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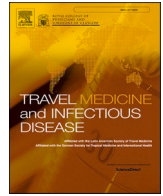
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Sharp decrease in malaria incidence among the French armed forces in French Guiana

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1. Background

Malaria incidence has decreased over the past 20 years in the Americas, with a 67% reduction between 2000 and 2020, but the epidemiological situation remains contrasted in South America. Paraguay and Argentina have been reported malaria-free by the World Health Organization (WHO), and Suriname is counted among the malaria-eliminating countries. Malaria incidence decreased by more than 40% (2015–2020 WHO Global Technical Strategy milestone) in Peru and French Guiana (FG), but increased from 2015 to 2020 in Bolivia, Venezuela, Guyana, and Colombia. During the same period, incidence remained stable in Brazil [1].

FG is a French overseas entity located on the northeast coast of South America, with a population of 294,436 in 2022 [2]. It is bordered by two countries, Suriname and Brazil, and more than 90% of its territory is covered by the Amazon rainforest (Fig. 1).

While the transmission of malaria was high at the beginning of the 20th century, indoor spraying with DDT and mass distribution of

chloroquine and then amodiaquine salts led to a significant reduction in malaria transmission between the 1950s and the 1970s [4]. At the end of these campaigns, local malaria transmission stopped in the coastal region, where 85% of the population lives. But malaria transmission persisted in hotspots in the interior, with a mean annual number of close to 3000 confirmed cases reported during the 1980–1999 period [5]. Over the last 20 years, reported cases peaked, with 4494 cases in 2005 (23 per 1000 person-years (PYs)), and then decreased to 900 cases in 2012 (4 per 1000 PYs) and 153 cases in 2020 (0.5 per 1000 PYs) [6–8]. The main species in FG are *Plasmodium falciparum* and *Plasmodium vivax*, which co-circulate. *P. falciparum* was predominant among notified cases until 2004. The proportion then decreased to 30% in 2014, 9% in 2018, and 3% in 2020 [6]. Some cases of *P. malariae* are also described [7]. The main mosquito vector for malaria in FG is *Anopheles darlingi* [9]. Its biting activity usually increases in the evening, but latest studies in forested areas highlighted activity during the day as well [10,11]. Recently, other species have also been found to be infected with *Plasmodium*: *An. nuneztovari sensu lato (s.l.)*, *An. intermedius*, and *An. oswaldoi*

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s.l. by *P. falciparum*, and *An. marajoara*, *An. nuneztovari s.l.*, and *An. ininii* by *P. vivax* [12–14].

However, the epidemiological situation of malaria in FG was still concerning in illegal gold mining areas in the rainforest. Illegal mining activities, which take place in remote areas with no access to health care, led to widespread gametocyte carriage and sustained malaria transmission. Several studies conducted among gold miners' in illegal situation (GMISs) between 2014 and 2017 revealed a high prevalence of malaria infections (22%–60%); a high proportion of *Plasmodium* asymptomatic carriers (48–84% of malaria infections), with a predominance of *P. falciparum* infections [15–17]. The consistent results of these studies supported the role of GMISs as a reservoir for malaria parasites. Approximately six to ten thousand GMISs are estimated to work in French Guiana's forest, so the incidence of malaria in FG may be higher than the official reported cases [18].

About 4000 French service members (FSMs) are present in FG, arriving from metropolitan France for short (4 months) or long (2–3 years) stays. Since 2002, they have been deployed in remote forest areas to control illegal gold mining activities. From forward operating bases, FSMs conduct short (24–48 h, camping in the forest) or long (3–4 weeks) interventions on illegal gold mining positions (Fig. 1). During these missions, the malaria prevention strategy of the French Armed Forces is

based on four axes: (1) Individual protection against vectors including skin-applied repellent, the wearing of long sleeves and long pants from dusk to dawn, permethrin-impregnated battle dress uniforms, long lasting permethrin-impregnated bed nets, and hammocks with mosquito nets; (2) Chemoprophylaxis based on 100 mg of doxycycline daily throughout the stay and for four weeks after leaving the malaria transmission zone; (3) Health education to promote compliance with the preventive measures described; and (4) prevention of *P. vivax* relapses with a primaquine radical cure (dosing regimen: 30 mg/day for 14 days) after the chloroquine treatment, from the first *P. vivax* attack since 2009 [19,20]. Despite such strategies, deployments at illegal gold mining sites were associated with a significant increase in malaria cases and repeated outbreaks [13,21–23]. Indeed, a high risk of malaria transmission existed at gold mining sites, with high rates of *Anopheles* infections from 0.4% to 12.5% [13,14].

