

# Fighting adult mortality through etiology of fever studies: Description of high mortality in an adult inpatient population in Mozambique

Justina Bramugy<sup>1</sup>, Sham Lal<sup>3</sup>, Marta Valente<sup>1,2</sup>, Sara Ajanovic<sup>1,2</sup>, Oliver Baerenbold<sup>3</sup>, Heidi Hopkins<sup>3</sup>, David Mabey<sup>3</sup>, Quique Bassat<sup>1,2,4,5,6</sup>

<sup>1</sup> Centro de Investigação em Saúde de Manhiça (CISM), Maputo, Mozambique. <sup>2</sup> ISGlobal, Hospital Clínic - Universitat de Barcelona, Barcelona, Spain. <sup>3</sup> London School of Hygiene and Tropical Medicine, London, United Kingdom <sup>4</sup> ICREA, Pg. Lluís Companys 23, 08010 Barcelona, Spain; <sup>5</sup> Pediatric Department, Hospital Sant Joan de Déu (Universidade de Barcelona), Barcelona, Spain; <sup>6</sup> CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain.

## Background

Fever is a common symptom leading to health care seeking and hospital admission in Africa. Mortality rates in febrile adult inpatients in Mozambique are high and are associated with high underlying prevalence of co-morbidities like HIV and cardiovascular diseases, and delays in care-seeking. Better characterization of febrile teenage and adult patients in terms of clinical presentation, diagnostic laboratory findings, and outcomes may be important for a more evidence-based evaluation of current clinical management algorithms, with the aim of decreasing preventable mortality.

## Methods

The observational study “**FIEBRE: Febrile illness evaluation in a broad range of endemicities**” recruited febrile patients in Mozambique, Zimbabwe, Malawi and Lao PDR to identify infectious causes of fever and antimicrobial susceptibility of bacterial pathogens. Comprehensive clinical and laboratory testing was conducted, including local and centralised analyses in reference laboratories.

We hereby present mortality data from adult Mozambican outpatients and inpatients (Jan 2019-Feb 2021) at Manhiça District Hospital, Mozambique.

- Patients presenting with fever were enrolled and provided clinical data, pharyngeal swabs and a venous blood sample; selected participants also provided a urine sample (those who had urinary symptoms and all HIV positive).
  - Laboratory assessments target infections that are treatable and/or preventable.
  - Selected point-of-care tests (POCT) [urine dipstick, malaria and HIV testing, serum cryptococcal antigen (CrAg) and urine lipoarabinomannan (uLAM), as well as blood and urine cultures and antimicrobial susceptibility testing, were performed on site.
  - On day 28, patients provided a second venous blood sample for serology and information on clinical outcomes.
- Further diagnostic assays were performed at international reference Laboratories including:
- blood parasites; bacterial, mycobacterial and fungal bloodstream infections; typhus group and spotted fever group Rickettsia spp; Orientia tsutsugamushi; Coxiella burnetii; Leptospira spp; Brucella spp; Borrelia spp that cause relapsing fever; Leishmania spp; and arboviruses (1)

(1)- Hopkins H, Bassat Q, Chandler CIR, et al. Febrile Illness Evaluation in a Broad Range of Endemicities (FIEBRE): protocol for a multisite prospective observational study of the causes of fever in Africa and Asia. *BMJ Open* 2020;10:e035632. doi:10.1136/bmjopen-2019-035632

## Results

During the study period, a total of 792 teenage (>15 yo) and adult patients were recruited (445 (56,1%) outpatients, 347 (43,8%) inpatients). 92 died within the first 28 days of recruitment, yielding a case fatality rate of 11.6%.

Table 1: Adult Study Population, by site

Variable	Inpatient N = 347	Outpatient N = 445
Age (years)		
Median (IQR)	38.0 (29.0, 52.0)	31.0 (24.0, 41.0)
Range	16.0-90.0	17.0-76.0
Age group, n (%)		
15 - <25	53 (15%)	123 (28%)
25 - <35	84 (24%)	135 (30%)
35 - <40	90 (26%)	99 (22%)
45 - <55	45 (13%)	46 (10%)
55 - <65	47 (14%)	28 (6.3%)
65+	28 (8.1%)	14 (3.1%)
Gender, n (%)		
Female	192 (55%)	335 (75%)
Male	155 (45%)	110 (25%)
Temperature (°C)		
Median (IQR)	38.2 (37.8, 38.9)	38.0 (37.7, 38.4)
Range	37.5, 41.0	37.5, 40.5
Day 28 outcome n (%)		
Alive	262 (76%)	438 (98%)
Dead	85 (24%)	7 (1.6%)
HIV status, n (%)		
Positive	187 (54%)	186 (42%)
Negative	153 (44%)	252 (57%)
Unknown	4 (1.2%)	3 (0.7%)
Indeterminate	3 (0.9%)	4 (0.9%)

