

Steps towards the pre-elimination of malaria in the Republic of Djibouti

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Abstract

This review was written in 2011. At this time Djibouti MoH was undergoing the preelimination phase and was successful in control phase of malaria national program. Because of the 2015 Millennium Development Goals and the risk of malaria outbreaks to individuals in Djibouti, the elimination of malaria in Djibouti is a major goal of the Djiboutian Ministry of Health. The purpose of this review is to describe the current malaria situation in Djibouti (epidemiological data and anti-vectorial and anti-malarial strategies) so that the feasibility of Djibouti to eliminate malaria in the Country can be evaluated. A three-fold decrease in the *P. falciparum* seroprevalence was observed between 2002 and 2009 and the percentage of positive examination for *P. falciparum* dropped from 2004 to 2009, suggesting that there have been significant decreases in local malaria transmission and malaria importation. These data indicate the evolution of Djiboutian plasmodia populations towards a

situation that is favourable for malaria elimination due to the presence of only a few genetically distinct strains that originate from the same source and spread throughout the country. The Republic of Djibouti is likely on the correct path to achieve pre-elimination if in depth actions are undertaken in areas highlighted by this study.

Keywords: Malaria, Plasmodium falciparum, anti-malarial drug, resistance, Djibouti

Résumé

Cette revue a été rédigée en 2011 durant le passage de la phase de contrôle de la maladie à la phase de pré-élimination conformément aux critères de l'OMS pour les pays à faible endémicité palustre. Dans un souci d'atteindre les objectifs de développement du millénaire et de circonscrire tout risque d'épidémie de malaria, le Ministère de la Santé de la République met tout en œuvre afin d'éliminer le malaria à Djibouti. La finalité de la présente étude scientifique est de décrire la situation du paludisme en République de Djibouti (données épidémiologiques et stratégies anti-vectorielles et antipaludiques) afin d'évaluer la capacité du pays à éradiquer ce fléau. La séroprévalence *P. falciparum* a diminué de trois fois entre 2002 et 2009 et le pourcentage de l'examen positif pour *P. falciparum* a chuté de 2004 à 2009, ce qui suggère qu'il y a eu des diminutions significatives de la transmission locale du paludisme et le paludisme importé des pays limitrophes. Ces données indiquent que l'évolution des populations plasmodiales sont en faveur d'une situation favorable pour l'élimination du paludisme en raison de la présence de très peu de souches génétiquement distinctes qui proviennent de la même source et se propagent par la suite uniquement dans tout le pays. La République de Djibouti est probablement sur la bonne voie pour atteindre la pré-élimination du paludisme si des actions réelles et en profondeur sont entreprises sur les points et domaines mis en lumière dans cette étude sur la lutte antipaludique.

Mot Clefs : Paludisme, Plasmodium falciparum, Djibouti

List of abbreviations used

ACT: Artemisinin-based combination therapy

AS: Artesunate

DDT: Dichlorodiphenyltrichloroethane

H.e.: Expected heterozygosity

IPT: Intermittent preventive treatment

ITNs: Insecticide-treated nets

LLINs: Long lasting insecticidal nets

MDGs: Millennium Development Goals

msp1: Merozoite surface protein 1 gene

msp2: Merozoite surface protein 2 gene

Pfcr1: *P. falciparum* chloroquine resistance transporter gene

Pfdhfr: *P. falciparum* dihydrofolate reductase gene

Pfdhps: *P. falciparum* dihydropteroate synthetase gene

PNLP: Programme National de Lutte Contre le Paludisme

SP: Sulfadoxine-pyrimethamine

SPR: Slide positivity rate

WHO: World Health Organisation

Introduction

The Republic of Djibouti is a country of 23000 Km² in the Horn of Africa (11°36'N 43°10'E). This country borders Eritrea (15°20'N,38°55'E) in the north, Ethiopia (9°1'0"N, 38°44'0"E) from the northwest to the southwest and Somalia in the southeast (2°02'N, 45°21'E) [1] (Figure 1).



Figure 1. Map of the Republic of Djibouti

(Source:<http://www.un.org/depts/Cartographic/map/profile/Djibouti.pdf>)

Djibouti is a natural port on the Red Sea that serves Djibouti's landlocked neighbour Ethiopia, with which Djibouti has strong trade in goods and people via National Road N°1 [2].