Malaria incidence among FSMs, a sentinel population, can indirectly reflect the trend in malaria transmission among GMISs, a hidden malaria reservoir, and could provide an understanding of the malaria situation in FG.

The objective of the study was to describe the evolution of malaria incidence among FSMs from 2000 to 2021, and the factors that may have influenced it.

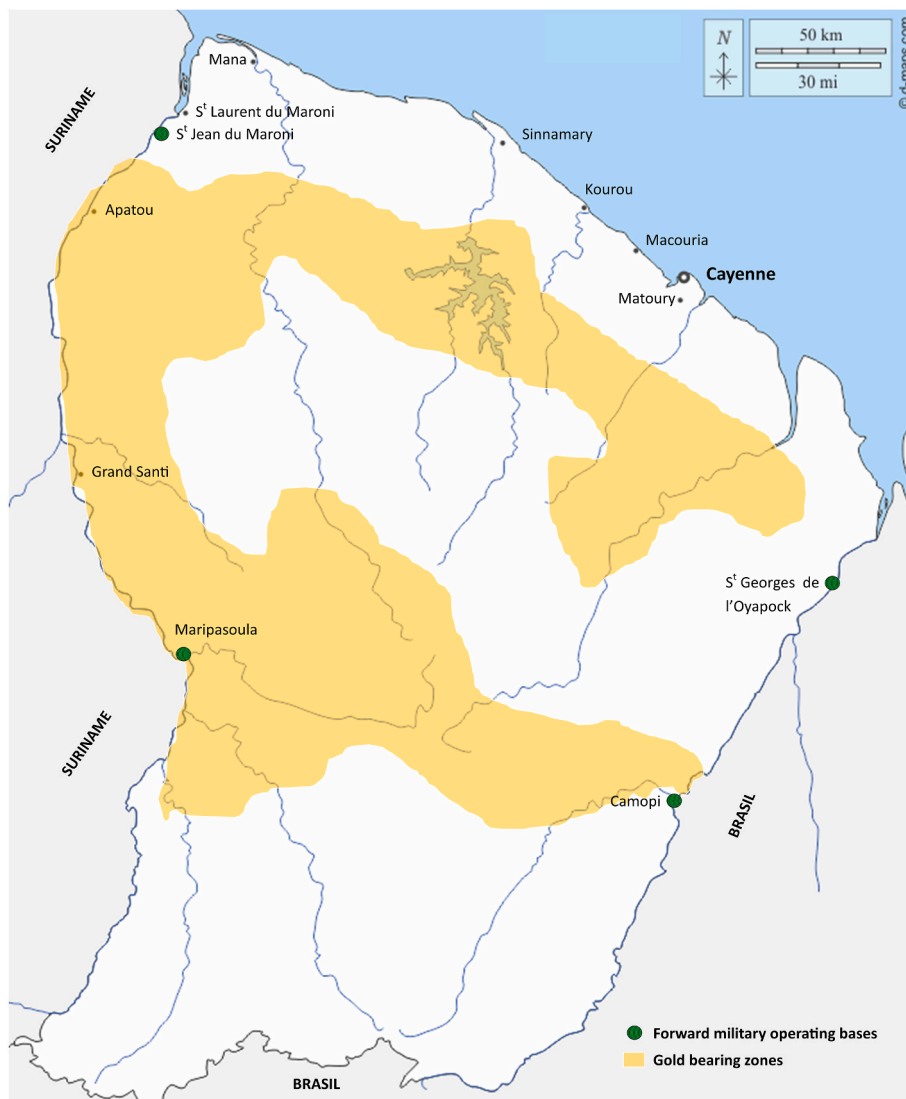


Fig. 1. French Guiana map, military operating bases and gold bearing zones adapted from [3]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2. Methods

2.1. Type of study

Epidemiological surveillance of malaria among the French Armed Forces consists of continuous and systematic collection, analysis, and interpretation of epidemiological data. Cases were reported by all military physicians. This retrospective study analyzed surveillance data over the period 2000–2021. As surveillance evolved, some of the data collected were introduced over time and were thus not available over the entire period.

