Causes of non-malarial fever in Africa: A systematic review and meta-analysis

Martin Wainaina[1,2,3,*], David Attuy Vey da Silva[1,2], Ian Dohoo[4], Anne Mayer-Scholl[1], Kristina Roesel[2,3], Dirk Hofreuter[1], Uwe Roesler[2], Johanna Lindahl[3,5,6], Bernard Bett[3], Sascha Al Dahouk[1,7]

1. German Federal Institute for Risk Assessment, Berlin, Germany **2.** Freie Universität Berlin, Berlin, Germany **3.** International Livestock Research Institute, Nairobi, Kenya
4. University of Prince Edward Island, Charlottetown, Canada **5.** Swedish University of Agricultural Sciences, Uppsala, Sweden **6.** Uppsala University, Uppsala, Sweden
7. RWTH Aachen University Hospital, Aachen, Germany

Introduction

The awareness of non-malarial fevers has been on the rise over the last decades. This is because, despite tremendous success in the control of malaria (*Plasmodium falciparum*) across Africa, fever continues to be commonly reported in both hospital and community settings. Therefore, we conducted this systematic review and meta-analysis to determine the commonly reported causes of non-malarial febrile illnesses in African fever patients. We also presented them using proportional morbidity rates. Additionally, we computed the summary effects of selected commonly occurring non-malarial febrile agents and lastly determined study and population characteristics that predict their occurrence. Significant predictors of non-malarial fevers are important considerations for future fever studies on the continent.

