Changes in malaria epidemiology in France and worldwide, 2000–2015

M. Thellier, F. Simard, Lise Musset, M. Cot, G. Velut, E. Kendjo, Bruno Pradines

Changes in malaria epidemiology in France and worldwide, 2000–2015

M. Thellier, F. Simard, Lise Musset, M. Cot, G. Velut, E. Kendjo, Bruno Pradines

Changes in malaria epidemiology in France and worldwide, 2000–2015

Évolution épidémiologique du paludisme au niveau mondial et national, 2000–2015

M. Thellier [a,b,c], F. Simard [d], L. Musset [e,f], M. Cot [g], G. Velut [h,i], E. Kendjo [a,b,c], B. Pradines [j,k,l,m,*]

[a] *Service de parasitologie-mycologie, Centre national de référence du paludisme, hôpital Pitié-Salpêtrière, Assistance publique Hôpitaux de Paris, 47, boulevard de l'Hôpital, 75013 Paris, France*

[b] *UMRS 1136, iPLESP, institut Pierre-Louis d'épidémiologie et de santé publique, Sorbonne université, 27, rue Chaligny, 75571 Paris 12, France*

[c] *UPMC, faculté de médecine, Sorbonne université, université Pierre-et-Marie-Curie, 91, boulevard de l'Hôpital, 75013 Paris, France*

[d] *MIVEGEC, IRD-CNRS-university Montpellier, 911, avenue Agropolis, BP 64501, 34394 Montpellier, France*

[e] *Laboratoire de parasitologie, Centre collaborateur OMS pour la surveillance des résistances aux antipaludiques, institut Pasteur de la Guyane, 23, avenue Louis Pasteur, 97300 Cayenne, France*

[f] *Centre national de référence du paludisme, institut Pasteur de la Guyane, 23, avenue Louis Pasteur, 97300 Cayenne, France*

[g] *UMR2016, unité Mère et enfant face aux infections tropicales, institut de recherche pour le développement, 4, avenue de l'Observatoire, 75006 Paris, France*

[h] *Centre d'épidémiologie et de santé publique des armées, GSBdD Marseille Aubagne, BP 40026, 13568 Marseille cedex 02, France*

[i] *Direction interarmées du service de santé des armées, Quartier La Madeleine, 97306 Cayenne, France*

[j] *Unité parasitologie et entomologie, institut de recherche biomédicale des armées, institut hospitalo-universitaire Méditerranée Infection, 19-21, boulevard Jean-Moulin, 13005 Marseille, France*

[k] *Aix Marseille université, IRD, AP–HM, SSA, VITROME, institut hospitalo-universitaire Méditerranée Infection, 19-21, boulevard Jean-Moulin, 13005 Marseille, France*

[l] *Institut hospitalo-universitaire Méditerranée Infection, 19-21, boulevard Jean-Moulin, 13005 Marseille, France*

[m] *Centre national de référence du paludisme, institut hospitalo-universitaire Méditerranée Infection, 19-21, boulevard Jean-Moulin, 13005 Marseille, France*

Keywords:
Malaria
Plasmodium falciparum
Plasmodium vivax
Travelers

A B S T R A C T

In 2015, 212 million new cases of malaria were reported, causing 429,000 deaths. The World Health Organization (WHO) estimated a 41% decrease in the number of new cases worldwide between 2000 and 2015. The number of deaths from malaria fell by 62% worldwide and by 71% in Africa. In mainland France, malaria is mainly imported by travelers or migrants from endemic areas, in particular sub-Saharan Africa (95%). In France, the number of imported malaria cases, mainly due to *Plasmodium falciparum* (85%), was estimated at about 82,000 for the period 2000–2015. Over the same period, 6,468 cases of malaria were reported in the French armed forces, of which 2,430 cases (37.6%) were considered as imported because occurring outside of endemic areas. The number of malaria cases also fell between 2000 and 2015 in Mayotte and French Guiana, a malaria transmission zone. Mayotte has entered the elimination of malaria with less than 15 cases per year. In French Guiana, between 300 and 500 cases have been reported annually in recent years. The decline in morbidity and mortality is usually attributed to vector control measures and improved access to effective treatments. However, the *Anopheles* mosquitoes that transmit the disease have developed resistance against most insecticides. Similarly, malaria parasites have developed resistance against most of the antimalarial drugs used as prevention or treatment, even the latest marketed combinations such as artemisinin-based combination therapies.

* Corresponding author. Unité parasitologie et entomologie, institut de recherche biomédicale des armées, institut hospitalo-universitaire Méditerranée Infection, 19-21, boulevard Jean-Moulin, 13005 Marseille, France.
E-mail address: bruno.pradines@gmail.com (B. Pradines).

RÉSUMÉ

Mots clés :
Paludisme
Plasmodium falciparum
Plasmodium vivax
Voyageurs

En 2015, 212 millions de nouveaux cas de paludisme étaient répertoriés, causant 429 000 morts. L'Organisation mondiale de la santé (OMS) estimait la réduction de nouveaux cas entre 2000 et 2015 à 41 % pour l'ensemble du monde. Les décès dus au paludisme chutaient parallèlement de 62 % dans le monde et de 71 % en Afrique. Le paludisme est essentiellement importé par des voyageurs ou migrants en provenance de zones endémiques, essentiellement d'Afrique subsaharienne (95 %) pour la France métropolitaine. Ce nombre de cas de paludisme d'importation, majoritairement dû à *Plasmodium falciparum* (85 %), a été estimé à environ 82 000 pour la période 2000–2015. Pour la même période, 6468 cas de paludisme ont été déclarés dans les armées, dont 2430 (37,6 %) importés hors zone d'endémie. Le nombre de cas de paludisme a aussi chuté entre 2000 et 2015 à Mayotte et en Guyane, zone de transmission du paludisme. Mayotte est en phase d'élimination (< 15 cas par an). En Guyane, le nombre de cas déclarés se situent entre 300 et 500 cas par an ces dernières années. La baisse de morbidité et de mortalité est attribuée à la lutte antivectorielle et à l'accès généralisé à des traitements efficaces. Mais les anophèles, insectes vecteurs de la maladie développent des résistances contre la plupart des insecticides. Les parasites du paludisme développent aussi des résistances contre la plupart des antipaludiques utilisés en prévention ou traitement, même aux dernières associations commercialisées comme les combinaisons thérapeutiques à base d'artémisinine.

1. Trends in the global incidence of malaria since 2000

Reliable global epidemiological surveillance for malaria has only recently been implemented. In 1998, in the wake of the launch of the "Roll Back Malaria" program, the World Health Organization (WHO) and UNICEF joined forces to produce a statistical summary for the African continent [1], followed by the first World Malaria Report in 2005 based on the cases and deaths reported by 107 malaria-endemic countries. At present, these reports are the most comprehensive single source of information available on malaria. Each yearly report provides figures for nearly all areas worldwide where there is a risk of contracting malaria, estimates of global morbidity and mortality for all reporting countries, and information on the coverage of key interventions to prevent malaria in tropical Africa.

Based on data from disparate sources, the WHO estimated at the beginning of 2000 that 3.2 billion people worldwide were at risk of contracting malaria and that the previous year had seen 350 million new cases of malaria with 839,000 deaths, mainly children under the age of 5 years in sub-Saharan Africa.

In 2015, malaria was still endemic in 91 countries, of which 43 countries in sub-Saharan Africa, and 212 million new cases and 429,000 deaths were reported. Moreover, 90% of cases of malaria and 92% of deaths occurred in sub-Saharan Africa [2]. At the global level, more than 90% of deaths were due to *Plasmodium falciparum* (99% in Africa) and 7.2% of deaths were due to *Plasmodium vivax.*

From 2000 to 2015, 57 countries achieved a 75% decrease in the number of cases of malaria, whereas in 18 other countries the incidence fell by 50% to 75%. The WHO estimated that over this period the global decline in new cases of infection was 41%. At the same time, malaria-related deaths decreased by 61% globally and by 71% in Africa. Finally, a growing number of countries made remarkable progress towards the goal of malaria elimination with 33 countries reporting less than 1000 cases in 2015 compared with only 13 in 2000 [3]. To address these objectives, malaria funding increased from 960 million USD invested in 2000 to 2.9 billion USD in 2015.

Nevertheless, these impressive figures should be interpreted with caution bearing in mind the reservations on the completeness of the data collected at the beginning of the period. The WHO's procedure for estimating the number of cases and deaths was also rectified during this period, in particular at the time of the 2011 World Malaria Report [4] and lastly, the estimated incidences reported by the WHO's network of surveillance organizations (that collect data for 10–14% of cases worldwide) are inadequately documented to provide reliable trends for key countries in sub-Saharan Africa. Of particular concern, it seems that the WHO's estimations probably largely underestimate the number of malaria cases and related deaths in subjects over the age of 5 [5].

However, it is reasonable to consider that globally the numbers and the main trends described do not significantly depart from reality. Other studies using mathematical models but limited to African countries (in particular an international work group coordinated by Oxford university) reported results that were overall in line with the WHO's statistics [6,7].

The Global Technical Strategy for Malaria 2016–2030 approved by the World Health Assembly in May 2015 [8] defines the goal for 2030: a 90% decrease of the incidence rate of malaria and the related death rate, elimination of malaria in at least 35 countries with transmission in 2015, and the prevention of malaria re-establishment in countries free of the disease in 2015. However, the geographical distribution of malaria shows much disparity with 13 African countries accounting for the great majority of the global malaria burden with 80% of cases and 75% of reported deaths.

The decrease observed in the morbidity and mortality rates is generally imputed to vector control measures (insecticide-treated mosquito nets and indoors spraying of insecticides), improved malaria diagnosis using rapid diagnostic tests (RDTs), generalized access to effective antimalarial drugs (artemisinin-based combination therapy, ACT), and the efficacy of intermittent preventive treatment in pregnancy (IPTp).

In many of the countries affected, mostly in Africa, social unrest, conflicts, and humanitarian disasters are major obstacles to reaching the goals. Prevention measures are also particularly difficult to implement in cross-border areas [9] and it is often in these areas that resistance to antimalarials and insecticides first appear. The control of insect vectors is losing ground. In sub-Saharan Africa 278 million people out of a total at-risk population of 840 million live in households without any mosquito nets. In 2015, less than 50% of pregnant women took a dose of IPTp, and less than 25% took the minimum of two doses recommended by the WHO. Finally, despite considerable funding obtained for malaria control in 2015, the WHO believes that a substantial additional effort will be required to achieve the Millennium Development Goals for 2030. Annual funding will need to be increased to 6.2 billion USD by 2020, which seems difficult to attain in the current international setting.

A new malaria species that normally infects monkeys, *Plasmodium knowlesi*, has emerged in humans and is causing an increasing number of cases in South-East Asia. *P. knowlesi* is now the main species that causes malaria in humans in Malaysia [10,11]. Cases have also been reported in Indonesia, Thailand, Vietnam, and

Myanmar, as well as some cases of imported malaria out of endemic areas [2,12]. This species can cause severe malaria and death.

