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## Zoonotic causes of febrile illness in malaria endemic countries

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Abstract: Fever is one of the most common reasons for healthcare seeking globally and the majority of human pathogens are zoonotic. We conducted a systematic review to describe the occurrence and distribution of zoonotic causes of human febrile illness reported in malaria endemic countries. Articles included in the review yielded data from 53 (48.2%) of 110 malaria endemic countries. The 244 articles included described diagnosis of 30 zoonoses in febrile people. The majority of zoonoses were bacterial (n=17), with viruses (n=9), protozoa (n=3) and helminths (n=1) also identified. Leptospira spp. and nontyphoidal Salmonella serovars were the most frequently reported pathogens. Despite evidence of profound data gaps, this review reveals widespread distribution of a diverse range of zoonotic causes of febrile illness. Greater understanding of the epidemiology of zoonoses in different settings is needed to improve awareness and management of the multiple zoonotic causes of febrile illness.

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#### Abstract 64

- Fever is one of the most common reasons for healthcare seeking globally and the majority of 65
- human pathogens are zoonotic. We conducted a systematic review to describe the occurrence 66
- 67 and distribution of zoonotic causes of human febrile illness reported in malaria endemic
- 68 countries. Articles included in the review yielded data from 53 (48.2%) of 110 malaria
- 69 endemic countries. The 244 articles included described diagnosis of 30 zoonoses in febrile 70
- people. The majority of zoonoses were bacterial (n=17), with viruses (n=9), protozoa (n=3)71 and helminths (n=1) also identified. *Leptospira* spp. and nontyphoidal *Salmonella* serovars
- 72 were the most frequently reported pathogens. Despite evidence of profound data gaps, this
- 73 review reveals widespread distribution of a diverse range of zoonotic causes of febrile illness.
- 74 Greater understanding of the epidemiology of zoonoses in different settings is needed to
- 75 improve awareness and management of the multiple zoonotic causes of febrile illness.
- 76

#### 77 Introduction

- Fever is one of the most common symptoms prompting healthcare seeking globally.<sup>1-3</sup> Fever 78
- 79 has myriad causes and their non-specific clinical presentation means that clinical history and
- 80 physical examination are often insufficient to accurately identify causal pathogens.<sup>1</sup>
- 81 Limitations in laboratory services and available diagnostic tools further contribute to
- diagnostic challenges.<sup>4</sup> In malaria-endemic countries, fever is often assumed to be due to 82
- malaria.<sup>5</sup> The mortality and morbidity attributable to malaria remains considerable, but there 83
- is also evidence of widespread over-diagnosis within malaria-endemic areas.<sup>6-8</sup> The 84
- recognized over-diagnosis of malaria together with declines in malaria incidence since the peak in global malaria deaths in 2004<sup>9,10</sup> have prompted attention to non-malaria causes of fever in malaria-endemic areas.<sup>11,12</sup> Zoonotic pathogens are likely to play a substantial role as 85 86
- 87
- causes of fever globally. Almost two-thirds of all human pathogens are zoonotic,<sup>13</sup> and there 88
- is growing evidence that many zoonoses cause more cases of human febrile illness than 89
- previously appreciated.<sup>12,14-20</sup> Improved understanding of the impacts and burdens of zoonotic 90
- causes of fever in malaria-endemic countries would provide the epidemiological evidence 91
- base for disease control program development and also influence diagnostic and treatment 92
- 93 algorithms for fever, with the potential to improve clinical outcomes. The aim of this study
- 94 was to systematically review the published literature to describe the occurrence and
- 95 distribution of reported zoonotic causes of human febrile illness in countries where malaria is
- 96 endemic.
- 97

#### 98 **Methods**

#### 99 Search strategy and selection criteria

- 100 The target literature for this systematic review was peer-reviewed published articles that
- 101 described the testing of one or more febrile person from malaria-endemic countries for one or
- 102 more zoonotic pathogen using robust diagnostic testing criteria to demonstrate acute
- 103 infection. Literature searches of the Medline and Embase databases were run using the
- 104 OvidSP gateway. Searches were limited to English language articles published in the period
- 105 2004 to 2019 inclusive, to span the period from the described peak of global malaria
- mortality in 2004 to present.<sup>9</sup> The searches were last executed on 03 January 2019. Outputs 106
- of database searches were combined and de-duplicated using R.<sup>21</sup> Additional details of 107 108 searches, screening, review, and data extraction processes are given in the appendix.
- 109

110 Three search concepts for 'fever,' 'zoonoses,' and 'malaria endemic countries' were 111 constructed. To construct the 'fever' concept the exploded subject heading and keywords 112 were combined using database appropriate syntax (e.g., exp Fever/ OR fever\$1.mp. OR 113 febrile.mp.). For the 'zoonoses' concept, a reference list of eligible zoonotic pathogens was compiled using lists of zoonotic diseases from the World Health Organization (WHO)<sup>22</sup> and 114 World Organisation of Animal Health (OIE)<sup>23</sup> as well as literature-based searches to identify 115 frequently reported zoonotic causes of human fever. We conducted preliminary searches of 116 117 Medline and Embase using the search syntax '(exp Fever/ OR fever.mp.) AND (exp 118 Zoonoses/ OR zoonoses.mp OR zoonosis.mp)' limited to humans. Additional details of 119 search concept construction are given in the appendix. All pathogens identified through these 120 approaches were mapped to existing subject headings and keywords at the lowest taxonomic 121 level possible, typically genus or species. In instances where pathogen species or serovars 122 within the same genus varied in their zoonotic status, search concepts were constructed to 123 include all zoonotic and non-zoonotic species or serovars and articles relating to non-124 zoonotic species were excluded at the full text stage. The candidate pathogens were classified 125 to differentiate pathogens normatively acquired by people through direct or indirect 126 transmission from vertebrate animals to humans, as compared to pathogens where zoonotic 127 transmission has been recorded but where the majority of human infections are not acquired through zoonotic transmission. We classified pathogens using the stages in the process 128 towards human endemicity defined in Wolfe et al.<sup>24</sup> Pathogens classified at stages one to 129 three (normatively acquired through zoonotic transmission) were retained (appendix). The 130 131 search concept for each pathogen or disease included exploded subject headings for both the 132 pathogen and the diseases caused in humans and terms for both pathogen and disease were 133 also included as keywords (e.g., exp anthrax/ OR anthrax.mp. OR exp Bacillus anthracis/ OR 134 bacillus anthracis.mp.). The list of pathogen or disease specific searches was combined using 135 OR syntax to generate the full 'zoonoses' search concept (appendix). The 'malaria endemic 136 countries' concept was constructed by mapping country names for countries defined as 137 malaria endemic in the WHO global malaria reports for the years 2005 and 2016 to Medline and Embase subject headings.<sup>10,25</sup> Each country was searched for using both the exploded 138 subject heading where possible and keywords in all cases (e.g., exp Kenya/OR Kenya.mp.). 139 The three concepts, fever,' 'zoonoses,' and 'malaria endemic countries' were combined using 140 141 AND operators and database specific syntax (appendix).

142

## 143 Study selection and validity assessment

144 Articles that reported the diagnosis of a zoonotic pathogen in a population from a malaria 145 endemic country defined on the basis of febrile illness were selected for full-text review. 146 Conference proceedings and records that did not include any abstract text or an abstract in 147 English were excluded. Abstracts and titles were screened by two independent reviewers (two 148 of MC, MES, KJA, GAFL, DVH, JAC, SC and MPR) using pre-defined criteria (appendix 149 table S1). Articles were selected for inclusion if the abstract or title described clinical and/or 150 laboratory evaluation of a group of  $\geq 2$  people all of whom had fever and some of whom 151 were diagnosed of one or more pathogens from the reference list of zoonotic pathogens (table 152 1). Abstracts referring to the use of blood culture were also retained at this stage even if a 153 zoonosis was not explicitly mentioned in the abstract (appendix table S1). When two 154 reviewers disagreed on article classification, a third independent reviewer (one of JEBH, MC, 155 MES, GAFL, DVH or MPR) resolved the tiebreak. Full text articles were sought for all

156 articles not excluded during abstract review steps. All articles were searched for using

- 157 PubMed, Google and the libraries of the University of Glasgow, Duke University,
- 158 Washington University in St. Louis, and US Centers for Disease Control and Prevention (US
- 159 CDC). Articles were excluded if a full text for the citation could not be obtained. Two
- 160 independent reviewers (two of, JEBH, MC, MES, JB and MPR) evaluated full text articles
- using pre-defined inclusion and exclusion criteria (table 2, appendix table S2). Strict
- 162 diagnostic case definitions based on WHO and US CDC guidelines ensured that only studies
- 163 reporting robust and specific diagnostic methods were retained (table 2). Articles were
- 164 excluded if they did not meet one or more of the study inclusion criteria or if they did meet at
- 165 least one of the study exclusion criteria (table 2). In cases where reviewers disagreed on
- article classification, discrepancies were checked and resolved by JEBH in discussion withother reviewers.
- 168
- Table 1. Zoonoses included in the review, with details of species and serovars excludedwhere appropriate.

Pathogen	Species, subspecies, and serovars excluded	Pathogen
		type <sup>15</sup>
Alphaviruses	All species excluded with the exception of Eastern equine encephalitis virus (EEEV) complex, Venezuelan equine encephalitis (VEEV) complex, and Western equine encephalitis (WEEV) complex	Virus
Anaplasma spp.	-	Bacteria
Aphthoviruses	All species excluded with the exception of Foot-and- mouth disease virus	Virus
Avulaviruses	All species excluded with the exception of Newcastle disease virus	Virus
Babesia spp.	-	Protozoa
Bacillus antrhracis	-	Bacteria
Bartonella spp.	B. bacilliformis and B. quintana excluded	Bacteria
Borrelia spp.	B. recurrentis excluded	Bacteria
Bovine	-	Prion
spongiform		
encephalopathy		
Brucella spp.	-	Bacteria
Burkholderia spp.	B. cepacia complex and B. pseudomallei excluded	Bacteria
<i>Campylobacter</i> spp.	-	Bacteria
Chlamydia spp.	All species excluded with the exception of <i>C. psittaci</i>	Bacteria
Coxiella burnetii	-	Bacteria
<i>Cryptosporidium</i> spp.	C. hominis excluded	Protozoa
Ebolavirus	-	Virus
Echinococcus spp.	-	Helminth
Ehrlichia spp.	-	Bacteria
Enteroviruses	All species excluded with the exception of Swine vesicular disease virus	Virus
Escherichia spp.	All species excluded with the exception of Shiga-toxin producing <i>E. coli</i>	Bacteria

Flaviviruses	All species excluded with the exception of Japanese encephalitis virus (JEV), West Nile virus (WNV), and Tick-borne-encephalitis virus.	Virus
Francisella spp.	All species excluded with the exception of <i>F</i> . <i>tularensis</i>	Bacteria
Hantavirus	-	Virus
Henipaviruses	-	Virus
Lassa virus	-	Virus
Leishmania spp.	L. donovani excluded if detected in India	Protozoa
Leptospira spp.	-	Bacteria
<i>Listeria</i> spp.	-	Bacteria
Lyssavirus	All species excluded with the exception of Rabies virus	Virus
Marburg virus	-	Virus
Mycobacterium	All species excluded with the exception of <i>M. bovis</i> and <i>M. avis</i>	Bacteria
Nairovirus	All species excluded with the exception of Crimean- Congo haemorrhagic fever virus	Virus
<i>Orientia</i> <sup>1</sup>	-	Bacteria
Orthopox viruses	All species excluded with the exception of Cowpox virus, Monkeypox virus, and Vaccinia virus	Virus
Pasteurella spp.	-	Bacteria
Phleboviruses	All species excluded with the exception of Rift Valley fever (RVF) virus	Virus
<i>Rickettsia</i> spp. <sup>2</sup>	R. prowazekii excluded	Bacteria
Salmonella spp.	All species, subspecies, and serovars excluded with the exception of nontyphoidal <i>Salmonella</i> serovars	Bacteria
Schistosoma spp.	S. haematobium, S. intercalatum, and S. mekongi.excluded	Helminth
<i>Streptobacillus</i>	-	Bacteria
Streptococcus spp.	All species excluded with the exception of <i>S. canis</i> , <i>S. suis</i> , <i>S. equi</i> , and <i>S. iniae</i>	Bacteria
<i>Taenia</i> spp.		Helminth
Toxocara		Helminth
Toxoplasma gondii	-	Protozoa
Trichinella spp.	-	Helminth
<i>Trypanosoma</i> spp.	All species excluded with the exception of <i>T. brucei</i> rhodesiense and <i>T. cruzi</i>	Protozoa
Varicelloviruses	All species excluded with the exception of Pseudorabies virus	Virus
Vesiculoviruses	All species excluded with the exception of Vesicular Stomatitis virus	Virus
Yersinia spp.	All species excluded with the exception of <i>Y. pestis</i> , <i>Y. enterocolitica</i> and <i>Y. pseudotuberculosis</i>	Bacteria

171 <sup>1</sup> Orientia was covered by search syntax for *Rickettsia*.