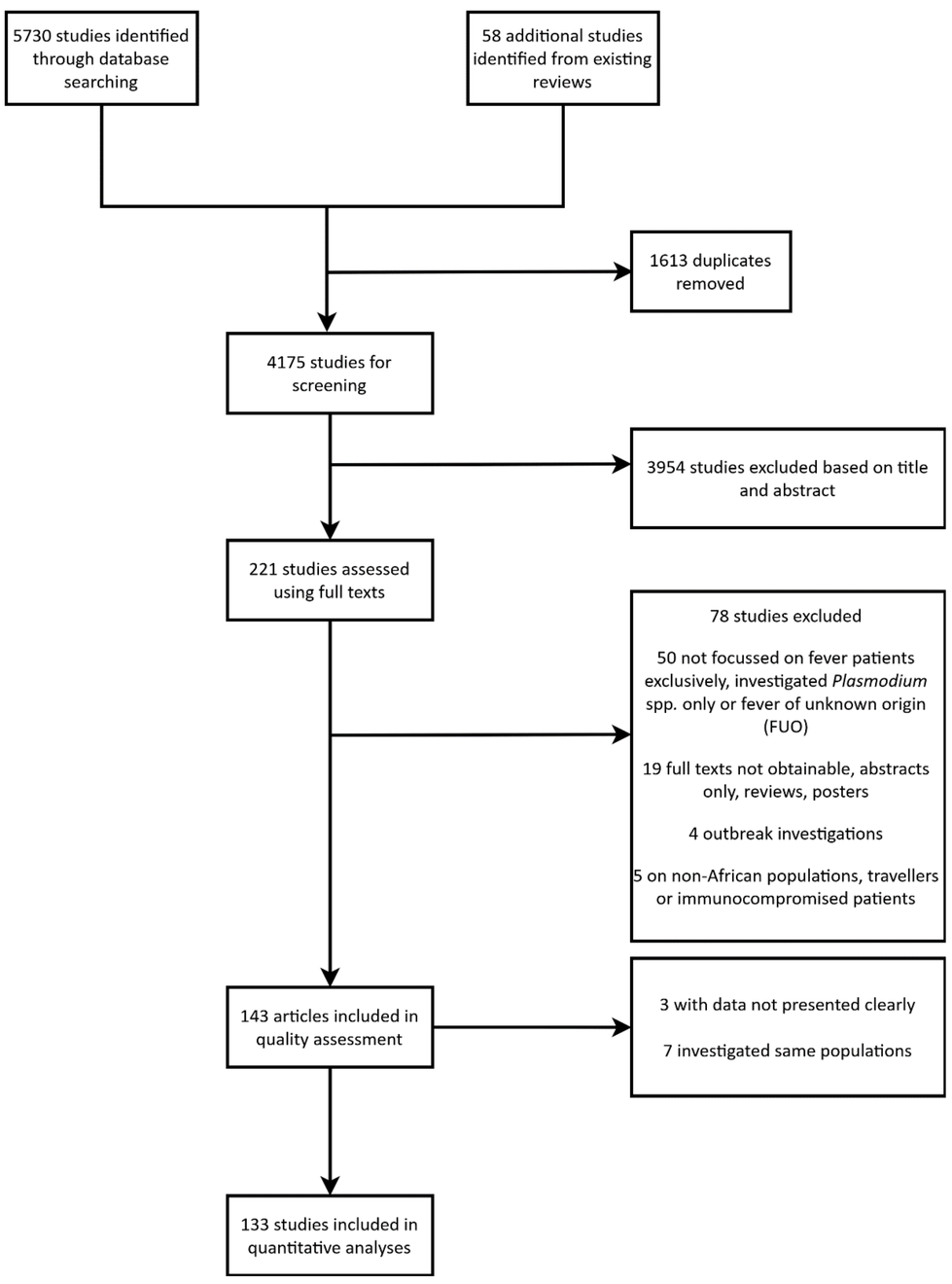
Methods

Databases: African Journals Online (AJOL), Embase, PubMed, Scopus, and Web of Science

Search terms: "undifferentiated" OR "unknown" OR "non*malaria*"AND "fever" OR "pyrexia" OR "hyperthermia" OR "febrile" AND "Africa".

Time and language restrictions: None

Data extracted: Country of study, Study start and end year, Number of agents investigated, Study season, Study design, Study setting, Place of recruitment of study participants, Minimum temperature, location of temperature measurement and duration of fever admitted in the study, Sample size, Aetiological agent tested, Samples tested, Diagnostic test, and Clinical signs and symptoms directly associated with agents.



Meta-analyses

- Calculation of proportional morbidity rates per study (patients positive for agent / total fever patients).
- Random effects models were used to determine summary effects and for meta-regression analyses.
- Tau squared (τ^2) and Higgins' I^2 were used to determine the between-study heterogeneity.
- Univariable and multivariable logistic meta-regression models were applied to variables. Final models comprised population status, African region, study end date (year), recruitment place, and diagnostics.
- Quality assessment (risk of bias) was done using a customised tool.

Results: Summary effects

Aetiologic agent	Number of studies	Study population sizes		Overall heterogeneity	Summary estimates (95% CI) with the diagnostic tests used			
		Median	IQR		Overall	Direct	Indirect	Direct & indirect
Brucella spp.	13	325	195 – 582	I^2 = 94.6%, τ^2 = 1.4	3.5% (1.7-7.1)	3.1% (0.9-10.5)	3.6% (1.2-10.5)	NA
Chikungunya virus	15	338	240 – 394	I^2 = 98.8%, τ^2 = 3.8	4.5% (1.5-12.7)	1.7% (0.2-11.5)	9.6% (2.7-29.2)	NA
Dengue virus	21	310	195 – 382	I^2 = 98.9%, τ^2 = 4.8	8.4% (3.2-20.0)	2.3% (0.6-7.9)	29.8% (13.8-53.0)	6.2% (0.0-100.0)
Haemophilus spp.	23	522	341 – 1,711	I^2 = 99.5%, τ^2 = 5.3	1.4% (0.5-3.6)	1.4% (0.5-3.8)	1.6% (0.2-10.7)	NA
Klebsiella spp.	31	300	150 – 842	I^2 = 98.9%, τ^2 = 2.3	1.8% (1.0-3.1)	1.8% (1.0-3.2)	1.6% (0.2-10.7)	NA
Leptospira spp.	15	223	180 – 379	I^2 = 95.5%, τ^2 = 4.2	3.2% (1.1-8.9)	0.5% (0.1-2.1)	9.6% (3.5-24.0)	22.9% (17.8-28.8)
Non-typhoidal *Salmonella*	28	437	235 – 1,076	I^2 = 99.5%, τ^2 = 3.5	1.6% (0.8-3.3)	1.6% (0.8-3.3)	NA	NA
Typhoidal *Salmonella*	34	449	243 – 1,156	I^2 = 97.8%, τ^2 = 1.8	2.0% (1.3-3.1)	1.4% (0.9-2.3)	8.5% (4.0-17.4)	3.4% (0.3-32.4)
Staphylococcus spp.	45	284	170 – 638	I^2 = 98.7%, τ^2 = 2.1	2.1% (1.4-3.3)	2.1% (1.4-3.3)	1.6% (0.2-10.7)	NA
Streptococcus spp.	43	277	119 – 636	I^2 = 99.1%, τ^2 = 2.9	3.2% (2.0-5.3)	3.2% (1.9-5.3)	4.9% (1.6-14.2)	NA