2. Incidence of imported malaria in mainland France from 2000 to 2015

Malaria is no longer endemic in many developed countries and was eliminated from most Western European countries between the 1930s and 1960s. However, the disease continues to represent a challenge in terms of prevention, diagnosis, and patient management. Malaria is imported both by travellers and migrants from endemic areas, as well as by visitors from endemic areas and armed forces personnel returning home after overseas operations. In mainland France, the developed country that reports the greatest number of cases of imported malaria, the disease is for the most part imported from sub-Saharan African countries (95% of cases) [13,14]. Imported malaria surveillance in mainland France relies on a network of about a hundred hospitals that report cases to the National Reference Center for Malaria (French acronym CNR). Member hospitals collect data for about 52% of cases of malaria that occur in mainland France (approximately 43,000 cases reported since 2000). The number of cases of imported malaria has thus been estimated at 82,000 for the period 2000–2015 [14], and shows varying, complex trends. A very significant decrease in the number of cases (−55%) was first observed between 2000 (8060 estimated cases/year) and 2011 (3600 estimated cases/year), followed by a substantial increase of more than 30% between 2012 (3600 estimated cases/year) and 2016 (4700 estimated cases/year) (Fig. 1). This recent increase seems inconsistent with the 41%–decrease in the number of cases of malaria estimated by the WHO for endemic areas since 2000 (−12% in Africa) which has further accelerated between 2012 and 2016 [2]. However, at the same time, the number of people traveling between France and endemic areas has risen (Fig. 1). The increase is of 49% for sub-Saharan Africa, and 32%, 35%, and 113% respectively for Western Africa, Eastern Africa (including Indian Ocean islands), and Southern Africa (CNR data based on figures from the French Civil Aviation Authority) [15]. A clear decrease in the incidence rate is still observed over the whole period for mainland France: 78% less cases of imported malaria with a considerable diminution between 2000 and 2007 followed by a stable rate afterwards (Fig. 2). By way of comparison, the global malaria incidence rate in endemic countries decreased steadily by 41% over the same period [2]. Many factors probably played a role in the trends observed, especially changes in the populations contracting malaria (origin, type), changes in behavior towards preventive medication, travel trends with different destinations, lengths of stay and repeated stays, and local trends in the malaria epidemic (incidence, geographical distribution, epidemic profile, resistance of isolates to antimalarials). In the great majority of the cases (95%), the patients contracted the disease in sub-Saharan Africa and this distribution is stable over the study period (mainly Ivory Coast, Cameroon, Mali, and Senegal). The patients were mainly of African origin, either French residents or newly arrived from Africa, with a marked increase between 2000 (63%) and 2015 (79%) (Fig. 3). Most cases were caused by *Plasmodium falciparum* (85%), followed by *Plasmodium ovale* (7%), *P. vivax* (5%), and lastly *P. malariae*. Two cases of malaria due to *Plasmodium knowlesi* were also reported, both successfully treated with chloroquine. Monthly case diagnosis distribution for all *Plasmodium* species revealed that diagnoses peaked between July and October, with a second peak of lesser intensity in January. This distribution reflects the periods when tourists return home after school holidays. In 90% of the cases, symptom onset occurred within two months after returning from the endemic area. A higher proportion of non-*falciparum* cases were observed during the months of lesser activity from February to March and from October to December. This is due to the longer incubation period for these species and, above all, to the ability to cause relapses due to the activation of hypnozoites in *P. vivax* and *P. ovale* malaria. At regular intervals, cases of airport malaria or "accidental" transmission (blood transfusion-induced malaria, posttransplant malaria) were reported [16,17]. On a more exceptional basis, cases of indigenous malaria were observed in France and in Italy, but also and of greater concern, in Greece [18,19]. The mosquito vectors are therefore still present.

The clinical course of imported malaria is sometimes dramatic. Patients who contract this curable disease still die in some cases today even if they are diagnosed rapidly and receive appropriate treatment. From 2008 to 2011, the case fatality rate for *Plasmodium falciparum* malaria was 5.5 per 1000) in the United States [20]. The figures are very similar in the main European Union countries (except for Italy, insufficient data), where 21,247 cases of *Plasmodium falciparum* malaria were reported between 2008 and 2012, and associated with 111 deaths, i.e. a case fatality rate of 5.2 per thousand [21]. In mainland France, the case fatality rate was 0.4% (mostly adults) and was stable over the whole period [14]. However, severe *P. falciparum* malaria is becoming increasingly frequent, both in proportion and absolute numbers, from 2.13% (84 cases) in 2000 to 12.4% (295 cases) in 2015 (Fig. 4). This is in contrast with the significant reduction in the case fatality rate for patients presenting with severe malaria which fell from 12% to 2%. Treatment with intravenous artesunate was introduced in 2011 and is now the most frequently prescribed treatment (75% of cases) for severe malaria [14]. There are several likely explanations for these two contrasting trends, observed even though no changes were made to the criteria used to define severe malaria over this period. A first plausible explanation is a change in the population presenting with imported malaria in France with a higher proportion of subjects of African origin who have been shown to have a lower mortality rate for severe malaria than subjects of Caucasian origin [22,23]. Another explanation, or a factor that adds to the previous explanation, is that the distribution of the criteria for severe malaria has shifted with time towards criteria of lesser severity (for example, the negative prognostic value of liver involvement with elevated serum bilirubin is less than that of respiratory distress or coma). A third explanation could be the improved management of severe cases, either because they are diagnosed faster or because treatment is more effective, in particular with the gradual replacement of intravenous quinine by intravenous artesunate. These points need to be further documented.

3. Incidence of imported malaria in overseas France

In the French Caribbean islands, imported malaria is relatively stable since 2000 with 10 to 15 cases per year in Martinique and the same number in Guadeloupe [24]. These cases are mostly imported from Central and West Africa (42%), French Guiana (32%), and Haiti (23%). Due to the presence of insect vectors in this region of the Caribbean, such cases must be reported to the health authorities to rapidly implement an entomo-epidemiological survey and vector control measures around the patients. The aim of such measures being to prevent new cases resulting from indigenous transmission. *P. falciparum* is the main species identified (74%), followed by *P. vivax* (17%). Cases of imported malaria are also reported in La Réunion. Between 2000 and 2009, 1319 cases of malaria were observed in travelers having spent time in Comoros or Mayotte [24]. The number of cases of imported malaria has fallen significantly over recent years (40 cases in 2013, 19 in 2014, and 26 in 2015) in La Reunion, as is the case in New Caledonia where about 20 cases are reported per year in travelers arriving from Vanuatu.

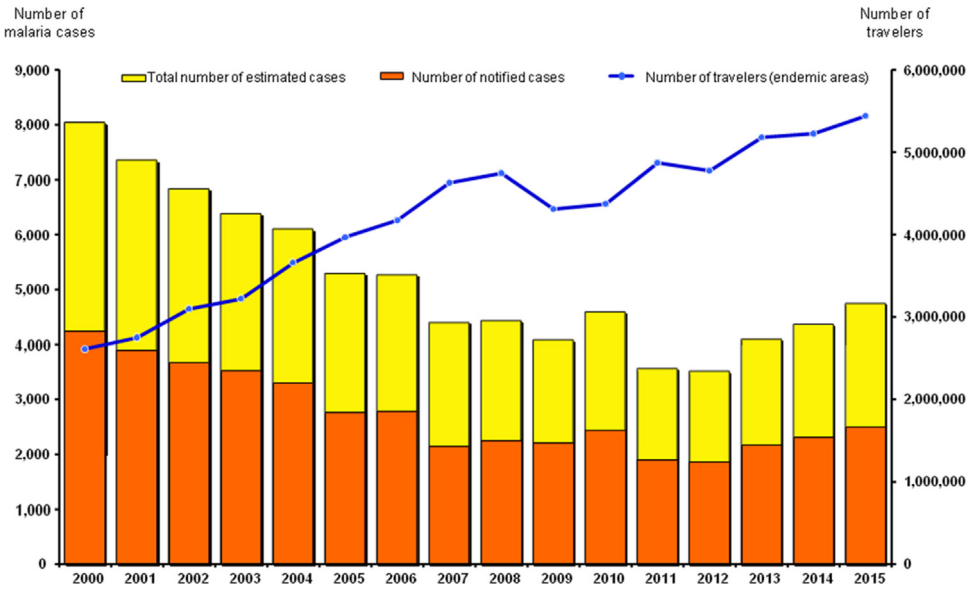

Fig. 1. Number of cases of imported malaria reported (orange) and estimated (yellow) and number of individuals traveling to malaria-endemic areas (blue line) between 2000 and 2015 in mainland France.
Nombre de cas de paludisme d'importation déclarés (orange) et estimés (jaune) avec le nombre de voyageurs vers les zones d'endémie pour le paludisme (courbe bleue) pour la période 2000–2015 en France métropolitaine.
French National Reference Center for malaria, October 2017.

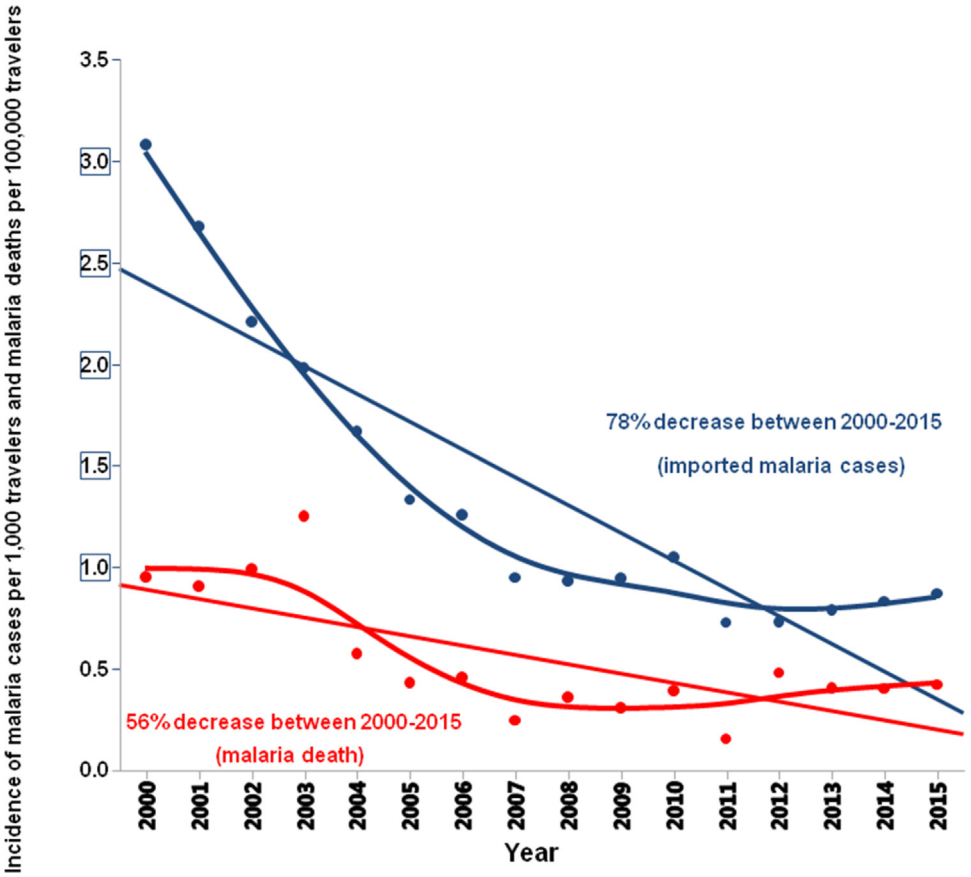

Fig. 2. Malaria incidence rate (cases per 1000 travelers) and death rate (cases per 100,000 travelers) between 2000 and 2015 in mainland France.
Évolution du taux d'incidence (cas pour 1000 voyageurs) et du taux de mortalité (cas pour 100 000 voyageurs) liés au paludisme pour la période 2000–2015 en France métropolitaine.
French National Reference Center for malaria, October 2017.

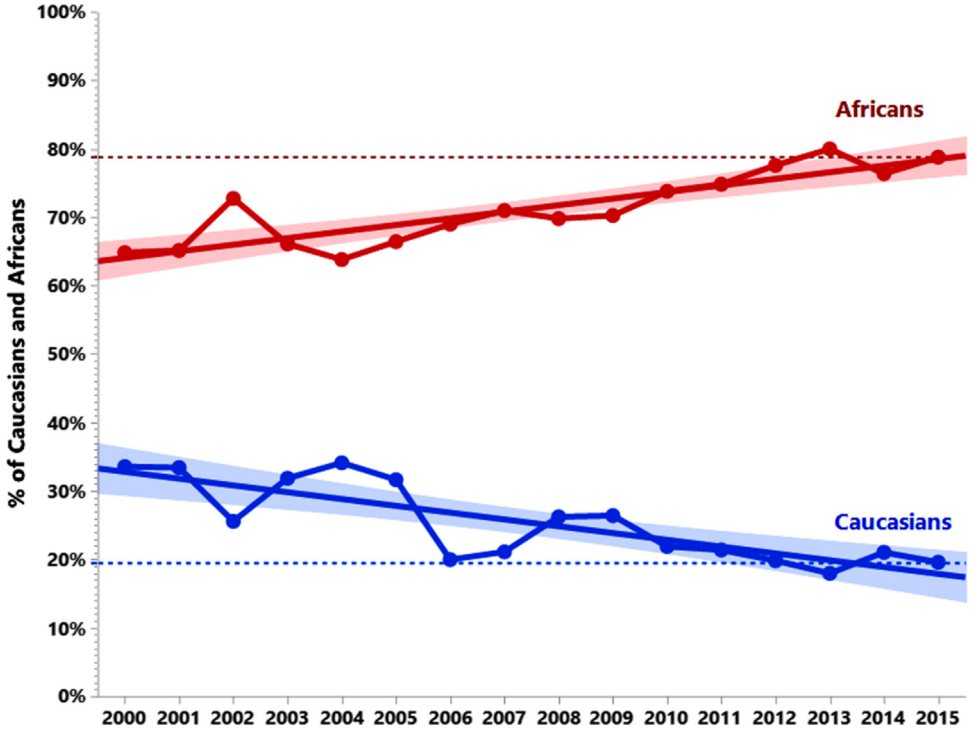

Fig. 3. Distribution of imported malaria cases in Caucasian (blue line) and African (red line) patients between 2000 and 2015 in mainland France.
Évolution de la proportion des cas de paludisme d'importation, pour la population d'origine caucasienne (courbe bleue) et la population d'origine africaine (courbe rouge), pour la période 2000–2015 en France métropolitaine.
French National Reference Center for malaria, October 2017.

