FIEBRE

Febrile Illness Evaluation in a Broad Range of Endemicities

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?

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FIEBRE at a glance

FIEBRE is a multi-disciplinary prospective 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.

The main research objectives are to:

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

Provide data on antimicrobial susceptibility of bacterial infections

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

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.

Whom we work with and where

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

Samples from study participants were 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.

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 St Montfort Mission Hospital in Nchalo, both in Chikwawa district, a rural area in southern Malawi.
Mozambique – Centro de Investigação em Saúde de Manhiça (CISM)	Manhiça District Hospital, the referral health facility for a rural area located 90 km from the capital city of Maputo and Hospital Geral José Macamo in Maputo, an urban centre.
Zimbabwe – Biomedical Research and Training Institute (BRTI)	Harare Central Hospital and Chitungwiza General Hospital (urban setting) and Budiriro, Glen View and Rutsanana polyclinics in peri-urban communities in south-western Harare.

Partner institutions

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
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

Collaborating reference laboratories

10. Australian Rickettsial Reference Laboratory, Australia
11. Institut Pasteur, France
12. Leibniz-Centre for Medicine and Life Sciences, National and Supranational Reference Mycobacterium Laboratory, Germany
13. Liverpool Clinical Laboratories, UK
14. Liverpool School of Tropical Medicine, UK
15. London School of Hygiene & Tropical Medicine, UK
16. Mahidol Oxford Tropical Medicine Research Unit, Thailand
17. Micropathology Ltd, UK
18. MiraVista Diagnostics, USA
19. Southern Community Laboratories and University of Otago, New Zealand
20. Unité des virus émergents, L'Institut de Recherche pour le Développement, France

Participant recruitment centres

21. Biomedical Research and Training Institute, Harare
22. Centro de Investigação em Saúde de Manhiça, Manhiça
23. Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit, Vientiane
24. Malawi-Liverpool Wellcome Trust Clinical Research Programme, Blantyre

Social science activities

25. Chikwawa, Malawi
26. Harare, Zimbabwe
27. Yangon, Myanmar

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
rapid diagnostic test and microscopy for malaria (*Plasmodium* species)
HIV rapid diagnostic test/s (African sites)
blood culture and antimicrobial susceptibility testing
urine dipstick and culture (small children, and older patients with urinary tract infection symptoms)
mycobacterial blood culture (HIV-infected adult patients)
urinary lipoarabinomannan rapid test (uLAM) to detect *Mycobacterium tuberculosis* (HIV-infected patients)
cryptococcal antigen lateral flow assay (inpatients and HIV-infected outpatients)

Further pathogen-based diagnostic tests is being 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, malaria	expert microscopy
brucellosis	IgM EIA[1]; microagglutination test for EIA positives
histoplasmosis	EIA[1]
leishmaniasis (visceral)	IgG ELISA and PCR
leptospirosis	microagglutination test
Q fever, scrub typhus, spotted fever group rickettsioses, typhus group rickettsioses	IgG and IgM IFA[3]; qPCR[2] for IFA[3] positives
respiratory pathogens: influenza A and B, respiratory syncytial virus (RSV)[4]	Luminex respiratory panel
External quality assessment for testing performed at study sites	
malaria (*Plasmodium* 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
potential future testing for paediatric viraemia and/or bacteraemia	PCR

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, *Legionella pneumoniae, Chlamydia pneumoniae and Mycoplasma pneumoniae*.
5. MALDI-TOF MS: matrix-assisted laser desorption ionization time-of-flight mass spectrometry
6. EUCAST: European Committee of Antimicrobial Susceptibility Testing

FIEBRE in numbers

FIEBRE enrolled children and adult inpatients and outpatients who presented with fever. Over the course of 24 months, outpatients and inpatients who presented with a fever were recruited and enrolled if they met study selection criteria (including informed consent). All participating patients provided a venous blood sample and pharyngeal swab samples, and selected patients provided a urine sample. Patients were followed up 28 days after enrolment to record clinical outcome and to obtain a convalescent blood sample.

