



# Causes of febrile illnesses in hospitalized patients in a referral center in Madagascar: a retrospective study

Les causes des maladies fébriles des patients hospitalisés dans un centre de référence à Madagascar : une étude rétrospective.

V ANDRIANANJA <sup>(1)</sup>, J ANDRIAMAMONJISOA <sup>(1)\*</sup>, E RAKOTOMIJOLO <sup>(1)</sup>, R D RAKOTOMALALA <sup>(1)</sup>, M RABERAHONA <sup>(1)</sup>,  
R ANDRIANASOLO <sup>(2,4)</sup>, R RAKOTOARIVELO <sup>(3,5)</sup>, M RANDRIA <sup>(1,4)</sup>

(1) Department of Infectious Diseases, Joseph Raseta Befelatanana University Hospital, Antananarivo, Madagascar

(2) Department of Endocrinology, Joseph Raseta Befelatanana University Hospital, Antananarivo, Madagascar

(3) Department of Infectious Diseases, Tambohobe University Hospital, Fianarantsoa, Madagascar

(4) Faculty of Medicine, Antananarivo, Madagascar

(5) Faculty of Medicine, Fianarantsoa, Madagascar

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## ABSTRACT

**Introduction:** Fever is the most frequent symptom of infectious diseases, often prompting patients to consult. The causes can be benign but sometimes serious, and the delay in diagnosis and therefore in treatment increases the morbidity and mortality of patients. The objectives of our study were to determine the causes of febrile illnesses and to determine the outcome of patients. **Methods:** This is a descriptive retrospective study, carried out over 12 months from January to December 2018. The study population was the medical records of patients hospitalized for fever of infectious origin in an Infectious Disease department of a tertiary care hospital in Madagascar. **Results:** Four hundred and seventy-two (72.8%) patients were included out of 650 hospitalised patients. The main reasons for consultation were: rash (23.7%; n=112), infectious syndrome (20.3%; n=96), cough/dyspnoea (16.3%; n=77) and altered consciousness (15.9%; n=75). The main causes of hospitalisation were: measles (26.7%; n=126), tuberculosis (21.4%; n=101), malaria (15.5%; n=73) and Human Immunodeficiency Virus (HIV) infection (13.4%; n=63). The association of tuberculosis and HIV infection was found in 47.6% (n=224) of subjects. The most frequent location of tuberculosis was the lung (38.1%; n=180), followed by the meninges (35.9%; n=169), and pleura (19.8%; n=93). The overall mortality rate was 15%. Tuberculosis was the main cause of death (46.5%; n=33), followed by HIV infection (18.3%; n=13), bacterial pneumonia (11.3%; n=8), malaria (11.3%; n=8) and bacterial meningitis (9.9%; n=7). **Conclusion:** Measles, tuberculosis, malaria and HIV infection were the main causes of hospitalization. Tuberculosis and HIV infection were the main causes of death. Increase screening, research for strategies and capacity building of healthcare workers should be a priority to improve the management of these diseases in tropical countries like Madagascar.

**Keywords :** Febrile illnesses; Measles; Tuberculosis; Malaria; HIV; Madagascar.

## RESUME

**Introduction:** La fièvre est le symptôme le plus fréquent des maladies infectieuses, incitant souvent les patients à consulter. Les causes peuvent être bénignes mais parfois graves, et le retard de diagnostic et de traitement augmente la morbidité et la mortalité des patients. L'objectif de notre étude était de déterminer les causes des maladies fébriles et de déterminer le devenir des patients. **Méthodes :** Il s'agit d'une étude rétrospective descriptive, réalisée sur 12 mois de janvier à décembre 2018. La population étudiée était les dossiers médicaux des patients hospitalisés pour fièvre d'origine infectieuse dans un service de maladies infectieuses d'un hôpital de soins tertiaires à Madagascar. **Résultats :** Quatre cent soixante-douze (72,8%) patients ont été inclus sur 650 patients hospitalisés. Les principaux motifs de consultation étaient : l'éruption cutanée (23,7 % ; n=112), le syndrome infectieux (20,3 % ; n= 96), la toux/dyspnée (16,3 % ; n=77) et le trouble de la conscience (15,9 % ; n=75). Les principales causes d'hospitalisation étaient les suivantes : la rougeole (26,7% ; n=126), la tuberculose (21,4% ; n=101), le paludisme (15,5% ; n=73) et l'infection par le virus de l'immunodéficience humaine (VIH) (13,4% ; n=63). L'association de la tuberculose et de l'infection par le VIH a été constatée chez 47,6 % (n=224) des sujets. La localisation la plus fréquente de la tuberculose était les poumons (38,1% ; n=180), suivi des méninges (35,9% ; n=169), et de la plèvre (19,8% ; n=93). Le taux de mortalité global était de 15 %. La tuberculose était la principale cause de décès (46,5% ; n=33), suivie de l'infection par le VIH (18,3% ; n=13), de la pneumonie bactérienne (11,3% ; n=8), du paludisme (11,3% ; n=8) et de la méningite bactérienne (9,9% ; n=7). **Conclusion :** La rougeole, la tuberculose, le paludisme et l'infection par le VIH sont les principales causes d'hospitalisation. La tuberculose et l'infection par le VIH étaient les principales causes de décès. L'augmentation du dépistage, la recherche de stratégies et le renforcement des capacités du personnel soignant devraient être une priorité pour améliorer la prise en charge de ces maladies dans les pays tropicaux comme Madagascar.

