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## Completeness of malaria notification in Tunisia assessed by capture recapture method

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## ABSTRACT

**Objective:** To estimate the completeness of malaria notification to the public healthcare system (PHCS) and to describe retrospectively data of malaria cases in Tunisia. **Methods:** We conducted a retrospective epidemiological survey using a standardized questionnaire for all cases of malaria reported to PHCS and those diagnosed in parasitological laboratory or infectious disease service between January 2002 and December 2007. To estimate the total number of cases, we used a two sources capture–recapture analysis. **Results:** After record–linkage and cross–validation 317 cases of malaria were identified, of whom 231 were notified, resulting in an observed under–notification of 17%. The estimated number of malaria cases using capture–recapture analysis was 366.3 (95% CI: 335.8–396.8) for the period of study with a completeness of 63.1% which increased from 44.8% for 2002 to 78.7% for 2007. One hundred and sixty two patients (51.1%) had been born in sub–Saharan Africa, 113 (35.6%) in Tunisia, 35 (11.0%) in North Africa and 7 (2.2%) in Europe with predominance of men (87.1% of all cases). The median age was 25.0 years (21–30) for sub–Saharan Africans, 38.0 years (23.5–45.5) for North Africans, 38.5 years (30.75–38.5) for Tunisian and 39.0 (26–43) for European ( $P<0.01$ ). The most predominant malaria species was *Plasmodium falciparum* with 216 cases (72.5%), and the most frequent area of acquisition was sub–Saharan Africa. In our study, information on compliance with malaria prophylaxis was only sporadically available and 34% of infected individuals had not used any chemoprophylaxis. Our study showed delayed identification of malaria that indicated a deficit in medical awareness and management of this infection. **Conclusions:** Our survey has marked variety in the type and availability of key data and shown an underreporting of malaria cases. Furthermore, it demonstrates that the two different sources of malaria registration are substantially incomplete. Of particular interest is the observation that a considerable number of patients could only be found in the records of PHCS, they were unknown to the laboratories, although malaria confirmation by thick or thin smear is obligatory in Tunisia.

### 1. Introduction

Malaria is one of the most severe public health problems worldwide and the re–emerging risk of this disease in malaria–free countries is higher now than it ever was as a result of international travel, migration and climate change. Recently, several outbreaks of autochthonous malaria transmission have been reported in malaria–free USA and Europe because of the introduction of infected mosquitoes

or infection of local mosquitoes that have fed on infected persons returning from endemic areas[1–3].

During the late 1970s, a combination of improved housing and socioeconomic conditions, water management, vector–control efforts, and case management was successful at interrupting malaria transmission in Tunisia[4]. The country became malaria free since 1979 and the majority of notified malaria cases in Tunisia acquired the infection in malaria endemic countries. Infections resulting from exposure to blood or blood products are also reported in Tunisia[5]. However, the re–emergence risk of local foci is not considered impossible because *Anopheles labranchiae* and *Anopheles sergenti*, the former vectors of malaria in Tunisia, are still present and are increasing following the building of dams and manmade lakes[6]. Consequently, malaria case surveillance has been maintained to detect locally acquired

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cases that could indicate the reintroduction of transmission and to monitor patterns of resistance to anti-malarial drugs. Notification of malaria cases is obligatory but national authorities considered that data underestimate the true situation and that underreporting is considerable<sup>[6,7]</sup>. The completeness of surveillance data can be increased through record-linkage between datasets of cases reported from different sources<sup>[8]</sup>. The number of cases missed can then be estimated using the overlap between two data sources through capture-recapture analysis<sup>[9]</sup>. Capture-recapture analysis has been used to evaluate surveillance systems of various infectious diseases in several countries<sup>[10]</sup>.

Therefore, the objective of this study was to describe malaria surveillance data and to estimate the total number of malaria cases and the completeness of malaria notification in Tunisia between 2002 and 2007 using record-linkage and capture-recapture methodology.