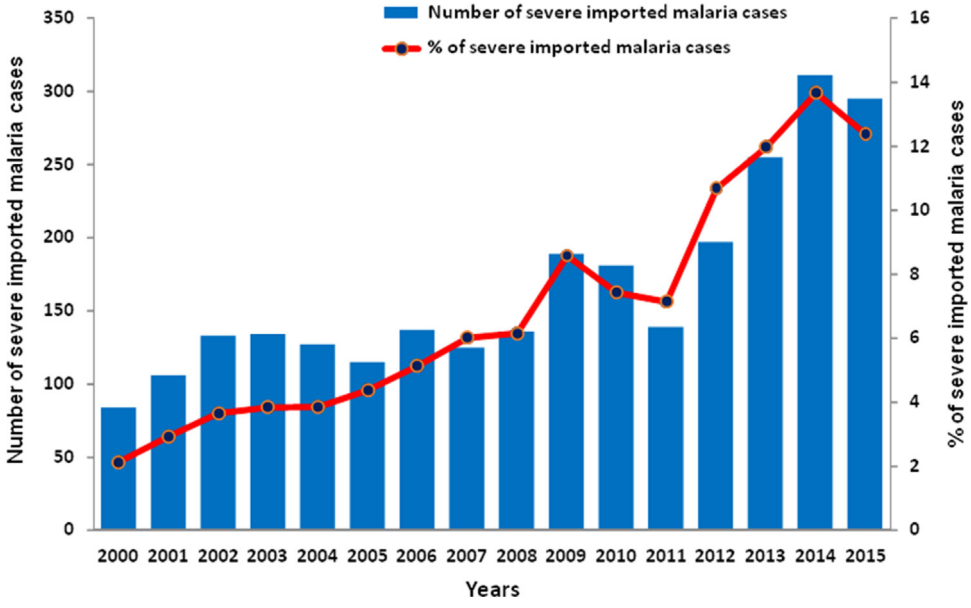

Fig. 4. Number (blue rectangles) and proportion (red line) of patients presenting with severe imported malaria between 2000 and 2015 in mainland France.
Évolution des cas graves de paludisme d'importation, en valeur (rectangles bleus) et en proportion (courbe rouge), pour la période 2000–2015 en France métropolitaine.
French National Reference Center for malaria, October 2017.

4. French overseas territories with endemic malaria: the situations in Mayotte and French Guiana

Mayotte and French Guiana are French overseas territories where malaria can be contracted.

Geographically-speaking part of the Comoros islands, Mayotte became an overseas department of France (101st department) in 2011. Faced with a regular increase in malaria-related morbidity and mortality, the health authorities reinforced in 2001 the measures taken to control the disease. Indoor residual deltamethrin spraying was initiated in 2001 at the same time as the use of rapid diagnostic tests (RDTs) to actively screen patients presenting with fever. In 2007 artemether-lumefantrine was included in new treatment protocols [25]. Finally in 2010, the authorities conducted a

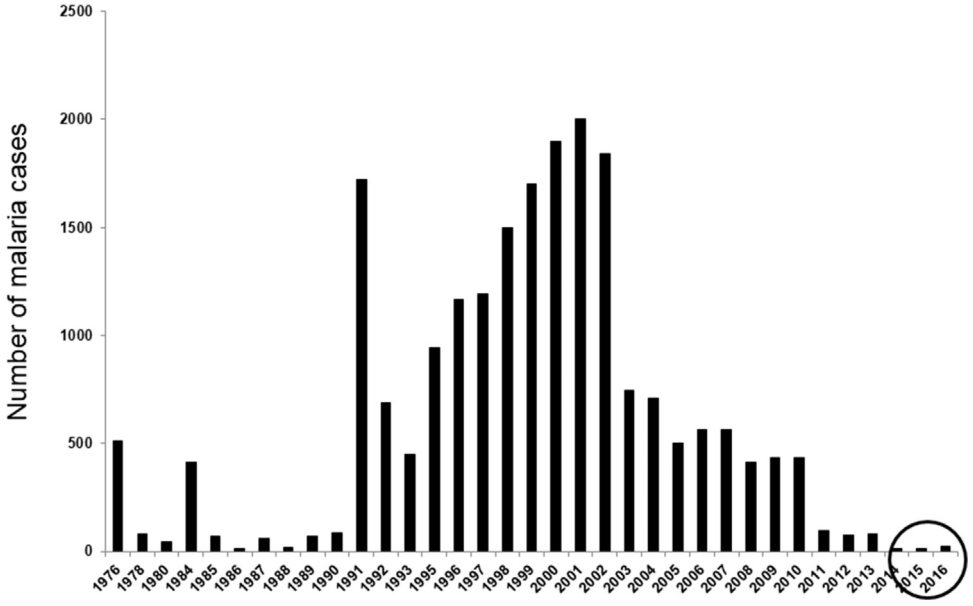

Fig. 5. Number of malaria cases in Mayotte from 1976 to 2016.
Évolution du paludisme à Mayotte de 1976 à 2016.

Table 1
Number of malaria cases reported, both indigenous and imported, in Mayotte from 2006 to 2016.
Nombre de cas de paludisme déclarés, autochtones et importés, à Mayotte de 2006 à 2016.

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Reported	565	562	411	399	433	97	74	80	15	14	22
Indigenous	348	294	195	88	160	42	25	2	1	1	11
Imported	88	136	155	268	236	50	47	70	13	13	8
Unknown origin	129	132	61	43	37	5	2	8	1	0	3

campaign of mass distribution of long-lasting insecticidal mosquito nets (LLINs). All these measures have significantly reduced the number of cases of malaria in Mayotte, from more than 500 cases in 2006–2007 to less than 25 cases per year since 2014 (Fig. 5) [26]. In addition, the number of cases of imported malaria that increased from 2006 to 2009 started to decrease after 2010 reaching less than 15 cases in 2014 (Table 1). After a first decline in 2011, malaria transmission has shown a marked decrease since 2013 with less than 5 cases per year. Since 2011, Mayotte is considered to have entered the elimination phase of malaria. Nevertheless, 11 cases of indigenous malaria were reported in Mayotte in 2016. This demonstrates the difficulty of completely eliminating indigenous malaria when many people travel to and from malaria endemic countries, even on an island where substantial prevention and vector control measures are implemented.

French Guiana is part of France since 1604. This European territory located on the Guiana Shield, a massive formation of Precambrian rock that is covered with tropical rainforest and has exceptionally abundant mineral resources such as gold and bauxite. French Guiana has a population of about 250,000 inhabitants who nearly all live along the Atlantic coast. Eighty per cent of the territory is covered by tropical rainforest and the road network is limited to the coastal area so some inland communities can only be reached by plane or boat.

At the beginning of the 1950s, malaria was widespread in all regions of French Guiana despite there being little data on the level of endemicity. Anti-malarial measures combining indoor residual spraying of dwellings and widespread prescription of 4-aminoquinolines, in particular the distribution of salts of amodiaquine from 1967 to 1978, were successful and eliminated malaria transmission in coastal regions [27,28]. Inland and along the rivers, varying levels of endemicity remain depending on both the disease-control measures taken and population changes. An important increase in the number of cases was reported in the 1980s [29], with sometimes more than 5000 cases per year and an incidence rate ranging from 360 to 485 cases per 1000 inhabitants. During the 1990s, French Guiana was one of the three countries in America with the highest number of malaria cases, mostly due to *P. falciparum*. At that time, the two main regions of malaria outbreak were the border areas along the Maroni River to the West (Suriname) and the Oyapock River to the East [30]. *P. vivax* is the most common *Plasmodium* species since 2005 (70% of cases in 2015) and the annual number of cases has been on the decline with only 258 cases reported in 2016 (Fig. 6) [31,32]. Imported malaria is extremely limited in French Guiana with only one or two cases every year from Haiti or Africa (data from the Endemic area service of the CNR). However, even if the number of cases reported is useful to monitor trends, the figures are underestimated because a certain number of individuals are not diagnosed and managed by the French health care system. Many of the infected people working in the rainforest mines practice self-medication or cross the border for diagnosis out of fear of prosecution by the French authorities [33,34].

At present it should be considered that there are two distinct patterns of malaria transmission in French Guiana (Fig. 7): on the one hand a high and probably stable transmission rate in the gold-mining regions in the center of the country and, on the other hand, seasonal outbreaks of "indigenous" malaria in some villages in the region around Saint-Georges and along the upper reaches of the Maroni River. The most recent study conducted in the gold-mining region between January and June 2015 included 421 gold-miners, mostly men (70.6%) and mostly Brazilian (93.8%) [35]. The average prevalence of *Plasmodium* parasite carriage determined by PCR

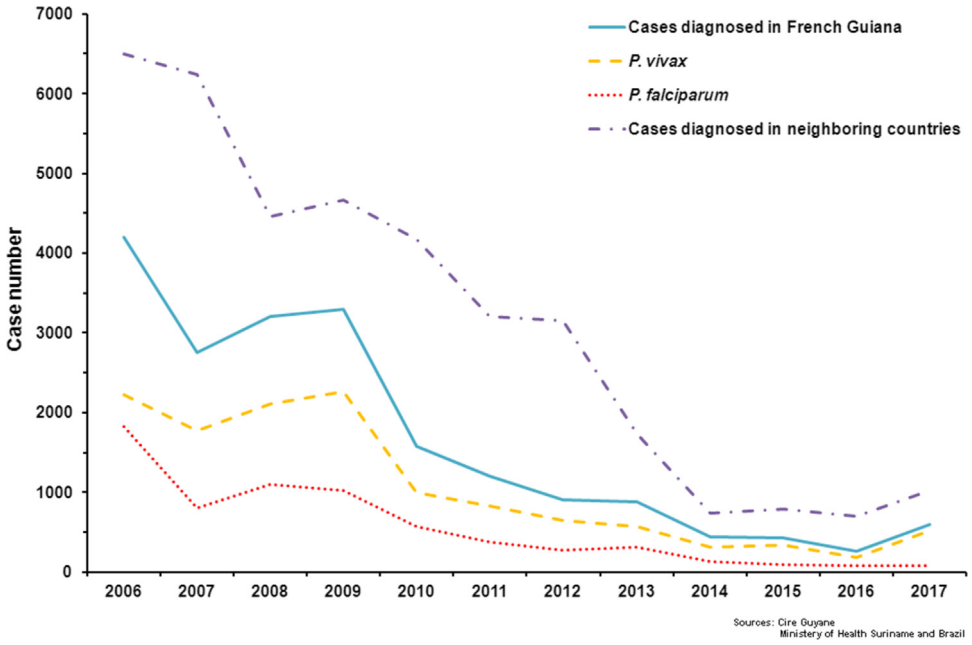

Fig. 6. Number of cases of malaria confirmed by laboratory testing in French Guiana or diagnosed in Brazil and Suriname between 2006 and 2017.
Évolution du nombre de cas de paludisme biologiquement confirmés recensés en Guyane ou diagnostiqués au Brésil et au Suriname entre 2006 et 2017. French Guiana Interregional Epidemiology Cell (CIRE Guyane).