<sup>2</sup> For data extraction, data on *Rickettsia* were classified as *Rickettsia* (SFGR) or *Rickettsia* 

- 173 (TGR) where the data resolution allowed. When details on the species of *Rickettsia* were not 174 given, these data were classified as *Rickettsia* spp.
- 175

176	Table 2. Inclusion	and exclusion	criteria for	full text review
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Outcome	Criterion
Inclusion:	• Febrile population ( $\geq 2$ people with a fever, defined as body temperature $\geq 38.0^{\circ}$ C)
	• Diagnosis of one or more zoonotic pathogens from pre-defined reference list of eligible aetiological agents (table 1)
	Diagnostic test criteria:
	i) Culture of the pathogen from sample(s) collected from a febrile person
	ii) Direct detection of the pathogen (e.g., by PCR based techniques) from sample(s) collected from a febrile person
	<ul> <li>iii) Serological diagnosis of acute infection based on testing of both acute and convalescent phase serum samples and demonstration of seroconversion</li> </ul>
	<ul> <li>iv) Diagnosis of acute infection based on detection of pathogen-specific antibody or antigens in a single serum sample only for selected pathogens, for which widely accepted case definitions deemed pathogen-specific antibody or antigen detection sufficiently accurate<sup>1</sup></li> <li>v) IgM detection in cerebrospinal fluid (CSF) for selected pathogens for which widely accepted case definitions include IgM detection in CSF<sup>2</sup></li> </ul>
Exclusion:	<ul> <li>Failure to meet inclusion criteria described above</li> </ul>
	• Lack of study detail e.g., number of people tested for each pathogen
	Negative diagnostic test results in all patients
	• Study designed to evaluate diagnostic test and/or vaccine performance without presenting novel data on number or proportion of patients
	of febrile people.
	• Study described as a group of $\geq 2$ people principally classified based on a shared (100% frequency) aetiological diagnosis.
	• Review

177 The following met study criteria for valid diagnostics for pathogen detection based on single sera only: *Leptospira* spp. agglutination titer of  $\geq$  800 by microscopic agglutination test in 178 one serum specimen <sup>26</sup>; detection of Hantavirus-specific IgM in a serum sample <sup>27</sup>; detection 179 180 of virus-specific IgM antibodies in serum with confirmatory virus-specific neutralizing antibodies for Eastern equine encephalitis virus (EEEV), West Nile virus (WNV), Western 181 equine encephalitis virus (WEEV), and Venezuelan equine encephalitis virus (VEEV)<sup>28</sup>; 182 identification of lyssavirus specific antibody by indirect fluorescent antibody test or complete 183 rabies virus neutralization at 1:5 dilution in the serum of an unvaccinated person <sup>29</sup>; detection 184 of viral antigens in blood by enzyme-linked immunosorbent assay for Ebola <sup>30,31</sup>, Marburg 185 <sup>31,32</sup>, Lassa <sup>31,33</sup>, and Crimean-Congo haemorrhagic fever viruses <sup>31</sup>; detection of Rift Valley 186 fever antigens or IgM in blood by enzyme-linked Immunosorbent assay<sup>34</sup>; and 187 <sup>2</sup> IgM detection in CSF was considered a valid diagnostic for EEEV, Japanese encephalitis 188 virus (JEV), rabies virus, WEEV, WNV and VEEV <sup>28,29,35</sup>. 189

190

## 191 Data extraction and bias assessment

192 Data extraction was conducted independently by one of two reviewers (JEBH and MC). 193 Article-level data were extracted on the location (country and WHO regional classification), <sup>36</sup> study period (start and end year of data collection), and eligibility criteria used in the study. 194 195 Each population was classified according to the clinical presentation as undifferentiated or 196 differentiated. Differentiated febrile populations were further classified as: i) febrile 197 neurologic; ii) febrile haemorrhagic; iii) febrile gastrointestinal; iv) febrile respiratory; v) specific febrile aetiology suspected; vi) febrile co-morbid group (i.e., malignancy, 198 immunocompromise).<sup>37-39</sup> Data extracted on each population included any demographic 199 restriction of the study population, the age range of the study participants, whether the 200 201 population was described as inpatient or outpatient, urban or rural, and whether data were 202 collected during a reported disease outbreak or not. To extract data on zoonotic pathogens, 203 every article was classified to record if the study reported looking for or diagnosing one or 204 more febrile individuals with any of the zoonotic pathogens included in the study reference 205 list (table 1), irrespective of the diagnostics used. Additional data were extracted when the 206 article reported application of a diagnostic approach that met study validity criteria. For each 207 combination of article and pathogen, details of the valid diagnostic methods used, the type 208 and number of samples tested, and the number of positive samples were recorded (appendix 209 table S3, S4). In instances where more than one valid diagnostic method was used in the 210 same study for a given pathogen (e.g., culture-based and serologic case definitions), data on 211 the total number of individuals tested and positive for each pathogen using valid methods 212 were aggregated. Some articles contributed data on more than one pathogen but no data on 213 participant numbers were extracted for pathogens not identified using diagnostic approaches 214 that met study inclusion criteria.

215

216 The principal source of potential bias affecting the interpretation of the findings of this study 217 is the lack of standardization of the febrile populations included in different studies. Criteria 218 were defined to classify potential bias in study representativeness and prevalence estimate precision (appendix table S5).<sup>40-42</sup> The representativeness bias criterion was designed to 219 220 classify the representativeness of the study population, relative to the general population 221 where the study was conducted. This was based on the description of the febrile population, 222 the restriction (if any) of the study sample to specific clinical or demographic sub-populations 223 and the reporting of disease outbreaks at the time of data collection. Each population was 224 classified as follows: i) populations classified as undifferentiated febrile with no demographic 225 restriction and no clinical aetiologies excluded were classified as low risk; ii) populations 226 classified as undifferentiated febrile with demographic restriction and/or reporting exclusion 227 of specific aetiologies or syndromes were classified as medium risk; iii) differentiated febrile 228 populations and those from studies reporting disease outbreaks at the time of data collection 229 were classified as high risk. The second, outcome-level, bias criterion was designed to 230 classify risk of bias in the estimated precision of the proportion of fevers attributed to each 231 pathogen. Thresholds used for this criterion are the sample sizes needed to estimate 232 proportions of 50% and 10% with 95% confidence and 0.05 precision respectively, assuming 233 an infinite population size. Each population was classified as follows: i) proportion estimates 234 based on a sample size of greater than or equal to 385 were classified as low risk; ii) 235 proportion estimates based on a sample size of greater than 385 but less than 139 were 236 classified as medium risk; iii) proportion estimates based on a sample size of less than 139 237 were classified as high risk.

- 238
- 239 Additional potential sources of bias included variation in the pathogens tested for, and
- 240 variation in the diagnostic approaches applied. For included studies, data on the pathogens
- 241 tested for (with any diagnostic approach) were summarized alongside pathogens for which
- 242 diagnostic test criteria were met to qualitatively evaluate the biases introduced by only
- 243 extracting data on pathogens diagnosed using methods meeting study inclusion criteria.
- 244

#### 245 **Data analysis**

- 246 Extracted data on the zoonotic pathogens diagnosed using valid methods, number of
- 247 individuals tested for each pathogen, and number of individuals positive for each pathogen
- 248 were used to estimate the proportion of fevers attributable to each pathogen for each unique 249 pathogen and study combination. All analyses were conducted in R<sup>21</sup> and plots were made 250 using the package ggplot2.<sup>43</sup>
- 251

#### 252 **Role of the funding source**

253 The funders of the study had no role in study design, data collection, data analysis, data 254 interpretation, or writing of the report. The corresponding author had full access to all the

- 255 data in the study and had final responsibility for the decision to submit for publication.
- 256

#### 257 **Results**

- 258 Database searches yielded a total of 16,332 and 10,574 records through Embase and Medline, 259 respectively, resulting in a total of 17,852 unique records following de-duplication (figure 1). 260
- A total of 4,531 (25.4%) records were excluded during pre-screening, 13,321 (74.6%)
- 261 records were screened and 962 (7.2%) of these were retained after title and abstract review.
- 262 In total, 718 (74.6%) articles were excluded during full text review and 244 (25.4%) articles 263 met all study inclusion criteria and were included (figure 1, appendix table S6).
- 264

265 Articles included in the review yielded data from 53 ( $48 \cdot 2\%$ ) of the 110 malaria endemic

- 266 countries (figure 2). The majority of articles with a single country origin (n=235) reported
- 267 data from Africa (83 of 235 articles, 35.3%) or South-East Asia (81 of 235 articles, 34.5%)
- 268 (appendix table S7, figure S1). One hundred and six  $(45 \cdot 1\%)$  of the 235 articles with a single
- 269 country origin were conducted in one of six dominant countries: India (n=31), United 270 Republic of Tanzania (n=22), Thailand, (n=20), Nepal (n=12), Bangladesh (n=11), and
- 271 Nigeria (n=10). The data reported in the review were gathered between 1994 and 2017
- 272 inclusive.
- 273
- 274 The 244 articles included for data extraction reported looking for and diagnosing 40 and 31
- 275 zoonoses, respectively, in these populations (figure 3). The number of included zoonoses was
- 276 reduced to 30 after the criteria for diagnostic testing approach were applied. The 244 articles
- 277 yielded data that met diagnostic test criteria for 30 zoonoses that included 17 bacterial
- 278 pathogens (56.7%), nine viruses (30.0%), three protozoa (10.0%), and one helminth (3.3%). 279
- Leptospira spp., nontyphoidal Salmonella serovars (NTS) and rickettsioses were the most 280 frequently reported bacteria, while Japanese encephalitis virus (JEV), Hantavirus, and West
- 281 Nile virus (WNV) dominated among reported viruses (figures 3, 4).
- 282
- 283 The number of febrile individuals included in each study population ranged from 4 to 13,845, 284 with a median of 300 (IQR: 120 - 812). In total, 309 records of zoonotic pathogens causing

- 285 fever were extracted from the 244 articles. The proportion of fevers attributed to each
- 286 pathogen reported ranged from <1.0% to 95.0% (figure 4). The risk of bias classification in
- 287 the precision of the proportion of fevers attributed to each zoonosis was 136 (44.0%) of 309
- 288 low risk, 79 (25.6%) of 309 medium risk, and 94 (30.4%) of 309 high risk.
- 289

290 Of the 244 studies, 87 (35.7%) described the clinical setting as inpatient, 36 (14.8%) as 291 outpatient, 39 (16.0%) as mixed, and 82 (33.6%) gave no clear classification of the clinical 292 setting. Thirty (12.3%) studies described the study area as urban, 59 (24.2%) as rural, 45 293 (18.4%) mixed or both, and 110(45.1%) gave no clear classification of the study area. 294 Eighteen (7.4%) studies included adult participants, 43 (17.6%) included children, 153 295 (62.7%) included both adults and children and 30 (12.3%) gave no clear classification of the 296 ages included. Of the 244 studies, twelve (4.9%) described a demographically restricted 297 population, 55 (22.5%) reported some exclusions from the population, and 32 (13.1%) 298 mentioned exclusion of malaria-infected individuals specifically (appendix table S6). Of the 299 244 studies, 73 (29.9%) reported looking for more than one zoonosis, 43 (17.6%) diagnosing 300 more than one zoonosis and 37 (15.2%) contributing data on more than one zoonosis. Of the 301 244 studies, 10 (4.1%) were described as outbreak investigations and 169 (69.3%) 302 populations were classified as undifferentiated febrile populations. Among the 75 303 differentiated populations, 36 (48.0%) had specific febrile aetiologies suspected, 17 (22.7%)304 were classified as febrile neurological, eight (10.7%) as comorbid populations, eight (10.7%)305 as febrile haemorrhagic, five (6.7%) as febrile gastrointestinal and one (1.3%) as febrile 306 respiratory. The associations between clinical presentation of febrile populations and the