**Mots clés:** Fièvre; Rougeole; Tuberculose; Paludisme; VIH; Madagascar.

## INTRODUCTION

Febrile diseases in tropical countries are defined as infections prevalent in tropical and subtropical regions, some of which occur throughout the year while others are influenced by season and/or climate [1,2]. However, non-tropical countries can also be affected by these tropical infectious diseases due to the increase in international movements, especially in recent years [3].

From the Department of Infectious Diseases,  
Joseph Raseta Befelatanana University Hospital, Antananarivo

\*Corresponding author :

Volatiana ANDRIANANJA, MD

Address : Department of Infectious Diseases  
Joseph Raseta Befelatanana University Hospital  
Antananarivo, Madagascar

Telephone : -

E-mail : volatiana.andriananja@gmail.com

The three main causes are respiratory tract infections, human immunodeficiency virus infection and diarrheal diseases [4]. Infections are responsible for significant mortality and morbidity, particularly in sub-Saharan Africa [5,6]. On the one hand, some aetiologies are potentially fatal, such as malaria, febrile diarrheal diseases, dengue, HIV infection and its opportunistic infections. On the other hand, some etiologies can cause epidemics or re-emergent infections, such as measles [7]. The knowledge of the main aetiologies of fever is an essential part of the diagnostic process and the management of patients in order to improve the lethality and the public health strategy. In that context, in this study we aimed to determine the causes of febrile illnesses as well as their respective case fatality rates in order to enhance the management of these illnesses.

## MATERIALS AND METHODS

This was a retrospective descriptive study. The study population was hospitalized patients with fever  $\geq 38^{\circ}\text{C}$ . Inclusion criteria included all inpatients who presented fever ( $T^{\circ} \geq 38^{\circ}\text{C}$ ) diagnosed at discharge as an infection, all inpatients who present clinical signs and symptoms associated with a fever  $\geq 38^{\circ}\text{C}$  were recorded. We included all hospitalized patients with fever  $T^{\circ} \geq 38^{\circ}\text{C}$  at axillary measurement at mealtime intervals and at admission with clinical signs and symptoms with clinical signs and symptoms associated with fever  $\geq 38^{\circ}\text{C}$ . These patients are diagnosed at discharge as a Community Acquired Infection. We excluded from the study patients presenting with fever due to non-infectious diseases. The exclusion criteria were established by the absence of clinical and paraclinical arguments for infection, including negative microbiological documentation. Concerning the management of fever in the department, antibiotics and antipyretics are not routinely taken during fever, unless signs of gravity or clinical intolerance are present. Sociodemographic and clinical data (age, sex, duration of fever, length of hospital stay) were collected for each patient.

Simple random sampling was performed, with a 95% confidence interval, a 5% margin of error, and an expected frequency of 70% of patients admitted with febrile illness. A minimum of 215 patients had to be included for the sample size to be representative.

This was a retrospective descriptive study conducted in the Infectious Diseases Department of the Joseph Raseta Befelatanana University Hospital. This is a reference center for infectious diseases in the capital city of Madagascar. The duration of the study was 12 months, from January 01, 2018 to December 31, 2018, the estimated time to include a representative study population.

A questionnaire was developed based on data from the literature. Data were collected from patients' hospital records. The questionnaire was anonymized by an identification code assigned to each patient's file. The collected data were entered into a database created with Epi Info 7.2.2 software.

For the definition of variables, they are described

and compared by the variables age, gender, sector of activity, symptoms, suspected diagnosis, diagnostics, patients issues recovery and mortality rate.

