



Febrile Illness Evaluation in a Broad Range of Endemicities (FIEBRE)

What are the leading causes of fever in children and adults in sub-Saharan Africa and Southeast Asia, and how should they be treated?

FIEBRE at a glance

FIEBRE is a multi-disciplinary study investigating the causes of febrile illness at multiple sites in sub-Saharan Africa and Southeast Asia where there is currently little information and very limited diagnostic capacity for the management of patients with fever.

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The study aims to recruit a total of 9,600 patients overall, both children and adults, and more than 2,400 community controls in order to generate, for the first time, a detailed description of the infectious causes of fever in the study regions.

The main research objectives are to:



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Identify the most common infectious causes of fever that are treatable and/or preventable



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Provide data on antimicrobial susceptibility of bacterial infections



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Learn how local perceptions of fever affect treatment practices, including the use of diagnostics and antimicrobial drugs



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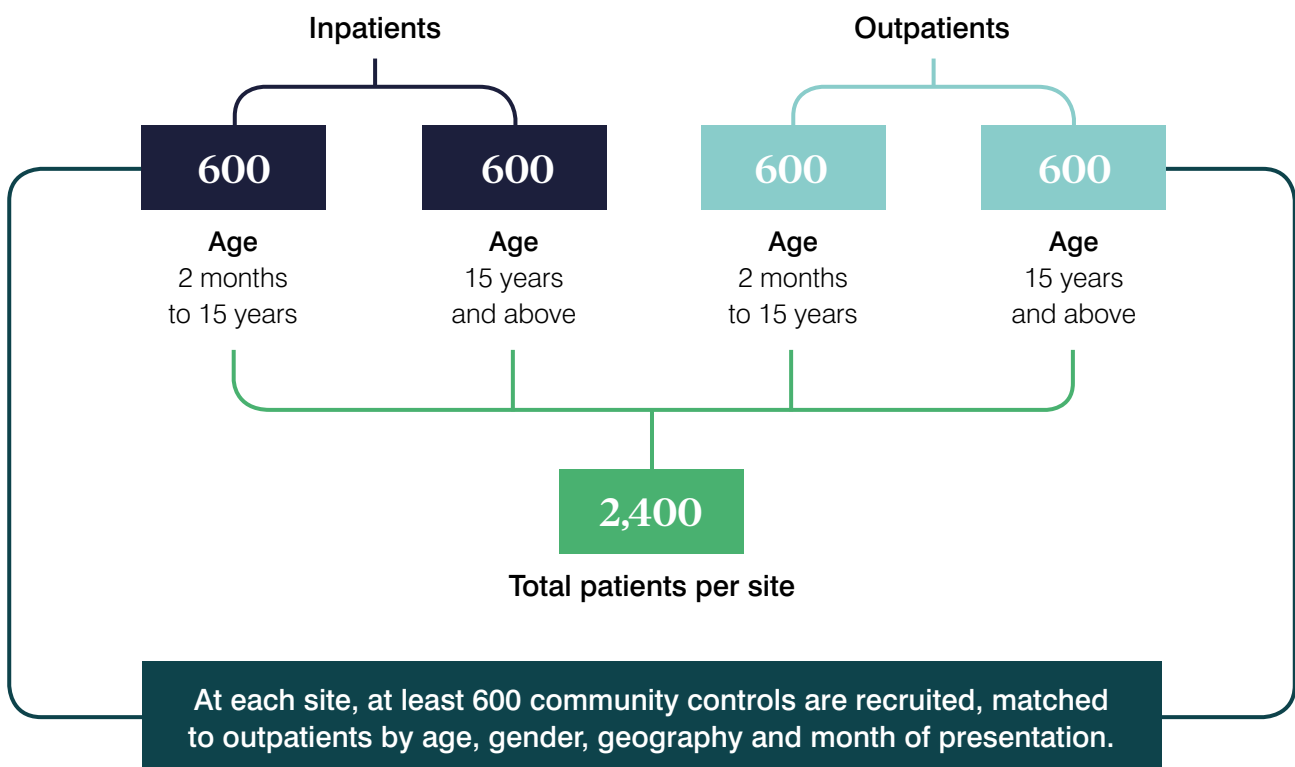
Inform clinical guidelines and algorithms on how to manage patients with fever

The data collected will contribute to updated recommendations for the clinical management and prevention of febrile illnesses, and help with the design of new evidence-based guidelines for fever case management, adapted to local contexts. It will also provide a platform for monitoring antimicrobial susceptibility in the study areas. These data will help to ensure patients receive treatments that give them the best chance of recovery, as well as help stop the spread of antimicrobial resistance.