307 subset of 25 pathogens identified in the differentiated populations are shown in figure 5. The 308 risk of bias classification in the representativeness of febrile populations was 121 (49.6%) of

- 309 244 low risk, 45 (18.4%,) of 244 medium risk, and 78 (32.0%,) of 244 high risk.
- 310

#### 311 Discussion

312 This systematic review reveals diverse zoonoses causing febrile illness within multiple 313 malaria-endemic countries, often at high prevalence. However, sparse and patchy reporting 314 suggests that the prevalence of zoonoses is widely under-estimated. Knowledge of probable 315 infecting pathogen is crucial to inform clinical management of febrile illness and there is a

- 316 clear need for further investigation of the zoonotic causes of febrile illness to generate data
- 317 relevant to clinicians, epidemiologists, and health policy makers globally. This study should
- 318 generate greater awareness of the clinical importance of zoonoses and provide a pragmatic
- 319 starting point for actions to better manage these diseases, for example through improved
- 320 diagnostic and clinical treatment algorithms. These findings demonstrate the need for
- 321 enhanced epidemiological understanding of multiple zoonoses to inform disease prevention. 322

323 This review reveals substantial gaps in the evidence base, including a complete absence of

- eligible studies from more than half of the 110 countries included in the review (figure 2). 324
- 325 There are multiple steps and biases in the processes from a patient seeking care with febrile
- 326 illness to the publication of an English language scientific paper on the occurrence and
- 327 prevalence of a specific zoonosis that could be included in this review. The underlying
- 328 distribution and relative clinical importance of individual pathogens varies, as do patient
- 329 healthcare seeking behaviour, clinical, and patient awareness of different pathogens,
- 330 diagnostic capacities, and probability of publication. It is therefore not plausible to expect this
- 331 review to yield data on all zoonoses in all countries. However, considering the inclusion of

- 332 110 countries and construction of searches for 50 pathogens or pathogen groups, the
- 333 identification of just 244 eligible studies underscores the profound overall shortage of robust
- 334 quantitative data describing the role of any zoonoses as causes of fever in most malaria-
- 335 endemic countries.
- 336

337 The geographic variation in the distribution of studies by country (figure 2) and region 338 (appendix table S7, figure S2) is likely to be strongly influenced by variation in research and 339 publication effort. There is noticeable geographic segregation for some zoonoses, with NTS 340 and SFGR reported more frequently in Africa, and Leptospira spp., Orientia tsutsugamushi, 341 and typhus-group rickettsioses (TGR) reported more frequently in South-East Asia and 342 Western Pacific regions (appendix figure S2). For viruses, Lassa virus was reported only in 343 Africa and JEV predominantly in South-East Asia. The distribution of studies cannot be 344 interpreted as an accurate reflection of the underlying distribution of zoonotic pathogens, 345 their prevalence or clinical importance. The pathogens that are looked for depend on factors 346 such as the diagnostic capacity available, existing data, and local assessment of the likely 347 causes of febrile illness in a specific location. Once pathogens are identified in any location 348 there will likely be increased clinical, patient, and community awareness of those pathogens, 349 as well as improved diagnostic capacity to detect them. In this way, dogma about the 'known' 350 important causes of febrile illness in specific locations can arise and contribute to the neglect 351 of other pathogens. The findings of this review may help indicate potential gaps in what is 352 looked for and can highlight pathogens and locations where these dogmas should be 353 questioned.

354

355 The majority of the 30 zoonotic causes of fever contributing data for this review were 356 bacteria (56.7%). This proportion is greater than expected from the taxonomic distribution of all zoonotic pathogens, which comprise 30.1% bacteria<sup>44</sup> and also contrasts with the 357 taxonomic distribution of emerging zoonoses, which are dominated by viruses.<sup>13</sup> This finding 358 359 reinforces the clinical importance of endemic bacterial zoonoses. The comparisons between 360 the number of articles that looked for, diagnosed, and contributed data for each of 40 361 zoonoses reveals the range of zoonotic pathogens investigated and indicates the relative 362 investigative effort used for each pathogen (figure 3). However, the figures for number of 363 articles where a pathogen was looked for but not identified must be interpreted with caution 364 given the high probability of reporting bias and how rarely negative results are reported. For 365 several pathogens, the number and proportion of articles that reported a zoonotic diagnosis 366 but did not contribute further data for analysis (because the diagnostic approaches described 367 did not meet study quality criteria) are substantial (figure 3). This demonstrates that for 368 many, predominantly bacterial pathogens, suboptimal diagnostic tests or imprecise case 369 definitions are in widespread use, highlighting the challenges of accurately quantifying 370 disease prevalence and comparing studies.

371

372 Persistent challenges in the diagnosis of febrile patients include limited laboratory capacity, 373 reliance on demonstration of seroconversion for confirmed diagnosis of many pathogens.

- 374 unsustainable costs associated with more advanced diagnostic technologies, and lack of
- 375 simple and affordable tests for the accurate and timely diagnosis of several zoonotic
- 376 pathogens. In addition, the delays in patient presentation that are typical in many resource
- 377 limited settings, low magnitude bacteraemia at presentation and, presentation of patients
- 378 during the immune phase of illness, all limit the sensitivity of culture or PCR-based

diagnostic approaches when available. These challenges necessitate syndromic approaches topatient management and broad-spectrum treatment. One specific issue relates to tetracycline

381 use. This study identified rickettsioses and *O. tsutsugamushi* as common causes of fever.

382 These would benefit from treatment with tetracyclines, which are not currently included in

the Integrated Management of Adolescent and Adult Illness (IMAI) algorithms for septic

- 384 shock and severe respiratory distress without shock.<sup>45</sup> In light of the extensive contribution of
- tetracycline-responsive infections to fever in malaria-endemic countries, revisions to clinical
- 386 guidelines may be warranted to suggest the empirical use of tetracyclines in addition to beta-387 lactams in scenarios where the infection with tetracycline-responsive pathogens cannot be
- 388

excluded.

389

390 The findings of this review show that one or more zoonotic causes of fever are likely to 391 present a threat to health in all of the countries included in this review. Only a small 392 proportion of the febrile populations included in the study were defined as demographically 393 restricted and most were not clinically differentiated. Even zoonoses commonly linked with 394 specific syndromes (e.g., Crimean-Congo haemorrhagic fever virus and JEV) were diagnosed 395 in undifferentiated populations and should thus be considered in the differential diagnosis of 396 undifferentiated febrile illness. Within populations at risk, it is important that aetiologic 397 studies are followed by epidemiologic risk factor studies to determine whether certain sub-398 groups are at higher risk for specific zoonotic diseases. Robust febrile illness surveillance 399 systems help inform local epidemiology and febrile illness management, and are also 400 essential for detection of disease outbreaks.<sup>46</sup>

401

402 There are several important limitations to this study. We examined the contribution of 403 zoonotic pathogens to febrile illness only in malaria-endemic countries and excluded articles 404 not available in English from our analysis. The restriction of this review to English language 405 texts will have reduced the probability that studies from French and Spanish speaking 406 countries were included and may partially account for some gaps, such as the 23 countries in 407 Africa and 15 in the Americas for which no eligible studies were identified. Studies reporting 408 all negative test results were excluded. This strategy was motivated by the inevitable 409 influence of publication bias and challenges of systematically quantifying the non-reporting 410 of either diagnostic test performance or the non-detection of specific pathogens. Biases in 411 testing practices for different pathogens in different locations and with different clinical 412 febrile presentations will influence the pathogens looked for, detected and reported. The 413 application of diagnostic criteria that are strictly comparable across pathogens is not feasible. 414 In this study, strict diagnostic criteria were applied, preferentially including diagnostic 415 approaches with a high specificity, to minimize the influence of false positives within the 416 analyses. The bias assessments for study representativeness and precision in the estimates of 417 proportion of fevers attributable to a given pathogen both reveal that the majority of data 418 points had medium or high risk of one or both types of bias. This emphasizes the need for 419 cautious and essentially non-quantitative interpretation of the data extracted from these 420 studies. Many studies with risk of precision bias due to smaller sample size tended to report 421 the highest prevalences of disease attribution to a given pathogen (figure 5); and, 422 interestingly, these studies were often also classified as high risk for representativeness bias. 423 Figure 5 shows clear variation in risk of representativeness bias across pathogens, potentially 424 linked to variation in clinical presentation. For example, the majority of data points for 425 Japanese encephalitis virus and indeed all data points for Leishmania donovanii are

426 classified as high risk of representativeness bias. This review focused on studies reporting 427 diagnostic investigation of patient populations that were principally defined by fever and 428 populations principally defined by a common aetiological diagnosis were excluded (e.g., 429 populations defined by presence or suspicion of one or more zoonosis, some of whom were 430 febrile). This review therefore had an inherently low sensitivity for studies describing disease 431 outbreaks. This focus explains, for example, the absence of studies describing the 2014-2016 432 Ebola West Africa outbreak. The design of this review did not allow explicit investigation of 433 co-infections, either of zoonoses with malaria or of multiple zoonoses. Co-infections are 434 likely to be an important factor underlying both the distribution and prevalence of some zoonotic pathogens, including for example nontyphoidal *Salmonella* serovars.<sup>47</sup> Serological 435 436 diagnosis of acute infection based on testing of both acute and convalescent phase sera is 437 central to the confirmed diagnosis of multiple pathogens included in the study. As a 438 consequence, individuals who die prior to the collection of convalescent samples are unlikely 439 to contribute data (in the absence of other valid test options) and the proportions of fevers 440 attributable to pathogens with high probability of acute fatality will be under-estimated. 441 Furthermore, no validity criteria regarding the timing of sample collection for acute and 442 convalescent samples were imposed, leading potentially to false negative results (e.g., 443 seroconversion not detected because of premature convalescent sampling). For these reasons, 444 our findings are unlikely to capture the full extent of morbidity and mortality attributable to 445 zoonoses.