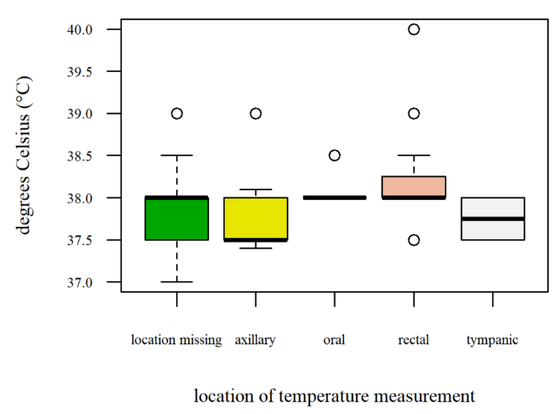
CI; confidence intervals, IQR; interquartile range, NA; not available

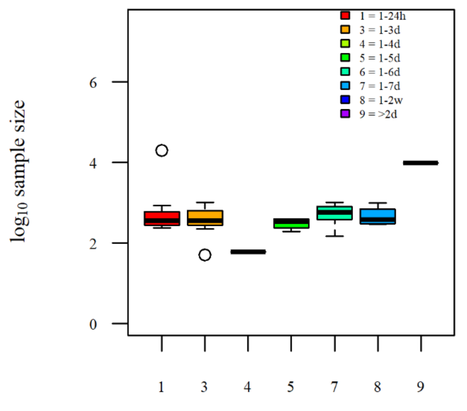
Meta-regression analyses

Variables	Coefficient	SE	p value	95% CI of coefficient lower	95% CI of coefficient upper
Dengue					
Intercept	0.07	0.07	0.29	-0.07	0.22
Study end date	-0.00	0.00	0.37	-0.01	0.00
Diagnostics (p value = 0.02)					
direct and indirect	0.22	0.16	0.19	-0.12	0.57
indirect	0.29	0.10	0.01	0.09	0.50
Haemophilus spp.					
Intercept	-0.01	0.05	0.87	-0.11	0.09
Population status (p value = 0.01)					
inpatient/outpatient	0.29	0.09	0.00	0.12	0.50
outpatient	0.02	0.12	0.86	-0.23	0.27
Study end date	0.01	0.00	0.08	-0.00	0.01
Klebsiella spp.					
Intercept	0.08	0.02	0.01	0.02	0.13
Population status (p value = 0.81)					
inpatient/outpatient	0.02	0.04	0.63	-0.07	0.11
outpatient	-0.01	0.04	0.81	-0.08	0.07
Study end date	-0.00	0.00	0.04	-0.01	-0.00
Typhoidal *Salmonella* spp.					
Intercept	0.03	0.01	0.00	0.01	0.04
Study end date	-0.00	0.00	0.67	-0.00	0.00
Diagnostics (p value = 0.00)					
direct and indirect	0.01	0.02	0.58	-0.03	0.06
indirect	0.07	0.02	0.00	0.03	0.10

CI; confidence intervals, SE; standard error

Case definitions





Conclusions

- Generally low summary effects perhaps from the poor performance of diagnostic tests. Large variety of causes of non-malarial fevers, mainly bacterial agents. Less focus on studies investigating parasitic and fungal causes.
- Significant heterogeneity between studies, with the type of diagnostic used being a significant predictor for Dengue and typhoidal *Salmonella*. Harmonisation of case definition, study designs, and diagnostics used is key for comparable data. This is possible with large multi-centred studies and standardised protocols.
- Good estimates of disease presence can help in the prioritisation of limited resources to tackle the most pertinent hazards.

Martin Wainaina
markimwa@gmail.com ● Diedersdorfer Weg 1, 12277 Berlin ● Tel: +49 30 18412-24703

DAAD Deutscher Akademischer Austauschdienst German Academic Exchange Service