes by multivariable analysis.

**Figure 3.** Delay between return and onset of symptoms in patients treated with atovaquone-proguanil or one of the four other chemoprophylaxis (doxycycline, mefloquine, chloroquine, chloroquine-proguanil), compared to those who did not followed prophylaxis, for *P. vivax* (A) and *P. ovale* (B).

Abbreviations: IQR, interquartile range; OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval.

Multivariable analyses were made on imputed data with only those having non-missing outcome data.

\*Adjusted OR: variables for adjustment were region of malaria acquisition, reason of travel, duration of stay, Personal Protection Against Vectors (PPAV), residence area, age, sex, ethnicity.

Doxycycline, mefloquine, chloroquine and chloroquine-proguanil were grouped because of their particular mechanism of action (blood stage acting drugs only), leading to their prescription for 21 to 28 days after return. Atovaquone-proguanil being effective on liver schizonts of *Plasmodium*, it is prescribed for up to 7 days after return.

The Forest plot displays the association between the use of atovaquone-proguanil or one of the four other prophylaxis (doxycycline, mefloquine, chloroquine, chloroquine-proguanil) and delayed onset illness after 60 days, compared to no prophylaxis, by multivariable analysis.

**Figure 4.** Density of time from return to onset of symptoms (1) and time from return to diagnosis (2) according to the different types of chemoprophylaxis, for *P. vivax* (A) and *P. ovale* (B).

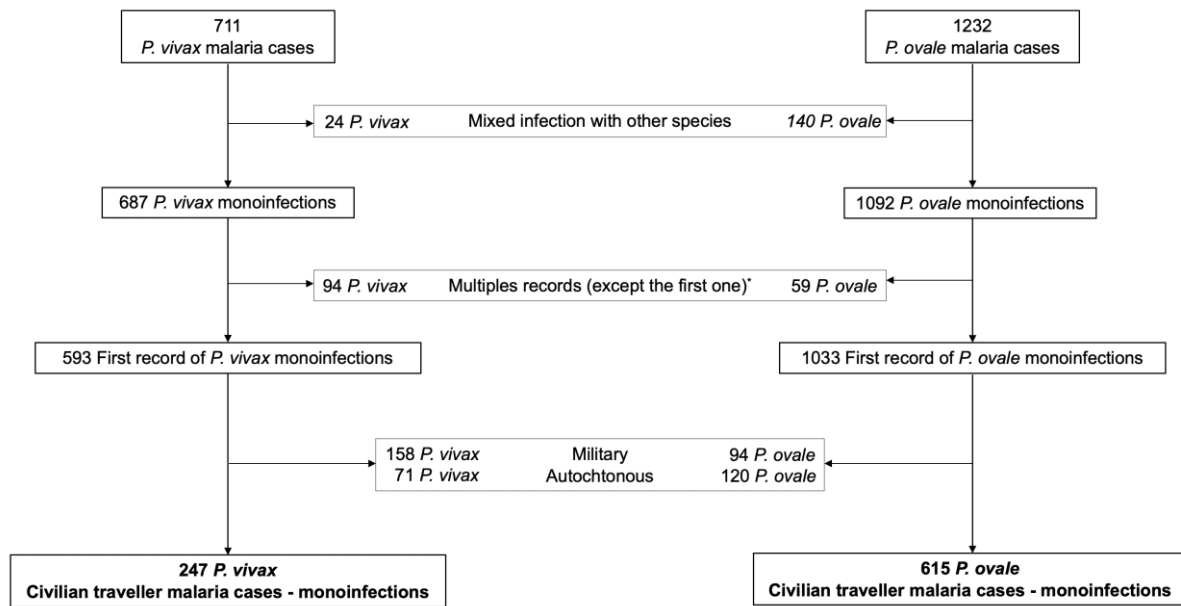
d: days

Kernel density plot show the distribution of time from return to onset of symptoms (1) and time from return to diagnosis (2) for patients who did not follow prophylaxis during travel, followed atovaquone-proguanil, or followed one of the four other chemoprophylaxis. Atovaquone-proguanil (yellow arrow) is prescribed for up to 7 days after return, other prophylaxis (green arrow) for up to 21 (mefloquine) to 28 days (chloroquine, doxycycline, chloroquine-proguanil) after return.