The sector of activity was: the primary sector includes all activities whose purpose is the exploitation of natural resources: agriculture, fishing, forestry, mining, deposits. The secondary sector includes all activities consisting of a more or less elaborate transformation of raw materials such as manufacturing industries, but also construction. The tertiary sector includes all commercial activity (trade, transport, financial activities, services to companies, services to individuals, accommodation and catering, real estate, information and communication); the mainly non-market tertiary sector (public administration, education, human health, social action)

The mortality rate proportion of patients reported dead from the infection in question, the recovery rate is the proportion of patients reported and discharged cured.

We define different infectious cases according to the World Health Organization (WHO) guidelines. Malaria is defined by fever associated with clinical symptoms: neurological symptoms, digestive symptoms, circulatory disorders, renal failure, bleeding, with positive rapid diagnostic test and/or microscopy test [8]. Tuberculosis: tuberculosis is confirmed bacteriologically when the biological sample is positive by smear microscopy, culture or WHO-approved by Rapid Diagnostic Test (RDT) (e.g. genxpert Mycobacterium tuberculosis /Rifampicin Xpert MTB/RIF). These cases should be reported every time, regardless of whether treatment has been initiated [9]. According to WHO suspect cases measles: a case where a patient presented fever and a maculopapular (non-vesicular) rash, or in whom a health worker suspects measles [10]. Clinically compatible measles: a suspected case with fever and maculopapular rash and at least one cough, coryza, or conjunctivitis, but no adequate clinical specimen was collected, and the case was not epidemiologically linked to a laboratory-confirmed case of measles or to another communicable disease [10]. Community-acquired pneumonia is an acute infection of the lung parenchyma, acquired outside the hospital or if, in the hospital, it occurs before the 48th hour after admission [11]. Severe community-acquired pneumonia is a community-acquired pneumonia with symptoms of severity as impaired higher functions (impaired consciousness), impaired vital functions: systolic blood pressure  $< 90$  mmHg, heart rate  $> 120$  / min, respiratory rate  $> 30$  / min, temperature  $< 35^{\circ}\text{C}$  or  $\geq 40^{\circ}\text{C}$  associated neoplasia (active cancer or cancer diagnosed within the year, other than basal cell), known or suspected inhalation pneumonia or tracheobronchial obstruction [11].

Bacterial central nervous system is defined as a fever associated with neurological disorders and confirmed by the lumbar puncture as meningitis due to tuberculosis or other pathogens, or by imagery as a brain abscess. Other bacterial infections are infections diagnosed at discharge such as diarrhoeal infectious dis-

ease, typhoid fever, urinary tract infection. When there was more than one diagnosis for fever, the most likely etiology based on clinical and paraclinical data was selected as the main etiological diagnosis.

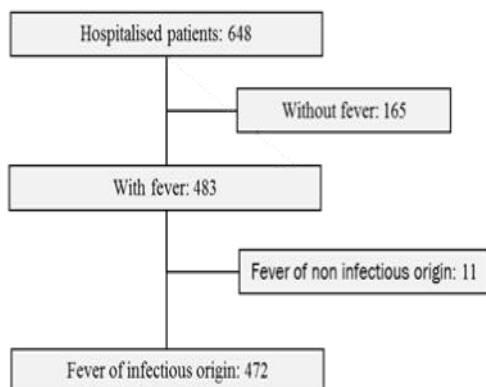
Categorical variables were represented by proportions. Quantitative variables were represented by the median and its interquartile range (IQR). Categorical variables were compared using the chi-square test or Fischer's exact test. Statistical analysis was performed with Epi info<sup>®</sup> 7.2.2 software.

We obtained the agreement of the competent authority for the analysis to use the archived medical records of the patients. Data collection was carried out in an anonymous manner.

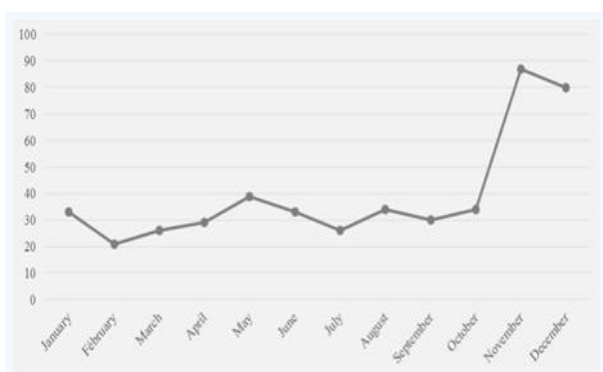
## RESULTS

During the study period, 648 patients were hospitalised of whom 472 (72.8%) presented with fever due to infectious disease (Figure 1).