## 2. Materials and methods

Three sources of malaria cases in Tunisia were examined between January 2002 and December 2007 *i.e.* patients notified by physicians to the public healthcare system (notification), patients diagnosed in parasitological laboratory and hospitalized patients recorded by infectious disease services.

We conducted a retrospective epidemiological survey using a standardized questionnaire, in which sociodemographic (sex, age, country of birth, place of residence, reporting center, hospitalization, country of travel), diagnostic (species, technique), chemoprophylaxis and treatment variables were collected, as well as the dates of onset of symptoms, diagnosis, and hospital admission. In addition, the following information was collected: the endemic geographic areas visited in the 30 days prior to the onset of symptoms, or the last country visited if the patient returned from travel more than 30 days previously and the reason for travel. Information about completion of the chemoprophylaxis treatment was also noted.

Imported malaria is defined as an infection acquired in an endemic area by an individual (either Tunisian or other nationalities) and diagnosed in Tunisia.

A descriptive analysis of the data was carried out. The quantitative variables were described by median (md) and interquartile range (IR) if the data did not follow a normal distribution and for the categorical variables the percentages were calculated. The *Chi*-square test was used to compare qualitative variables, while *t*-test or ANOVA and the corresponding non-parametric tests were used to compare the quantitative variables. SPSS version 13.0 was used for statistical analysis.

The completion of notification was assessed by searching for cases which were also reported to the public healthcare system (PHCS) and diagnosed in parasitological laboratory using two-source-capture-recapture method (CRM)<sup>[11,12]</sup>. Completion refers to the proportion of cases detected by the notification system.

The two-source method is a relatively simple, feasible and reproducible method used to estimate the total number

of cases, including the ones which were not observed, and subsequently to assess the completeness of the sources. On the basis of previous literature<sup>[12,13]</sup>, the estimated number of cases (*n*) is:

$$n = \frac{(a+b+1) \times (a+c+1)}{(a+1)} - 1$$

where *a* is the number of cases in both sources and *b* and *c* are the number in only one of the sources.

The 95% *CI* of *n* is:  $n \pm 1.96 [Var(n)]^{1/2}$  and

$$Var(n) = \frac{(a+b+1) \times (a+c+1) \times b \times c}{(a+1)^2 \times (a+2)}$$

To calculate the completion of notification relative to the estimated number of cases (*C*) we used the formula:

$$C = \frac{(a+b)}{n} \times 100$$

Where *b* is the number of malaria cases only known to PHCS and “*a+b*” are the number of cases known to PHCS.

## 3. Results

During the study period, a total of 317 cases of malaria were registered, 231 (73%) of them were reported to PHCS. Figure 1 showed the trend of registered malaria and the proportion of cases that had been reported to PHCS per year.

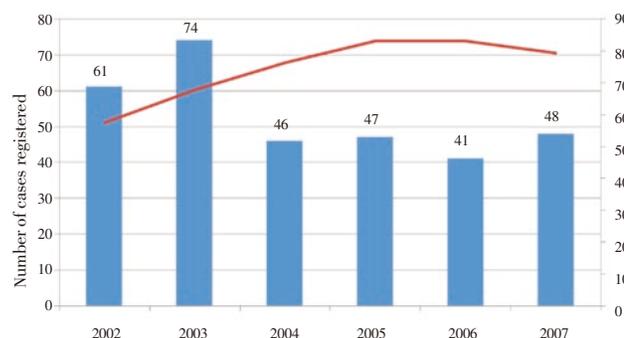


Figure 1. Trend of registered malaria and the proportion of cases reported to PHCS per year.

The estimated number of malaria cases in capture-recapture method was 366.3 (95% *CI*: 335.8–396.8) for the study period with a completeness rate of 63.1%.

Based on the estimated numbers of total cases, as demonstrated in Table 1, the completeness of notification increased from 44.8% in 2002 to 78.7% in 2007.