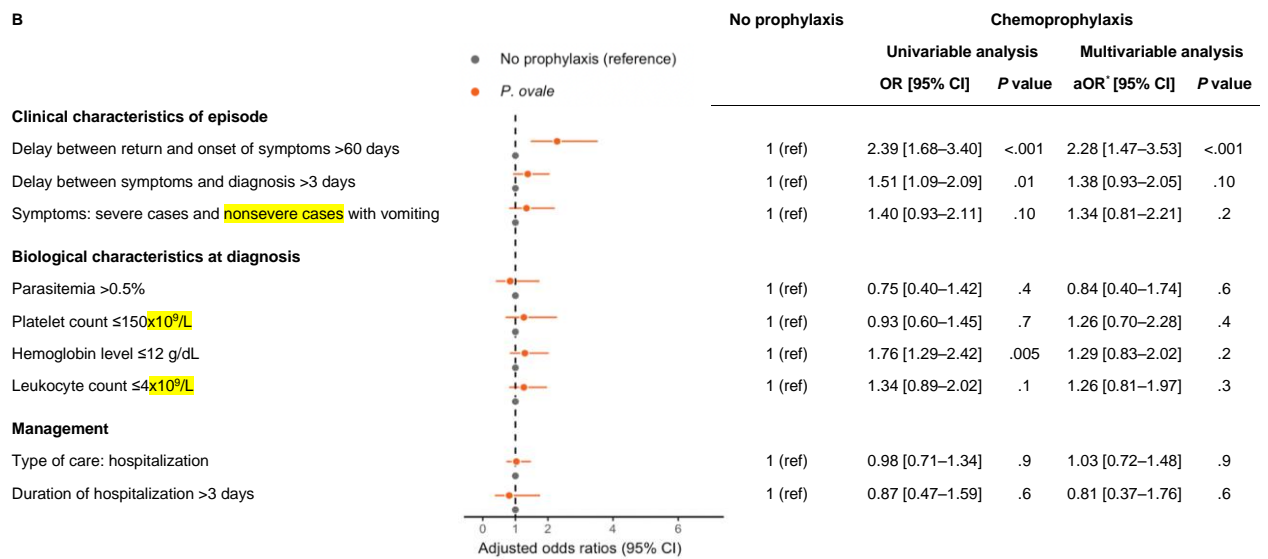
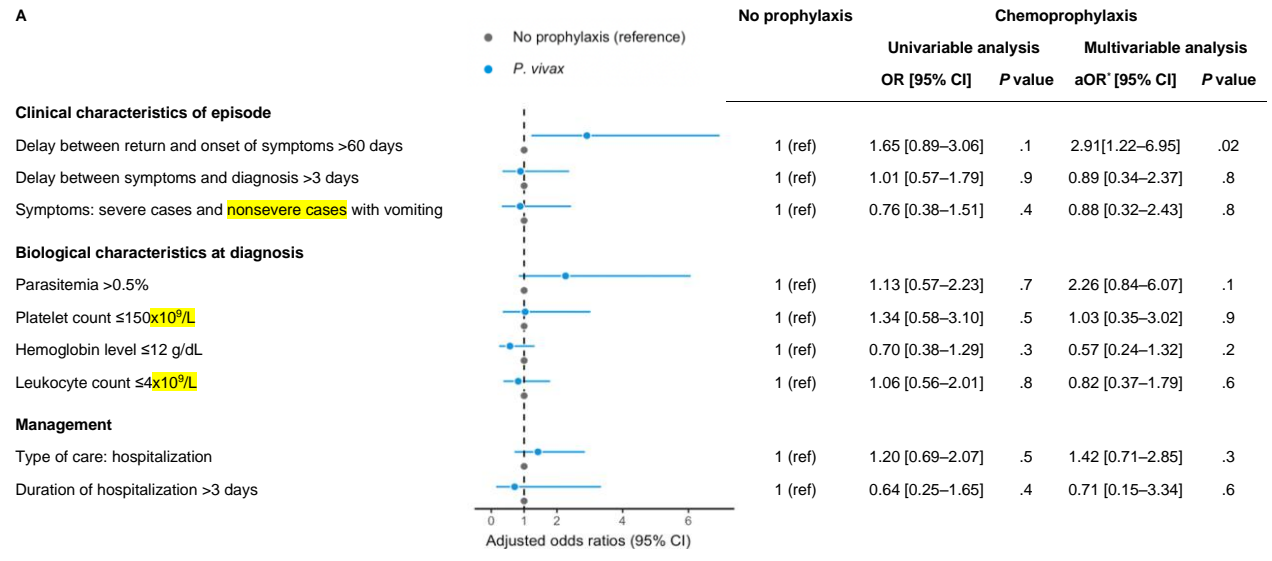
The height of the curve is scaled such that the area under the curve equals one. The peak of the density plot gives the data of concentrated values over the time.



**Figure 1.** Flow Chart of *Plasmodium vivax* (*P. vivax*) and *Plasmodium ovale* (*P. ovale*) imported malaria cases diagnosed in Metropolitan France, 2006–2017\*.