2.2. Inclusion criteria

A malaria case was defined as any patient with any symptom combined with confirmed parasitological evidence (*Plasmodium* spp. in blood smears or quantitative buffy coat or a positive malaria rapid diagnosis test). All cases were contracted in FG. Each malaria attack was counted as a separate case.

2.3. Data collected and definitions

For each malaria case, sociodemographic information, clinical outcomes, chemoprophylaxis compliance, diagnostic tests, and treatment data were provided by the military physicians using a mandatory specific form.

The diagnosis date was used for chronological description. The denominator for the incidence rate was the average number of FSMs present in FG during a given year. Incidence was described annually, and monitoring indicators were grouped into consecutive 2-year periods.

An indigenous malaria case was defined as a case occurring in FG. An imported malaria case was defined as a case occurring in metropolitan France or in another malaria-free country after a stay in FG.

Starting in 2005, for each *P. vivax* case, the number of *P. vivax* attacks during the previous six months was reported, which made it possible to identify relapses. The impact of the implementation in 2009 of the primaquine radical cure after the first *P. vivax* attack could only be studied for imported malaria cases (formally excluding new exposure to malaria). Relapse occurrences were compared before and after the implementation of this measure. In addition, for each *P. vivax* attack, information about primaquine radical cure was available starting in 2012, providing details on two indicators:

- planning for a radical cure after the attack (first attack or relapse),
- in the event of relapse, whether any primaquine radical cure had been undergone since the last attack.

Data about chemoprophylaxis compliance prior to diagnosis were available starting in 2005. Appropriate compliance was defined as chemoprophylaxis taken within eight days before the diagnosis, excluding malaria cases diagnosed more than four weeks after the service member's return from the malaria endemic area. The date of first clinical signs was available from 2012 onwards, hospitalization in an intensive care unit from 2007.

2.4. Statistical analysis

Statistical analyses were performed using Epi Info 7.2.4 (Centers for Disease Control and Prevention, Atlanta, GA, USA). Comparisons over time were made using the Chi² test for trend, and mean comparisons were done with ANOVA. Seasonality was analyzed by comparing monthly cumulative cases and monthly cumulative rainfall during the same period (available on the NOAA website) [24] using binomial negative regression, with a time lag of zero to three months, using R 4.0.3. A *p* value < 0.05 was considered significant.

2.5. Ethics and regulation

Ethical approval and consent to participate were not required for mandatory epidemiological surveillance. All the data collected were anonymized. The database was declared to the CNIL, the French data protection authority (Registration no. 2035221), on February 15, 2017. This surveillance activity was carried out in accordance with the General Data Protection Regulation (EU Regulation 2016/679).

3. Results

3.1. Malaria cases and trends from 2000 to 2021

A total of 2433 malaria cases were reported among FSMs deployed in FG over the study period. The incidence rate increased from 27 per 1000 PYs in 2000 to 78 per 1000 PYs in 2009 (*p* < 0.001), and then dramatically decreased to 1 per 1000 PYs in 2021 (*p* < 0.001) (Fig. 2).

The male/female ratio was 70 (98.6% were men). Median age was 28 years (interquartile range: 24–33; minimum: 17; maximum: 56). Imported cases occurring outside FG, upon return to metropolitan France or to other countries without malaria transmission, represented 30.9% of cases (*n* = 753). This proportion decreased over the period, from 45.9% in 2000–2001 to 26.7% in 2020–2021 (*p* < 0.01) (Table 1).