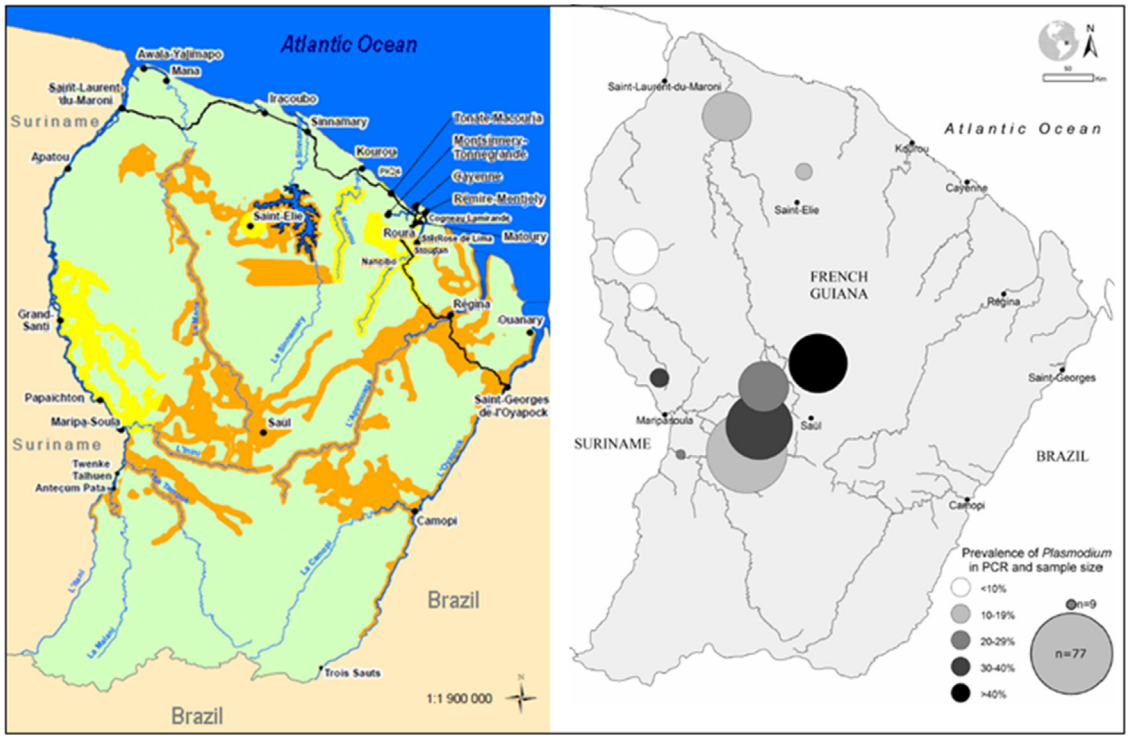

Fig. 7. Left: risk of malaria infection in French Guiana; yellow – low; orange – high. (Source: Regional Health Agency for French Guiana, 2017). Right: contrasted distribution of asymptomatic carriers of *Plasmodium* spp. as determined by PCR in illegal gold-mining regions of French Guiana, 2015. (Source: Douine et al., 2017 [35]).
Carte de gauche : risque de paludisme en Guyane – En jaune : risque faible et en orange : risque fort (Source : ARS de Guyane 2017). Carte de droite: hétérogénéité de la prévalence du portage de Plasmodium *spp. déterminée par PCR sur les sites d'orpaillage illégale en Guyane, 2015 (Source : Douine et al., 2017 [35]).*

was 22.3% (95% CI: 18.3–26.3) with 84% of asymptomatic carriers. Species identified were mainly *P. falciparum* (47.9%) followed by *P. vivax* (37.2%), with 10.6% of mixed *P. falciparum/vivax* infections. These results confirm clinical observations and previous studies that demonstrated that the main malaria transmission area in the gold-mining region is found in the localities of Maripasoula and Saül [33]. Furthermore, this transmission causes frequent outbreaks in the armed forces that fight illegal gold mining and in the villages where gold miners reside, even temporarily [36–39]. This alarming situation is however quite contrasted, and some gold mining areas are only marginally (3–5% of cases) or not at all affected by malaria (Fig. 7). Apart from the transmission in gold mining regions,

sporadic, seasonal outbreaks of indigenous malaria are observed today in the Oyapock region of French Guiana in some neighborhoods of the localities of Saint-Georges and Maripasoula. In these localities, 3–4% of the inhabitants are asymptomatic carriers, mostly infected with *P. vivax* [40]. In these regions, malaria also affects children [32].

ACT was only introduced in French Guiana in 2007 even though recommended for use in this region since 2002. Malaria control strategies are difficult to implement in this region for several reasons: French regulations still prohibit the use of single doses of primaquine to eliminate circulating gametocytes, patient management is delayed by the requirement to obtain individual temporary use authorization before using primaquine to kill hypnozoites during indigenous malaria outbreaks, health centers lack the diagnostic capacity required to diagnose G6PD deficiency and finally, malaria transmission in gold mining areas occurs in illegal immigrants living in remote regions that are not readily accessible. Taken together, these conditions facilitate continuing malaria transmission. *P. vivax* is most common along the rivers and its continued transmission relies on the relapses it causes, and *P. falciparum* is predominant in the rainforest and is an effective indicator of delayed diagnosis and patient management. Nonetheless, no malaria-related deaths have been reported since 2014. In 2013, three deaths were reported in gold miners who sought medical care at a very late stage and had other significant comorbidities. Each year 8–14% of the patients diagnosed with malaria are admitted to hospital.

5. Particular case of armed forces personnel

Although globally on the decline throughout the world, malaria is still a particular issue for the French armed forces. This can be explained by the frequent involvement of French armed forces in operations in endemic areas where the local situation increases the risk of contracting the disease: crisis situations, displaced populations, illegal immigrants, and disorganized health services. In such settings, soldiers are exposed to a high risk of malaria, as was the case during operations in the Ivory Coast [41] and the Central African Republic, or during gold mine monitoring operations in French Guiana [38]. During such operations, the lack of compliance with preventive measures can lead to significant outbreaks [41–45]. Exposure was shown to be maximum during the initial phases of an operation, crisis situations during the course of an operation, troop rotations, and when back to mainland France [41].

From January 2000 to December 2015, 6468 cases of malaria were reported in the French armed forces, of which 2430 (37.6%) were imported and occurred outside of endemic areas. Fig. 8 shows the trends for the incidence and incidence rate over this period. The peak incidence rates observed in 2003–2004, 2008–2009, and 2014 respectively reflect the beginning of the *Opération Licorne* in the Ivory Coast, *Opération Harpie* in French Guiana (against illegal gold mining), and the beginning of the *Opération Sangaris* in the Central African Republic. The main region of malaria infection was Central and Western Africa with 60.8% of reported cases, followed by French Guiana with 33.5% of cases, and the Sahel-Saharan strip with 4% of cases. Troops infected in Africa presented with *P. falciparum* (predominant species), *P. ovale,* and *P. malariae* infections (Fig. 9), whereas *P. vivax* malaria was most common in French Guiana.

Severe *P. falciparum* malaria accounted for 2.1% of cases and occurred more frequently after returning to mainland than in the endemic areas (2.8% vs. 1.7%; $P = 0.003$). Eight deaths were reported, five of which occurred between 2011 and 2015. In one of these cases, failure of prophylaxis was confirmed: the phenotype and genotype of the isolated *P. falciparum* strain revealed reduced susceptibility to doxycycline [46].

Doxycycline is the most frequently used antimalarial prophylactic drug since 2003 (92.5%). A lack of compliance with malaria prophylaxis was demonstrated in 53.2% of cases, more frequently after returning to France than in the endemic country (61.5% vs. 49.5%, $P < 10^{-4}$). The most frequently prescribed treatment for uncomplicated *P. falciparum* malaria was quinine from 2000 to 2009, atovaquone-proguanil from 2010 to 2014, and dihydroartemisinin-piperaquine since 2015. In 2015, out of the 181 cases of uncomplicated *P. falciparum* malaria, 54.7% were treated with dihydroartemisinin-piperaquine, 28.2% with atovaquone-proguanil, 9.4% with quinine, 8.8% with artemether-lumefantrine, and 1.7% with mefloquine. Patients with severe *P. falciparum* malaria were most often prescribed intravenous quinine up to 2014, and then artesunate from 2015 on.

The impact of malaria on the operations of the French armed forces can be considerable, temporarily saturating evacuation capabilities and medical facilities [47,48] with a median period of unavailability of 7 days (extreme values: 0–90 days) adding up to more than 41,000 days of soldiers' unavailability from 2010 to 2015.

6. Trends in resistance to antimalarial drugs

The first-line treatment of non-vomiting patients presenting with uncomplicated *P. falciparum* malaria is artemisinin-based combination therapy (ACT): artemether-lumefantrine and dihydroartemisinin-piperaquine (available since 2013). A third combination is also available: atovaquone-proguanil. For severe *P. falciparum* malaria, a study conducted in 2005 demonstrated that intravenous artesunate was simpler to administer, acted faster, and decreased the mortality rate more efficiently than intravenous quinine in adults [49]. Intravenous artesunate is now the first-line treatment recommended for severe malaria.

Quinine, with a loading dose, is still recommended for severe malaria if artesunate is not available, while waiting for artesunate to become available, and to treat patients who contracted the disease in an area of known resistance to artemisinin (combination of artesunate, quinine, and doxycycline). The administration of quinine does not prevent the use of artesunate a few hours later.

Resistance to artemisinin and its derivatives first emerged in South-East Asia in 2007 [50,51] on the border between Thailand and Cambodia. It spread to the whole of Cambodia and Thailand in 2011, and then to Laos in 2014. Another form of resistance with a different genetic profile was reported in Myanmar in 2014. According to the WHO, artemisinin resistance is characterized by an increased parasite clearance time (PCT) during treatment (resistance if PCT > 5 hours) and/or persisting parasites on the third day of treatment, whereas resistance to the other molecule used in ACT is assessed by monitoring therapeutic efficacy in the patient for 28 days for lumefantrine or 42 days for piperaquine. Resistance to artemisinin alone does not result in ACT failure. To qualify a region as a suspected area of artemisinin resistance, at least 10% of treated subjects must display an increased parasite clearance time or persisting parasites on day 3 of treatment. Moreover to document resistance to ACT, resistance to both artemisinin and its partner molecule, either piperaquine or lumefantrine, must be demonstrated. In Cambodia, parasites have developed resistance even to the most recent ACTs marketed such as dihydroartemisinin-piperaquine [52–54]. In this country, the number of new cases increased from 15.4% between 2011 and 2013 to 39% between 2012 and 2014 in the period of frequent treatment with dihydroartemisinin-piperaquine, with a PCT > 5 hours for 84% of treated patients and persisting parasites on day 3 of treatment in 57% of patients. Resistance to the combination dihydroartemisinin-piperaquine was also confirmed in Vietnam in 2015 with a treatment failure rate of 35% [55]. In South

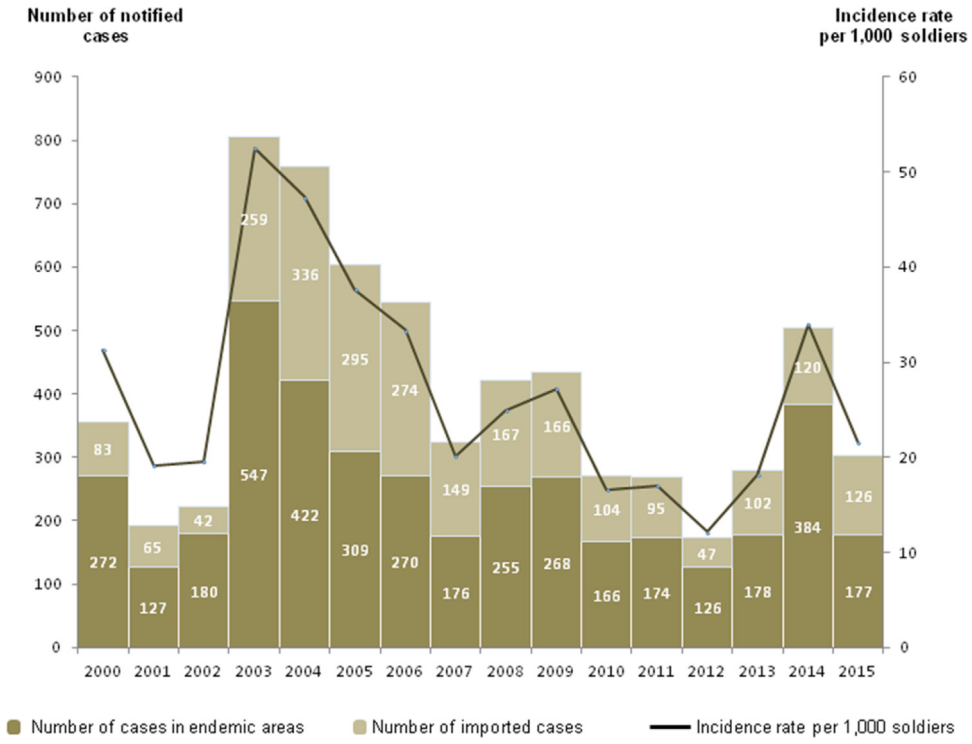

Fig. 8. Malaria in endemic areas and imported malaria: incidence rate per 1000 person-years reported by the French armed forces. Period: 2000–2015.
Incidence et taux d'incidence pour 1000 personnes années (PA) du paludisme déclaré par fiche spécifique dans les armées. Période : 2000–2015.
Epidemiology and Public Health Center of the French armed forces [CESPA], October 2017.