A total of 162 patients (51.1%) had been born in sub-Saharan Africa, 113 (35.6%) in Tunisia, 35 (11.0%) in North Africa and 7 (2.2%) in Europe with predominance of men (87.1% of all cases). The median age was 25.0 years (21–30) for sub-Saharan Africans, 38.0 years (23.5–45.5) for North Africans, 38.5 years (30.75–38.5) for Tunisian and 39.0 (26–43) for European (*P*<0.01) (Figure 2).

**Table 1**

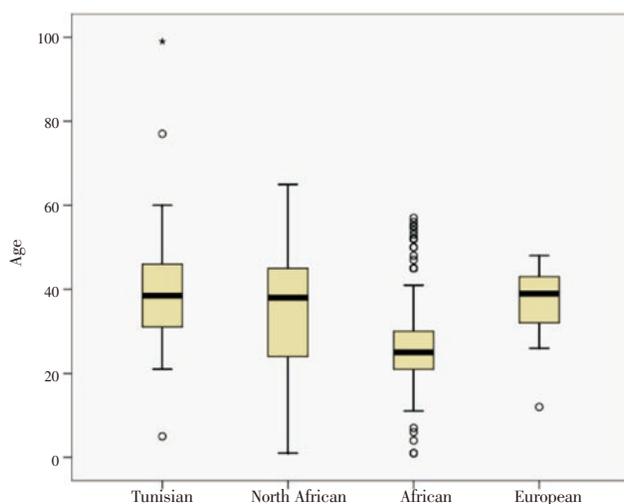
Results of capture–recapture method of malaria cases in Tunisia and completeness of declaration by year.

Year of diagnosis	Two sources of notification (a)	PHCS declaration (b)	Laboratory confirmation and notification (c)	Total number of cases by capture–recapture (n)	95% CI	Completeness (%)
2002	19	16	24	78.2	63.1–93.3	44.8
2003	27	23	20	86.4	72.2–100.6	57.9
2004	20	15	7	47.0	39.7–54.3	74.5
2005	17	22	8	56.8	43.5–70.0	68.7
2006	18	16	6	45.1	37.1–53.0	75.5
2007	18	20	5	48.3	39.3–57.3	78.7
Total	119	112	70	366.3	335.8–396.8	63.1

**Table 2**

Comparison of epidemiological characteristics of Tunisian patients with imported malaria to others nationalities [n (%)].

Characteristics	Tunisian	Other nationalities
Age (md, IR) years	98 (38.5, 15)	145 (26.0, 16)**
Sex	Male	153 (84.1)
	Female	29 (15.9)
Purpose of travel	Missionary work	13 (13.1)
	Tourism	1 (1.0)
	Study	74 (74.4)
	Sport manifestation	5 (5.1)
	Others	6 (6.1)
Hospital admission (yes/total)	81/99 (81.8)	87/130 (66.9)*
Hospitalization duration (md, IR) days	47 (5.0, 4)	30 (3.5, 2)**
Delay before care (md, IR) days	54 (5.0, 6)	39 (5.0, 3)
Delay before diagnosis (md, IR) days	55 (14.0, 15)	52 (12.5, 20)
Chemoprophylaxis	Received	–
	None	–

\* $P<0.05$ ; \*\* $P<0.01$ .**Figure 2.** Age comparison of malaria patients by nationalities.

All cases were contracted outside Tunisia except five that were induced by transfusion among Tunisian people that had never been travelled. The mean age of transfusion transmitted malaria group was  $(60.8 \pm 16.6)$  years and the median age was 59.

For the other cases of imported malaria, sub-Saharan Africa appeared to be the most common region of infection acquisition. The major purpose of travel to malaria endemic countries for Tunisian patients was missionary work (95.4%). However, the most purpose of travel to Tunisia from malaria endemic countries was to study (74.4%). In 56.5% the length

of stay for Tunisian patients in endemic area was more than 30 days. Chemoprophylaxis was prescribed for 42 Tunisian patients among 63 (66.7%) for which information was available.