FIEBRE in numbers

Outpatients and inpatients who present with fever are recruited and enrolled if they meet study selection criteria (including informed consent). Recruitment of community controls is based on matching with outpatients by age, gender and area of residence.

Target sample size at each site



FIEBRE social science

We currently know little about the antibiotics being used to treat febrile illnesses and how we could safely reduce antimicrobial use. Social science research has been called for to understand our relationships with antibiotics and how we can optimise their use in fever case management. The FIEBRE social science study seeks to understand how fever is understood by different communities of practice and how this affects treatment practices.

In order to shed light on how patients with fever are managed in practice, the FIEBRE social science study uses an ethnographic approach derived from medical anthropology. This includes participant observation and interviews in a variety of settings including clinics, hospitals, pharmacies, markets and households, as well as a medicines survey to identify broader patterns of antibiotic use and access at the community level. Findings will be used alongside clinical data to inform revised guidelines for fever case management that are sensitive to the contexts in which they are used.

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FIEBRE social science is working in three countries:

Malawi

Our researchers in Malawi are based at the Malawi-Liverpool Wellcome Trust Clinical Research Programme (MLW) with a field site in rural Chikwawa District.

Myanmar

Our team in Myanmar are primarily based in the city of Yangon with some activities possibly taking them to other regions.

Zimbabwe

Our Zimbabwe team is based at the Biomedical Research and Training Institute (BRTI). The field site is Harare, the capital city.

Whom we work with and where

FIEBRE is co-ordinated by the London School of Hygiene & Tropical Medicine, in collaboration with Barcelona Institute for Global Health (ISGlobal), Liverpool School of Tropical Medicine, the Universities of Otago and Oxford, partner institutions in Lao PDR, Malawi, Mozambique and Zimbabwe.

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Samples from patients will be sent to internationally recognised reference laboratories in Australia, France, Germany, New Zealand, Thailand, the UK and the USA for the diagnosis of specific infections, using state of the art methodology.

FIEBRE partners

The study sites in each country cover a variety of rural, urban and peri-urban areas.

LOMWRU.

Laos – Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit (LOMWRU)

Vientiane Provincial Hospital, a hospital which serves a rural community approximately 70 km from the capital city of Vientiane and the LOMWRU base.



Malawi – Malawi-Liverpool Wellcome Trust Clinical Research Programme (MLW)

Chikwawa District Hospital and a local clinic in Nchalo, both in Chikwawa district, a rural area in southern Malawi.



Mozambique – Centro de Investigação em Saúde de Manhica (CISM)

Manhiça District Hospital, the referral health facility for a rural area located 90 km from the capital city of Maputo.



Zimbabwe – Biomedical Research and Training Institute (BRTI)

Harare Central Hospital and Chitungwiza General Hospital (urban setting) and Budiro, Glen View and Rutsanana polyclinics in peri-urban communities in south-western Harare.

What are we looking for?

Infectious causes of fever that are preventable and/or treatable.

Some diagnostic tests are performed at or near the point of care at each study site, both to inform patient care and to contribute to study data:

Diagnostic tests performed at/or near point of care

microscopy and rapid diagnostic test for malaria (*Plasmodium species*)

HIV rapid diagnostic tests (African sites)

cryptococcal antigen lateral flow assay

urinary lipoarabinomannan rapid test (uLAM) to detect *Mycobacteria tuberculosis* (HIV infected African adults)

urine dipstick and culture (small children and older patients with urinary tract infection symptoms)

blood culture and antimicrobial susceptibility testing

mycobacterial blood culture (HIV infected African adults)



Further pathogen-based diagnostic tests will be performed on participant samples at internationally recognised reference laboratories:

Diagnostic tests performed at reference laboratories	
Infection or pathogen	Diagnostic test/s
arboviruses: chikungunya, dengue, Japanese encephalitis, o'nyong 'nyong, West Nile, yellow fever, Zika	IgG ELISA ¹ and qPCR ² ; microneutralisation for ELISA positives
borreliosis (louse- and tick-borne relapsing fevers)	expert microscopy
brucellosis	IgM EIA ¹ ; microagglutination test for EIA positives
histoplasmosis	EIA ¹
leishmaniasis (visceral)	direct agglutination test
leptospirosis	microagglutination test
paediatric viremia and/or bacteraemia	PCR
Q fever, scrub typhus, spotted fever group rickettsioses, typhus group rickettsioses	IgG and IgM IFA ³ ; qPCR ² for IFA positives
respiratory pathogens: influenza A and B, respiratory syncytial virus (RSV) ⁴	Luminex respiratory panel
<ol style="list-style-type: none"> 1. EIA, ELISA: enzyme immunoassay, enzyme-linked immunosorbent assay 2. qPCR: quantitative polymerase chain reaction 3. IFA: immunofluorescence assay 4. The Luminex respiratory panel also detects: adenovirus, parainfluenza virus 1-4, enterovirus, rhinovirus, B virus, corona viruses (229E, OC43, HKU1, NL63), metapneumovirus, Boca virus, <i>Legionella pneumoniae</i>, <i>Chlamydia pneumoniae</i> and <i>Mycoplasma pneumoniae</i>. 	