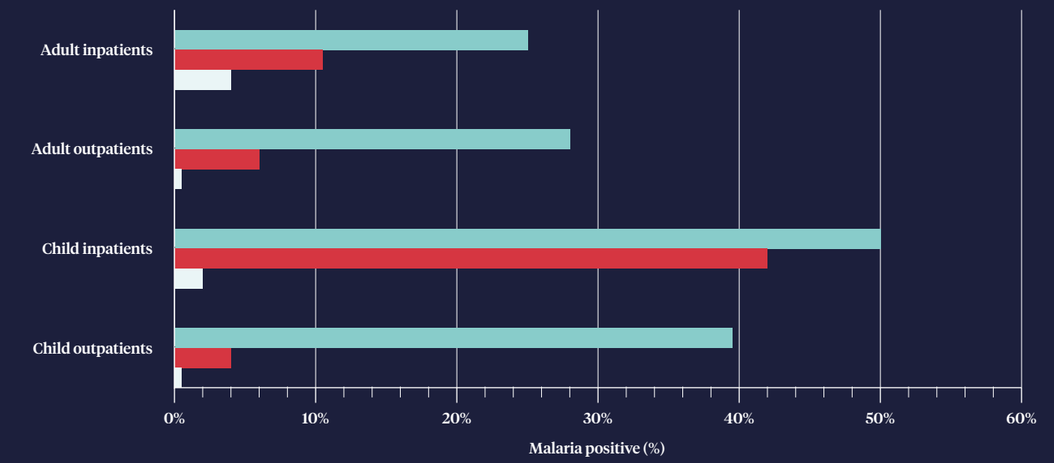
In addition, community controls were recruited, matched with outpatients by age, gender and area of residence. Community controls provided blood and pharyngeal samples to allow estimation of background prevalence of specific pathogens. The controls were also surveyed to obtain representative data about treatment seeking and medicine use.

Patient enrolment and participant characteristics

	Laos	Malawi	Mozambique	Zimbabwe	All sites
Total patients enrolled	**1,972**	**1,767**	**2,141**	**1,924**	**7,804**
Female	50%	56%	55%	49%	53%
Male	50%	44%	45%	51%	47%
Aged <15 years	39%	54%	53%	46%	48%
Aged ≥15 years	61%	46%	47%	55%	52%
Inpatient	52%	32%	46%	42%	43%
Outpatient	48%	68%	54%	58%	57%
Total controls	**484**	**908**	**561**	**436**	**2,389**

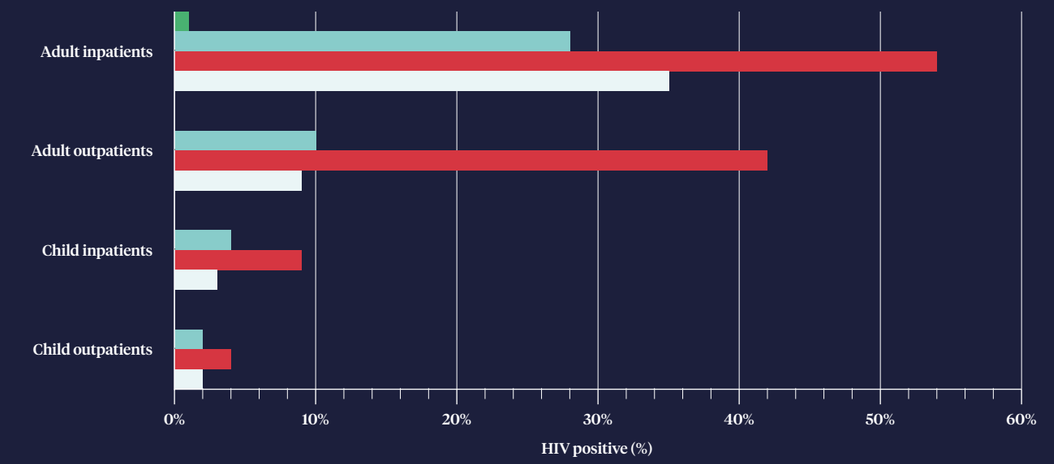
Point of care test results

Malaria
Malaria RDT results by patient group



Malaria test positive (HRP2-pLDH combination RDT)
Malaria testing was done in Laos, but all results were negative.