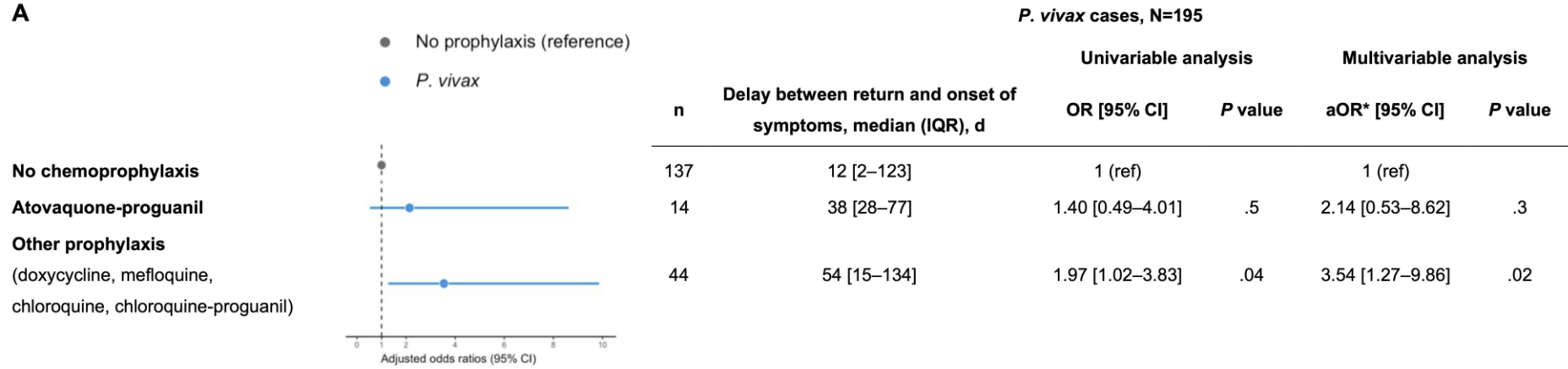


**Figure 2.** Association between the use of chemoprophylaxis and characteristics of civilian traveller malaria episodes, for (A) *P. vivax*, and (B) *P. ovale*.

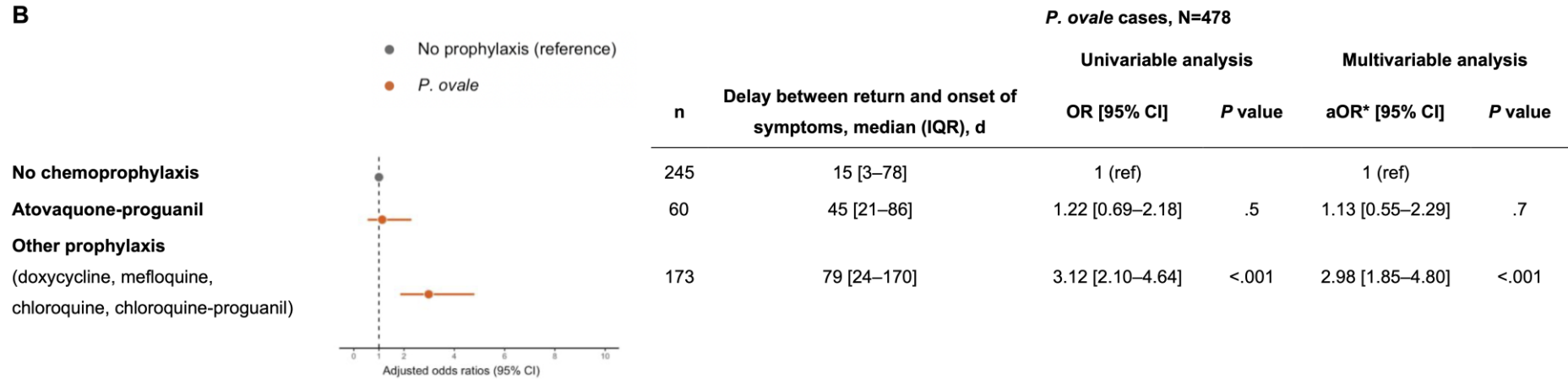


**Figure 3.** Delay between return and onset of symptoms in patients treated with atovaquone-proguanil or one of the four other chemoprophylaxis (doxycycline, mefloquine, chloroquine, chloroquine-proguanil), compared to those who did not followed prophylaxis, for *P. vivax* (A) and *P. ovale* (B).

**A**



**B**



**Figure 4.** Density of time from return to onset of symptoms (1) and time from return to diagnosis (2) according to the different types of chemoprophylaxis, for *P. vivax* (A) and *P. ovale* (B).