## 446

447 The data compiled in this review demonstrate the need to consider multiple zoonoses among 448 the potential causes of febrile illnesses in malaria-endemic countries. Different zoonoses are 449 likely to be important in different settings. Our study provides a starting point for improving 450 awareness of first the zoonoses that are known to contribute to febrile illness in different 451 malaria-endemic regions and second the fever-causing zoonoses with widespread distribution 452 that should be considered in patient evaluation. The demonstration of major data gaps should 453 encourage a more open-minded approach when considering zoonoses as a potential cause of 454 febrile illness. Continued efforts are needed to develop multi-pathogen diagnostics, ideally 455 with formats appropriate for point of care use. To avoid perpetuation of self-fulfilling 456 prophesies that can arise when only pathogens tested for (and detected) are assumed to be 457 present, the development and evaluation of such diagnostics should be informed by data 458 describing the pathogens present in specific settings and also the wider context. Untapped 459 sources of information on the distribution and occurrence of fever-causing zoonoses almost 460 certainly exist, particularly in the animal health sector. One Health efforts to share data and 461 knowledge between animal and human health sectors could help raise clinician awareness of locally relevant zoonoses, inform history taking, and guide diagnostic and management 462 463 decision making. Control of disease in animal populations and prevention of transmission 464 from animals to humans are likely to be the most effective ways to reduce human disease risk 465 with many zoonoses, necessitating active engagement with populations at risk to develop 466 sustainable disease control interventions. There are substantial challenges to clinicians and 467 epidemiologists in revealing the true impacts of many zoonoses. The enormous global burden of febrile illness and scope for improvements in the diagnosis and treatment of zoonotic 468 469 pathogens necessitate efforts to overcome these challenges and translate findings into 470 important public health gains. 471

Page 13 of 18

## 473 **Contributors**

- The author contributions are as follows. Study design: JEBH, KJA, JAC, SC, and MPR.
- 475 Searches, screening and article review: JEBH, MC, MES, KJA, JB, GAFL, DVH, PH, JAC,
- 476 SC, and MPR. Data extraction: JEBH and MC. Data analysis: JEBH. Manuscript writing:
- 477 JEBH, MC, MES, KJA, JAC, SC, and MPR.
- 478

## 479 **Declaration of interests**

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- 484 and Infectious Diseases and contracted research with BioFire Defense, LLC, outside the
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- 486

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- 497
- 498

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- 622 *Salmonella* Disease, Other Bacterial Bloodstream Infections, and Malaria in Sub-Saharan 623 Africa. *Clin Infect Dis* 2016; **62 Suppl 1**: S23-31.
- 624

# 626 Figures627

- 628 Figure 1: Flow diagram of records and articles assessed for the review.
- 629 Among the 46 articles excluded because the full text was not accessible in English, the
- 630 breakdown of languages was as follows: French (13 articles); Spanish (11 articles); Turkish
- 631 (9 articles); Mandarin (6 articles); Portuguese (2 articles); Hebrew (2 articles); Arabic (1
- 632 article); Danish (1 article) and Russian (1 article).
- 633
- Figure 2: Map illustrating the malaria-endemic countries included in the study and number of articles contributing data for each country (indicated by colour shading).
- 636
- Figure 3: Barchart showing the number of articles that looked for, reported diagnosis of andcontributed data for each of 40, 31 and 30 zoonoses respectively.
- 639 These data were tabulated for all zoonoses (n=40) and articles included in the review
- 640 (n=244). Bar colour indicates pathogen type and shading differentiates studies that i)
- 641 contribute data meeting study diagnostic criteria (left hand bar sections with darkest shading,
- 642 n=30 pathogens indicated by \*), ii) report diagnosis with approaches that do not meet study
- 643 diagnostic criteria (central bar sections with lighter shading, n=31 pathogens that comprised
- 644 the 30 with extracted data and *Escherichia coli*), iii) report looking for but not diagnosing a
- 645 zoonosis (right hand bar section with lightest shading, n=40 pathogens, also including
- 646 Burkholderia spp. Tick borne encephalitis virus, Marburg virus, Rabies virus, Newcastle
- 647 Disease virus, Mycobacterium bovis, Francisella tularensis, Ebola virus and
- 648 *Cryptosporidium parvum*).649
- 650 Figure 4: Proportion of fevers attributed to each zoonosis.
- 651 The plot includes one data point per study and pathogen combination. The different panels
- 652 include data from different WHO regions. Point colour indicates the coding for the risk of
- bias for the representativeness of the febrile population and point size is proportional to the
- number of individuals tested. Points are jittered on the x axis and shaded to visualize
- 655 overlapping points.
- 656
- Figure 5: Venn diagram illustrating the associations between febrile population clinical presentation and pathogens identified
- 658 presentation and pathogens identified.
- 659 Circles are scaled to the number of pathogens detected in each type of febrile population.
- 660 Undifferentiated, shown in green, 23 pathogens (including pathogens also seen in other 661 populations): fabrila nourological, shown in red, four archagenes, fabrila gasterintering
- 661 populations); febrile neurological, shown in red, four pathogens; febrile gastrointestinal, 662 shown in blue, two pathogens; febrile respiratory, shown in purple, one pathogen, febrile
- haemorrhagic, shown in yellow, seven pathogens. Five pathogens are not represented in the
- 664 figure as they were only detected in febrile populations classified as co-morbid (*Listeria spp.*,
- 665 *Pasteurella* spp. and *Toxoplasma gondii*) or in febrile populations with a specific febrile
- 666 aetiology suspected (Leishmania donavani, and Yersinia pestis).
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Figure 3 Leptospira spp.\* -Salmonella (non-Typhi)\* -Rickettsia (TGR)\* -Rickettsia (SFGR)\* -Orientia tsutsugamushi\* Coxiella burnetii\* Brucella spp.\* Japanese encephalitis virus\* Hantavirus\* West Nile virus\* Borrelia spp.\* Streptococcus spp.\* Escherichia spp. Rickettsia spp.\* Crimean-Congo haemorrhagic fever virus\* -Bartonella spp.\* -Rift valley fever virus\* -Lassa virus\* Leishmania donovani\* Anaplasma phagocytophilum\* -Venezuelan equine encephalitis virus\* *Ehrlichia* spp.\* *Campylobacter* spp.\* Burkholderia spp. Tick borne encephalitis virus -Schistosoma mansoni\* Pasteurella spp.\* Marburg virus -Babesia microti\* Yersinia pestis\* -Toxoplasma gondii\* Rabies virus Nipah virus\* Newcastle disease virus Mycobacterium bovis -Listeria spp.\* Francisella tularensis -Ebola virus Eastern equine encephalitis virus\* -Cryptosporidium parvum



# Pathogen





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## Zoonotic causes of febrile illness in malaria endemic countries: a systematic review **Supplementary Information**

#### **Zoonoses Search Concept Construction**

To construct a list of frequently reported zoonotic causes of human fever, we conducted preliminary searches of Medline and Embase using the search syntax '(exp Fever/ OR fever.mp.) AND (exp Zoonoses/ OR zoonoses.mp OR zoonosis.mp)' limited to humans.

3456789 The outputs of these searches were combined and de-duplicated in R.<sup>1</sup> The complete list of all subject headings associated with these articles was extracted and each heading was classified by two independent reviewers to 10 identify headings for named disease causing agents or named diseases. Headings that referred to non-specific 11 pathogen groups e.g., 'arboviruses' and those that referred to non-specific clinical symptoms, signs, syndromes, 12 13 or diseases e.g., 'jaundice' and 'parasitic diseases' were excluded. All headings classified as either a pathogen or disease by one or both reviewers (JEBH and PH) were matched to a list of 1,415 infectious organisms known to 14 be pathogenic to humans<sup>2</sup>. Non-zoonotic pathogens or diseases based on the classification by Taylor et al.<sup>2</sup> were 15 excluded. The frequency of appearance of each zoonosis-related heading in the initial search output dataset was 16 tabulated. Pathogen/disease subject headings that appeared in >10 references identified through the initial 'Fever 17 and Zoonoses' searches were retained. 18

19 For the 'zoonoses' concept, the list of zoonotic pathogens identified above was combined with lists of zoonotic 20 diseases from the World Health Organization (WHO)<sup>3</sup> and World Organisation of Animal Health (OIE)<sup>4</sup>.

21 22 23 24 25 All identified pathogens or diseases were then classified to differentiate pathogens that are normatively acquired by people through direct or indirect transmission from vertebrate animals to humans, as compared to pathogens where zoonotic transmission has been recorded but where sustained transmission within human populations also occurs and the majority of human infections are not acquired through zoonotic transmission. This classification 26 was made following the definitions used in Wolfe et al.<sup>5</sup> Three reviewers (JAC, SC, and MPR) independently 27 classified listed pathogens or diseases using the stages in the transformation of an animal pathogen into a 28 specialized pathogen of humans described in Wolfe et al.:5

- 29 Stage 1. A microbe that is present in animals but that has not been detected in humans under natural 30 conditions (that is, excluding modern technologies that can inadvertently transfer microbes, such as blood 31 transfusion, organ transplants, or hypodermic needles).
- 32 Stage 2. A pathogen of animals that, under natural conditions, has been transmitted from animals to humans 33 ('primary infection') but has not been transmitted between humans ('secondary infection'). 34
  - Stage 3. Animal pathogens that can undergo only a few cycles of secondary transmission between humans, so that occasional human outbreaks triggered by a primary infection soon die out.
- 36 Stage 4. A disease that exists in animals, and that has a natural (sylvatic) cycle of infecting humans by 37 primary transmission from the animal host, but that also undergoes long sequences of secondary 38 transmission between humans without the involvement of animal hosts.
- 39 Stage 5. A pathogen exclusive to humans.<sup>5</sup>

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41 Tie-breaks were resolved by a fourth independent reviewer (JEBH). Pathogens classified as stages 1 to 3 were 42 retained. Pathogens classified as stage 4 or 5, where sustained chains of transmission between humans occur, 43 were excluded from the review. 44

45 Pathogens or diseases included in the list of study zoonoses therefore included all pathogens and diseases that 46 were:

- Identified through the WHO list, OIE list or preliminary zoonoses search approach AND •
- Classified as a zoonoses<sup>2</sup> AND .
- Classified as a stage 1, 2 or 3 zoonosis.<sup>5</sup> •

50 51 52 The search concept for each pathogen or disease included exploded subject headings for both the pathogen and the diseases caused in humans and terms for both pathogen and disease were also included as keywords (e.g., 53 54 exp anthrax/ OR anthrax.mp. OR exp Bacillus anthracis/ OR bacillus anthracis.mp.). In instances where pathogen species within the same genus varied in their zoonotic status, search concepts were constructed to 55 include all zoonotic and non-zoonotic species and articles relating to non-zoonotic species were excluded at a 56 later stage. Finally, the list of pathogen- or disease-specific searches were combined using OR syntax to generate

57 the full 'zoonoses' search concept (Medline Search Syntax and Embase Search Syntax sections below).