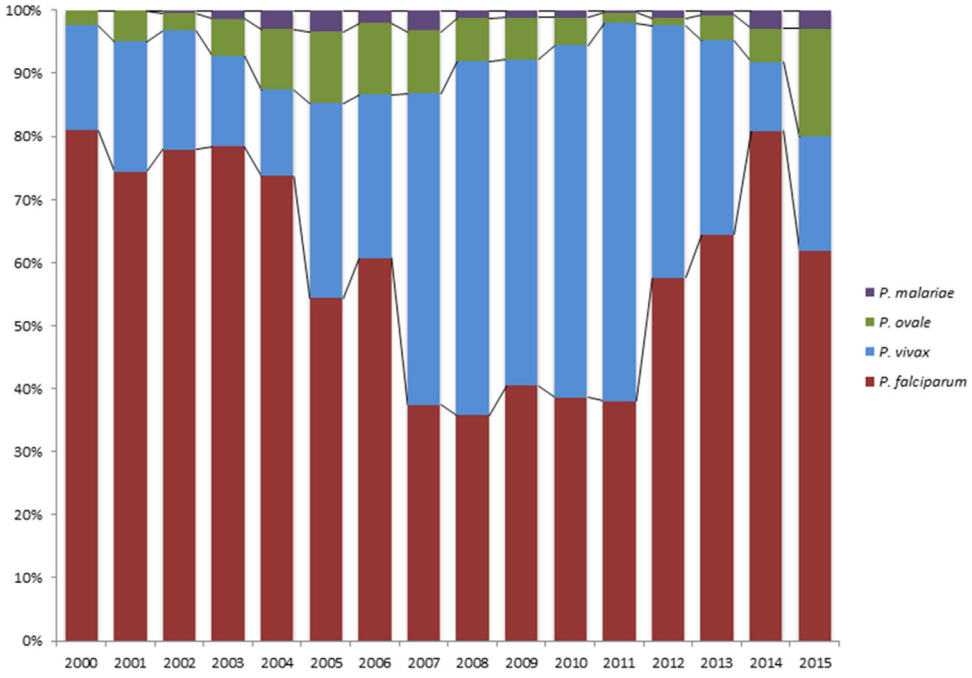

Fig. 9. *Plasmodium* species diagnosed in the French armed forces. Period 2000–2015.
Évolution de la répartition des espèces plasmodiales diagnostiquées dans les armées. Période 2000–2015.
Epidemiology and Public Health Center of the French armed forces (CESPA), October 2017.

Vietnam, the proportion of patients with detectable parasitemia on day 3 of treatment with dihydroartemisinin-piperaquine increased from 38% to 57% between 2011 and 2015 [56]. Over the same period, the parasite clearance half-life lengthened significantly from 3.75 hours to 6.60 hours [56]. The resistance to artemisinin derivatives observed in South-East Asia is associated with parasite phenotypes that are found to exhibit in vitro resistance [57,58] and the presence of certain mutations of the *pfk13* gene that encodes the *Plasmodium* Kelch protein, such as the C580Y mutation [51,59]. The presence of more than 5% of *Plasmodium* strains containing the

C580Y mutation is sufficient to classify a region as a suspected area of resistance to artemisinin and its derivatives. A region in which more than 5% of treated patients are infected with parasites carrying the C580Y mutation and where all patients display an increased parasite clearance time or persisting parasites on day 3 of treatment is considered a region of confirmed resistance to artemisinin and its derivatives. Since the *pfk13* gene has been identified as linked to resistance to artemisinin and its derivatives, more than a hundred point mutations have been described worldwide for this gene. As of yet very few have been validated by homologous recombination [60].

Resistance to artemisinin has not yet spread to Africa even if therapeutic failures are reported at regular intervals, for example in a traveler returning from Ethiopia 32 days after treatment with dihydroartemisinin-piperaquine [61]. Treatment with artemether-lumefantrine remains efficient in the African countries in which most patients treated for imported malaria in mainland France contract the disease. The current efficacy rates are 98–100% for Mali [62,63], 92–100% for the Central African Republic [64,65], 66–98% for the Republic of Congo [66,67], and 98–100% for Senegal [68,69]. No resistance mutations of the *pfk13* gene, especially the C580Y mutation, have been detected in Africa [70–73], including Senegal [74,75], Mali [76], and Mayotte [77]. New mutations of the *pfk13* gene have however been identified in African parasites but do not seem to be associated with artemisinin derivative resistance [70,78–81]. The cases of therapeutic failure following treatment with artesunate or ACT observed in Africa or in cases of imported malaria from Africa are all associated with the presence of wild-type parasites that do not harbor mutations on the *pfk13* gene [82–84].

The situation in the Guiana Shield region of South America is quite different because the *pfk13* C580Y mutation was identified in isolates collected in French Guiana in 2010 [85]. In addition, the results of studies conducted in 2013 on the efficacy of artemisinin treatment in Suriname demonstrated that some patients exhibited positive parasitemia on day 3 [86]. Although these results still need to be confirmed, as does the involvement of the *pfk13* gene in artemisinin resistance in parasites of South American genetic background, this situation is reminiscent of the emergence of chloroquine and sulfadoxine-pyrimethamine resistance in the past with resistant parasites developing independently and practically simultaneously in the same regions, South-East Asia and Amazonia [87]. In French Guiana, the *pfk13* gene was sequenced in 541 isolates between 2009 and 2016 and led to the identification of a single mutation, M671I, in only one isolate (data from the Endemic area service of the CNR). Data from in vitro survival assays did not show any cause for alarm.

Besides resistance to artemisinin and its derivatives, resistance to the partner drugs to artemisinin should also be monitored for, in particular lumefantrine and piperaquine which are used in France. Two genes that respectively encode Plasmepsin II and an exonuclease may be predictive of piperaquine resistance in Cambodia although this has not been confirmed in other endemic countries [88,89]. An absence of mutation at codon 86 (N86) associated with a mutation at codon 184 (184F) of the *P. falciparum* multidrug resistance 1 (*pfmdr1*) gene that encodes an efflux pump are predictive of therapeutic failure with artemether-lumefantrine in Africa [90,91], especially in Burkina Faso [92,93] and Senegal [94]. An absence of mutation at codon 86 of the *pfmdr1* gene was also reported after therapeutic failure in patients treated with artemether-lumefantrine or artesunate-mefloquine in Eastern Africa [95–97] whereas the mutant form (86Y) was observed after failure of treatment with the combination dihydroartemisinin-piperaquine in Uganda [98,99]. In French Guiana, all sequenced parasites exhibited the same *pfmdr1* gene sequence which was therefore not predictive of resistance [100]. The parasites from isolates from this region all remained sensitive to lumefantrine in vitro (data from the Endemic area service of the CNR).

The first-line treatment of non-vomiting patients presenting with uncomplicated *P. vivax* malaria is based on chloroquine. *P. vivax* resistance to chloroquine (CQ) first appeared in Papua New Guinea in 1989, 32 years after the first case of *P. falciparum* resistance [101]. Since then it has spread to neighboring countries endemic for *P. vivax* infections: with cases reported as early as 1991 in the Indonesian island of Nias, 1993 in Myanmar, and 1995 in Bombay in India. In South America, the first cases of suspected resistance to CQ were described in Colombia (1989) and then in Brazil (1992) (Fig. 10). However, plasma levels did not confirm that these therapeutic failures were caused by parasite resistance to CQ [103]. Since then cases of documented resistance have been reported in isolates collected in French Guiana and Brazil [104,105]. In the Amazonian region, the chloroquine resistance rate ranges from 1.1% to 10.1% in the Manaus area ($n = 11/109$) after supervised treatment with CQ alone and 5.2% ($n = 7/135$) after concomitant treatment with CQ and primaquine (PQ) [106,107]. More recently in the Oiapoque region on the border between Brazil and French Guiana, therapeutic failure due to parasite resistance was reported in 95 patients who received supervised treatment with CQ and PQ, i.e. a resistance rate of 1.1% [108]. The therapeutic efficacy of CQ for the treatment of uncomplicated *P. vivax* mono-infections between 2009 and 2015 in French Guiana was estimated at 95% (95% CI: 91.7–98.3; $n = 164/172$) (data from the Endemic area service of the CNR). Most cases of failure were associated with the use of subclinical concentrations of chloroquine ($n = 5/8$). It may therefore be considered that *P. vivax* chloroquine resistance is found in French Guiana, but at the very low rate of 1.2% (95% CI: 0–2.8; $n = 2/172$). There is no need to update the recommended treatment guidelines for uncomplicated *P. vivax* malaria with such a low level of resistance. To prevent the spread of CQ resistance, primaquine should be prescribed to all carriers of *P. vivax* as quickly and as often as possible. In consequence, it seems important to assess the use of rapid diagnostic tests for G6PD deficiency or systematic screening for G6PD deficiency in all individuals who live in regions of malaria transmission.

7. Status and trends for malaria vectors

Only about sixty species of mosquitoes out of the more than 3500 species currently identified worldwide, all of which belong to the *Anopheles* genus, can transmit the *Plasmodium* parasites that cause malaria in humans. Less than 10 of these species are responsible for more than 99% of malaria transmission worldwide. *Anopheles* mosquitoes are not invasive insects and each continent has its own particular species [109].

In mainland France, where malaria was endemic until the beginning of the 20th century in the marshy areas of the Landes, Dombes, Brittany, Alsace, Corsica, and in the Rhone delta, 13 *Anopheles* species have been described. Among these species, *An. atroparvus* (mainland France) and *An. labranchiae* (Corsica) were considered to be the main vectors of the disease. A recent study conducted in the Camargue (Rhone delta) region demonstrated that *A. hyrcanus*, which is found in large numbers in the rice fields and is an aggressive human biter, could still harbor and transmit *Plasmodium* parasites [110]. *An. plumbeus*, that lays its eggs in water-filled tree-holes, was incriminated in two cases of indigenous malaria in Germany [111]. Although based on the presence of these species in France and Europe, there is potential for the resurgence of malaria transmission in certain areas, the risk is currently believed to be negligible [112].

In Africa, where malaria mortality is highest, the *An. gambiae* and *An. funestus* complex are the main vectors. In the wet savanna

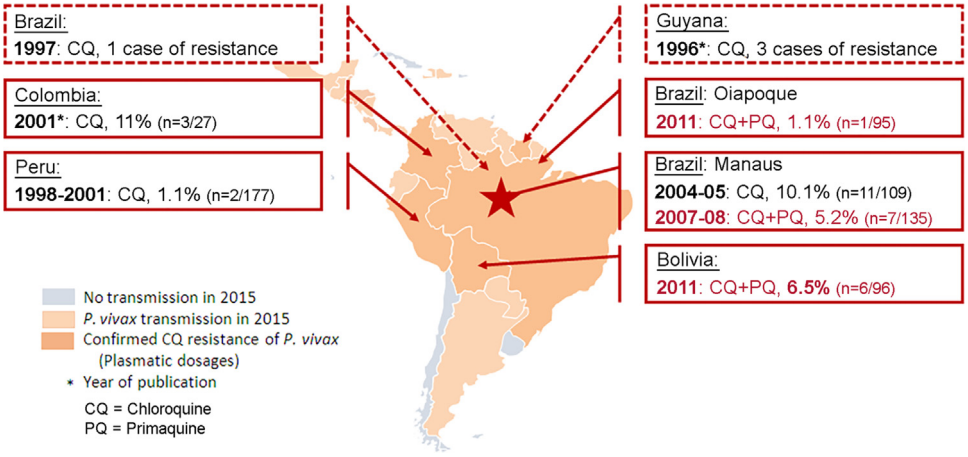

Fig. 10. Areas of *P. vivax* resistance to chloroquine in South America, 1999–2015 (according to Price et al., 2014 [102]).
Les différents foyers de résistance à la chloroquine de P. vivax *en Amérique du Sud, 1999–2015 (d'après Price et al., 2014 [102]).*

grasslands and the forests of Central Africa, other species such as *An. nili* and *An. moucheti* are also involved in the transmission of malaria and can locally be the predominant species when their population density is high [113]. They preferentially bite humans rather than animals, at night, and follow people inside buildings and homes. Although originally considered to be found only in rural areas, some species are now colonizing the outskirts of large African cities, and can even be found in the center of towns, in polluted environments into which they had not yet ventured [114].

In South America and in particular French Guiana, the main malaria vector is *An. darlingi*. The species is widespread throughout the continent and very much prefers to feed on humans. It is a natural host for *P. falciparum*, *P. vivax,* and *P. malariae* [115]. Other species have however been shown to contribute to malaria transmission, especially in gold-mining regions, such as *An. intermedius*, *An. oswaldoi*, *An. nuneztovari,* and *An. marajoara* [116,117].