Quality assessment tests	
malaria (<i>Plasmodium</i> species)	expert microscopy
bacteria and fungi isolated from blood and urine at sites	MALDI-TOF MS ⁵ for identification and antimicrobial susceptibility testing to EUCAST ⁶ standards
mycobacteria isolated from blood at sites	sub-culture and molecular testing, antimicrobial susceptibility testing
<ol style="list-style-type: none"> 5. MALDI-TOF MS: matrix-assisted laser desorption ionization time-of-flight mass spectrometry 6. EUCAST: European Committee of Antimicrobial Susceptibility Testing 	



Main organisations

- 1 London School of Hygiene & Tropical Medicine, UK
- 2 Barcelona Institute for Global Health
- 3 Liverpool School of Tropical Medicine
- 4 University of Otago
- 5 University of Oxford

Partner institutions

- 6 Biomedical Research and Training Institute, Harare
- 7 Centro de Investigação em Saúde de Manhiça, Manhiça
- 8 Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit, Vientiane
- 9 Malawi-Liverpool Wellcome Trust Clinical Research Programme, Blantyre

Laboratories

- 10 Australian Rickettsial Reference Laboratory, Australia
- 11 Leibniz-Centre for Medicine and Life Sciences, National and Supranational Reference Mycobacterium Laboratory, Germany
- 12 Liverpool Clinical Laboratories, UK
- 13 Liverpool School of Tropical Medicine, UK
- 14 London School of Hygiene & Tropical Medicine, UK
- 15 Mahidol Oxford Tropical Medicine Research Unit, Thailand
- 16 Micropathology Ltd, UK
- 17 MiraVista Diagnostics, USA
- 18 Queensland Health Leptospirosis Reference Laboratory, Australia
- 19 Southern Community Laboratories and University of Otago, New Zealand



Laboratories

- 20 Unité des virus émergents,
L'Institut de Recherche pour
le Développement, France

Social science

- 21 Chikwawa, Malawi
- 22 Harare, Zimbabwe
- 23 Yangon, Myanmar

Participant samples also will be analysed for markers of host immune and endothelial activation, to identify markers that may be associated with severity of disease and/or presence of certain infections:

Markers of immune and endothelial activation

Biomarker	Name
CRP	C-reactive protein
PCT	procalcitonin
Chitinase	chitinase
Ang-1	angiopoietin-tie-1
Ang-2	angiopoietin-tie-2
Azu/HBP	azuroidin 1/heparin binding protein
FLT-1	fms-like tyrosine kinase-1
sTNFR-1	soluble tumour necrosis factor receptor-1
TREM-1	triggering receptor expressed on myeloid cells-1
TRAIL	TNF-related apoptosis-inducing ligand
IL-6	interleukin-6
IL-8	interleukin-8
IL-10	interleukin-10
IP-10	interferon gamma-induced protein 10
MxA	myxovirus resistance protein A

Looking forward

This study will inform the development of new, context specific clinical algorithms for the management of patients with fever.

It also provides a unique opportunity to collect and store biomedical samples alongside clinical data from a large and well-characterised group of febrile patients and controls.

The archive will be useful for identification of novel diagnostic targets, and for development and evaluation of new point-of-care diagnostic tests intended to guide the management of febrile patients. New tests could include those that predict severity of illness, detect specific infections, and/or differentiate between bacterial and viral infections.



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Image accreditations

Front page (bottom left) – Pipetting samples, Mozambique
(top left) – Malaria rapid diagnostic test, Laos
(top right) – Blood samples, Antonio Mendes

Page 3 – Laboratory technology aliquots blood samples, Mozambique
Page 6 – Patient recruitment, Malawi, Thoko Chikondi, Wellcome Trust
Page 10 – Agar plate streaked with specimen, Mozambique



Funding

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