### 58 59 **Medline Search Syntax**

- 60
- 61 (exp Anaplasmosis/ OR anaplasmosis.mp. OR exp Anaplasma/ OR anaplasma.mp.) [set database shortcode to
- 62 'pmez']
- 63 (exp Babesiosis/ OR babesiosis.mp. OR exp Babesia/ OR babesia.mp.)
- 64 (exp Anthrax/ OR anthrax.mp. OR exp Bacillus anthracis/ OR bacillus anthracis.mp.)
- 65 (exp Bartonella Infections/ OR bartonellosis.mp. OR exp Bartonella/ OR bartonella.mp.)
- 66 (exp Borrelia Infections/ OR borrelia Infection\$1.mp. OR exp Borrelia/ OR borrelia.mp.)
- 67 (exp brucellosis/ OR brucellosis.mp. OR exp Brucella/ OR brucella.mp.)
- 68 (exp Burkholderia Infections/ OR glanders.mp. OR exp Burkholderia/ OR burkholderia.mp.)
- 69 (exp Campylobacter Infections/ OR exp Campylobacter/ OR campylobacter\$.mp.)
- 70 (exp Psittacosis/ OR psittacosis.mp. OR exp Chlamydophila psittaci/ OR chlamydophila psittaci.mp.)
- 71 (exp Cowpox/ OR exp Cowpox virus/ OR cowpox.mp.)
- 72 (exp Q Fever/ OR q fever.mp. OR exp Coxiella/ OR coxiella.mp.)
- 73 (exp Hemorrhagic Fever, Crimean/OR crimean-congo h?emorrhagic fever.mp. OR exp Hemorrhagic Fever
- 74 Virus, Crimean-Congo/ OR crimean-congo h?emorrhagic fever virus.mp.)
- (exp Hemorrhagic Fever, Ebola/ OR ebolavirus infection\$1.mp. OR exp Ebolavirus/ OR ebola\$.mp.)
- (exp Echinococcosis/ OR echinococcosis.mp. OR exp Echinococcus/ OR echinococcus.mp.)
- 75 76 77 (exp Ehrlichiosis/ OR ehrlichiosis.mp. OR exp Ehrlichia/ OR ehrlichia.mp.)
- 78 79 (exp Encephalomyelitis, Equine/ OR exp Encephalitis Virus, Eastern Equine/ OR exp Encephalitis Virus,
- Venezuelan Equine/ OR exp Encephalitis Virus, Western Equine/ OR equine encephalitis.mp. OR equine 80 encephalomyelitis.mp.)
- 81 (exp Escherichia coli Infections/ OR exp Escherichia coli/ OR escherichia coli.mp.)
- 82 (exp "Foot-and-Mouth Disease"/ OR exp "Foot-and-Mouth Disease Virus"/ OR "foot and mouth disease".mp.
- 83 OR "foot-and-mouth".mp.)
- 84 (exp Tularemia/ OR tular?emia.mp. OR exp Francisella tularensis/ OR francisella tularensis.mp.)
- 85 (exp Hantavirus Infections/ OR hantavirus infection\$1.mp. OR exp Hantavirus/ OR hantavirus.mp.)
- 86 (exp Henipavirus Infections/ OR exp Henipavirus/ OR hendra.mp. OR nipah.mp. OR henipavirus.mp.)
- 87 (exp Encephalitis, Japanese/ OR exp Encephalitis Virus, Japanese/ OR japanese encephalitis.mp.)
- 88 (exp Lassa Fever/ OR exp Lassa virus/ OR lassa.mp.)
- 89 (exp Leishmaniasis/ OR leishmaniasis.mp. OR exp Leishmania/ OR leishmania.mp.)
- 90 (exp Leptospirosis/ OR leptospirosis.mp. OR exp Leptospira/ OR leptospira.mp.)
- 91 (exp Listeriosis/ OR listeriosis.mp. OR exp Listeria/ OR listeria.mp.)
- 92 (exp Marburg Virus Disease/ OR marburg h?emorrhagic fever.mp. OR exp Marburgvirus/ OR marburg\$.mp.)
- 93 (exp Monkeypox/ OR exp Monkeypox virus/ OR monkeypox.mp.)
- 94 (exp Tuberculosis, Bovine/ OR bovine tuberculosis.mp. OR exp Mycobacterium bovis/ OR mycobacterium
- 95 bovis.mp.)
- 96 (exp Paratuberculosis/ OR paratuberculosis.mp. OR exp "Mycobacterium avium subsp. paratuberculosis"/ OR
- 97 mycobacterium paratuberculosis.mp.)
- 98 (exp Newcastle Disease/ OR exp Newcastle disease virus/ OR newcastle disease.mp.)
- 99 (exp Pasteurella Infections/ OR pasteurellosis.mp. OR exp Pasteurella/ OR pasteurella.mp.)
- 100 (exp Prion Diseases/ OR exp Prions/ OR prion.mp.)
- 101 (exp Rabies/ OR rabies.mp. OR exp Rabies virus/ OR rabies virus.mp.)
- 102 (exp Rat-Bite Fever/ OR rat-bite.mp. OR rat bite.mp. OR exp Streptobacillus/ OR exp Spirillum/ OR
- 103 streptobacillus.mp. OR spirillum.mp.)
- 104 (exp Rickettsiaceae Infections/ OR rickettsiaceae infection\$1.mp. OR rickettsiosis.mp. OR exp Rickettsieae/ OR 105 rickettsia.mp.)
- 106 (exp Rift Valley Fever/ OR rift valley fever.mp. OR exp Rift Valley fever virus/ OR rift valley fever virus.mp.)
- 107 (exp Salmonella Infections/ OR salmonellosis.mp. OR exp Salmonella/ OR salmonella.mp.)
- 108 (exp Schistosomiasis/ OR schistosomiasis.mp. OR exp Schistosoma/ OR schistosoma.mp.)
- 109 (exp Streptococcal Infections/ OR streptococcal.mp. OR exp Streptococcus/ OR streptococcus.mp.)
- 110 (exp Pseudorabies/ OR pseudorabies.mp. OR exp Herpesvirus 1, Suid/ OR suid herpesvirus.mp. OR
- 111 aujeszky\$.mp.)
- 112 (exp Swine Vesicular Disease/ OR swine vesicular.mp. OR exp Enterovirus/ OR enterovirus.mp.)
- 113 (exp Cysticercosis/ OR cysticercosis.mp. OR exp Taenia/ OR taenia.mp.)
- 114 (exp Encephalitis, Tick-Borne/ OR tick borne encephalitis.mp. OR exp Encephalitis Viruses, Tick-Borne/ OR
- 115 tick borne encephalitis virus.mp.)
- 116 (exp Toxocariasis/ OR toxocariasis.mp. OR exp Toxocara/ OR toxocara.mp.)
- 117 (exp Toxoplasmosis/ OR toxoplasmosis.mp. OR exp Toxoplasma/ OR toxoplasma.mp.)

- 118 (exp Trichinellosis/ OR trichinellosis.mp. OR exp Trichinella/ OR trichinella.mp.)
- 119 (exp Trypanosomiasis/ OR trypanosomiasis.mp. OR exp Trypanosoma/ OR trypanosoma.mp.)
- 120 (exp Vaccinia/ OR exp Vaccinia virus/ OR vaccinia.mp.)
- 121 (exp Vesicular Stomatitis/ OR exp Vesiculovirus/ OR vesicular stomatitis.mp.)
- 122 (exp West Nile Fever/ OR west nile fever.mp. OR exp West Nile virus/ OR west nile virus.mp.)
- 123 (exp Yersinia Infections/ OR yersinia infection\$1.mp. OR exp Yersinia/ OR yersinia.mp. OR plague.mp.)
- 124 (exp "Georgia (Republic)"/ OR "Georgia (Republic)".mp.)
- 125 (exp Afghanistan/ OR Afghanistan.mp.)
- 126 (exp Algeria/ OR Algeria.mp.)
- 127 (exp Angola/ OR Angola.mp.)
- 128 (exp Argentina/ OR Argentina.mp.)
- 129 (exp Armenia/ OR Armenia.mp.)
- 130 (exp Azerbaijan/ OR Azerbaijan.mp.)
- 131 (exp Bahamas/ OR Bahamas.mp.)
- 132 (exp Bangladesh/ OR Bangladesh.mp.)
- 133 (exp Belize/ OR Belize.mp.)
- 134 (exp Benin/ OR Benin.mp.)
- 135 (exp Bhutan/ OR Bhutan.mp.)
- 136 (exp Bolivia/ OR Bolivia.mp.)
- 137 (exp Botswana/ OR Botswana.mp.)
- 138 (exp Brazil/ OR Brazil.mp.)
- 139 (exp Burkina Faso/ OR Burkina Faso.mp.)
- 140 (exp Burundi/ OR Burundi.mp.)
- 141 (exp Cambodia/ OR Cambodia.mp.)
- 142 (exp Cameroon/ OR Cameroon.mp.)
- 143 (exp Cape Verde/ OR Cape Verde.mp.)
- 144 (exp Central African Republic/ OR Central African Republic.mp.)
- 145 (exp Chad/ OR Chad.mp.)
- 146 (exp China/ OR China.mp.)
- 147 (exp Colombia/ OR Colombia.mp.)
- 148 (exp Comoros/ OR Comoros.mp.)
- 149 (exp Congo/ OR Congo.mp.)
- 150 (exp Costa Rica/ OR Costa Rica.mp.)
- 151 (exp Cote d'Ivoire/ OR Cote d'Ivoire.mp.)
- 152 (exp Democratic People's Republic of Korea/ OR Democratic People's Republic of Korea.mp.)
- 153 (exp Democratic Republic of the Congo/ OR Democratic Republic of the Congo.mp.)
- 154 (exp Djibouti/ OR Djibouti.mp.)
- 155 (exp Dominican Republic/ OR Dominican Republic.mp.)
- 156 (exp East Timor/ OR East Timor.mp.)
- 157 (exp Ecuador/ OR Ecuador.mp.)
- 158 (exp Egypt/ OR Egypt.mp.)
- 159 (exp El Salvador/ OR El Salvador.mp.)
- 160 (exp Equatorial Guinea/ OR Equatorial Guinea.mp.)
- 161 (exp Eritrea/ OR Eritrea.mp.)
- 162 (exp Ethiopia/ OR Ethiopia.mp.)
- 163 (exp French Guiana/ OR French Guiana.mp.)
- 164 (exp Gabon/ OR Gabon.mp.)
- 165 (exp Gambia/ OR Gambia.mp.)
- 166 (exp Ghana/ OR Ghana.mp.)
- 167 (exp Guatemala/ OR Guatemala.mp.)
- 168 (exp Guinea/ OR Guinea.mp.)
- 169 (exp Guinea-Bissau/ OR Guinea-Bissau.mp.)
- 170 (exp Guyana/ OR Guyana.mp.)
- 171 (exp Haiti/ OR Haiti.mp.)
- 172 (exp Honduras/ OR Honduras.mp.)
- 173 (exp India/ OR India.mp.)
- 174 (exp Indonesia/ OR Indonesia.mp.)
- 175 (exp Iran/ OR Iran.mp.)
- 176 (exp Iraq/ OR Iraq.mp.)
- 177 (exp Jamaica/ OR Jamaica.mp.)

178 (exp Kenya/ OR Kenya.mp.) 179 (exp Kyrgyzstan/ OR Kyrgyzstan.mp.) 180 (exp Laos/ OR Laos.mp.) 181 (exp Liberia/ OR Liberia.mp.) 182 (exp Madagascar/ OR Madagascar.mp.) 183 (exp Malawi/ OR Malawi.mp.) 184 (exp Malaysia/ OR Malaysia.mp.) 185 (exp Mali/ OR Mali.mp.) 186 (exp Mauritania/ OR Mauritania.mp.) 187 (exp Mauritius/ OR Mauritius.mp.) 188 (exp Mexico/ OR Mexico.mp.) 189 (exp Morocco/ OR Morocco.mp.) 190 (exp Mozambique/ OR Mozambique.mp.) 191 (exp Myanmar/ OR Myanmar.mp.) 192 (exp Namibia/ OR Namibia.mp.) 193 (exp Nepal/ OR Nepal.mp.) 194 (exp Nicaragua/ OR Nicaragua.mp.) 195 (exp Niger/ OR Niger.mp.) 196 (exp Nigeria/ OR Nigeria.mp.) 197 (exp Oman/ OR Oman.mp.) 198 (exp Pakistan/ OR Pakistan.mp.) 199 (exp Panama/ OR Panama.mp.) 200 (exp Papua New Guinea/ OR Papua New Guinea.mp.) 201 (exp Paraguay/ OR Paraguay.mp.) 202 (exp Peru/ OR Peru.mp.) 203 (exp Philippines/ OR Philippines.mp.) 204 (exp Republic of Korea/ OR Republic of Korea.mp.) 205 (exp Russia/ OR Russia.mp.) 206 (exp Rwanda/ OR Rwanda.mp.) 207 (exp Sao Tome/ OR Sao Tome.mp.) 208 (exp Saudi Arabia/ OR Saudi Arabia.mp.) 209 (exp Senegal/ OR Senegal.mp.) 210 (exp Sierra Leone/ OR Sierra Leone.mp.) 211 (exp Solomon Islands/ OR Solomon Islands.mp.) 212 (exp Somalia/ OR Somalia.mp.) 213 (exp South Africa/ OR South Africa.mp.) 214 (exp Sri Lanka/ OR Sri Lanka.mp.) 215 (exp Sudan/ OR Sudan.mp.) 216 (exp Suriname/ OR Suriname.mp.) 217 (exp Swaziland/ OR Swaziland.mp.) 218 (exp Syria/ OR Syria.mp.) 219 (exp Tajikistan/ OR Tajikistan.mp.) 220 (exp Tanzania/ OR Tanzania.mp.) 221 (exp Thailand/ OR Thailand.mp.) 222 (exp Togo/ OR Togo.mp.) 223 (exp Turkey/ OR Turkey.mp.) 224 (exp Turkmenistan/ OR Turkmenistan.mp.) 225 (exp Uganda/ OR Uganda.mp.) 226 (exp Uzbekistan/ OR Uzbekistan.mp.) 227 (exp Vanuatu/ OR Vanuatu.mp.) 228 (exp Venezuela/ OR Venezuela.mp.) 229 (exp Vietnam/ OR Vietnam.mp.) 230 (exp Yemen/ OR Yemen.mp.) 231 (exp Zambia/ OR Zambia.mp.) 232 (exp Zimbabwe/ OR Zimbabwe.mp.) 233 (exp Africa/ OR africa.mp) 234 (exp Fever/ OR fever\$1.mp. OR febrile.mp.) 235 or/1-52 236 or/53-162 237 164 AND 165

