

# The main pathogens causing febrile illness and implications for fever management in Laos; preliminary results from the FIEBRE study



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## Introduction

Management of febrile illness in Laos typically relies on clinical assessment and empiric treatment, as laboratory confirmation is often not available, except for malaria and dengue rapid tests. The standard empirical treatment of inpatients with sepsis or febrile illness in Laos is parenteral ceftriaxone. Vientiane Provincial Hospital in northern Laos was one site of the multicentre FIEBRE (Febrile Illness in a Broad Range of Endemicities) study which performed a comprehensive evaluation of the causes of febrile illness in in- and outpatients of all ages. We aimed to describe the leading pathogens diagnosed from FIEBRE patients recruited in Laos.

## Study methods

- Prospective observational study, conducted between October 2018 and 2020, in Vientiane Provincial Hospital, Lao PDR.
- In- and out-patients with fever, aged 2 months and above were recruited. Matched community controls were enrolled to enable calculation of attributable fractions.
- Blood and nasopharyngeal specimens were tested using pathogen-based diagnostics:
  - a) Performed at or near the point of care: blood culture and malaria RDT/blood smear microscopy;
  - b) Performed at reference laboratories: Arboviruses, respiratory pathogens, rickettsial diseases, histoplasma and Leptospira
- Patients' usual care and antibiotic prescriptions from hospital clinicians were documented by the study team.
- Results of point of care tests (POCTs) and blood cultures performed at Mahosot hospital were reported immediately.

## Results

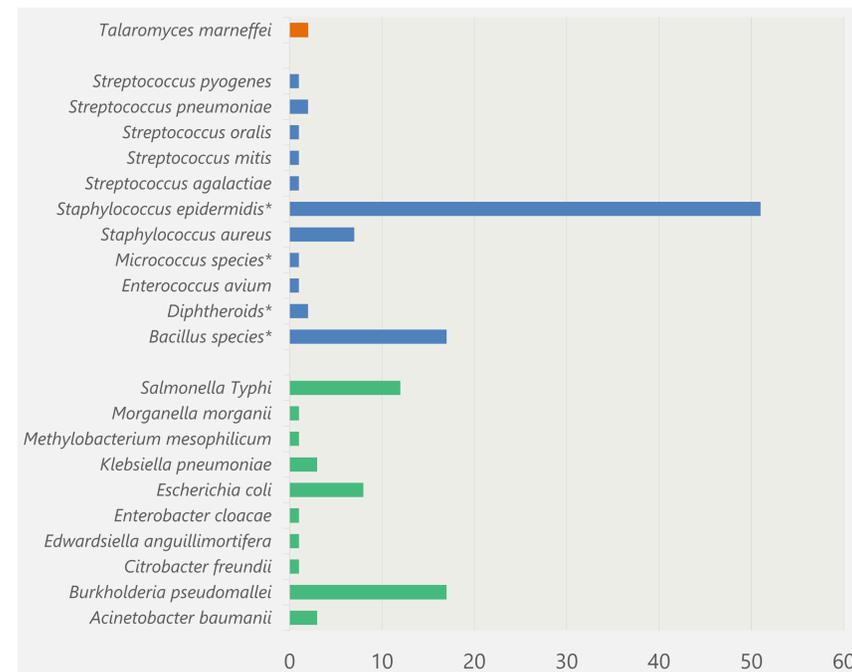
Preliminary results of investigations performed in Laos (blood culture, pending confirmation, malaria rapid test & microscopy) are reported:

- 1,980 blood cultures from 1,972 patients, 135 (6.8%) isolates were identified. Of these, 17 (12.6%) grew *Burkholderia pseudomallei*, 12 (8.9%) *Salmonella* Typhi, 8 (5.9%) *Escherichia coli* (5 were ESBL-producing), 7 (5.2%) *Staphylococcus aureus* (2 were Methicillin-resistant *S. aureus*), 3 (2.2%) *Klebsiella pneumoniae*, 2 (1.5%) *Streptococcus pneumoniae*, and 2 (1.5%) *Talaromyces marneffei* [Fig. 1]. No positive test for malaria.