The *Plasmodium* species involved were *P. vivax* (*n* = 1836 cases; 75.5%), *P. falciparum* (*n* = 416 cases; 17.1%), mixed *P. vivax* and *P. falciparum* infection (*n* = 89 cases; 3.7%), and *P. malariae* infection (*n* = 9; 0.4%). The proportion of malaria attacks caused by single *P. falciparum* decreased from 30.4% in 2000–2001 to 0% in 2020–2021 (*p* < 0.001) (Table 1). The diagnosis was confirmed less than 48 h after the onset of symptoms in 53% of cases. The mean diagnostic delay was 2.7 days (95% CI [2.3 days, 3 days]), with no difference between periods (*p* = 0.13). This mean delay was higher for imported cases than for indigenous cases in FG (3.4 days (95% CI [2.6, 4.1]) vs 2.4 days (95% CI [2.1, 2.8])) (*p* = 0.02).

The median number of lost workdays was seven per attack (interquartile range: 4–8; minimum: 0; maximum: 90). Since 2007, two *P. falciparum* infections were hospitalized in an intensive care unit. No death was reported.

Monthly cumulative cases were not significantly associated with concomitant monthly cumulative rainfall in FG (*p* = 0.62). But, a significant association was observed with rainfall with a time lag of two (*p* = 0.01) and three months (*p* = 0.03) before cases. Thus, the number of malaria cases increased as rainfall decreased during the previous two or three months.

3.2. Malaria chemoprophylaxis

This measure remains the best way to protect FSMs against malaria when exposure is high. Since chemoprophylaxis is mandatory for them, when outbreaks occurred, supervision of compliance was implemented in the field, reinforced by daily reminders upon return from the mission. Despite those measures, between 2005 and 2021, only 48.1% of FSMs reported appropriate compliance, with no trend towards improved declared compliance over the period (*p* = 0.18) (Table 1).

3.3. Preventing *P. vivax* relapses

The proportion of *P. vivax* relapses after leaving FG (imported cases) decreased from 52.4% during the 2005–2009 period to 43.6% during the 2010–2021 period (*p* = 0.04). From 2012 onwards, at the time of *P. vivax* case notification (regardless of whether it was indigenous or imported), the primaquine radical cure was reported by clinicians as planned (81.8%) or begun (6.8%), but only 29.7% of cases that had had a prior attack during the past six months underwent a primaquine radical cure.