- 238 239 240 241 163 AND 166
- ..l/167 yr=2004-2019

## 243 Embase Search Syntax

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- 245 (exp anaplasmosis/ OR exp human granulocytic anaplasmosis/ OR anaplasmosis.mp. OR exp Anaplasma/ OR
- anaplasma.mp.) [set database shortcode to 'emczd']
- 247 (exp babesiosis/ OR babesiosis.mp. OR exp Babesia/ OR babesia.mp.)
- 248 (exp anthrax/ OR anthrax.mp. OR exp Bacillus anthracis/ OR bacillus anthracis.mp.)
- 249 (exp bartonellosis/ OR bartonellosis.mp. OR exp Bartonella/ OR bartonella.mp.)
- 250 (exp Borrelia infection/ OR borrelia Infection\$1.mp. OR exp Borrelia/ OR borrelia.mp.)
- 251 (exp brucellosis/ OR brucellosis.mp. OR exp Brucella/ OR brucella.mp.)
- 252 (exp Burkholderia infection/ OR glanders.mp. OR exp Burkholderia/ OR burkholderia.mp.)
- 253 (exp campylobacteriosis/ OR exp Campylobacter/ OR campylobacter\$.mp.)
- 254 (exp ornithosis/ OR psittacosis.mp. OR exp Chlamydophila psittaci/ OR chlamydophila psittaci.mp.)
- 255 (exp cowpox/ OR exp Cowpox virus/ OR cowpox.mp.)
- 256 (exp Q fever/ OR q fever.mp. OR exp Coxiella/ OR coxiella.mp.)
- 257 (exp Crimean Congo hemorrhagic fever/ OR crimean-congo h?emorrhagic fever.mp. OR exp Nairo virus/ OR
- crimean-congo h?emorrhagic fever virus.mp.)
- 259 (exp Ebola hemorrhagic fever/ OR ebolavirus infection\$1.mp. OR exp Ebola virus/ OR ebola\$.mp.)
- 260 (exp echinococcosis/ OR echinococcosis.mp. OR exp Echinococcus/ OR echinococcus.mp.)
- 261 (exp ehrlichiosis/ OR ehrlichiosis.mp. OR exp Ehrlichia/ OR ehrlichia.mp.)
- 262 (exp Eastern equine encephalitis/ OR exp Venezuelan equine encephalitis/ OR exp Western equine encephalitis/
- 263 OR exp Eastern equine encephalomyelitis virus/ OR exp Venezuelan equine encephalomyelitis alphavirus/ OR
- 264 exp Western equine encephalomyelitis alphavirus/ OR equine encephalitis.mp. OR equine
- 265 encephalomyelitis.mp.)
- 266 (exp Escherichia coli infection/ OR exp Escherichia coli/ OR escherichia coli.mp.)
- (exp "foot and mouth disease"/ OR exp "Foot and mouth disease virus"/ OR "foot and mouth disease".mp. OR
   "foot-and-mouth".mp.)
- 269 (exp tularemia/ OR tular?emia.mp. OR exp Francisella tularensis/ OR francisella tularensis.mp.)
- 270 (exp Hantavirus infection/ OR hantavirus infection\$1.mp. OR exp Hantavirus/ OR hantavirus.mp.)
- 271 (exp Nipah virus infection/ OR exp Hendra virus infection/ OR exp Nipah virus/ OR exp Hendra virus/ OR
- 272 hendra.mp. OR nipah.mp. OR henipavirus.mp.)
- 273 (exp Japanese encephalitis/ OR exp Japanese encephalitis virus/ OR japanese encephalitis.mp.)
- 274 (exp Lassa fever/ OR exp Lassa virus/ OR lassa.mp)
- 275 (exp leishmaniasis/ OR leishmaniasis.mp. OR exp Leishmania/ OR leishmania.mp.)
- 276 (exp leptospirosis/ OR leptospirosis.mp. OR exp Leptospira/ OR leptospira.mp.)
- 277 (exp listeriosis/ OR listeriosis.mp. OR exp Listeria/ OR listeria.mp.)
- 278 (exp Marburg hemorrhagic fever/ OR marburg h?emorrhagic fever.mp. OR exp Marburg virus/ OR
- 279 marburg\$.mp.)
- 280 (exp monkeypox/ OR exp Monkeypox virus/ OR monkeypox.mp.)
- 281 (exp bovine tuberculosis/ OR bovine tuberculosis.mp. OR exp Mycobacterium bovis/ OR mycobacterium
- 282 bovis.mp.)
- (exp paratuberculosis/ OR paratuberculosis.mp. OR exp Mycobacterium paratuberculosis/ OR mycobacterium
   paratuberculosis.mp.)
- 285 (exp Newcastle disease/ OR exp Newcastle disease paramyxovirus/ OR newcastle disease.mp.)
- 286 (exp pasteurellosis/ OR pasteurellosis.mp. OR exp Pasteurella/ OR pasteurella.mp.)
- 287 (exp prion disease/ OR exp prion/ OR prion.mp.)
- 288 (exp rabies/ OR rabies.mp. OR exp Rabies virus/ OR rabies virus.mp.)
- 289 (exp rat bite fever/ OR rat-bite.mp. OR rat bite.mp. OR exp Streptobacillus/ OR exp Spirillum/ OR
- 290 streptobacillus.mp. OR spirillum.mp.)
- (exp Rickettsiaceae infection/ OR rickettsiaceae infection\$1.mp.OR rickettsiosis.mp. OR exp Rickettsiaceae/ OR
   rickettsia.mp.)
- (exp Rift Valley fever/ OR rift valley fever.mp. OR exp Rift Valley fever bunyavirus/ OR rift valley fever
   virus.mp.)
- 295 (exp salmonellosis/ OR exp animal salmonellosis/ OR salmonellosis.mp. OR exp Salmonella/ OR
- 296 salmonella.mp.)
- 297 (exp schistosomiasis/ OR schistosomiasis.mp. OR exp Schistosoma/ OR schistosoma.mp.)
- 298 (exp Streptococcus infection/ OR streptococcal.mp. OR exp Streptococcus/ OR streptococcus.mp.)
- 299 (exp pseudorabies/ OR pseudorabies.mp. OR exp Pseudorabies herpetovirus/ OR suid herpesvirus.mp. OR
- 300 aujeszky\$.mp.)
- 301 (exp swine vesicular disease/ OR swine vesicular.mp. OR exp Enterovirus/ OR enterovirus.mp.)

- 302 (exp cysticercosis/ OR cysticercosis.mp. OR exp Taenia/ OR taenia.mp.)
- 303 (exp tick borne encephalitis/ OR tick borne encephalitis.mp. OR exp Tick borne encephalitis flavivirus/ OR tick
- 304 borne encephalitis virus.mp.)
- 305 (exp toxocariasis/ OR toxocariasis.mp. OR exp Toxocara/ OR toxocara.mp.)
- 306 (exp toxoplasmosis/ OR exp congenital toxoplasmosis/ OR toxoplasmosis.mp. OR exp Toxoplasma/ OR
- 307 toxoplasma.mp.)
- 308 (exp trichinosis/ OR trichinellosis.mp. OR exp Trichinella/ OR trichinella.mp.)
- 309 (exp trypanosomiasis/ OR trypanosomiasis.mp. OR exp Trypanosoma/ OR trypanosoma.mp.)
- 310 (exp vaccinia/ OR exp Vaccinia virus/ OR vaccinia.mp.)
- 311 (exp vesicular stomatitis/ OR exp Vesicular stomatitis virus/ OR vesicular stomatitis.mp.)
- 312 (exp West Nile fever/ OR west nile fever.mp. OR exp West Nile flavivirus/ OR west nile virus.mp.)
- 313 (exp Yersinia infection/ OR yersinia infection\$1.mp. OR exp Yersinia/ OR yersinia.mp. OR plague.mp.)
- 314 (exp "Georgia (republic)"/ OR "Georgia (republic)".mp.)
- 315 (exp "Turkey (republic)"/ OR "Turkey (republic)".mp.)
- 316 (exp Afghanistan/ OR Afghanistan.mp.)
- 317 (exp Algeria/ OR Algeria.mp.)
- 318 (exp Angola/ OR Angola.mp.)
- 319 (exp Argentina/ OR Argentina.mp.)
- 320 (exp Armenia/ OR Armenia.mp.)
- 321 (exp Azerbaijan/ OR Azerbaijan.mp.)
- 322 (exp Bahamas/ OR Bahamas.mp.)
- 323 (exp Bangladesh/ OR Bangladesh.mp.)
- 324 (exp Belize/ OR Belize.mp.)
- 325 (exp Benin/ OR Benin.mp.)
- 326 (exp Bhutan/ OR Bhutan.mp.)
- 327 (exp Bolivia/ OR Bolivia.mp.)
- 328 (exp Botswana/ OR Botswana.mp.)
- 329 (exp Brazil/ OR Brazil.mp.)
- 330 (exp Burkina Faso/ OR Burkina Faso.mp.)
- 331 (exp Burundi/ OR Burundi.mp.)
- 332 (exp Cambodia/ OR Cambodia.mp.)
- 333 (exp Cameroon/ OR Cameroon.mp.)
- 334 (exp Cape Verde/ OR Cape Verde.mp.)
- 335 (exp Central African Republic/ OR Central African Republic.mp.)
- 336 (exp Chad/ OR Chad.mp.)
- 337 (exp China/ OR China.mp.)
- 338 (exp Colombia/ OR Colombia.mp.)
- 339 (exp Comoros/ OR Comoros.mp.)
- 340 (exp Congo/ OR Congo.mp.)
- 341 (exp Costa Rica/ OR Costa Rica.mp.)
- 342 (exp Cote d'Ivoire/ OR Cote d'Ivoire.mp.)
- 343 (exp Democratic Republic Congo/ OR Democratic Republic Congo.mp.)
- 344 (exp Djibouti/ OR Djibouti.mp.)
- 345 (exp Dominican Republic/ OR Dominican Republic.mp.)
- 346 (exp Ecuador/ OR Ecuador.mp.)
- 347 (exp Egypt/ OR Egypt.mp.)
- 348 (exp El Salvador/ OR El Salvador.mp.)
- 349 (exp Equatorial Guinea/ OR Equatorial Guinea.mp.)
- 350 (exp Eritrea/ OR Eritrea.mp.)
- 351 (exp Ethiopia/ OR Ethiopia.mp.)
- 352 (exp French Guiana/ OR French Guiana.mp.)
- 353 (exp Gabon/ OR Gabon.mp.)
- 354 (exp Gambia/ OR Gambia.mp.)
- 355 (exp Ghana/ OR Ghana.mp.)
- 356 (exp Guatemala/ OR Guatemala.mp.)
- 357 (exp Guinea/ OR Guinea.mp.)
- 358 (exp Guinea-Bissau/ OR Guinea-Bissau.mp.)
- 359 (exp Guyana/ OR Guyana.mp.)
- 360 (exp Haiti/ OR Haiti.mp.)
- 361 (exp Honduras/ OR Honduras.mp.)