Figure 1: FIEBRE study nurse with adult patient recruited into study



Table 2: Demographic and clinical characteristics of patients by day 28 outcome

Variable	Alive N= 700	Dead N = 92	Overall N = 792
Age (years)			
Median (IQR)	34.0 (25.0, 44.0)	41.0 (33.0, 56.5)	35.0 (26.0, 46.0)
Range	16.0, 90.0	20.0, 86.0	16.0, 90.0
Age group, n (%)			
15 - <25	170 (97%)	6 (3.4%)	176 (100%)
25 - <35	197 (90%)	22 (10%)	219 (100%)
35 - <40	162 (86%)	27 (14%)	189 (100%)
45 - <55	81 (89%)	10 (11%)	91 (100%)
55 - <65	58 (77%)	17 (23%)	75 (100%)
65+	32 (76%)	10 (24%)	42 (100%)
Gender, n (%)			
Female	481 (91%)	46 (8.7%)	527 (100%)
Male	219 (83%)	46 (17%)	265 (100%)
Patient group, n (%)			
Inpatient	262 (76%)	85 (24%)	347 (100%)
Outpatient	438 (98%)	7 (1.6%)	445 (100%)
Temperature (°C)			
Median (IQR)	38.0 (37.7, 38.6)	38.2 (37.9, 38.9)	38.0 (37.7, 38.6)
Range	37.5, 40.6	37.5, 41.0	37.5, 41.0
HIV status, n (%)			
Positive	316 (85%)	57 (15%)	373 (100%)
Negative	373 (92%)	32 (7.9%)	405 (100%)
Unknown	5 (71%)	2 (29%)	7 (100%)
Indeterminate	6 (86%)	1 (14%)	7 (100%)
HIV result POCT, n (%)			
indet	6 (86%)	1 (14%)	7 (100%)
neg	342 (92%)	28 (7.6%)	370 (100%)
pos	89 (79%)	24 (21%)	113 (100%)
(Missing)	263	39	302
Malaria POCT, n (%)			
indet	2 (40%)	3 (60%)	5 (100%)
neg	637 (88%)	87 (12%)	724 (100%)
pos	61 (97%)	2 (3.2%)	63 (100%)
CrAg POCT, n (%)			
indet	43 (81%)	10 (19%)	53 (100%)
neg	391 (84%)	75 (16%)	466 (100%)
pos	5 (83%)	1 (17%)	6 (100%)
(Missing)	261	6	267
uLAM POCT, n (%)			
indeterminate	2 (100%)	0 (0%)	2 (100%)
negative	222 (89%)	27 (11%)	249 (100%)
positive	20 (87%)	3 (13%)	23 (100%)
(Missing)	456	62	518
Diabetes, n (%)			
no	383 (87%)	59 (13%)	442 (100%)
Unknown	300 (91%)	28 (8.5%)	328 (100%)
yes	17 (77%)	5 (23%)	22 (100%)
Sickle cell, n (%)			
no	615 (90%)	71 (10%)	686 (100%)
Unknown	18 (86%)	3 (14%)	21 (100%)
yes	67 (79%)	18 (21%)	85 (100%)
Blood culture results, n (%)			
contaminated	10 (67%)	5 (33%)	15 (100%)
negative	594 (92%)	52 (8.0%)	646 (100%)
positive	43 (83%)	9 (17%)	52 (100%)
(Missing)	53	26	79

Figure 2: Point of care tests collected as part of the FIEBRE procedures (Photo: Heidi Hopkins)



## Discussion and conclusions

- The FIEBRE multi-site study will provide an invaluable set of data on febrile illness across Africa and Asia
- Mortality among adult Mozambican inpatients with febrile illness remains unacceptably high
- Malaria plays an important role in febrile illness, but a minor role in terms of teenager and adult mortality
- Tuberculosis remains highly prevalent as a cause of febrile illness in this population, but with low short-term associated mortality
- Cryptococcal invasive diseases affected ~1% of patients in this population with very high prevalence of HIV (47%)
- Invasive bacterial infections were detected in 6.6% of patients, with a high associated mortality. However, the low yield of a single blood culture may have led to an important underestimate of the real burden
- HIV infection significantly increased the risk of dying among our febrile patients (p<0.001)
- Most deaths were related to preventable and treatable opportunistic infections in the context of underlying HIV infection
- Comprehensive strategies to address HIV infection at all stages (prevention, diagnosis and treatment) are needed to decrease mortality.
- While awaiting final centralized diagnostic results from reference laboratories, local laboratory results already reveal a number of causes of preventable deaths
- The detailed analysis of all patient's results will provide a roadmap upon which to base policy change to improve the management of fever in teenagers and adults, and ultimately increase their survival

## Contact details/email

Justina Bramugy: justina.bramugy@manhica.net  
Quique Bassat: quique.bassat@isglobal.org

www.lshtm.ac.uk/febre  
@FeverStudies

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