Preliminary results from the international reference laboratories:

- 5/382 (1.3%) blood samples were positive for Histoplasma-Ag. From 1,556 samples, 218 (14%) were PCR-positive for dengue with no patients confirmed PCR-positive for Japanese encephalitis, Zika or chikungunya viruses [Table 1].
- Of 669 nasopharyngeal samples tested so far, 218 (32.6%) tested positive for respiratory viruses. (Results from controls to follow).
- 1,207 (61.4%) patients received antibiotics. Among 1,431 antibiotic prescriptions, 837 (58.5%) were for cephalosporins [Fig. 2].

**Figure 1: Organisms identified from 1,972 patients (1,980 blood cultures)**



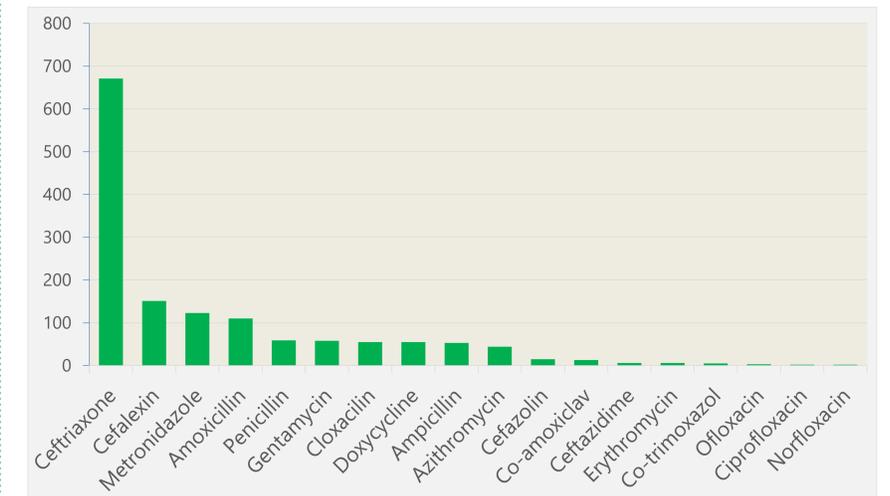
\*considered as contaminant organisms

**Table 1: Preliminary results of Arbovirus testing**

	Patients, N=1556	
	Confirmed	Presumptive
<b>Results for each virus analysed separately</b>		
Dengue virus	218 (14%)	147 (9.4%)
Japanese encephalitis virus	0	125 (8%)
Zika virus	0	9 (0.6%)
Chikungunya virus	0	101 (6.5%)
<b>Overall results (PCR is confirmatory over Ab)</b>		
Dengue virus	218 (14%)	92 (5.9%)
Japanese encephalitis virus	0	37 (2.4%)
Zika virus	0	1 (0.1%)
Chikungunya virus	0	43 (2.8%)
Multi (POS for >1 V)	0	76 (4.9%)
Overall positive	218 (14%)	249 (16%)

Viral RNA detection using real-time RT-PCR; specific ELISAs to look for serological evidence of Infection, with confirmation by microneutralization (pending).  
Confirmed = PCR positive, Presumptive = ELISA IgM positive.

**Figure 2: Antibiotics prescribed in the first 24 hours of admission**



## Conclusion

- From these preliminary results, we confirm that malaria is no longer a leading cause of fever in northern Laos.
- Dengue was a common reason for presentation to the hospital with fever, reflecting the fact that there was an epidemic in the country while the study was recruiting.
- We demonstrated melioidosis, enteric fever and ESBL-producing Enterobacterales bacteraemia as causes of bloodstream infection in this part of Laos, with important implications for empiric prescribing in severely ill patients with sepsis.



FIEBRE-Laos team recruiting control participants at home, 2018

## References:

- Hopkins H, Bassat Q, Chandler CI, et al. ; FIEBRE Consortium. 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 Jul 21;10(7):e035632. doi: 10.1136/bmjopen-2019-035632. Erratum in: *BMJ Open*. 2020 Aug 31;10(8):e035632corr1. PMID: 32699131; PMCID: PMC7375419.

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