362 (exp India/ OR India.mp.) 363 (exp Indonesia/ OR Indonesia.mp.) 364 (exp Iran/ OR Iran.mp.) 365 (exp Iraq/ OR Iraq.mp.) 366 (exp Jamaica/ OR Jamaica.mp.) 367 (exp Kenya/ OR Kenya.mp.) 368 (exp Kyrgyzstan/ OR Kyrgyzstan.mp.) 369 (exp Laos/ OR Laos.mp.) 370 (exp Liberia/ OR Liberia.mp.) 371 (exp Madagascar/ OR Madagascar.mp.) 372 (exp Malawi/ OR Malawi.mp.) 373 (exp Malaysia/ OR Malaysia.mp.) 374 (exp Mali/ OR Mali.mp.) 375 (exp Mauritania/ OR Mauritania.mp.) 376 (exp Mauritius/ OR Mauritius.mp.) 377 (exp Mexico/ OR Mexico.mp.) 378 (exp Morocco/ OR Morocco.mp.) 379 (exp Mozambique/ OR Mozambique.mp.) 380 (exp Myanmar/ OR Myanmar.mp.) 381 (exp Namibia/ OR Namibia.mp.) 382 (exp Nepal/ OR Nepal.mp.) 383 (exp Nicaragua/ OR Nicaragua.mp.) 384 (exp Niger/ OR Niger.mp.) 385 (exp Nigeria/ OR Nigeria.mp.) 386 (exp North Korea/ OR North Korea.mp.) 387 (exp Oman/ OR Oman.mp.) 388 (exp Pakistan/ OR Pakistan.mp.) 389 (exp Panama/ OR Panama.mp.) 390 (exp Papua New Guinea/ OR Papua New Guinea.mp.) 391 (exp Paraguay/ OR Paraguay.mp.) 392 (exp Peru/ OR Peru.mp.) 393 (exp Philippines/ OR Philippines.mp.) 394 (exp Russian Federation/ OR Russian Federation.mp.) 395 (exp Rwanda/ OR Rwanda.mp.) 396 (exp Sao Tome and Principe/ OR Sao Tome and Principe.mp.) 397 (exp Saudi Arabia/ OR Saudi Arabia.mp.) 398 (exp Senegal/ OR Senegal.mp.) 399 (exp Sierra Leone/ OR Sierra Leone.mp.) 400 (exp Solomon Islands/ OR Solomon Islands.mp.) 401 (exp Somalia/ OR Somalia.mp.) 402 (exp South Africa/ OR South Africa.mp.) 403 (exp South Korea/ OR South Korea.mp.) 404 (exp Sri Lanka/ OR Sri Lanka.mp.) 405 (exp Sudan/ OR Sudan.mp.) 406 (exp Suriname/ OR Suriname.mp.) 407 (exp Swaziland/ OR Swaziland.mp.) 408 (exp Syrian Arab Republic/ OR Syrian Arab Republic.mp.) 409 (exp Tajikistan/ OR Tajikistan.mp.) 410 (exp Tanzania/ OR Tanzania.mp.) 411 (exp Thailand/ OR Thailand.mp.) 412 (exp Timor-Leste/ OR Timor-Leste.mp.) 413 (exp Togo/ OR Togo.mp.) 414 (exp Turkmenistan/ OR Turkmenistan.mp.) 415 (exp Uganda/ OR Uganda.mp.) 416 (exp Uzbekistan/ OR Uzbekistan.mp.) 417 (exp Vanuatu/ OR Vanuatu.mp.) 418 (exp Venezuela/ OR Venezuela.mp.) 419 (exp Viet Nam/ OR Viet Nam.mp.) 420 (exp Yemen/ OR Yemen.mp.) 421 (exp Zambia/ OR Zambia.mp.)

- 422 (exp Zimbabwe/ OR Zimbabwe.mp.)
- 423 (exp Africa/ OR africa.mp)
- 424 (exp fever/ OR fever\$1.mp. OR febrile.mp.)
- 425 or/1-52
- 426 or/53-162
- 427 164 AND 165
- 428 163 AND 166
- 429 ..1/167 yr=2004-2019
- 422 423 424 425 426 427 428 429 430
- 431

# 432 433 434 435 **Abstract Screening**

Conference proceedings, records that did not include any abstract text, and records that did not have an abstract

in English were excluded. Remaining records were evaluated against the criteria listed in table S1. Records that

436 437 did not present data from a malaria-endemic country were also excluded. Full text articles were sought for all articles not excluded at the abstract review step.

438 439

#### Table S1. Criteria applied for abstract screening.

Criterion	Guidance	Outcome
Inc1FeverPopn	Does the Title/Abstract refer to clinical and/or laboratory evaluation	If Yes, retain and evaluate
	of a group of two or more humans that are explicitly described using	Inc1ZooPath.
	one or more of the of the following terms:	
	Febrile / fever(s) / pyrexia(s) /temperature $\geq$ 38.0C / body	If No, exclude.
	temperature elevation?	
Inc1ZooPath	Does the Title/Abstract refer to diagnosis of this febrile population	If Yes, retain and evaluate
	with one or more of the pathogens/diseases included in this study	Exc1PathogenFocus.
	(table 1 in main paper)?	
		If No, evaluate Inc1Bcx.
Inc1Bcx	Does the Title/Abstract refer to the use of blood culture for the	If Yes, retain and evaluate
	diagnosis of this febrile population?	Exc1PathogenFocus.
		If No, exclude.
Exc1PathogenFocus	Does the Title/Abstract refer to a group of two or more humans that	If Yes, exclude.
	are principally classified on the basis of a common (i.e. 100%	
	frequency) aetiological diagnosis, some proportion of which may	If No, retain for full text review.
	also have fever?	

440

#### 441 **Full Text Review**

442 Full text articles were evaluated by two independent reviewers against the criteria listed in table S2.

443 444

### Table S2. Criteria applied for full text review of articles.

Criterion	Guidance	Outcome
Inc2FP	Does the article provide details/inclusion criteria for one or more human population(s) (of more than one person) that explicitly includes acute fever/febrile illness as part of the inclusion criteria?	If Yes, retain and evaluate Inc2ZP.
		If No, exclude.
Inc2ZP	Does the article provide data on the diagnosis of a zoonotic pathogen as defined on the species level list (table 1 in main paper)?	If Yes, retain and evaluate Inc2DT. If No. exclude.
Inc2DT	<ul> <li>Does the article provide details of one or more diagnostic test procedure(s) for one or more of the zoonotic pathogens included in this study that meets &gt;1 of the following criteria and are used to test &gt;1 febrile people?</li> <li>1 – culture of the pathogen from sample(s) collected from a febrile person</li> <li>2 – direct detection of the pathogen (e.g., by PCR based techniques) from sample(s) collected from a febrile person</li> <li>3 – serological diagnosis of acute infection based on testing of both acute and convalescent phase serum samples and demonstration of seroconversion</li> <li>4 – diagnosis of acute infection based on detection of pathogen-specific antibody or antigens in a single serum sample only for selected pathogens, for which widely accepted case definitions deemed pathogen specific antibody or antigen detection sufficiently accurate (table 2 in main paper)</li> <li>5 – IgM detection in CSF for selected pathogens for which widely accepted case definitions include IgM detection in CSF (table 2 in main paper)</li> </ul>	If Yes, retain, record coding of valid tests and evaluate Exc2nTests. If No, exclude.
Exc2nTests	Does the article lack detail on the number of people tested for each study pathogen with each testing method/case definition that meets the above criteria?	If Yes, exclude. If No, retain and evaluate Exc2AllNeg.
Exc2AllNeg	Does the article give the number of people tested for a study pathogen with a test method/case definition that meets the above criteria, but all tested individuals are negative?	If Yes, exclude. If No, retain and evaluate Exc2DV.
Exc2DV	Does the article present data from a study designed to evaluate diagnostic test and/or vaccine performance without presenting 'new data' on the number/proportion of patients diagnosed with pathogen x from a described population of febrile humans?	If Yes, exclude. If No, retain and evaluate Exc2Rev.
Exc2Rev	Does the article provide a review of previously published data only, without presenting 'new' primary data on the number/proportion of patients diagnosed with pathogen x?	If Yes, exclude. If No, retain and evaluate Exc2PF.

Exc2PF	Does the article refer to a group of two or more humans that are principally	If Yes, exclude.
	classified on the basis of a common (e.g., 100% frequency) aetiological	
	diagnosis, some proportion of which may also have fever?	If No, retain and carry forward
		for data extraction.

#### 446 Data extraction

447 Articles were excluded during data extraction if they did not meet one or more of the study inclusion criteria or 448 did meet one or more of the exclusion criteria described above for full text review. For all included studies, data 449 were extracted in two stages. First, article level data were extracted following the guidance given in table S3. 450

451 Article level data collection on individual pathogens included the names of each of the zoonotic pathogens that 452 the article described diagnostic methods for and the names of the zoonotic pathogens that were diagnosed in the 453 study. These classifications record the named zoonoses that each study reported looking for and diagnosing,

- 454 irrespective of the diagnostic approach used or level of detail given.
- 455

456 At the second step, data were extracted the for each combination of zoonotic pathogen and diagnostic test 457 approach that met study validity criteria following the guidance given in table S4. In instances where more than 458 one diagnostic method was used for a given pathogen (e.g., culture and serology-based case definitions), data on 459 the total number of individuals tested and positive using valid diagnostics for a given pathogen were aggregated. 460 Data were only extracted for diagnosed pathogens and no data were extracted for pathogens not identified, even 461 when common diagnostic approaches were used. For example, in studies conducting blood cultures the number 462 of individuals tested and positive for each identified zoonosis were extracted but no data were extracted on the 463 number of individuals who tested negative for other pathogens that could be identified by that blood culture.

When duplicate records were identified, e.g., when two articles reported identical data on pathogen detection in the same population, the later duplicate record was removed from the dataset for analysis.

467

464

468 Extracted data were used to classify study and outcome level attributes according to the pre-defined criteria for 469 bias assessment given in table S5.

470 471

Data to be extracted	Guidance
Country and WHO region	Record the country or countries in which the reported study was conducted (i.e. the country where the febrile population was identified, and data were collected).
	Country name spellings and regional classifications are as defined by the WHO.
Start year of data collection	Record the start year for the period over which the reported study was conducted (i.e. the period when the febrile population was identified, and data were collected).
End of data collection	Record the end year for the period over which the reported study was conducted (i.e. the period when the febrile population was identified, and data were collected).
Fever population description	Record a general description of the febrile population investigated in this study.
Fever population eligibility	Record the inclusion and exclusion criteria used to define eligibility of participants in this study.
Specific aetiologies excluded	Record if patients with any specific actiologies or syndromes were excluded in this study. Generalised exclusions such as "known causes of fever", "obvious focus of infection" or 'obvious explanations of febrile illness" were not classified here.
Details of exclusions	Record the details of the named aetiologies and/or syndromes excluded.
Differentiated or undifferentiated fever	Classify each study population as undifferentiated febrile population or differentiated febrile population according to the reported clinical presentation.
Febrile population classification	Classify differentiated febrile populations as: i) febrile neurologic presentation; ii) febrile haemorrhagic presentation; iii) febrile gastrointestinal presentation; iv) febrile respiratory presentation; v) specific febrile aetiology suspected (i.e., leishmaniasis, leptospirosis, plague, and rickettsiosis); vi) fever in a high specific co-morbid group (i.e. malignancy, immunocompromise).
Age	Record details provided about the ages of the febrile population
Demographic restriction	Record the details of any demographic restriction of the study population e.g., restriction of the study population to individuals meeting specific criteria for age or sex.
Urban or rural population	Record whether or not the study was conducted in a predominantly urban population, predominantly rural or mixed.
Inpatient or outpatient population	Record whether or not the febrile population described were inpatients (e.g., admitted to a healthcare facility), outpatients (e.g., patients seeking care at a healthcare facility but apparently not admitted) or if the study was population- based.
Outbreak	Record whether or not the study reports that data collection was conducted during a reported outbreak or not and the disease/syndrome described if Yes.
Zoonotic pathogens diagnosed among febrile	Was any proportion of the reported febrile population diagnosed with a zoonotic
--	--
patients	pathogen?
Pathogens looked for	For each zoonosis mentioned in the article record 1 if the article describes a
	diagnostic approach taken to identify individuals infected with that pathogen.
	Record 0 for each zoonosis where this is not the case.
Pathogens diagnosed	For each zoonosis mentioned in the article record 1 if the article reports more than
	one member of a febrile population diagnosed with this pathogen (irrespective of
	the diagnostics used). Record 0 for each zoonosis where this is not the case.

#### 473 Table S4. Data extracted for each zoonotic pathogen diagnosed by a valid method.

Data to be extracted	Guidance
Zoonotic pathogen identified	Record the pathogen diagnosed using valid diagnostic methods.
Type of sample	Record the details of the sample(s) tested with each specific test/approach.
Diagnostic method used	Record the type of diagnostic test(s) used for each specific test/approach.
Number of individuals tested for that pathogen by	Record the number of febrile patients tested using the valid diagnostics described
valid methods	in this row of the dataset specifically.
Number of individuals diagnosed as positive for that	Record the number of febrile patients classified as positive using the valid
pathogen by valid methods	diagnostics described in this row of the dataset specifically.
Indicator for multiple diagnostic methods for given	Record Yes (1) if there is more than one row of data for this pathogen and
pathogen in this reference	reference combination.