Recent progress in fighting malaria, in terms of the significant decrease in the number of cases of severe malaria, has been largely attributed to enhanced vector control in many countries, in particular the large-scale distribution of long-lasting insecticidal mosquito nets (LLINs), sometimes associated with indoor residual spraying (IRS) of insecticides. It has been estimated that the use of LLINs alone prevented more than 450 million cases of malaria from 2000 to 2015 [6]. These gains are impressive, but remain fragile. The widespread use in human health, farming, and market gardening of an ever-smaller number of insecticide molecules has resulted in the emergence of vector resistance [118]. Parasite resistance is today a major issue and impacts most of the countries with the highest malaria burden. According to the WHO [2], out of the 73 malaria endemic countries that reported surveillance data on vector resistance to insecticides between 2010 and 2015, 60 countries detected resistance to at least one class of insecticides, and 50 to at least two classes. This is currently the case for pyrethroids, the only insecticides approved for LLINs [119]. The consequences of the loss of efficacy of LLINs, a major tool in the fight against malaria, would be disastrous and it is urgent that resistance management strategies be implemented [120]. Nevertheless, the operational impact of resistance to pyrethroids on the efficacy of LLINs is yet to be demonstrated. Various organochlorine, carbamate, or organophosphorus compounds could also be used for IRS. But again, resistance has been reported and some vector populations have developed multiple insecticide resistance, as observed in Cameroon [121] and Burkina Faso [122].

Various mechanisms of resistance to insecticides have been described. The best known and documented mechanisms involve point mutations in the genes that encode the protein targets of the insecticides. For example, the knockdown resistance (kdr) mutations of the voltage-gated sodium channel gene result in resistance to DDT (organochlorine pesticide) and pyrethroids [119], and the Ace1R mutations of the acetylcholinesterase gene in resistance to carbamates and organophosphorus compounds. Gene duplication has also been reported, especially in Benin and Burkina Faso [123]. Another mechanism of resistance to insecticides is to enhance the activity of detoxifying enzymes that directly metabolize the insecticide molecule, accelerate its elimination or inhibit the toxic activity of some of its metabolites. Several classes of enzymes are involved in such enhanced detoxifying mechanisms, including P450 cytochrome oxidases, esterases, and glutathione-S-transferases [124]. The upregulation of the expression of these enzymes can be due to gene duplication or enhanced gene transcription [125]. However the enzymes are rarely selective and generally display a broad spectrum of activity. The insecticide resistance mechanisms acquired generation after generation by mosquitoes might therefore allow them to better tolerate other toxic molecules, such as urban pollutants, and help mosquitoes adapt to these new man-made environments [126,127].

In addition to genetic and metabolic resistance to insecticides, reports of changes in vector behavior are more and more common. Such changes include shifts in the peak biting activity from the middle of the night to dawn and dust when people are less likely to be protected by mosquito nets [128]. In the same way, the high selection pressure due to the massive use of insecticides indoors (LLINs and IRS) favor the development of exophilic species (that live and bite outdoors) that are not in contact with LLINs. None of the currently used vector control measures target the "residual transmission" of malaria parasites that takes place outdoors. Hence, the conditions of malaria transmission in Africa are changing. From a disease transmitted in rural areas by mosquitoes biting preferentially indoors during the night, malaria is today transmitted by mosquitoes resistant to insecticides, that are colonizing urban areas and have changed their biting times and places. New tools and integrated vector control strategies must now be developed, assessed, and implemented to address these new issues of resistance to insecticides and control of residual transmission [129].

8. Conclusion

Over the last 15 years, the rate of new malaria infections and the malaria death rate have significantly declined around the world. This trend is confirmed in French Guiana and Mayotte. Imported malaria in mainland France, however, has increased over the last 5 years. *Plasmodium* species are developing resistance to most of

the antimalarial drugs used to prevent and treat malaria, even to the latest combination therapies marketed such as ACTs. Likewise, *Anopheles* mosquitoes, the insects that transmit the disease, are currently developing resistance to most insecticides. Continuous urgent effort is therefore required to reach the recently defined goals of malaria control and elimination. To fight the disease more effectively, the guidelines for the prevention and treatment of malaria should be updated, when necessary, and surveillance of the different epidemiological features and resistance patterns implemented to develop relevant strategies that include innovative initiatives taking into account the specific characteristics of each geographical area.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgments

The authors would like to thank all the partners of the French National Reference Center for Malaria (*CNR Paludisme*) involved in monitoring malaria in mainland France and French overseas territories. A considerable portion of the data discussed would not exist without their involvement. The authors are also grateful to *Santé publique France* for its long-term financial support via the French National Reference Center for Malaria.

References

[1] WHO UNICEF. The Africa malaria report 2003. Geneva: World Health Organization; 2003.
[2] WHO. World Malaria Report 2016. Geneva: World Health Organization; 2016 [cited 2019 May 17]. (Available from: http://www.who.int/entity/malaria/publications/world-malaria-report-2016/report/en/index.html).
[3] Cibulskis RE, Alonso P, Aponte J, Aregawi M, Barrette A, Bergeron L, et al. Malaria global progress 2000–2015 and future challenges. Infect Dis Poverty 2016;5:61.
[4] WHO. World Malaria Report 2011. Geneva: World Health Organization; 2011 [cited 2019 May 17]. (Available from: http://www.who.int/malaria/world_malaria_report_2011/burdenestimatesbriefing2011.pdf).
[5] Murray CJ, Ortblad KF, Guinovart C, Lim SS, Wolock TM, Roberts DA, et al. Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014;384:1005–70.
[6] Bhatt S, Weiss DJ, Cameron E, Bisanzio D, Mappin B, Dalrymple U, et al. The effect of malaria control on Plasmodium falciparum in Africa between 2000 and 2015. Nature 2015;526:207–11.
[7] Gething PW, Casey DC, Weiss DJ, Bisanzio D, Bhatt S, Cameron E, et al. Mapping Plasmodium falciparum mortality in Africa between 1990 and 2015. N Engl J Med 2016;375:2435–45.
[8] WHO. Global Technical Strategy for Malaria 2016–2030. Geneva: World Health Organization; 2015 [cited 2019 May 17]. (http://apps.who.int/iris/bitstream/10665/176712/1/9789241564991_eng.pdf?ua=1&ua=1).
[9] Wangdi K, Gatton ML, Kelly GC, Clements AC. Cross-border malaria: a major obstacle for malaria elimination. Adv Parasitol 2015;89:79–107.
[10] William T, Rahman HA, Jelip J, Ibrahim MY, Menon J, Grigg MJ, et al. Increasing incidence of *Plasmodium knowlesi* malaria following control of *P. falciparum* and *P. vivax* malaria in Sabah, Malaysia. PLoS Negl Trop Dis 2013;7:e2026.
[11] Ysof R, Lau YL, Mahmud R, Fong MY, Jelip J, Ngian HU, et al. High proportion of knowlesi malaria cases in Malaysia. Malar J 2014;13:168.
[12] Daneshvar C, Williams T, Davis TM. Clinical features and management of *Plasmodium knowlesi* infections in humans. Parasitology 2017;26:1–14.
[13] Danis M, Mouchet M, Giacomini T, Guillet P, Legros F, Belkaid M. Paludisme autochtone et introduit en Europe. Med Mal Infect 1996;26(Suppl 3):393–6.
[14] Centre National de Référence du Paludisme CNRP. Rapport d'activités 2016 de l'année d'exercice 2015. Paris, France: Santé Publique France, SPF; 2016, 15 avril 2016.
[15] Direction Générale de l'Aviation Civile DGAC. Bulletin statistique du trafic aérien commercial pour l'année 2015. Paris, France. 2016. [cited 2019 May 17]. (Available from: https://www.ecologique-solidaire.gouv.fr/sites/default/files/Bulletin_Statistique_2015_20160831.pdf).
[16] Bruneel F, Thellier M, Eloy O, Mazier D, Boulard G, Danis M, et al. Transfusion-transmitted malaria. Intensive Care Med 2004;30:1851–2.
[17] Mejia GA, Alvarez CA, Pulido HH, Ramirez B, Cardozo C, Suarez Y, et al. Malaria in a liver transplant recipient: a case report. Transplant Proc 2006;3:3132–4.
[18] Danis K, Lenglet A, Tseroni M, Baka A, Tsiodras S, Bonovas S. Malaria in Greece: historical and current reflections on a re-emerging vector borne disease. Travel Med Infect Dis 2013;11:8–14.
[19] Armengaud A, Legros F, D'Ortenzio E, Quatresous I, Barre H, Houze S, et al. A case of autochthonous Plasmodium vivax malaria, Corsica, August 2006. Travel Med Infect Dis 2008;6:36–40.
[20] Cullen KA, Arguin PM. Centers for Disease Control Prevention. Malaria surveillance - United States, 2011. MMWR Surveill Summ 2013;62:1–17.
[21] World Health Organization WHO, Regional Office Europe CISID. Imported Malaria in Europe 2012–2014. Geneva, Centralized Information System for Infectious Diseases–World Health Organization, 2016. [cited 2017 Nov 26]. (Available from: http://data.euro.who.int/cisid/?TabID=417432).
[22] Danis M, Thellier M, Jauréguiberry S, Bricaire F, Buffet P. Le paludisme grave à *Plasmodium falciparum* en France, 2000–2011 : évolution épidémiologique et nécessité d'une nouvelle prise en charge thérapeutique. Bull Acad Natl Med 2013;197:699–714.
[23] Checkley AM, Smith A, Smith V, Blaze M, Bradley D, Chiodini PL, et al. Risk factors for mortality from imported falciparum malaria in the United Kingdom over 20 years: an observational study. BMJ 2012;344:e2116.
[24] Tarantola A, Eltges F, Ardillon V, Lernout T, Sissoko D, Kendjo E, et al. Malaria in France: mainland and territories. Med Mal Infect 2011;41:301–6.
[25] Toyb M, Ouledi A, Gauzère B-A, Anbry P. Le paludisme dans l'Archipel des Comores: état des lieux en 2015 après quinze années de lutte. Bull Soc Pathol Exot 2015;109:107–13.
[26] Maillard O, Lernout T, Olivier S, Achirafi A, Aubert L, et al. Major decrease in malaria transmission on Mayotte Island. Malar J 2015;14:323.
[27] Juminer B, Robin Y, Pajot FX, Eutrope R. Features of malaria in Guyana. Bull Soc Pathol Exot Filiales 1981;74:176–92.
[28] Lepelletier L, Gay F, Nadire-Galliot M, Poman JP, Bellony S, Claustre J, et al. Malaria in Guiana. I. General status of the endemic. Bull Soc Pathol Exot Filiales 1989;82:385–92.
[29] Mouchet J, Nadire-Galliot M, Gay F, Poman JP, Lepelletier L, Claustre J, et al. Malaria in Guiana. II. The characteristics of different foci and antimalarial control. Bull Soc Pathol Exot Filiales 1989;82:393–405.
[30] Carme B, Venturin C. Malaria in the Americas. Med Trop 1999;59:298–302.
[31] Carme B, Ardillon V, Girod R, Crenier C, Joubert M, Djoussou F, et al. Update on the epidemiologiy of malaria in French Guiana. Med Trop 2009;69:19–25.
[32] Musset L, Pelleau S, Girod R, Ardillon V, Carvalho L, Dusfour I, et al. Malaria on the Guiana Shield: a review of the situation in French Guiana. Mem Inst Oswaldo Cruz 2014;109:525–33.
[33] Pommier de Santi V, Djossou FC, Barthes N, Bogreau H, Hyvert G, Nguyen C, et al. Malaria hyperendemicity and risk for artemisinin resistance among illegal gold miners, French Guiana. Emerg Infect Dis 2016;22:903–6.
[34] Douine M, Lazrek Y, Blanchet D, Pelleau S, Chanlin R, Corlin F, et al. Predictors of antimalarial self-medication in illegal gold miners in French Guiana: a pathway towards artemisinin resistance. J Antimicrob Chemother 2017;73:231–9.
[35] Douine M, Musset L, Cortin F, Pelleau S, Pasquier J, Mutricy L, et al. Prevalence of *Plasmodium spp.* In illegal gold miners in French Guiana in 2015: a hidden but critical malaria reservoir. Malar J 2016;15:315.
[36] Verret C, Cabianca B, Haus-Cheymol R, Lafille JJ, Loran-Haranqui G, Spiegel A. Malaria outbreak in troops returning from French Guiana. Emerg Infect Dis 2006;12:1794–5.
[37] Queyriaux B, Texier G, Ollivier L, Galoisy-Guibal L, Michel R, Meynard JB, et al. Plasmodium vivax malaria among military personnel, French Guiana, 2010. Emerg Infect Dis 2011;17:1280–2.
[38] Pommier de Santi V, Dia A, Adde A, Hyvert G, Galant J, Mazevet M, et al. Malaria in French Guiana: reality of a situation closely linked to illegal gold mining. Emerg Infect Dis 2016;22:344–6.
[39] Berger F, Flamand C, Musset L, Djossou F, Rosine J, Sanquer MA, et al. Investigation of a sudden malaria outbreak in the isolated Amazonian village of Saul, French Guiana, January–April 2009. Am J Trop Med Hyg 2012;86:591–7.
[40] Mosnier E, Douine M, Epelboin L, Pelleau S, Pommier de Santi V, Dangel Y, et al. Asymptomatic *Plasmodium falciparum* and *vivax* infection in the neighborhood of Blondin, Saint-Georges-de-l'Oyapock District, French Guiana. Bull Soc Pathol Exot 2017;110:265–9.
[41] Migliani R, Ollivier L, Romand O, Verret C, Haus-Cheymol R, Todesco A, et al. Paludisme chez les militaires français en Côte-d'Ivoire de 1998 à 2006. Bull Epid Hebd 2008:209–12.
[42] Ollivier L, Michel R, Carlotti M-P, Mahé P, Romand O, Todesco A, et al. Chemoprophylaxis compliance in a French battalion after returning from malaria-endemic area. J Travel Med 2008;15:355–7.
[43] Resseguier N, Machault V, Ollivier L, Orlandi-Pradines E, Texier G, Pradines B, et al. Determinants of compliance with malaria chemoprophylaxis among French soldiers during missions in inter-tropical Africa. Malar J 2010;9:41.
[44] Sagui E, Resseguier N, Machault V, Ollivier L, Orlandi-Pradines E, Texier G, et al. Determinants of compliance with anti-vectorial protective measures among non-immune travellers during missions to tropical Africa. Malar J 2011;10:232.
[45] Créach M-A, Velut G, Laval F de, Briolant S, Aigle L, Marimoutou C, et al. Factors associated with malaria chemoprophylaxis compliance among French service members deployed in Central African Republic. Malar J 2016;15:174.
[46] Javelle E, Madamet M, Gaillard T, Velut G, Surcouf C, Michel R, et al. Delayed onset of *Plasmodium falciparum* malaria after doxycycline prophylaxis in a soldier returning from the Central African Republic. Antimicrob Agents Chemother 2016;60:2592–3.