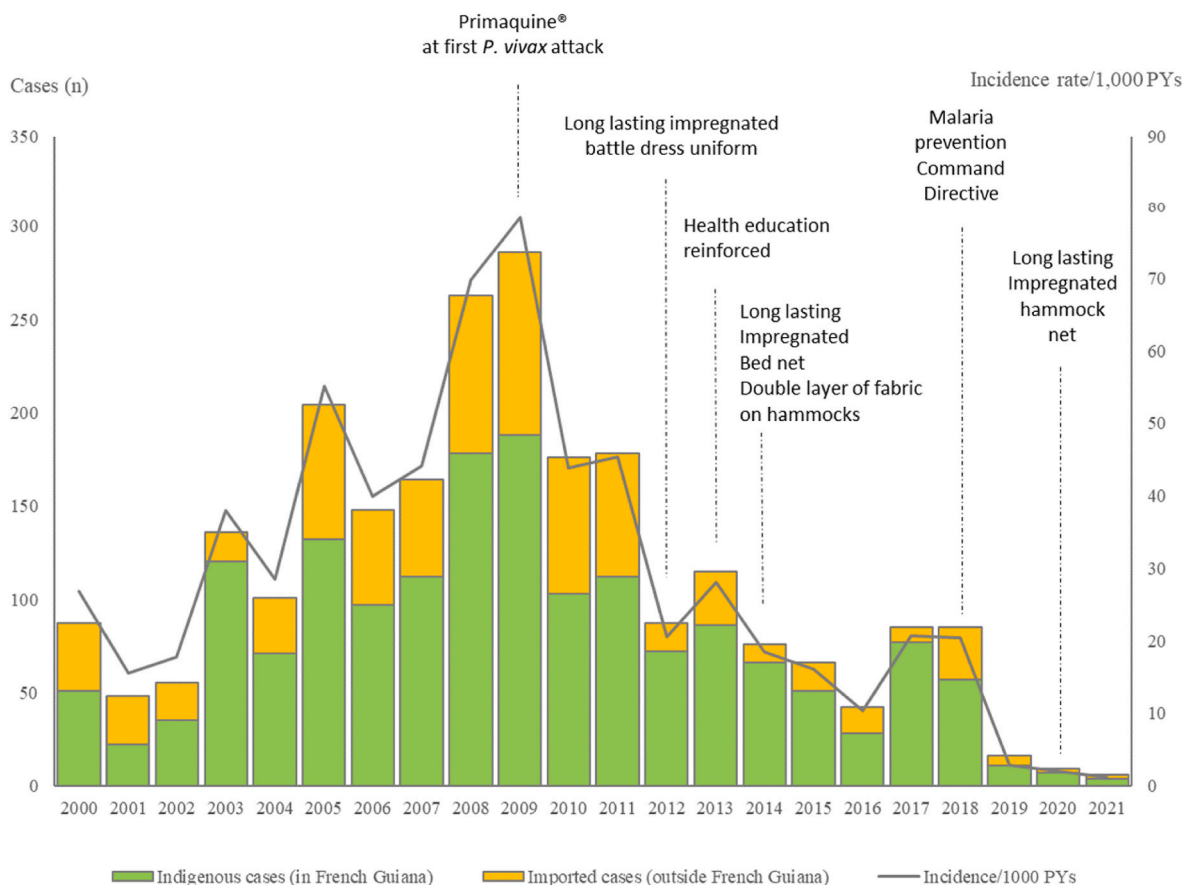


Fig. 2. French Armed Forces malaria cases, incidence rate, and main implemented measures, French Guiana, 2000–2021.

3.4. Other preventive measures

The collective military response has been strengthened by other preventive measures. Long lasting permethrin-impregnated jungle battle dress uniforms were distributed to all FSMs for forest missions starting in 2012. Targeted health education actions were strengthened from 2013 onwards. Starting in 2014, long lasting permethrin pre-impregnated mosquito bed nets were distributed in the semi-permanent military camps, and the bottom of the hammocks used for sleeping during night missions in the forest was doubled to limit biting through the fabric. A specific plan was supported by the military command in 2018, aiming to reinforce compliance with preventive measures, but also to limit exposure to vectors by having FSMs sleep away from mining sites during police operations. Finally, hammock mosquito nets were also impregnated with long lasting permethrin starting in 2020.

4. Discussion

This study highlights a significant decrease in the incidence of malaria among FSMs in French Guiana. These results can be explained by the measures successively implemented which may have contributed to this reduction and common issues with the civilian population and the GMISs which constitute persistent challenges to the elimination of malaria in this territory.

4.1. Evolution of malaria incidence among FSMs: a sharp decrease in recent years

This study may have limitations, since the data are from epidemiological surveillance. Underreporting can occur, even in a military

context. This could be possible for imported malaria cases, as FSMs may more frequently choose a civilian practitioner for primary care during leave taken after their mission in FG. Nevertheless, the decreasing trend of malaria incidence is also observed for indigenous cases reported in FG. It is therefore unlikely that this practice could have influenced the trends described in this study. Information about previous stays in malaria endemic areas was not available. However, the interval between two missions for FSMs is one year. Thus, malaria infections from another endemic territory were very unlikely.

Since 2009, there has been a sharp decline in the incidence of malaria among FSMs. This decrease has also been observed among the French Guianese civilian population [6].