Species was isolated in 298 patients (94%). The most frequently isolated species was *Plasmodium falciparum* (*P. falciparum*) with 216 cases (72.5%), followed by *Plasmodium ovale* (*P. ovale*) with 26 cases (8.7%), *Plasmodium vivax* (*P. vivax*) with 16 cases (5.4%) and *Plasmodium malariae* with 11 cases (3.7%). In 5 cases (1.7%), the diagnosis was of *P. falciparum* in association with *P. ovale* or *P. vivax*.

Information about hospitalization was available for 229 and a total of 168 cases (73.4%) required hospital admission. Hospital admission and duration of hospitalization were significantly higher within Tunisian patients ( $P<0.05$  and  $P<0.01$ , respectively). Information about delay before diagnosis and care were available for respectively 93 and 107 patients. The median delays before diagnosis and care were not different according to nationalities. During the period of the study one death among Tunisian patient was observed. Mefloquine was the most frequently prescribed medication (50/99, 50.5%) (Table 2).

#### 4. Discussion

In Tunisia, the majority of malaria infections occur among persons who have travelled to area with ongoing malaria transmission. Few cases can occur through exposure to infected blood products. Malaria surveillance is conducted

to identify risk of local transmission and to guide prevention recommendation for travelers.

This study describes and summarizes trends of malaria cases that occurred in Tunisia during the period between 2002 and 2007. Our objective is to estimate the total number of malaria cases and the completeness of notification using capture–recapture analysis of two sources of malaria registration: the public health care system and laboratories.

For the study period, the total number of malaria notification showed a decreasing trend and the completeness rate of notification showed an increasing trend.

Our results showed an underreporting of malaria cases and confirmed that more malaria cases occur in Tunisia than that are reflected by the number officially notified to the PHCS. Furthermore, it demonstrates that the two different sources of malaria notification are substantially incomplete. Of particular interest is the observation that a considerable number of patients could only be found in the records of PHCS, but they were unknown to the laboratories.

Notification of malaria cases seems to be good (44.8% in 2002 to 78.7% in 2007) comparing to other country as France for example (only 32% of all cases are notified); and shows an increase in recent years<sup>[3,14]</sup>. But it is clear that the official notification often understates the true position. Some limitations are inherent in the survey system because reporting is passive, incomplete and not standardized; however, collection of surveillance data is important to allow monitoring of trends. Irregular surveillance and lack of homogeneity in the collected data hinder the assessment of incidence, risk groups and the efficacy of chemoprophylaxis. Our survey marked heterogeneity in the type and availability of key data such as chemoprophylaxis used, traveler status, country of origin of infection, and information on recovery and death, which were infrequently collected despite the recommendations and proposals for standardized reporting by national authorities.

Five cases of transfusion–transmitted malaria were reported in our study. Ensuring that, in non–endemic countries, the blood supply which is free from malaria is problematical, especially as travel to malarious areas is increasing and there is some spread of the disease into new areas, as well as a resurgence of malaria in areas where previously it had been eradicated. In non–endemic countries, donor deferral can be effective, but clear guidelines are needed. Thus, other strategies are needed to ensure safety with sufficiency. In non–endemic countries, donor deferral in combination with screening for specific antimalarial immunoglobulin provides an effective measure of minimizing the risk of transmission. Nonetheless, no matter what strategy is adopted, it is likely that cases of transfusion–transmitted malaria may still occur, so malaria must always be considered in any patient with a febrile illness post–transfusion<sup>[15,16]</sup>. Preventive measures have been undertaken to screen blood donors such as discarding red cell donations according to the medical history, travel history and detection of malarial antibodies. However, these measures may be not sufficient and reliable to avoid the risk of transmission. Preliminary data indicate that combination of travel history, detection of malarial antibodies and antigens by commercialized kits adapted to blood transfusion centers either in endemic or non endemic areas may improve malaria transfusion risk management<sup>[15]</sup>.