[47] Sauvet F, Lebeau C, Foucher S, Flusain O, Jouanin JC, Debonne J-M. Operational impact of health problems observed during a four-month military deployment in Ivory Coast. Mil Med 2009;174:921–8.
[48] Rapp C, Aoun O, Ficko C, Andriamanantena D, Flateau C. Infectious diseases related aeromedical evacuation of French soldiers in a level 4 military treatment facility: a ten-year retrospective analysis. Travel Med Infect Dis 2014;12:355–9.
[49] Dondorp A, Nosten F, Stepniewska K, Day N, White N. South East Asian quinine artesunate malaria trial (SEAQUAMAT) group. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. Lancet 2005;366:717–25.
[50] Dondorp AM, Nosten F, Yi P, Das D, Phyo AP, Tarning J, et al. Artemisinin resistance in *Plasmodium falciparum* malaria. N Engl J Med 2009;361:455–67.
[51] Ashley EA, Dhorda M, Fairhurst RM, Amaratunga C, Lim P, Suon S, et al. Spread of artemisinin resistance in *Plasmodium falciparum* malaria. N Engl J Med 2014;371:411–23.
[52] Leang R, Taylor WRJ, Bouth DM, Song L, Tarning J, Char MC, et al. Evidence of *Plasmodium falciparum* malaria multidrug resistance to artemisinin and piperaquine in Western Cambodia: dihydroartemisinin-piperaquine open-label multicenter clinical assessment. Antimicrob Agents Chemother 2015;59:4719–26.
[53] Spring MD, Lin JT, Manning JE, Vanachayangkul P, Somethy S, Bun R, et al. Dihydroartemisinin-piperaquine failure associated with a triple mutant including kelch13 C580Y in Cambodia: an observational cohort study. Lancet Infect Dis 2015;15:683–91.
[54] Amaratunga C, Lim P, Suon S, Sreng S, Mao S, Sopha C, et al. Dihydroartemisinin-piperaquine resistance in *Plasmodium falciparum* malaria in Cambodia: a multisite prospective cohort study. Lancet Infect Dis 2016;16:357–65.
[55] Phuc BQ, Rasmussen C, Duong TT, Dong LT, Loi MA, Menard D, et al. Treatment failure of dihydroartemisinin/piperaquine for *Plasmodium falciparum* malaria, Vietnam. Emerg Infect Dis 2017;23:715–7.
[56] Thanh NV, Thuy-Nhien N, Tuyen NT, Tong NT, Nha-Ca NT, Dong LT, et al. Rapid decline in the susceptibility of *Plasmodium falciparum* to dihydroartemisinin-piperaquine in the south of Vietnam. Malar J 2017;16:27.
[57] Witkowski B, Amaratunga C, Khim N, Sreng S, Chim P, Kim S, et al. Novel phenotypic assays for the detection of artemisinin-resistant *Plasmodium falciparum* malaria in Cambodia: in-vitro and ex-vivo drug-response studies. Lancet Infect Dis 2013;13:1043–9.
[58] Amaratunga C, Witkowski B, Khim N, Menard D, Fairhurst RM. Artemisinin resistance in *Plasmodium falciparum*. Lancet Infect Dis 2014;14:449–50.
[59] Ariey F, Witkowski B, Amaratunga C, Beghain J, Langlois A-C, Khim N, et al. A molecular marker of artemisinin-resistant *Plasmodium falciparum* malaria. Nature 2014;505:50–5.
[60] Straimer J, Gnadig NF, Witkowski B, Amaratunga C, Duru V, Ramadani AP, et al. Drug resistance K13-propeller mutations confer artemisinin resistance in *Plasmodium falciparum* clinical isolates. Science 2015;347:428–31.
[61] Gobbi F, Buonfrate D, Menegon M, Lunardi G, Angheben A, Severini C, et al. Failure of dihydroartemisinin-piperaquine treatment of uncomplicated *Plasmodium falciparum* malaria in a traveller coming from Ethiopia. Malar J 2016;15:525.
[62] Denoeud-Ndam L, Dicko A, Baudin E, Guindo O, Grandesso F, Diawara H, et al. Efficacy of artemether-lumefantrine in relation to drug exposure in children with and without severe acute malnutrition: an open comparative intervention study in Mali and Niger. BMC Med 2016;14:167.
[63] Niaré K, Dara A, Sagara I, Sissoko MS, Guindo CO, Cissé NH, et al. In vivo efficacy and parasite clearance of artesunate + sulfadoxine-pyrimethamine versus artemether-lumefantrine in Mali. Am J Trop Med Hyg 2016;94:634–9.
[64] Djallé D, Njuimo SP, Manirakiza A, Laganier R, Le Faou A, Rogier C. Efficacy and safety of artemether + lumefantrine, artesunate + sulphamethoxypyrazine-pyrimethamine and artesunate + amodiaquine and sulphadoxine-pyrimethamine + amodiaquine in the treatment of uncomplicated *falciparum* malaria in Bangui, Central African Republic: a randomized trial. Malar J 2014;13:9.
[65] Nambei WS, Lango Yaya E, Pounguinza S, Achonduh O, Bogon A, Lengande R, et al. Efficacy and safety of antimalarial combinations for treatment of uncomplicated malaria in children in Bangui, Central African Republic. Med Sante Trop 2013;23:313–9.
[66] Singana BP, Bogreau H, Matondo BD, Dossou-Yovo LR, Casimiro PN, Mbouka R, et al. Malaria burden and anti-malarial drug efficacy in Owando, northern Congo. Malar J 2016;15:16.
[67] Ndounga M, Pembe Issamou M, Casimiro PN, Koukouikila-Koussounda F, Bitemo M, Diassivy Matondo B, et al. Artesunate-amodiaquine versus artemether-lumefantrine for the treatment of acute uncomplicated malaria in Congolese children under 10 years old living in a suburban area: a randomized study. Malar J 2015;14:423.
[68] Sylla K, Abiola A, Tine RCK, Faye B, Sow D, Ndiaye JL, et al. Monitoring the efficacy and safety of three artemisinin based-combinations therapies in Senegal: results from two years surveillance. BMC Infect Dis 2013;13:598.
[69] Dieye B, Affara M, Sangare L, Joof F, Ndiaye YD, Gomis JF, et al. West Africa international centers of excellence for malaria research: drug resistance patterns to artemether-lumefantrine in Senegal, Mali, and the Gambia. Am J Trop Med Hyg 2016;95:1054–60.
[70] Ménard D, Khim N, Beghain J, Adegnika AA, Shafiul-Alam M, Amodu O, et al. A worldwide map of *Plasmodium falciparum* K13-propeller polymorphisms. N Engl J Med 2016;374:2453–64.
[71] Taylor SM, Parobek CM, DeConti DK, Kayentao K, Coulibaly SO, Greenwood BM, et al. Absence of putative artemisinin resistance mutations among *Plasmodium falciparum* in Sub-Saharan Africa: a molecular epidemiologic study. J Infect Dis 2015;211:680–8.
[72] Cooper RA, Conrad MD, Watson QD, Huezo SJ, Ninsiima H, Tumwebaze P, et al. Lack of artemisinin resistance in *Plasmodium falciparum* in Uganda based on parasitological and molecular assays. Antimicrob Agents Chemother 2015;59:5061–4.
[73] Ocan M, Bwanga F, Okeng A, Katabazi F, Kigozi E, Kyobe S, et al. Prevalence of K13-propeller gene polymorphisms among *Plasmodium falciparum* parasites isolated from adult symptomatic patients in northern Uganda. BMC Infect Dis 2016;16:428.
[74] Torrentino-Madamet M, Fall B, Benoit N, Camara C, Amalvict R, Fall M, et al. Limited polymorphisms in K13 gene in *Plasmodium falciparum* isolates from Dakar, Senegal in 2012–2013. Malar J 2014;13:472.
[75] Boussaroque A, Fall B, Madamet M, Camara C, Benoit N, Fall M, et al. Emergence of mutations in the K13 propeller gene of *Plasmodium falciparum* isolates from Dakar, Senegal, in 2013–2014. Antimicrob Agents Chemother 2015;60:624–7.
[76] Ouattara A, Kone A, Adams M, Fofana B, Maiga AW, Hampton S, et al. Polymorphisms in the K13-propeller gene in artemisinin-susceptible *Plasmodium falciparum* parasites from Bougoula-Hameau and Bandiagara, Mali. Am J Trop Med Hyg 2015;92:1202–6.
[77] Torrentino-Madamet M, Collet L, Lepère JF, Benoit N, Amalvict R, Ménard D, et al. K13-propeller polymorphisms in Plasmodium falciparum isolates from patients in Mayotte in 2013 and 2014. Antimicrob Agents Chemother 2015;59:7878–81.
[78] Kamau E, Campino S, Amenga-Etego L, Drury E, Ishengoma D, Johnson K, et al. K13-propeller polymorphisms in *Plasmodium falciparum* parasites from sub-Saharan Africa. J Infect Dis 2015;211:1352–5.
[79] Muwanguzi J, Henriques G, Sawa P, Bousema T, Sutherland CJ, Beshir KB. Lack of K13 mutations in *Plasmodium falciparum* persisting after artemisinin combination therapy treatment of Kenyan children. Malar J 2016;15:36.
[80] Hawkes M, Conroy AL, Opoka RO, Namasopo S, Zhong K, Liles WC, et al. Slow clearance of *Plasmodium falciparum* in severe pediatric malaria, Uganda, 2011–2013. Emerg Infect Dis 2015;21:1237–9.
[81] Dorkenoo AM, Yehadji D, Agbo YM, Layibo Y, Agbeko F, Adjeloh P, et al. Therapeutic efficacy trial of artemisinin-based combination therapy for the treatment of uncomplicated malaria and investigation of mutations in K13 propeller domain in Togo, 2012–2013. Malar J 2016;15:331.
[82] Plucinski MM, Dimbu PR, Macaia AP, Ferreira CM, Samutondo C, Quivinja J, et al. Efficacy of artemether-lumefantrine, artesunate-amodiaquine, and dihydroartemisinin-piperaquine for treatment of uncomplicated Plasmodium falciparum malaria in Angola, 2015. Malar J 2017;16:62.
[83] Sutherland CJ, Lansdell P, Sanders M, Muwanguzi J, van Schalkwyk DA, Kaur H, et al. *Pfk13*-independent treatment failure in four imported cases of *Plasmodium falciparum* malaria treated with artemether-lumefantrine in the United Kingdom. Antimicrob Agents Chemother 2017;61:e02382–2416.
[84] Madamet M, Kounta MB, Wade KA, Lo G, Diawara S, Fall M, et al. Absence of association between polymorphisms in the K13 gene and the presence of *Plasmodium falciparum* parasites at day 3 after treatment with artemisinin derivatives in Senegal. Int J Antimicrob Agents 2017;49:754–6.
[85] Chenet SM, Akinyi Okoth S, Huber CS, Chandrabose J, Lucchi NW, Talundzic E, et al. Independent emergence of the *Plasmodium falciparum* Kelch propeller domain mutant allele C580Y in Guyana. J Infect Dis 2016;213:1472–5.
[86] Vreden SG, Jitan JK, Bansie RD, Adhin MR. Evidence of an increased incidence of day 3 parasitaemia in Suriname: an indicator of the emerging resistance of *Plasmodium falciparum* to artemether. Mem Inst Oswaldo Cruz 2013;108:968–73.
[87] Packard RM. The origins of antimalarial-drug resistance. N Engl J Med 2014;371:397–9.
[88] Amato R, Lim P, Miotto O, Amaratunga C, Dek D, Pearson RD, et al. Genetic markers associated with dihydroartemisinin-piperaquine failure in *Plasmodium falciparum* malaria in Cambodia: a genotype-phenotype association study. Lancet Infect Dis 2017;17:164–73.
[89] Witkowski B, Duru V, Khim N, Ross LS, Saintpierre B, Beghain J, et al. A surrogate marker of piperaquine-resistant *Plasmodium falciparum* malaria: a phenotype-genotype association study. Lancet Infect Dis 2017;17:174–83.
[90] Venkatesan M, Gadalla NB, Stepniewska K, Dahal P, Nsanzabana C, Moriera C, et al. Polymorphisms in *Plasmodium falciparum* chloroquine resistance transporter and multidrug resistance 1 genes: parasite risk factors that affect treatment outcomes for *P. falciparum* malaria after artemether-lumefantrine and artesunate-amodiaquine. Am J Trop Med Hyg 2014;91:833–43.
[91] Otienoburu SD, Maïga-Ascofaré O, Schramm B, Jullien V, Jones JJ, Zolia YM, et al. Selection of *Plasmodium falciparum pfcrt* and *pfmdr1* polymorphisms after treatment with artesunate-amodiaquine fixed dose combination or artemether-lumefantrine in Liberia. Malar J 2016;15:452.
[92] Sondo P, Derra K, Diallo Nakanabo S, Tarnagda Z, Kazienga A, Zampa O, et al. Artesunate-amodiaquine and artemether-lumefantrine therapies and selection of *Pfcrt* and *Pfmdr1* alleles in Nanoro, Burkina Faso. PLoS One 2016;11:0151565.
[93] Baraka V, Tinto H, Valea I, Fitzhenry R, Delgado-Ratto C, Mbonye MK, et al. In vivo selection of *Plasmodium falciparum Pfcrt* and *Pfmdr1* variants by artemether-lumefantrine and dihydroartemisinin-piperaquine in Burkina Faso. Antimicrob Agents Chemother 2015;59:734–7.
[94] Mbaye A, Dieye B, Ndiaye YD, Bei AK, Muna A, Deme AB, et al. Selection of N86F184D1246 haplotype of Pfmdr1 gene by artemether–lumefantrine