For FSMs, this decrease may be linked to reduced exposure. First, in recent years, the fight against illegal gold mining has led to smaller and more transitory illegal gold mining sites being set up [25]. This could have limited a sustainable establishment of the malaria transmission cycle in the French Guianese forest. In addition, the implementation of protective measures for FSMs, including long lasting impregnated nets and jungle battle dress uniforms, has potentially limited malaria exposure [26,27]. The use of doxycycline for chemoprophylaxis may have limited infections, but the need to take a daily dose and the perceived side effects remain barriers to compliance [28,29]. Furthermore, there was no change in chemoprophylaxis compliance among malaria cases over the study. The choice of doxycycline as first-line chemoprophylaxis, rather than atovaquone-proguanil, was made for reasons of cost, but also for its action against other infections present in French Guiana, such as leptospirosis. Nevertheless, atovaquone-proguanil malaria chemoprophylaxis is now recommended for short-term missions (<14 days), in order to facilitate compliance upon return from malaria risk areas.

Malaria transmission is present all year round among FSMs in FG. But

Table 1
Malaria cases, where diagnosed, species, *P. vivax* imported relapses, chemoprophylaxis compliance, and diagnostic delay. Cumulative data covering two-year periods. French Armed Forces, French Guiana, 2000–2021.

Year	2000–2001	2002–2003	2004–2005	2006–2007	2008–2009	2010–2011	2012–2013	2014–2015	2016–2017	2018–2019	2020–2021	Total
Malaria cases (n)	135	191	305	312	549	354	202	142	127	101	15	2433
Population (n)	6342	6674	7242	7428	7416	7941	8340	8210	8143	9734	9686	87,156
Malaria incidence rate (p 1000 PYs)	21.3	28.6	42.1	42.0	74.0	44.6	24.2	17.3	15.6	10.4	1.5	27.9
Cases												
Indigenous cases in French Guiana (n)	73	155	203	209	366	215	158	117	105	68	11	1680
Imported cases outside French Guiana (n)	62	36	102	103	183	139	44	25	22	33	4	753
Imported cases outside French Guiana (%)	45.9%	18.8%	33.4%	33.0%	33.3%	39.3%	21.8%	17.6%	17.3%	32.7%	26.7%	30.9%
Species												
<i>P. vivax</i> (n)	83	117	216	249	425	293	144	96	106	92	15	1836
<i>P. falciparum</i> (n)	41	54	57	40	96	39	39	32	13	5	0	416
Mixed <i>P. falciparum</i> - <i>P. vivax</i> infection (n)	1	17	16	10	18	13	3	5	3	3	0	89
<i>P. malariae</i> (n)	0	1	4	2	0	2	0	0	0	0	0	9
Not specified (n)	10	2	12	11	10	7	16	9	5	1	0	83
<i>P. falciparum</i> (%)	30.4%	28.3%	18.7%	12.8%	17.5%	11.0%	19.3%	22.5%	10.2%	5.0%	0.0%	17.1%
<i>P. vivax</i> (%)	61.5%	61.3%	70.8%	79.8%	77.4%	82.8%	71.3%	67.6%	83.5%	91.1%	100.0%	75.5%
Imported <i>P. vivax</i>^a												
First attack (n)	–	–	24	36	89	66	23	14	9	23	1	285
Relapse (n)	–	–	32	52	80	62	14	11	9	6	3	269
Relapse (%)	–	–	57.1%	59.1%	47.3%	48.4%	37.8%	44.0%	50.0%	20.7%	75.0%	48.6%
Chemoprophylaxis compliance^a												
Non-compliant (n)	–	–	94	114	198	97	84	67	41	26	5	726
Compliant (n)	–	–	49	105	210	124	61	39	50	31	5	674
Compliant (%)	–	–	34.3%	47.9%	51.5%	56.1%	42.1%	36.8%	54.9%	54.4%	50.0%	48.1%
Diagnostic delay^b												
Mean 95% CI	–	–	–	–	–	–	2.2 [1.7,2.7]	2.9 [2.2,3.6]	2.5 [1.8,3.1]	3.2 [2.4,4.0]	4 [2.4,5.6]	2.7 [2.3,3.0]

^a Data available starting in 2005.

^b Data available starting in 2012.

a seasonal rise in the number of cases is observed two to three months after rainfall decreases. This time lag has been observed in other studies and could be explained by the time lag between the larval cycle of the mosquito, the sporogonic cycle of the parasite, and the incubation period required before the onset of the disease [30].