The climate and landscape are primarily desertic. Climate is marked by a cool season (20 to 25°C) and a hot season (38 to 47°C). There is no perennial streams, only wadies, temporary ponds and salty lakes [3].

The country is divided in six major regions with 5 regional capitals (Arta, Ali-Sabieh, Dikhil, Tadjourah and Obock) and the national capital of Djibouti City [4].

The population is 879000 inhabitants, and more than 70% are under 25 years old [5, 6]. A total of 65% of the population lives in Djibouti City [7].

The national capital has a substantial growth rate [8], and the movement of the population (essentially traders, nomads and sailors) is very important [4].

The health facilities are developing but still insufficient to manage this rapidly growing population [5].

Most tropical and communicable diseases have existed and still exist [7], including cholera, dengue and other communicable diseases [8].

Djibouti has a geographically strategic position across the Red Sea from the Arabian Peninsula and not too far from Europe and the Middle East (by sea, it is 10 days to Marseille and 7 days to Afghanistan) [9].

This location is coveted by foreign military powers, which have set up military bases and facilities (US, France, Japan, Germany, Spain and China).

The foreign military population is approximately 5,000 individuals [4].

Because of the 2015 MDGs (Millennium Development Goals) [10] and the risk of malaria outbreaks for the population, the elimination of malaria in Djibouti is a major goal of the Djiboutian Ministry of Health [11].

The purpose of this review is to present the updated malaria situation in Djibouti (epidemiological data and anti-vectorial and anti-malarial strategies) to evaluate the ability of Djibouti to eliminate malaria from the country.

Transmission and prevalence of malaria

The first cases of malaria were described by Bouffard in 1901 [12], with two hotbeds outside Djibouti City (4 km away). These areas are currently known as Doraleh and Ambouli and are home to an autochthonous population. The major vector of malaria, *Anopheles gambiae*, was described in 1905 by Chabaneix [13] for the first time.

Until 1970, no malaria cases were described in the literature, and vector surveillance revealed no *Anopheles* mosquitoes [3].

In 1978, a retrospective study showed the occurrence of malaria in micro and localised outbreaks between 1973 and 1976 [14].

Carteron *et al.* [15,14] highlighted the existence of local foci for both the vector and the parasite near Ambouli. In his medical thesis work in 1990, Goulan [16] described two periods of historical malaria epidemiology in Djibouti. From 1973 to 1976, when malaria cases were

rare and outbreaks quasi-inexistent, the north of the country was rarely affected by malaria. The transmission was seasonal [16], and *Anopheles arabiensis complex gambiae* was the predominant vector [13, 14,17].

From 1978 to 1989, malaria transmission became annual with *P. falciparum* as the main parasite[16].

The first well-documented outbreak was reported in 1989, with more than 3000 confirmed cases [18-20]. In 1991, 7338 cases were reported.

These outbreaks occurred after heavy rains [18].

Fox *et al.* suggested that the parasite and its anopheline vector have been imported from Ethiopia since 1991 [19,20], and they estimated that 10 parasitised humans with gametocyte stages entered Djibouti by train every day.

In 1993, 4770 malaria cases were reported. Though less severe than in the past, outbreaks occurred in 1998, 1999 and 2002 [21].

From 1999 to 2009, excluding the outbreak years (1998, 1999, 2002), the epidemiological pattern returned to seasonal transmission with a decrease in the *Anopheles* population.

The vector *Anopheles arabiensis* was replaced by *Anopheles dthali* and *Anopheles sergentii* [22], which are known in the countries of the Arab gulf as occasional vectors [23].

In 2002, the *P. falciparum* and *P. vivax* seroprevalence rates were 31.5% and 17.5%, respectively, in 1910 adults aged 15-54 distributed in 30 clusters in the city of Djibouti and 25 clusters in the other districts of the country (personal data).

In 2009, Noor *et al.* [24] showed that among 7151 individuals tested using rapid diagnostic tests (RDTs), only 42 (0.5%) were positive for *P. falciparum*. Overall, the *P. falciparum* seroprevalence was 9.9% for all ages, 6.9% in children under the age of five years and 14.2% in the oldest age group (≥ 50 years). The combined infection and antibody prevalence was 10.5%, with no significant regional differences.

Significant *P. falciparum* hot spots were observed in the Dikhil region where several outbreaks occurred previously.