drug pressure on Plasmodium falciparum populations in Senegal. Malar J 2016;15:433.
[95] Sisowath C, Stromberg J, Martensson A, Msellem M, Obondo C, Björkman A, et al. In vivo selection of *Plasmodium falciparum pfmdr1* 86 N coding alleles by artemether-lumefantrine (Coartem). J Infect Dis 2005;191:1014–7.
[96] Dokomajilar C, Nsobya SL, Greenhouse B, Rosenthal PJ, Dorsey G. Selection of *Plasmodium falciparum pfmdr1* alleles following therapy with artemether-lumefantrine in an area of Uganda where malaria is highly endemic. Antimicrob Agents Chemother 2006;50:1893–5.
[97] Price RN, Uhlemann AC, Brockman A, McGready R, Ashley E, Phaipun L, et al. Mefloquine resistance in *Plasmodium falciparum* and increased *pfmdr1* gene copy number. Lancet 2004;364:438–47.
[98] Conrad MD, LeClair N, Arinaitwe E, Wanzira H, Kakuru A, Bigira V, et al. Comparative impacts over 5 years of artemisinin-based combination therapies on *Plasmodium falciparum* polymorphisms that modulate drug sensitivity in Ugandan children. J Infect Dis 2014;210:344–53.
[99] Nankabirwa JI, Conrad MD, Legac J, Tukwasibwe S, Tumwebaze P, Wandera B, et al. Intermittent preventive treatment with dihydroartemisinin-piperaquine in Ugandan schoolchildren selects for *Plasmodium falciparum* transporter polymorphisms that modify drug sensitivity. Antimicrob Agents Chemother 2016;60:5649–54.
[100] Legrand E, Yrinesi J, Ekala MT, Péneau J, Volney B, Berger F, et al. Discordant temporal evolution of *Pfcrt* and *Pfmdr1* genotypes and *Plasmodium falciparum* in vitro drug susceptibility to 4-aminoquinolines after drug policy change in French Guiana. Antimicrob Agents Chemother 2012;56:1382–9.
[101] Rieckmann KH, Davis DR, Hutton DC. *Plasmodium vivax* resistance to chloroquine? Lancet 1989;2:1183–4.
[102] Price RN, von Seidlein L, Valecha N, Nosten F, Baird JK, White NJ. Global extent of chloroquine-resistant *Plasmodium vivax*: a systematic review and meta-analysis. Lancet Infect Dis 2014;14:982–91.
[103] Goncalves LA, Cravo P, Ferreira MU. Emerging *Plasmodium vivax* resistance to chloroquine in South America: an overview. Mem Inst Oswaldo Cruz 2014;109:534–9.
[104] Phillips EJ, Keystone JS, Kain KC. Failure of combined chloroquine and high-dose primaquine therapy for *Plasmodium vivax* malaria acquired in Guyana, South America. Clin Infect Dis 1996;23:1171–3.
[105] Alecrim MdG, Alecrim W, Macedo V. *Plasmodium vivax* resistance to chloroquine (R2) and mefloquine (R3) in Brazilian Amazon region. Rev Soc Bras Med Trop 1999;32:67–8.
[106] de Santana Filho FS, Arcanjo AR, Chehuan YM, Costa MR, Martinez-Espinosa FE, Vieira JL, et al. Chloroquine-resistant *Plasmodium vivax*, Brazilian Amazon. Emerg Infect Dis 2007;13:1125–6.
[107] Marques MM, Costa MR, Santana Filho FS, Vieira JL, Nascimento MT, Brasil LW, et al. *Plasmodium vivax* chloroquine resistance and anemia in the western Brazilian Amazon. Antimicrob Agents Chemother 2014;58:342–7.
[108] Gomes Mdo S, Vieira JL, Machado RL, Nacher M, Stefani A, Musset L, et al. Efficacy in the treatment of malaria by *Plasmodium vivax* in Oiapoque, Brazil, on the border with French Guiana: the importance of control over external factors. Malar J 2015;14:402.
[109] Carnevale P, Robert V. Les anopheles : biologie, transmission du Plasmodium et lutte antivectorielle. Marseille, France: IRD Eds; 2009, 391 p.
[110] Ponçon N, Toty C, L'Ambert G, Le Goff G, Brengues C, Schaffner F, et al. Biology and dynamics of potential malaria vectors in Southern France. Malar J 2007;6:18.
[111] Krüger A, Rech A, Su XZ, Tannich E. Two cases of autochthonous *Plasmodium falciparum* malaria in Germany with evidence for local transmission by indigenous *Anopheles plumbeus*. Trop Med Intl Hlth 2001;6:983.
[112] Ponçon N, Tran A, Toty C, Luty AJ, Fontenille D. A quantitative risk assessment approach for mosquito-borne diseases: malaria re-emergence in southern France. Malar J 2008;7:147.
[113] Antonio-Nkondjio C, Kerah CH, Simard F, Awono-Ambene HP, Chouaibou M, Tchuinkam T, et al. Complexity of the malaria vectorial system in Cameroon: contribution of secondary vectors to malaria transmission. J Med Entomol 2006;43:1215–21.
[114] Kamdem C, Fossog BT, Simard F, Etouna J, Ndo C, Kengne P, et al. Anthropogenic habitat disturbance and ecological divergence between incipient species of the malaria mosquito *Anopheles gambiae*. PLoS One 2012;7:e39453.
[115] Girod R, Gaborit P, Carinci R, Issaly J, Fouque F. *Anopheles darlingi* bionomics and transmission of *Plasmodium falciparum*, *Plasmodium vivax* and *Plasmodium malariae* in Amerindian villages of the Ypper-Maroni Amazonian forest, French Guiana. Mem Inst Oswaldo Cruz 2008;103:702–10.
[116] Dusfour I, Issaly J, Carinci R, Gaborit P, Girod R. Incrimination of *Anopheles (Anopheles) intermedius Peryassú, An. (Nyssorhynchus) nuneztovari Gabaldón, An. (Nys.) oswaldoi Peryassú* as natural vectors of *Plasmodium falciparum* in French Guiana. Mem Inst Oswaldo Cruz 2012;107:429–32.
[117] Dusfour I, Jarjaval F, Gaborit P, Mura M, Girod R, Pages F. Confirmation of the occurrence of *Anopheles (Nyssorhynchus) marajoara* in French Guiana. J Am Mosq Control Assoc 2012;28:309–11.
[118] Diabate A, Baldet T, Chandre F, Akogbeto M, Guiguemde TR, Darriet F, et al. The role of agricultural use of insecticides in resistance to pyrethroids in *Anopheles gambiae s.l.* in Burkina Faso. Am J Trop Med Hyg 2002;67:617–22.
[119] Ranson H, N'Guessan R, Lines J, Moiroux N, Nkuni Z, Corbel V. Pyrethroid resistance in African anopheline mosquitoes: what are the implications for malaria control? Trends Parasitol 2011;27:91–8.
[120] Hemingway J, Ranson H, Magill A, Kolaczinski J, Fornadel C, Gimnig J, et al. Averting a malaria disaster: will insecticide resistance derail malaria control? Lancet 2016;387:1785–8.
[121] Nwane P, Etang J, Chouaibou M, Toto JC, Koffi A, Mimpfoundi R, et al. Multiple insecticide resistance mechanisms in *Anopheles gambiae s.l.* populations from Cameroon, Central Africa. Parasit Vectors 2013;6:41.
[122] Namountougou M, Simard F, Baldet T, Diabaté A, Ouédraogo JB, Martin T, et al. Multiple insecticide resistance in *Anopheles gambiae s.l.* populations from Burkina Faso, West Africa. PLoS One 2012;7:e48412.
[123] Djogbenou L, Labbé P, Chandre F, Pasteur N, Weill M. Ace-1 duplication in *Anopheles gambiae*: a challenge for malaria control. Malar J 2009;8:70.
[124] Hemingway J, Ranson H. Insecticide resistance in insect vectos of human disease. Ann Rev Entomol 2000;45:371–91.
[125] Müller P, Chouaibou M, Pignatelli P, Etang J, Walker ED, Donnelly MJ, et al. Pyrethroid tolerance is associated with elevated expression of antioxidants and agricultural practice in *Anopheles arabiensis* sampled from an area of cotton fields in Northern Cameroon. Mol Ecol 2008;17:1145–55.
[126] Chouaibou M, Etang J, Brévault T, Nwane P, Hinzoumbé CK, Mimpfoundi R, et al. Dynamics of insecticide resistance in the malaria vector *Anopheles gambiae s.l.* from an area of extensive cotton cultivation in Northern Cameroon. Trop Med Int Health 2008;13:476–86.
[127] Tene-Fossog B, Antonio-Nkondjio C, Kengne P, Njiolou F, Besansky N, Costantini C. Physiological correlates of ecological divergence along an urbanization gradient: differential tolerance to ammonia among molecular forms of the malaria mosquito *Anopheles gambiae*. BMC Ecol 2013;13:1.
[128] Moiroux N, Damien GB, Egrot M, Djenontin A, Chandre F, Corbel V, et al. Human exposure to early morning *Anopheles funestus* biting behaviour and personnal protection provided by long-lasting insecticidal nets. PLoS One 2014;9:e104967.
[129] Beier JC, Keating J, Githure JI, Masdonald MB, Impoinvil E, Novak RJ. Integrated vector management for malaria control. Malar J 2008;7(Suppl 1):S4.