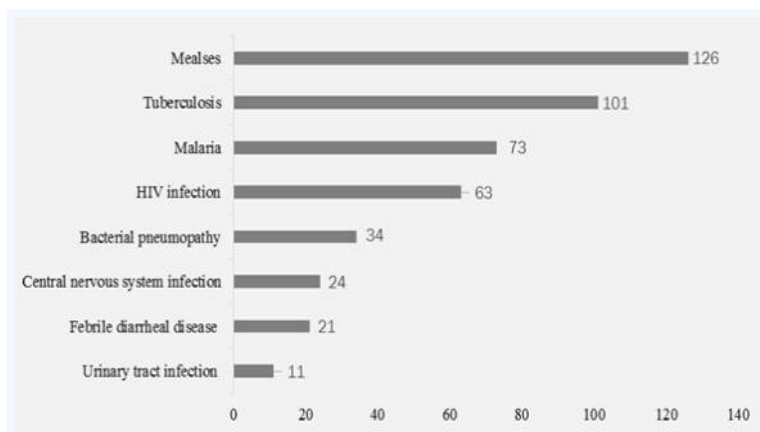
**Figure 1** : PRISMA flow chart



The mean age was  $32 \pm 5.3$  years. The study population was predominantly male ( $n=288$ ; 61%) with a sex ratio of 1.56. According to the sector of activity, half of them ( $n=242$ ; 51.3%) were in the tertiary sector. Figure 2 shows the monthly evolution of the number of hospitalised patients.



**Figure 2** : Monthly evolution of the number of hospitalisation



**Figure 3** : Main aetiologies of febrile illnesses

Among patients hospitalised in the Infectious Diseases Department, the main reasons for hospital admission were: skin rash ( $n=112$ ; 23.7%), infectious symptoms ( $n=96$ ; 20.3%), dyspnoea or cough ( $n=77$ ; 16.3%) and altered consciousness ( $n=75$ ; 15.9%).

The mean duration of symptom evolution before hospitalisation was 7 days  $\pm$  3.1. The mean duration was  $28 \pm 9.2$  days for patients diagnosed with tuberculosis and for patients with Human Immunodeficiency Virus / Acquired Immunodeficiency Syndrome (HIV/AIDS). Fever lasting less than 5 days was found in 138 (29.2%) patients, between 6 and 20 days in 202 (42.8%) patients and more than 21 days in 132 (28%) patients.

The main aetiologies of febrile illnesses were: measles ( $n=126$ ; 26.7%), tuberculosis ( $n=101$ ; 21.4%), malaria ( $n=73$ ; 15.5%), HIV infection ( $n=63$ ; 13.4%). Figure 3 shows the diagnoses of patients hospitalised for febrile illnesses. Of the patients diagnosed with HIV infection, 30 (47.6%) presented with tuberculosis. The most frequent forms of tuberculosis were pulmonary ( $n=39$ ; 38.1%), meningoencephalitis ( $n=36$ ; 35.9%), pleural ( $n=20$ ; 19.8%), miliary ( $n=11$ ; 10.7%) and lymph node ( $n=8$ ; 7.6%).

Measles was the main etiological diagnosis (126 patients) during this period. The median age of measles patients was 30 years  $\pm$  11.2 and the majority belong to the age group 26 to 35 years. The youngest is 15 years old and the oldest 47 years old. The sex ratio for the patients with measles was 0.8. No cases of death in adult measles patients have been recorded.

The median duration of hospitalisation was 4 days  $\pm$  3.1. The overall mortality rate was 15%, this rate was 32.7% for tuberculosis patients; 29.2% for central nervous system infections; 20.6% for patients living with HIV. Table I summarises the mortality rate for each disease (cf Table I)

## DISCUSSION

Febrile diseases were one of the main causes of hospitalization in the infectious diseases department, presented by 72.8% of patients.