Noor *et al.* concluded that malaria transmission in the Republic of Djibouti is very low across all regions and that there is evidence of microepidemiological heterogeneity and limited recent transmission.

These two studies indicate that *P. falciparum* transmission has decreased three-fold in the past 7 years, even though some hotspots were identified in the two studies in the same area, the Dikhil region. These data show that the Republic of Djibouti is likely on the path to achieve pre-elimination. However, the identification of the same hotspots seven years later represents a serious threat to the success of the announced goal.

In 2009, after studying the occurrence of malaria in the civilian population and in French and American soldiers over a period of 12 years (1998-2009), Ollivier et al. found a decline in the percentage of positive tests for *P. falciparum* [25].

They concluded that the chemoprophylaxis regimen used by the French soldiers stationed in Djibouti was useless, considering the balance of benefits versus risks, and the French army decided to stop the use of chemoprophylaxis in Djibouti in January 2011.

The German troops have also stopped using chemoprophylaxis.

Genetic diversity of *P. falciparum*

Before and after the 1999 epidemic, the *P. falciparum* genetic diversity in Djibouti was high, with $\approx 80\%$ and 63% heterozygosity, respectively [21]. This finding is somewhat surprising for an area where the disease endemicity and transmission are low [26] and thus most likely reflects the importation of strains from neighbouring areas such as Ethiopia and Somalia [19,21].

The *P. falciparum* genetic diversity was lower during the 1999 epidemic, reflecting the circulation of a restricted number of strains during that period [21].

Most of these strains harboured an *msp1* and *msp2* genotype that was detected before and after the epidemic [21].

The prevalence of mutant genotypes for *Pfcr* (*P. falciparum* chloroquine resistance transporter gene), which is involved in chloroquine resistance; *Pfdhfr* (*P. falciparum* dihydrofolate reductase gene), which is involved in pyrimethamine and proguanil resistance; and *Pfdhps* (*P. falciparum* dihydropteroate synthetase gene), which is involved in sulfadoxine resistance, did not vary significantly from 1998 to 1999 ([1]).

The hypothesis that a sudden increase in the level of drug resistance of the local *P.falciparum* population caused the epidemic is not supported by Rogier *et al.* [21].

They hypothesise that the epidemic was not caused by the massive invasion of a single strain/genotype but was instead caused by the expansion of a few strains that were already prevalent [21].

Bogreau *et al.* [27] analysed the *P. falciparum* population structure in Africa and found a lower genetic diversity in Djibouti than in other central or western African countries. In addition, they found significant linkage disequilibrium within the Djiboutian population of *P. falciparum* that has been sampled from 2001.

The Djiboutian plasmodial populations were analysed over an eleven-year period (1998, 1999, 2002 and 2009). Based on microsatellite markers, the expected heterozygosity (H.e.) and pairwise Fst index were determined to estimate the genetic diversity. Data indicated a significant decline in genetic diversity (0.51 to 0.0) (personal data). The significant decrease in H.e., with unexpected proportions, suggests a significant decrease in local malaria transmission and probably in malaria importation

Chemotherapy and Chemoprophylaxis used in Djibouti

From late 1960 until 1988, mass chloroquine chemoprophylaxis was used in areas where malaria cases were observed, especially during rainy periods, in combination with an anti-vectorial strategy [14, 17]. However, before 1973, more than 80% of the cases were imported cases [14, 16]. In 1990, despite the failure of treatment with chloroquine [21], the national recommendations were to use chloroquine as the firstline treatment. Rogier *et al.* reported a high level (>90%) of chloroquine resistance from 1998 to 2002 in strains circulating in Djibouti based on the analysis of molecular markers of resistance [21]. Sulfadoxine-pyrimethamine (SP) resistance also increased from 1999 to 2002 [21]. In 1999, an *in vitro* study of *P. falciparum* isolates showed that 93%, 11% and 8% of the strains were resistant *in vitro* to chloroquine, cycloguanil (the active metabolite of proguanil) and pyrimethamine, respectively [28].

These findings prompted the change of the first-line treatment to ACT (artemisinin-based combination therapy) using the artesunate-sulfadoxine-pyrimethamine combination in 2006. The French forces switched from chloroquine-proguanil in 2001 to mefloquine and then from mefloquine to doxycycline in 2002 for malaria chemoprophylaxis. The French army decided to stop the chemoprophylaxis in Djibouti in January 2011. The German troops have also stopped using chemoprophylaxis.

