FIEBRE

Febrile Illness Evaluation in a Broad Range of Endemicities

Leptospirosis among patients presenting with fever in the multi-center Febrile Illness Evaluation in a Broad Range of Endemicities (FIEBRE) study

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on behalf of the FIEBRE consortium

Good afternoon.
I will be discussing leptospirosis among patients presenting with fever in the multi-center Febrile Illness Evaluation in a Broad Range of Endemicities or FIEBRE study on behalf of the consortium.

Background

- **Fever is a common reason for health care seeking and hospital admission in sub-Saharan Africa and Asia, yet infectious causes of fever are incompletely understood**
- **An understanding of causes of fever is needed to inform empiric management of severe and non-severe febrile illness**
- **The Febrile Illness Evaluation in a Broad Range of Endemicities (FIEBRE) study is a multi-center study of causes of fever using reference diagnostics and standardized case definitions**

By way of background.
Fever is a common reason for health care seeking and hospital admission in countries in sub-Saharan Africa and Asia, yet infectious causes of fever are incompletely understood.
An understanding of causes of fever is needed to inform empiric management of severe and non-severe febrile illness.
The FIEBRE study is a multi-center study of causes of fever using reference diagnostics and standardized case definitions.

Methods

- **Febrile patients aged ≥2 months presenting for inpatient or outpatient care**
  - **Lao PDR**
  - **Malawi**
  - **Mozambique**
  - **Zimbabwe**
- **22 June 2018 through 31 March 2021**
- **Standardized clinical history, physical examination, and exposure questionnaire**
- **Acute and convalescent serum and acute plasma**

In brief, FIEBRE enrolled febrile patients aged 2 months and above presenting for inpatient or outpatient care in Laos, Malawi, Mozambique, and Zimbabwe.
From 22 June 2018 through 31 March 2021.
All participants had a standardized clinical history, physical examination, and an exposure questionnaire administered.
Among other samples, acute and convalescent serum and acute plasma were collected.

Methods

- ***Leptospira*** **microagglutination testing paired sera**
  - **Global *Leptospira* serovar panel supplemented with local or regional strains**
- ***Leptospira*** **direct detection**
  - **Polymerase chain reaction *lfb1* pathogenic *Leptospira* target**
  - **Sequencing of PCR positive for speciation**
- **Confirmed acute leptospirosis**
  - **≥4-fold rise in antibody titer between acute and convalescent sample**
  - **single reciprocal titer ≥800**
  - **Polymerase chain reaction positive**
- **Among serologically confirmed cases, *Leptospira* serogroup with highest titer was classified predominant reactive serogroup**

Perez J, et al. BMC Microbiol 2010; 10: 325
Bourhy P, et al. J Clin Microbiol 2011; 49: 2154-2160

The diagnosis of leptospirosis was by *Leptospira* microagglutination testing, or MAT, of paired sera at the French National Reference Center for Leptospirosis, Institut Pasteur.
…using a global *Leptospira* serovar panel supplemented with local or regional strains.
And by *Leptospira* direct detection was by polymerase chain reaction to the *lfb1* pathogenic *Leptospira* target on acute plasma.
Whole genome sequencing was used on PCR positive samples for speciation.
We defined confirmed acute leptospirosis as a ≥4-fold rise in MAT antibody titer between the acute and convalescent sample.
Or a single reciprocal MAT titer of 800 or above.
Or a positive polymerase chain reaction.
Among serologically confirmed cases, the *Leptospira* serogroup with highest titer was classified as the predominant reactive serogroup

Results

- **7,804 febrile participants**
  - **7,413 (95.0%) had ≥1 serum samples available for MAT testing**
  - **4,682 (63.2%) had paired sera**
  - **7,273 (93.2%) had acute plasma available for PCR testing**
- **149 (2.2%) had confirmed leptospirosis**
  - **94 (6.2%) from Lao PDR**
  - **20 (1.2%) from Malawi**
  - **9 (0.4%) from Mozambique**
  - **26 (1.6%) from Zimbabwe**
- **Trend towards those with confirmed leptospirosis being hospitalized (OR=1.37, p=0.063)**

Of 7,804 febrile participants

7,413 (95.0%) had at least one serum samples available for MAT testing,
4,682 (63.2%) had paired sera,
And 7,273 (93.2%) had serum available for PCR testing.
Of these, 149 (2.2%) had confirmed leptospirosis.
Including
94 (6.2%) participants from Laos,
20 (1.2%) from Malawi,
9 (0.4%) from Mozambique,
And 26 (1.6%) participants from Zimbabwe.
Compared with those without leptospirosis, there was a non-significant trend towards those with confirmed leptospirosis being hospitalized (OR=1.37, p=0.063).