**Table I** : Causes of death and lethality

	Patients n=472	Percentage %
<b>Causes of death</b>		
<i>Tuberculosis</i>	33	46.5
<i>HIV infection</i>	13	18.3
<i>Bacterial pneumonia</i>	8	11.3
<i>Malaria</i>	8	11.3
<i>Bacterial infection of the CNS</i>	7	9.9
<i>Others</i>	2	2.8
<b>Mortality rates</b>		
<i>Overall mortality</i>		15
<i>Tuberculosis</i>		32.7
<i>Bacterial infection of the CNS</i>		29.2
<i>Bacterial pneumonia</i>		23.5
<i>HIV infection</i>		20.6
<i>Malaria</i>		11

HIV : Human immunodeficiency virus; CNS : Central nervous system

The main etiological diagnoses were measles followed by malaria, tuberculosis, HIV infection. Measles was a re-emerging infection in Madagascar in 2018 [12-13]. It was the most common cause of hospitalization in adults during this period of study because of measles outbreak and it is mostly manifested by skin rash associated with fever. The combination of tuberculosis and HIV infection (HIV/TB) was found in 30 patients. This co-infection places a heavy burden on health systems and poses special diagnostic and therapeutic challenges [14]. According to the literature, the risk of tuberculosis increases by 2 to 5 times with early HIV-1 infection and by more than 20 times with advanced HIV-1 infection [15] [16]. Yet, TB is the leading cause of death among people living with HIV and accounts for one in three HIV-related deaths [17]. In addition, *Mycobacterium tuberculosis* co-infection negatively impacts immune responses to HIV, as evidenced by the higher incidence of new Acquired Immuno Deficiency Syndrome AIDS-defining opportunistic infections in HIV and TB co-infected individuals [18]. This is certainly a "cursed duo" and TB screening should not be neglected in HIV patients, especially if they have fever. This duo is the main reason for hospitalization of tuberculosis cases in the Infectious Diseases Department. In our results, tuberculosis was the leading cause of death (n=33; 46.5%), followed by HIV infection (n=13; 18.3%), bacterial pneumonia (n=8; 11.3%), malaria (n=8; 11.3%) and central nervous system infection (n=7; 9.9%). In Uganda, in two tertiary hospitals, after one month of follow-up for febrile illness, 16 (13.6%) of 118 patients died, and those who died were more tachypneic (median 24.5 breaths per minute, IQR: 22 to 31 breaths per minute) than survivors (median 20 breaths per minute; IQR: 18 to 24 breaths per minute). Fatal cases also had lower initial oxygen saturation (median 95.5%; IQR: 92.3 to

98% vs median 98.0%; IQR: 96.0 to 99.0%). Half of fatal cases had an initial Quick Sequential Organ Failure Assessment (qSOFA) score  $\geq 2$  compared with 16.7% of nonfatal cases. However, the leading causes of febrile illness were malaria and tuberculosis; tuberculosis remained the leading cause of death [19]. This highlights the severity of the disease and underscores the importance of early diagnosis through increased screening. In Madagascar, this high mortality may be related to a lack of ongoing training, inaccessible means of screening for some healthcare facilities, resulting in delayed diagnosis. A meta-analysis conducted in African countries on the causes of febrile illnesses other than malaria emphasizes that delay in diagnosis and treatment of these diseases leads to high mortality [20]. However, knowledge of infectious diseases is essential to refine pathogen-specific control measures, hence the need to train health workers in the management of febrile diseases and to establish a standardized protocol for better management of febrile diseases [19,20].

Our study is limited because only a few cases were identified, it was conducted during the measles outbreak and over a one-year period, it was a monocentric study. This contributes to a selection bias by overestimating the number of measles cases and masking other causes of febrile illness.

Most of the time, the lack of confirmation of the diagnosis did not identify the primary cause of the infections, such as blood culture, imaging. Some patients may have also an infection but no fever or may have taken antipyretics or antibiotics for more than 48 hours, which may underestimate the actual number of patients with febrile illness. However, we can show that tuberculosis and malaria are the main causes apart from measles. Moreover, the frequency of tropical infections and the causes of fever and death found in our result are different from those found in other tropical or subtropical countries or among immigrants from a tropical country, which vary from one country to another. This difference could be related to the differences in climate and geographical location of each tropical country [21]. This again emphasizes the need for each country and region to identify the main causes of febrile illnesses in order to improve the management and outcome of these illnesses. Capacity building is therefore crucial to help healthcare workers to manage these diseases and preventive measures can be put in place such as vaccination, preventive treatment (malaria) and early diagnosis to improve the prognosis of these diseases.

## CONCLUSION

Measles, tuberculosis, malaria and HIV infection were the main reasons for hospitalisation. The overall mortality rate was high; tuberculosis and HIV infection were the leading causes of death. Increase Screening, research for strategies and capacity building of healthcare workers are important in order to improve the management of these diseases in a tropical countries including Madagascar.

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