Anti-vectorial strategy in Djibouti

From late 1960 until 1988, several actions were taken: 1) fumigation of the town with derivatives of DDT or ABATE once or twice per week, 2) the introduction of larvivorous fish into ponds, wells and reservoirs, and 3) the identification of breeding sites and their regular treatment. The late 1980s was a difficult time for the Horn of Africa, as Djibouti, Somalia and Ethiopia experienced periods of civil war [8].

A substantial refugee population was displaced and came to Djibouti from the other countries and from the interior of Djibouti, leading to a high level of uncontrolled urbanisation [18].

During this period, the anti-vectorial strategy was discontinued until 1994, when the Djibouti peace agreement was signed [29].

From 1997 to 2004, the resumption of anti-vectorial activity was progressive and incomplete. The anti-larval activities were abandoned (no more larvivorous fish), and the urban spraying was very sporadic [29].

The Programme National de Lutte Contre le Paludisme (PNLP) was established in 2006, and the National Malaria Strategy was launched the same year with a goal of "pre-elimination" after demonstrating a decrease in malaria cases [30].

The major justification was to "*interrupt the transmission of malaria and eliminate the disease and its consequences to the socioeconomic development of the country as a major public health problem in Djibouti*" [30].

The evaluation of the actions was based on 1) the proportion of homes owning two insecticide-treated nets (ITNs) by 2010; 2) the introduction of larvivorous fish and Abate for larval control; 3) urban spraying with insecticides; 4) malaria case management involving the use of the combination of artesunate and sulphadoxinepyrimethamine (AS+SP) as the first-line therapy for uncomplicated malaria; and 5) an increase in the diagnostic capacity of all

health facilities. Politic leaders at the highest level planned to achieve pre-elimination before 2015 as part of MDGs (Millennium Development Goals) [30].

The PNLN increased the frequencies of urban spraying and vector monitoring and improved the quality of care for infected individuals, in addition to implementing the use of AS + SP [7]. In 2008-2009, the large scale distribution of LLINs [28,30] and the decrease in the malaria prevalence in Ethiopia [31] and in northern Somalia [32] coincided with the 0.5% prevalence of *P. falciparum* infection among 7151 reported by Noor *et al.* in Djibouti [24]. According to national program, almost 45 000 ITN/LLINs were distributed in 2008, eliminating 46% of the population at risk

Recommendations for pre-elimination or elimination status by WHO (Figure. 2)

The WHO recommends considering the following criteria before starting the next step of the strategy to eliminate malaria [33].

For the countries in which a control program is ongoing, the following actions should be taken:

- reduce morbidity and mortality; reduce the burden of malaria; reduce the transmission intensity; and achieve an SPR (slide positivity rate) of <5% at the Country level. To confirm these changes, population-based surveys are necessary.

For those countries where there is a pre-elimination program, the following actions should be taken:

- prevent local transmission nationwide; reduce the number of active foci to zero, reduce the number of locally acquired cases to zero; reduce onward transmission from existing cases; implement interventions at the focus level; and achieve an SPR of <1 case per 1000 population.