The decrease in malaria incidence both in the civilian population and among FSMs in FG may also reflect the implementation of the Malaria Control Plan in French Guiana since 2015, which strengthened the capacity for surveillance, vector control, diagnosis and treatment [31]. For example, a study was conducted in one of the main transmission towns on the border river with Brazil. The Palustop Project evaluated the effect of systematic mass PCR screening and treatment of symptomatic and asymptomatic plasmodial infections in 2017–2018 [32]. The results confirmed asymptomatic carriage in 73%–89% of PCR-positive participants and a 53.7% drop in malaria prevalence after the intervention (6.7%–2.5%) [33].

4.2. Does the evolution of malaria among FSMs in FG reflect the situation among GMISs?

A cohort study conducted between 2013 and 2015 among 1496 FSMs with a serology performed before the first stay at an illegal mine site (T0), and then after the last stay (T4), estimated the reality of malaria exposure. The incidence of serological evidence of malaria infection (positive IgG immune response between T0 and T4 for at least one plasmodial antigen) was very high, with more frequent exposure to *P. falciparum* (49.6 per 100 PYs) than to *P. vivax* (39.1 per 100 PYs), consistent with the incidence among GMISs described during this period [15,16]. This was in contrast to the incidence of malaria attacks among FSMs: 0.6 p. 100 PYs for *P. falciparum* and 6.1 p. 100 PYs for *P. vivax* [34]. The low incidence rates of malaria attacks in this cohort compared to the very high incidence rates observed in serological evidence of infections support the efficacy of antimalarial chemoprophylaxis with doxycycline. In fact, both GMISs and FSMs are exposed to the same level of transmission at illegal mining sites, but individual anti-vector protective measures used by FSMs reduce exposure to mosquito bites, and chemoprophylaxis reduces malaria incidence, especially for *P. falciparum* attacks [33]. Thus, the incidence of malaria among FSMs was indirectly related to that of GMISs, but species distribution was not.

4.3. Malaria among GMISs: a shrinking parasite reservoir?

The high mobility of GMISs and the remoteness of the areas where they work could be obstacles to the elimination of malaria in the Guiana Shield. Suriname has established a specific program, “Looking for Gold, Finding Malaria”, which deploys community health workers in the mines and remote areas to diagnose and treat malaria free of charge. This strategy has enabled the country to quickly move from an endemic situation to a malaria pre-elimination phase [35]. In Brazil, malaria treatment can be provided by non-medical personnel in remote areas without access to a physician, but there is no specific program for GMISs and malaria remains uncontrolled in some northern states [36]. In FG, regulations do not allow non-medical professionals to diagnose and treat malaria. The Malakit project evaluated a new intervention strategy to control malaria, based on the distribution in cross-border areas (Suriname and Brazil) of free self-diagnosis and self-treatment kits (artemether-lumefantrine with a single dose of primaquine) to GMISs, together with training on how to use them [37]. The results showed that over the intervention period (2018–2020), more than 4700 kits were distributed which helped prevent 42.9% of malaria cases from French gold mines diagnosed in Suriname and Brazil [38]. The Malakit pre/post surveys showed that PCR-*Plasmodium* prevalence among GMISs decreased from 22.3% in 2015 to 5.3% in 2019 on the Maroni river border with Suriname, and from 3.9% in 2018 to 2.5% in 2019 on the Oyapock river border with Brazil. Since GMISs constitute one of the main reservoirs of malaria in FG, these results may explain the marked decrease in malaria

incidence among FSMs over the 2019–2021 period, but asymptomatic carriage and accessibility remain obstacles to the elimination of malaria in this population [39].

4.4. Preventing *P. vivax* relapses: a persistent issue in FG

Both among FSMs and the civilian population, the proportion of *P. falciparum* is decreasing. One reason for this decline is that artemisinin-based combination therapies are more effective for treating *P. falciparum* attacks due to the absence of hypnozoites. Moreover, gametocytes circulate earlier in infections caused by *P. vivax*, which could promote its transmission [40]. In addition, for FSMs, chemoprophylaxis with doxycycline limits *P. falciparum* attacks, but does not prevent *P. vivax* relapses after chemoprophylaxis ends [41].

