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# Epidemiology of imported malaria give support to the hypothesis of 'long-term' semi-immunity to malaria in sub-Saharan African migrants living in France

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**Summary** *Background:* Short-term semi-immunity to malaria in sub-Saharan African migrants who have recently arrived in non-endemic countries results in less severe imported malaria. Our aim was to investigate the factors associated with imported malaria that would favour the hypothesis of a 'long-term' semi-immunity to malaria in adult travellers of sub-Saharan origin living in France and visiting family or relatives in their country of origin (VFR group).
*Method:* The epidemiological, clinical and biological characteristics of imported *Plasmodium falciparum* malaria in VFR were compared with those of travellers of European origin (TEO). Newly arrived African migrants and European expatriates were excluded.
*Results:* This retrospective study included 106 adult VFR (30%) and 240 adult TEO (70%) with imported *P. falciparum* malaria treated at the University Hospital Center of Bordeaux between 2000 and 2007. The main regions visited were West Africa (58%) and Central Africa (34%). *P. falciparum* was associated with severe malaria in 8% of patients (VFR 3% vs. TEO 11%), of which two TEO died. In univariate analysis, the factors associated with *P. falciparum* malaria in VFR vs. TEO were: female sex, younger age, less frequent use of mosquito nets, poor compliance with chemoprophylaxis, less severe malaria without death, less severe thrombocytopenia and a tendency towards a lower level of parasitaemia and higher haemoglobinaemia. In multivariate analysis, the only factor to be independently associated with *P. falciparum* malaria in VFR compared to TEO was less frequent severe malaria.

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*Conclusions:* Our results give support to the hypothesis of 'long-term' semi-immunity to malaria in VFR living in France.


## Introduction

France is the industrialised country most affected by imported malaria, accounting for 50% of all imported cases in Europe. The incidence of imported malaria in France has ranged from 4000 to 7000 cases per year over the past 10 years [1—4]. Although the annual incidence appears to be decreasing, national epidemiological data in France [1], like those from our cohort in Bordeaux [5], demonstrate a paradoxical increase in the proportion of malaria patients of sub-Saharan Africa origin living in France and visiting family or relatives in their country of origin (VFR). It is widely accepted that a prolonged duration of stay in a stable transmission zone for *Plasmodium falciparum* malaria [6,7] is associated with a certain level of protection against malaria, due to repeated exposure to the parasite, expressed as a reduced risk of severe malaria [8—12]. This state of protection, termed 'semi-immunity', is generally considered to be labile, partial and quick to disappear within months when 'semi-immune' individuals no longer live in an endemic area and are not regularly exposed to infecting bites of the *Anopheles* mosquito. However, the notion that semi-immunity to malaria is always transient may not be correct [10,11,13—15] and studies of imported malaria in Europe indicate that these cases are generally less severe when they occur in VFR [1—4,16—24]. These observations suggest that semi-immunity to malaria may persist in VFR, particularly since this group is less likely to use malarial prophylaxis than travellers of European origin (TEO) [4,18—23]. In this context, the milder severity of *P. falciparum* malaria in VFR could signify 'long-term' semi-immunity to malaria acquired following a history, albeit remote, of long-term residence in a stable transmission zone in sub-Saharan Africa. We therefore consider as strong the hypothesis of 'long-term' semi-immunity to malaria awaited to persist over a 12 months period following departure from an endemic area. From an epidemiological point of view, we hypothesize that VFR can be considered to be 'semi-immune' to *P. falciparum* malaria if the clinical and biological presentation of *P. falciparum* malaria in VFR is less severe than that in TEO.

Our aim was to investigate the factors associated with imported malaria that would favour the hypothesis of a 'long-term' semi-immunity to malaria in VFR by comparing the epidemiological, clinical and biological characteristics of imported *P. falciparum* malaria in VFR and TEO presenting at the University Hospital Center (CHU) of Bordeaux, France.

## Materials and methods

A retrospective, descriptive study was carried out using the medical files of adult patients treated for malaria in consultation or hospitalization at the CHU of Bordeaux, between 1st January 2000 and 31st December 2007. Inclusion criteria were a positive diagnosis of *P. falciparum* malaria, age $\geq$15-years and main residence in France. The patients were divided into two groups: group of travellers of sub-Saharan Africa origin and visiting family or relatives in their country of origin (VFR group) and group of travellers of European origin (TEO group), namely VFR and TEO. By definition, European expatriates living in Sub-Saharan Africa and immigrants from Sub-Saharan Africa newly arrived for less than 12 months were not included. The diagnosis of *P. falciparum* malaria should have been confirmed in at least one of the following biological tests: direct microscopic examination of a thin blood smear or a thick drop or positive polymerase chain reaction (detection and amplification of the *pBRK1-14* gene). Demographic, epidemiological, clinical and biological data were collected retrospectively from the medical file of each patient. The data collected included sex, age, nationality, country of residence, country of birth, main endemic country visited, the dates of travel or the duration of stay, the use of and compliance with malaria chemoprophylaxis (MP) and mosquito nets, the date of onset of symptoms, the date of the first consultation, the date of biological diagnosis, the clinical form (simple or severe) of disease according to the WHO criteria [25], the initial parasitaemia (% *P. falciparum* trophozoïtes) and haemogram parameters (haemoglobin in g/dl, leukocytes in cells/mm$^3$, platelets in cells/mm$^3$).

Descriptive, univariate and multivariate analyses were carried using SAS version 9.1.3. In a first step, variables whose distribution differed between the VFR and TEO groups were identified by univariate analysis. Simple logistic regression was used to compare the percentages of qualitative variables and the means of quantitative variables. Log-linearity of quantitative variables was verified and non-log linear quantitative variables were recoded in classes. Subsequently, multivariate analysis was carried out by logistic regression using a descending stepwise procedure in order to identify variables that were independently associated with VFR or TEO status. An initial multivariate model included the variables identified in the univariate analysis with a type 1 risk of error of $<$20% ($p < 0.2$) excluding non-relevant variables and variables with numerous missing data after a sensitivity analysis. The final multivariate model included variable(s) retained in the initial model with a final type 1 risk of error of 5% ($p < 0.05$). The appropriateness of the model was verified by the Hosmer and Lemeshow test.

## Results

This retrospective study identified 526 adult cases of imported malaria treated between 2000 and 2007 in the CHU of Bordeaux. These 526 cases have already been described