Results

- **Predominant reactive serogroups among serologically confirmed cases**
  - **African sites: Ballum and Icterohaemorrhagiae**
  - **Asian site: Australis**

- ***Leptospira* species among PCR positive confirmed cases**
  - **African sites (n=24): *L. interrogans,* 17 (70%); *L. kirschneri*, 4 (17%); *L. borgpetersenii,* 2 (8%)**
  - **Asian site (n=14): *L. interrogans,* 13 (93%); *L. kirschneri* 1 (7%)**

The predominant reactive serogroups among serologically confirmed cases at African sites were Ballum and Icterohaemorrhagiae.
And at the Asian site was Australis.
The *Leptospira* species among PCR positive confirmed cases at African sites were *L. interrogans, kirschneri*, and *borgpetersenii.*
And at the Asian site were *L. interrogans* and *kirschneri.*

Covariates associated with confirmed leptospirosis on univariable and multivariable analysis, FIEBRE study

		Confirmed leptospirosis				Univariable model		Multivariable model	
Covariate		Yes		No		OR	p-value	OR	p-value
Age, yrs	Ref 2 mnth - <5	7	(4.7)	1,532	(22.8)	1.0			
	5-<15	25	(16.8)	1,441	(21.4)	3.8	0.002	3.4	0.005
	15-<30	54	(36.2)	1,621	(24.1)	7.3	<0.001	6.0	<0.001
	30-<60	49	(32.9)	1,770	(26.3)	6.1	<0.001	4.2	0.001
	60-<100	14	(9.4)	360	(5.5)	8.3	<0.001	5.9	<0.001
Sex	Ref male	82	(55.0)	3,141	(46.7)	1.0			
	Female	67	(45.0)	3,591	(53.3)	0.71	0.044	0.78	0.143
Exposure to livestock	Ref no	132	(89.2)	6,286	(94.1)	1.0			
	Yes	16	(10.8)	391	(5.9)	2.0	0.013	1.0	0.934
Work in rice field	Ref no	95	(63.8)	6,158	(92.3)	1.0			
	Yes	54	(36.2)	513	(7.7)	6.8	<0.001	6.8	<0.001
Swim/bath in river	Ref no	111	(74.5)	6,076	(91.0)	1.0			
	Yes	38	(25.5)	604	(9.0)	3.4	<0.001	0.71	0.211
Jaundice	Ref no	140	(94.0)	6,528	(97.3)	1.0			
	Yes	9	(6.0)	180	(2.7)	2.3	0.016	1.6	0.232

This slide shows covariates associated with confirmed leptospirosis on univariable and multivariable analysis across all FEIBRE sites.
****CLICK****
As you can see, on univariable analysis increasing odds of leptospirosis was associated with increasing age band, exposure to livestock, working in a rice field, swimming or bathing in a river, and with jaundice.
Female sex was protective.
****CLICK****
****CLICK****
On multivariable analysis, increasing age band and working in a rice field remained significant.
****CLICK****

Conclusions

- **Leptospirosis was a common cause of fever in the Laos PDR site, but was identified as the cause of fever for <2% of participants in African sites**
- **Participants with leptospirosis were more likely to be older and male than those without**
- ***Leptospira interrogans* and *Leptospira kirschneri* were leading species but different patterns of *Leptospira* serogroup reactivity suggest geographic variation in leptospirosis ecology**

In conclusion, leptospirosis was a common cause of fever at the Laos site, but was identified as the cause of fever for less that 2% of participants in African sites.
Participants with leptospirosis were more likely to be older and to work in a rice field compared to those without.
While *Leptospira interrogans* and *kirschneri* were the leading species at African and the Asia site, different patterns of *Leptospira* serogroup reactivity were observed suggesting geographic variation in leptospirosis ecology.