The frequent observation of imported malaria in individuals of sub–Saharan African origin and in Tunisian who travelled to sub–Saharan Africa is consistent with that observed in European countries<sup>[1]</sup>.

One reason for conducting malaria surveillance is to monitor malaria prophylaxis that might indicate emergence of drug resistance<sup>[17]</sup>. In our study information, compliance with malaria prophylaxis was only sporadically available and 34% of infected individuals had not used any chemoprophylaxis. This proportion is comparable to other industrialized country as Germany (35%). Approximately 81% of imported malaria infections among US civilians occurred in those who had not taken a chemoprophylaxis as recommended<sup>[3]</sup>. It was demonstrated that compliance with chemoprophylaxis was effective in reducing the malaria risk<sup>[18–24]</sup>. Long–stay in endemic area is shown to be a risk factor of infection. The proportion of Tunisian peoples who travel to endemic area and don't take any chemoprophylaxis is unknown. Short–stay travelers often use no protective or inadequate regimens or are noncompliant with their medication. All travelers to risk areas need to be targeted with medical advice and protective measures prior to travel and should take one of the recommended chemoprophylaxis medications for the region of travel and use personal protection measures to prevent mosquito bites. Any person who has been to a malarious area and who subsequently has a fever or influenza–like symptoms should seek medical care immediately and report their travel history to the clinician; investigation should include a blood–film test for malaria<sup>[25]</sup>.

*P. falciparum* was the dominant pathogenic agent reflecting the geographical source of the infection dominated by sub–Saharan Africa but other species are imported reflecting the changing patterns of traveler origin in Tunisia with an increase of travel to Asia. *P. falciparum* continues to be the most frequent species in European countries and the USA<sup>[2]</sup>.

Our study shows delayed identification of malaria that indicates a deficit in medical awareness and expertise in the management of this infection.

Lack of homogeneity in the collected data has been the major obstacle to quantifying the problem of malaria in Tunisia and to estimate incidence. An active survey with a standardized form to collect key data variables on malaria cases could be introduced. Cooperation with the travel industry should lead to the development of preventive strategies to increase malaria awareness of travelers. In addition, the medical profession must be conditioned to consider malaria in the differential diagnosis of any explained fever. More studies are needed in order to better characterize the population at high risk of imported malaria and to improve awareness of the disease and the information provided to Tunisian travelers to malaria endemic areas. Improvement in surveillance and reporting would therefore help to quantify incidences, identify risk groups and provide an indication of the prophylactic efficacy<sup>[26]</sup>. A standardized form of data on malaria cases could be introduced with the creation of a one page short form with key data variables, including demographic information (age, sex, nationality, occupation) reason for travel, area of acquisition of infection, chemoprophylaxis used, date of diagnosis, species identification, and outcome<sup>[3]</sup>.

## Conflict of interest statement

We declare that we have no conflict of interest.

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- Direction Médicale Tunis Air
- Centre National de Médecine et des Sciences du Sport
- Service régional des Soins de Santé de Base Sfax
- Services des maladies infectieuses de:
  - Hôpital La Rabta
  - Hôpital Militaire
  - Hôpital F. Hached Sousse
  - Hôpital Menzel Bourguiba
  - Hôpital H. Chaker Sfax
  - Hôpital F. Bourguiba Monastir
- Les laboratoires :
  - Laboratoire de parasitologie de l’Hôpital La Rabta
  - Laboratoire de parasitologie de l’Institut Pasteur Tunis
  - Laboratoire de parasitologie de l’Hôpital F. Hached Sousse
    - Laboratoire d’hygiène DRSP de Sfax
    - Service laboratoire de l’Hôpital F. Bourguiba Monastir
    - Laboratoire H Bourguiba–de Sfax

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