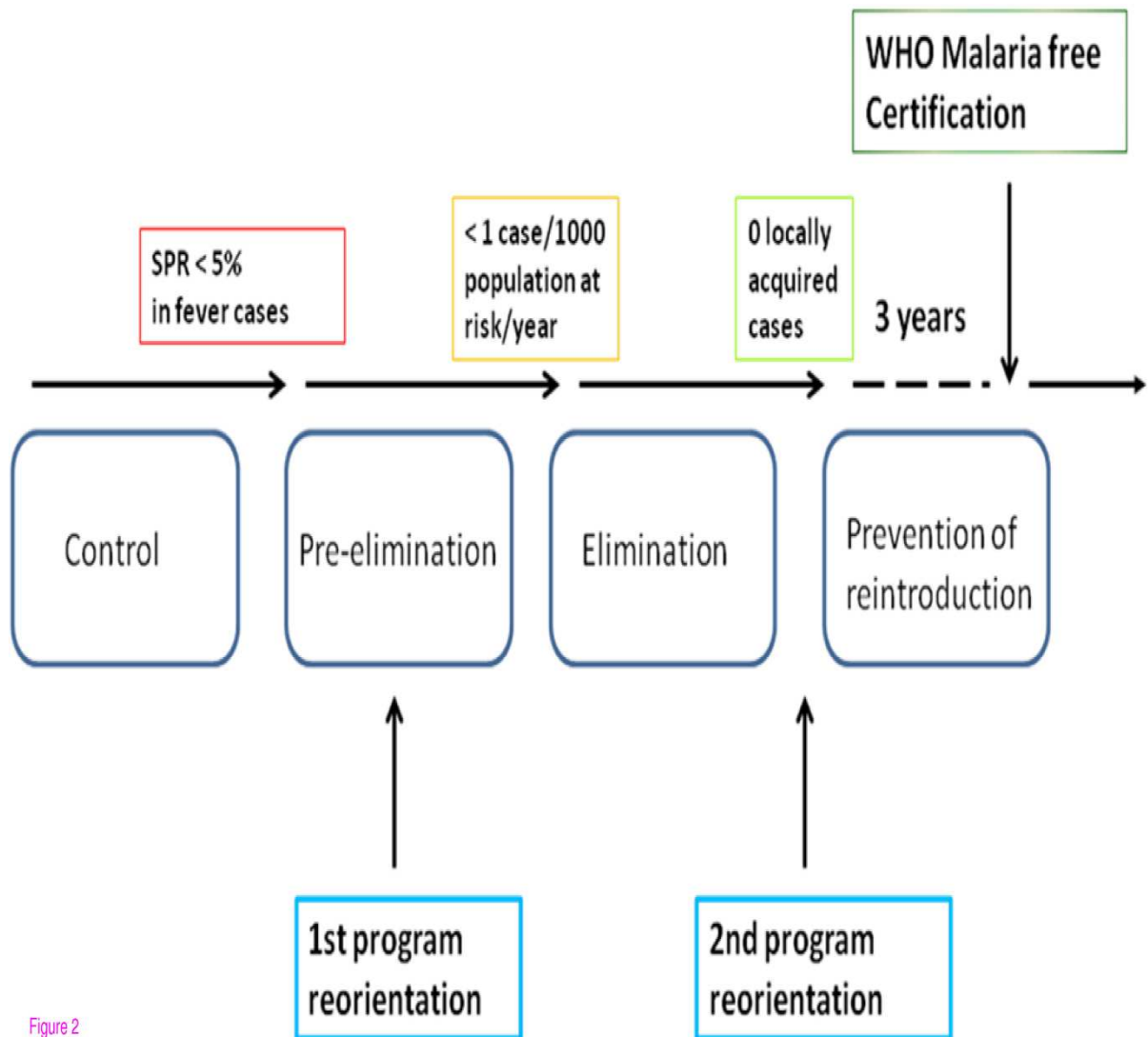


Figure 2

Figure 2. Malaria program phases and milestones on the path to malaria elimination

These changes must be confirmed with population-based surveys. In an elimination program, countries must achieve the following:

- end local transmission nationwide; reduce the number of active foci to zero; reduce the number of locally acquired cases to zero; reduce onward transmission from existing cases; act at the levels of foci and individual cases (locally acquired and imported); and reduce the number of locally acquired cases to zero.

These changes must be confirmed by genotyping and population-based surveys. Finally, when countries are on the path to malaria-free certification and when a program to prevent reintroduction is ongoing, countries must do the following:

- prevent the re-establishment of local transmission; prevent the introduction of cases and the development of local cases secondary to introduced cases; and prevent onward transmission from imported cases.

Current trends for malaria in the neighbouring area

The 4 countries of the Horn of Africa—Eritrea, Ethiopia, Djibouti and Somalia—are in the control phase of the WHO's plan for malaria, and all of these countries are expected to reach the next step in the future [31,32,34,35]. To reach the second step, i.e., pre-elimination, the definition of the WHO requires an incidence level below 5/1000 population at risk/year [36].

The technical feasibility of reaching this goal must be supported by a strong operational feasibility, which requires strong support from the government [36]. As international experts highly recommend progressing from small area to small area, from the sparsely affected areas to highly malarial geographic zones [37], the Horn of Africa should be considered a single geographical region in the fight against malaria. However, disparities exist in the progression towards pre-elimination because Djibouti and Eritrea may have biological advantages, such as the extreme decrease in the transmission levels [24, 25,38].