HIV
HIV results by patient group



HIV-infected (known at enrolment, or tested positive).
HIV testing was not done in Laos.

Social science findings

The social science research took place in Malawi, Myanmar and Zimbabwe. The teams began with a core shared research objective – to understand the roles of antimicrobials in fever case management for prescribers, local residents and a range of stakeholders. The focus of each study was defined by local priorities and access. In Malawi, the research focused on public sector primary care and residents in a rural area with limited resources. In Myanmar, the research focused on drug shops and labourers in an industrial zone of Yangon. In Zimbabwe, the research focused on public sector care as well as other sources of antibiotics in urban Harare, including non-governmental organisations and market places.

Research comprised 'drug bag' interviews with residents, immersive ethnography (observations) with providers and residents, interviews with a range of key informants, and documentary analysis of policies, media and historical materials (see table below).

Social science field research

	Malawi	Myanmar	Zimbabwe
Drug bag interviews	**925**	**50**	**436**
Residents, in-depth	100	50	100
Residents, survey	825	–	336
Ethnographic observation	**52 weeks**	**36 weeks**	**90 weeks**
Residential areas	24 weeks	12 weeks	20 weeks
Markets/drug shops	–	16 weeks	30 weeks
Pharmacies	–	–	20 weeks
Clinics	20 weeks	20 weeks	14 weeks
Hospitals	8 weeks	–	6 weeks
Stakeholders	–	–	–
Key informant interviews	**122**	**51**	**55**
Residents	60	17	10
Markets/drug shops	–	1	4
Pharmacy staff	–	–	3
Clinic staff	34	1	15
Hospital staff	16	–	6
Stakeholders	12	32	17

Findings were specific to each setting, in which particular relations with antimicrobials played out in the context of the management of fevers and other ailments. For example, in the Malawi study, antibiotics constituted care in a context of scarcity in which disease-specific programme drugs dominated; in the Zimbabwe site, antibiotics formed part of a global health architecture that constrained clinical choices and siloed the care options for residents, including sex workers; in Myanmar antibiotics were among medicines that enabled cheap labour, and antibiotic control efforts reinforced rather than alleviated reasons for informal antibiotic use.

Across the settings, commonalities emerged: antibiotics had come to prop-up particular systems of biomedical and biopolitical governance, and responses to fevers by providers and patients was mediated by prior experience with biomedical systems. This research points to the need for a wide-lens perspective to improve fever care and better target antimicrobial drugs; addressing the numerous registers and scales at which antibiotics have come to gain significance will be critical.

Participant samples are being 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
CH3L1	chitinase 3-like 1
Ang-1	angiopoietin-1
Ang-2	angiopoietin-2
Azu/HBP	azurocidin 1/Heparin binding protein
sTNFR-1	soluble tumour necrosis factor receptor-1
sTREM-1	soluble 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

FIEBRE results will inform the development of new and updated clinical algorithms for the management of patients with fever, tailored for local contexts. The study 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 sample 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.

Publications

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Justin Dixon, Eleanor MacPherson, Salome Manyau, Susan Nayiga, Yuzana Khine Zaw, Miriam Kayendeke, Christine Nabirye, Laurie Denyer Willis, Coll de Lima Hutchison, Clare I. R. Chandler
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The Lancet Infectious Diseases, Correspondence, Vol 19, Issue 9; Sept 2019 DOI: 10.1016/S1473-3099(19)30425-6

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European Journal of Clinical Microbiology & Infectious Diseases; July 2021 DOI:10.1007/s10096-021-04312-4

Negotiating authoritarian law and (dis)order: medicines, drug shops, and regulators in a poor Yangon suburb.

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Image accreditation

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Pipetting samples, Mozambique

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Malaria rapid diagnostic test, Laos

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Blood samples, Antonio Mendes

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Patient recruitment, Malawi, Thoko Chikondi, Wellcome Trust

Page 11
Drug bag interview, Malawi, Eleanor MacPherson

Page 12/13
Agar plate streaked with specimen, Mozambique

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