One primary factor for controlling malaria in FG is to prevent *P. vivax* relapses by administering a systematic radical cure with primaquine [42]. The implementation starting in 2009 of the primaquine cure at the first *P. vivax* attack was concomitant with the beginning of decreases in both malaria incidence in FSMs and imported *P. vivax* relapses. However, access to the primaquine cure remains limited. In France, its use is reserved for hospital treatment and requires a temporary authorization. In addition, G6PD deficiency tests can only be carried out in metropolitan France, which increases the delay in treatment for infected individuals in FG. These reasons and the sometimes-delayed medical follow-up of the FSMs, due to their operational activities, may explain why the implementation of this measure was not optimal. Since 2017, unfitness for field missions was recommended until the end of primaquine treatment. Furthermore, systematic screening for G6PD deficiency for military personnel at the time of their recruitment has been studied; but has not been retained for the time being due to the financial cost of its implementation in regard with the actual low incidences of *P. vivax* and *P. ovale* malaria among French armed forces.

For FSMs and travelers in malaria endemic areas in FG, a solution could be causal chemoprophylaxis with tafenoquine, which presents the advantage of requiring a single dose per week while preventing relapses, and which has been approved by the FDA in the United States [43]. However, that chemoprophylaxis regimen is still not authorized in Europe, requires systematic screening for G6PD deficiency, and is contraindicated if there is a history of psychiatric disorders. Another alternative could be presumptive anti-relapse therapy, by primaquine or tafenoquine, but such strategy is not authorized in France [44].

5. Conclusions

Malaria incidence is decreasing sharply among FSMs in FG. This is probably the result of a combination of several factors, including reduced exposure linked to a decrease in malaria among GMISs and the strengthening of prevention and treatment measures. For FSMs and travelers in malaria transmission areas in FG, residual *P. vivax* malaria poses the problem of chemoprophylaxis using doxycycline or atovaquone proguanil, which are ineffective against hypnozoites. Tafenoquine causal chemoprophylaxis could be a worthwhile alternative, with the advantages of requiring a single dose per week and preventing relapses, but it requires systematic screening for G6PD deficiency. Such screening is also necessary for radical treatment with primaquine. Implementing quantitative rapid G6PD tests could provide simple and quick access to treatment to prevent *P. vivax* relapses, and thus contribute to malaria control in FG. For civilian populations, screening and treatment of asymptomatic carriers in residual transmission hotspots could consolidate the observed decline in malaria incidence. Constant vigilance must also be maintained to detect the emergence of antimalarial drug resistance, as there are already signs of in vitro artemisinin resistance for *P. falciparum* and chloroquine resistance for *P. vivax* in this region [45,46]. Cooperation between all military, local, and cross-border health actors is essential to achieve malaria elimination in FG.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Disclaimer

The views expressed are solely those of the authors and do not reflect the official policy or position of the French Armed Forces Health Service.

CRediT authorship contribution statement

Guillaume Velut: Data curation, Data collection, Formal analysis, Writing – original draft, and, review final version. **Franck de Laval:** Data curation, Writing – original draft, additional expertise and review final version. **François Delon:** Data curation, Writing – review & editing, additional expertise and review final version. **Albane d'Oléon:** Data curation, and, review final version. **Maylis Douine:** Writing – review & editing, additional expertise, and, review final version. **Emilie Mosnier:** Writing – review & editing, additional expertise, and, review final version. **Bakridine Mmadi Mrenda:** Formal analysis, and, review final version. **Aissata Dia:** Data curation, and, review final version. **Lise Musset:** Writing – review & editing, additional expertise, and, review final version. **Sébastien Briolant:** Writing – original draft, additional expertise, and, review final version. **Vincent Pommier de Santi:** Supervision, Writing – original draft, Data curation, and, review final version.

Declaration of competing interest

The authors declare that they have no competing interests.

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