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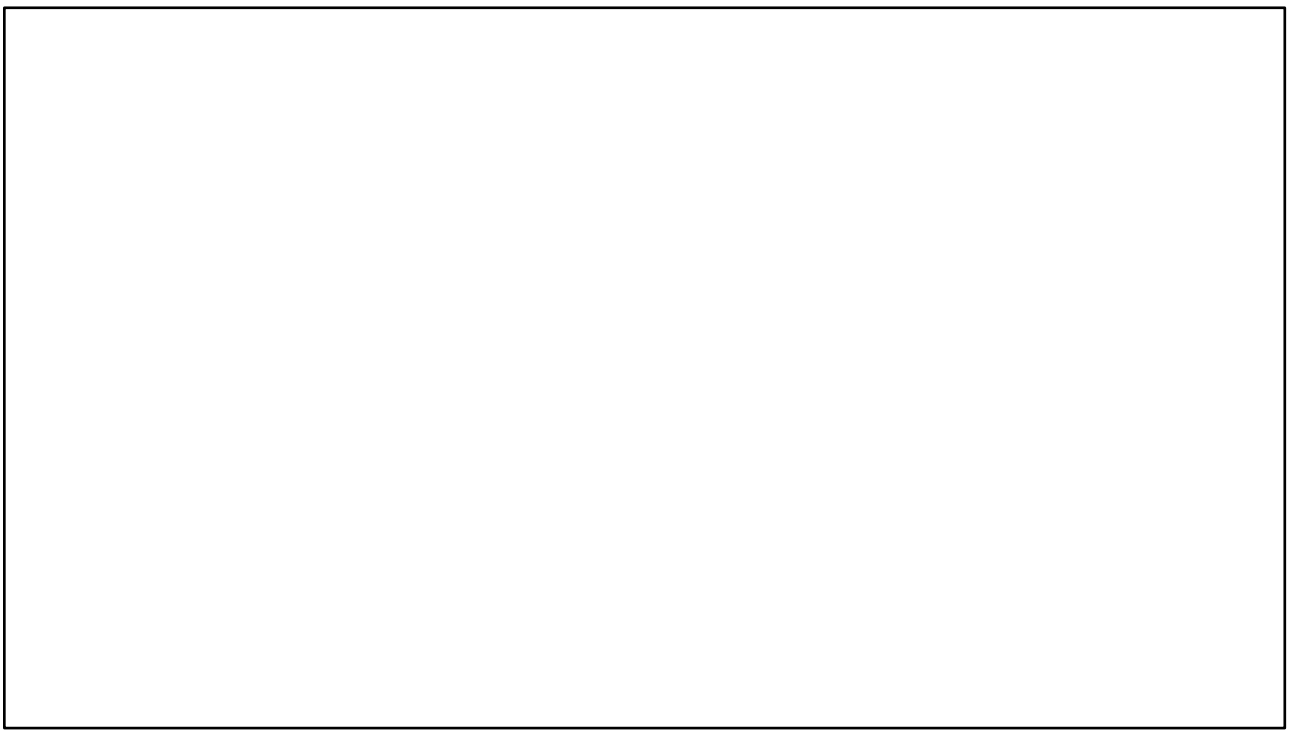
We thank UK aid for funding the FIEBRE study.
More information about FIEBRE is available via the QR code.
Thank you for your attention.



Thank you for your attention.

Africa *Leptospira* microagglutination test panel

Leptospira species	*kirschneri*	*borgpetersenii*	*kirschneri*	*borgpetersenii*	*interrogans*	*borgpetersenii*	*interrogans*	*borgpetersenii*	*kirschneri*	*interrogans*	*interrogans*	*borgpetersenii*	*interrogans*	*interrogans*	*interrogans*	*interrogans*	*borgpetersenii*	*borgpetersenii*
Serovar	Sokoine	Kenya	Unknown	Unknown	Lora	arborea	Kuwait	Unknown	Unknown	Unknown	Copenhageni	Sejroë	Australis	Canicola	Hebdomadis	Pomona	ND	
Serogroup	Icterohaemorrhagiae	Ballum	Autumnalis	Pyrogenes	Australis	Ballum	Canicola	Pomona	Grippotyphosa	Pyrogenes	Icterohaemorrhagiae	Sejroë	Australis	Canicola	Hebdomadis	Pomona	Mini	Mini

Asia *Leptospira* microagglutination test panel

Leptospira species	*borgpetersenii*	*interrogans*	*interrogans*	*interrogans*	*weilii*	*weilii*	*interrogans*	*interrogans*	*interrogans*	*weilii*	*interrogans*	*interrogans*	*interrogans*	*interrogans*	*borgpetersenii*	*interrogans*
Serovar	Javanica	Canicola	Autumnalis	Autumnalis	Mini	Celledoni	Australis	Grippotyphosa	Bataviae	Hebdomadis	Pomona	Icterohaemorrhagiae	Pyrogenes	Grippotyphosa	Sejroë	Ictero
Serogroup	201801754	201801169	akiyamiA	201801758	201801198	201801177	201801194	201801158	201801193	201801206	201801207	201801765	salinem	201801175	M 84	Verdun

Results

- **149 (2.2%) had confirmed leptospirosis**
  - **110 (2.1%) by ≥4-fold rise in MAT titer**
  - **15 (0.2%) by single reciprocal MAT titer ≥800**
  - **38 (0.5%) by PCR**

Of these, 149 (2.2%) had confirmed leptospirosis.
110 (2.1%) by ≥4-fold rise in MAT titer.
15 (0.2%) by single reciprocal MAT titer ≥800.
38 (0.5%) by PCR.