Although a regional decrease in transmission has been observed [24,38-40], it is necessary to coordinate the actions that are undertaken. As an example, the utilisation of intermittent preventive treatment (IPT) is only reported in Somalia [31], and in populations that were frequently displaced, there were different policies regarding treatment, despite reports of resistance [28,29], at each national level (Table 1).

The scientific data are also very informative, and Ethiopia is the primary provider of information on the disease. Despite these observations, regional transmission is favourable for certain countries, such as Djibouti. Djibouti is the latest country to adopt ITNs and ACTs and provides the least amount of scientific data.

However, Djibouti seems to be the most likely country to achieve pre-elimination [24, 37].

To achieve pre-elimination, it is essential for this desert country, which is nearly encircled by its giant neighbours, to establish very tight scientific and medical collaborations with the surrounding countries.

Table 1. Brief summary of regional current trends on malaria

Facts	Country			
	Eritrea	Ethiopia	Djibouti	Somalia
Anti -malaria fighting Phase(WHO)	Control	Control	Control	Control
Transmission currentTendency	Low Decrease	Low Decrease	Extreme Decrease	Low Decrease
ITN Coverage	>50%	25-50%	20%	20%
Year of adoption	2002	2002	2008	2006
IRS coverage	5%	50%	10%	1%
Year of adoption	1995	1960	2006	2004
First line drugs for <i>P. Falciparum</i>	Artesunate + amodiaquine	Artesunate + lumefantrine	Artesunate + sulfadoxine-pyrimethamine	Artesunate + sulfadoxine-
First line drugs for <i>P. Vivax</i>	Chloroquine + primaquine	Chloroquine	Chloroquine + primaquine	Chloroquine + primaquine
Year of adoption	2007	2004	2006	2006
Mortality tendency	Significant decrease	Significant decrease	Null	Significant decrease
Number of studies on Malaria (Pubmed)	32	395	20	79
Geographical area of	South border with	East border with	All the country	North-west border
Possible preelimination	Djibouti	Somalia and Djibouti		with Djibouti and Ethiopia

WHO= World Health Organisation, ITN= Insecticide Treated Nets, IRS= Indoor Residual Spraying.

Sources: http://www.who.int/malaria/publications/countryprofiles/profile_dji_en.pdf;

http://www.who.int/malaria/publications/country-profiles/profile_eri_en.pdf;

http://www.who.int/malaria/publications/countryprofiles/profile_som_en.pdf;

http://www.who.int/malaria/publications/country-profiles/profile_eth_en.pdf;

Conclusions

The primary threats to elimination are related to 1) the LLIN coverage rate, 2) the regularity of local-to-regional updating of the information on the disease, 3) the efficacy of the vector monitoring and alert system, 4) the capacity to impose and follow the regional guidelines to prevent and manage clinical cases, 5) the capacity to perform evaluations and informative scientific studies to adjust national programs and 6) the level of cooperation among neighbouring countries regarding the actions undertaken to fight malaria.

To reach pre-elimination, the level of population exposure to malaria, and not only to *P. falciparum* but *P. vivax*, must be taken into account because this parasite is the second most common parasite involved in malaria cases on the regional scale, with well-described hotbeds in Ethiopia and Somalia [31,35]. Knowledge about the level of importation of new malaria strains should be updated. To achieve the preelimination of falciparum malaria, it will be necessary to assess the flow of parasites from the neighbouring countries. An entomological surveillance system strengthened with additional human and material resources is also necessary.

The three-fold decrease in malaria prevalence observed in the two studies of *P. falciparum* seroprevalence between 2002 and 2009 [24, personal data] and the decrease from 2004 to 2009 in the percentage of positive tests for *P. falciparum* [25], suggest that the Republic of Djibouti is likely on the correct path to pre-elimination.

In addition, the significant decrease in the genetic diversity of the *P. falciparum* Population in unexpected proportions and the presence of a few genetically distinct strains originating from the same source and spreading throughout the country suggests a significant decrease in local malaria transmission and probably in malaria importation (personal data). These data indicate the evolution of Djiboutian plasmodial populations towards a situation that is favourable for the elimination of malaria due to the presence of only a few genetically distinct strains originating from the same source and spreading throughout the country.

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