### **Bias evaluation**

Each population was classified as low, medium or high risk of bias against the representativeness and precision criteria as detailed in table S5.

474 475 476 477 478 479

### Table S5. Criteria for bias assessment and classification of study and population level attributes.

Criteria	Risk of bias	Description
	classification	
Study representativeness	Low	Undifferentiated febrile population with no demographic restriction and no aetiologies or syndromes excluded.
	Medium	Undifferentiated febrile population with demographic restriction or one or more aetiologies and/or syndromes excluded.
	High	Febrile population classified as differentiated (table S4) or sampled during an identified disease outbreak.
Precision of percentage fevers attributed to zoonosis	Low	Number of individual tested > 385.
	Medium	Number of individuals tested > 139 and $\leq$ 385.
	High	Number of individuals tested $\leq 139$ .

### 482 **Results**

483

# 484 Table S6: Characteristics and summary of the 244 articles and 309 records of zoonosis diagnosis included in the review.

485 Study population abbreviations: UN = undifferentiated; D = differentiated; COMORBID = febrile co-morbid group GI = febrile gastrointestinal; HEM = febrile

- 486 haemorrhagic; NEU = febrile neurological; RESP; febrile respiratory; SP = specific febrile aetiology suspected.
- 487 Diagnostics abbreviations: ELISA = enzyme linked immunosorbent assay; HI = haemagglutination inhibition test; IFA = immunofluorescence assay; IgM = IgM detection;
- $\begin{array}{l} 488 \\ 489 \end{array} \text{MAT} = \text{microscopic agglutination test; PCR} = \text{polymerase chain reaction-based test; PRNT} = \text{plaque reduction neutralisation test. When multiple diagnostics used different} \\ 489 \end{array} \\ \begin{array}{l} \text{tests are separated by ",".} \end{array} \\ \end{array}$
- 490 An excel format version of this table, including additional data fields is accessible at: <u>http://dx.doi.org/10.5525/gla.researchdata.890</u>

Pathogen	First author, year of publication and reference	Country	Study Period	Study Population Classification	Diagnostics Used	Number Tested	Number Positive	Representativeness Bias Coding	Precision Bias Coding
Anaplasma	Lee et al. (2018) <sup>6</sup>	Republic of	2015-	UN	PCR	380	14	Medium	Medium
phagocytophilum	7	Korea	2017						
Anaplasma phagocytophilum	Yi et al. (2017)'	Republic of Korea	2003-2012	UN	PCR	70	5	Low	High
Ananlasma	Zhang et al. $(2011)^8$	China	2012	D SP	PCR IFA	26	8	High	High
phagocytophilum	Zhang et al. (2011)	Cillia	2004	0.01		20	0	1151	ingu
Anaplasma	Zhang et al. (2013)9	China	2009-	UN	Culture, IFA, PCR	421	46	Low	Low
phagocytophilum			2010						
Babesia microti	Zhou et al. (2013) <sup>10</sup>	China	2012-	UN	PCR	449	10	Low	Low
			2013						
Bartonella spp.	Chaudhry et al. (2018) <sup>11</sup>	India	2012-	UN	PCR	28	2	Medium	High
<b>D</b>			2016	101		500			-
Bartonella spp.	Faruque et al. $(2017)^{12}$	Thailand	2008-2009	UN	Culture	720	1	Medium	Low
Bartonella spp.	Hercik et al. (2017) <sup>13</sup>	United Republic	2014-	UN	PCR	842	4	Low	Low
Durionena oppi		of Tanzania	2015	011	1011	0.2			2011
Bartonella spp.	Kosoy et al. (2010) <sup>14</sup>	Thailand	2002-	UN	Culture, PCR	261	14	Low	Medium
			2003						
Bartonella spp.	Simpson et al. (2018) <sup>15</sup>	South Africa	2012-	UN	PCR	74	7	Medium	High
			2013						
Bartonella spp.	Sokhna et al. (2013) <sup>16</sup>	Senegal	2011-	UN	PCR	440	23	Low	Low
			2012						
Borrelia spp.	Aarsland et al. $(2012)^{17}$	Ethiopia	2009-	UN	PCR	102	2	Low	High
	10		2010						
Borrelia spp.	Elhelw et al. $(2014)^{18}$	Egypt	2008-	UN	PCR	15	4	Medium	High
			2009						
<i>Borrelia</i> spp.	Fotso Fotso et al.	Algeria	2012-	UN	PCR	257	4	Low	Medium
<b>D</b>	(2015)19	I	2012	101	DCD	1.5.4	11.5		-
Borrelia spp.	Mediannikov et al. $(2014)^{20}$	Senegal	2010-	UN	PCR	1566	115	Low	Low
Demaliner	(2014)	T	2011	LINI	DCD	227	21		Madin
<i>borrella</i> spp.	$(2007)^{21}$	Togo	2002-	UN	PUK	237	21	Low	wiedium
<i>Borrelia</i> spp	Parola et al $(2011)^{22}$	Senegal	2004	UN	PCR	206	27	Medium	Medium
Dorrena spp.		Senegui	2000			200	27		

Pathogen	First author, year of publication and	Country	Study Period	Study Population Classification	Diagnostics Used	Number Tested	Number Positive	Representativeness Bias Coding	Precision Bias Coding
	reference		1 crioù	Chassinearion		resteu	1 0010110	couning	Dias counig
Borrelia spp.	Reller et al. $(2011)^{23}$	United Republic of Tanzania	NA-NA	UN	PCR	310	13	Low	Medium
Borrelia spp.	Sarih et al. (2009) <sup>24</sup>	Morocco	2005- 2006	UN	PCR	127	23	Medium	High
Borrelia spp.	Sokhna et al. (2013) <sup>16</sup>	Senegal	2011- 2012	UN	PCR	440	35	Low	Low
Borrelia spp.	Toure et al. (2017) <sup>25</sup>	Mali	2012- 2012	UN	PCR	8	3	Medium	High
Brucella spp.	Afifi et al. (2005) <sup>26</sup>	Egypt	1999- 2003	D SP	Culture	9883	275	High	Low
Brucella spp.	Barua et al. (2016) <sup>27</sup>	India	2010- 2012	D SP	Culture	102	18	High	High
Brucella spp.	Boone et al. (2017) <sup>28</sup>	Madagascar	2011- 2013	UN	PCR	1020	15	Low	Low
Brucella spp.	Bouley et al. (2012) <sup>29</sup>	United Republic of Tanzania	2007- 2008	UN	MAT	455	16	Low	Low
Brucella spp.	Carugati et al. (2018) <sup>30</sup>	United Republic of Tanzania	2007- 2014	UN	MAT	1680	45	Low	Low
Brucella spp.	Cash-Goldwasser et al. (2018) <sup>31</sup>	United Republic of Tanzania	2012- 2014	UN	Microagglutination test	562	39	Low	Low
Brucella spp.	Ciftdogan et al. (2011) <sup>32</sup>	Turkey	2003- 2008	UN	Culture	92	3	Low	High
Brucella spp.	Crump et al. (2013) <sup>33</sup>	United Republic of Tanzania	2007- 2008	UN	MAT	453	16	Low	Low
Brucella spp.	Fadeel et al. (2006) <sup>34</sup>	Egypt	1999- 2003	UN	Culture	1177	202	Low	Low
Brucella spp.	Jennings et al. (2007) <sup>35</sup>	Egypt	2002- 2003	UN	Culture	4490	115	Medium	Low
Brucella spp.	Kamal et al. (2013) <sup>36</sup>	Saudi Arabia	2009- 2011	UN	PCR	101	50	Low	High
Brucella spp.	Kuila et al. (2017) <sup>37</sup>	India	2013- 2015	UN	PCR	2088	88	Low	Low
Brucella spp.	Manock et al. (2009) <sup>38</sup>	Ecuador	2001- 2004	UN	ELISA	275	4	Medium	Medium
Brucella spp.	Mattar et al. (2017) <sup>39</sup>	Colombia	2012- 2013	UN	Rose Bengal plate test	100	1	Medium	High
Brucella spp.	Migisha et al. (2018) <sup>40</sup>	Uganda	2017- 2017	D SP	Culture	235	10	High	Medium
Brucella spp.	Nandagopal et al. $(2012)^{41}$	India	2008- 2009	UN	PCR	301	3	Low	Medium
Brucella spp.	Paul et al. (2017) <sup>42</sup>	Saudi Arabia	2014- 2016	UN	Culture	377	37	Low	Medium
Brucella spp.	Rahman et al. $(2016)^{43}$	Bangladesh	2007- 2008	D SP	PCR	6	3	High	High

Pathogen	First author, year of publication and	Country	Study Period	Study Population	Diagnostics Used	Number Tested	Number Positive	Representativeness Bias	Precision Bias Coding
	reference		1 0110 u			resteu	1 0010110	coung	Dias counig
Campylobacter spp.	Ali et al. (2016) <sup>44</sup>	Pakistan	2011- 2014	D RESP	Culture	356	2	High	Medium
Campylobacter spp.	Bottieau et al. $(2011)^{45}$	No Specific	2000-	D GI	Stool examination,	512	47	High	Low
17 11		Country	2006		Culture				
Campylobacter spp.	Hogan et al. (2018) <sup>46</sup>	Ghana	2013- 2015	UN	PCR	240	21	Low	Medium
Campylobacter spp.	Naheed et al. (2008) <sup>47</sup>	Bangladesh	2003- 2004	UN	Culture	867	1	Low	Low
Coxiella burnetii	Angelakis et al. (2014) <sup>48</sup>	No Specific Country	2008- 2012	UN	PCR	1888	7	Low	Low
Coxiella burnetii	Crump et al. (2013) <sup>33</sup>	United Republic of Tanzania	2007- 2008	UN	IFA	482	24	Low	Low
Coxiella burnetii	Esmaeili et al. (2017) <sup>49</sup>	Iran (Islamic Republic of)	2013- 2013	UN	ELISA	116	16	Medium	High
Coxiella burnetii	Greiner et al. (2018) <sup>50</sup>	Thailand	2002- 2005	UN	IFA	1784	5	Medium	Low
Coxiella burnetii	Hamilton et al. (2011) <sup>51</sup>	Iraq	2008- 2008	UN	PCR, IFA	18	8	Low	High
Coxiella burnetii	Hercik et al. (2017) <sup>13</sup>	United Republic of Tanzania	2014- 2015	UN	PCR	842	2	Low	Low
Coxiella burnetii	Khalili et al. (2016) <sup>52</sup>	Iran (Islamic Republic of)	2014- 2015	UN	PCR	92	7	Low	High
Coxiella burnetii	Manock et al. (2009) <sup>38</sup>	Ecuador	2001- 2004	UN	ELISA	33	15	Medium	High
Coxiella burnetii	Mazyad et al. (2007) <sup>53</sup>	Egypt	2006- 2006	UN	PCR	150	5	Low	Medium
Coxiella burnetii	Metanat et al. (2014) <sup>54</sup>	Iran (Islamic Republic of)	2011- 2011	UN	IFA	105	23	Low	High
Coxiella burnetii	Njeru et al. (2016) <sup>55</sup>	Kenya	2014- 2015	UN	PCR	448	10	Low	Low
Coxiella burnetii	Pradeep et al. (2017) <sup>56</sup>	India	2016- 2016	UN	PCR	72	2	Medium	High
Coxiella burnetii	Ratmanov et al. $(2013)^{57}$	Senegal	2008- 2011	UN	PCR	874	4	Low	Low
Coxiella burnetii	Reller et al. (2016) <sup>58</sup>	Nicaragua	2008- 2009	UN	IFA	748	10	Low	Low
Coxiella burnetii	Sokhna et al. (2013) <sup>16</sup>	Senegal	2011- 2012	UN	PCR	440	2	Low	Low
Coxiella burnetii	Toure et al. $(2017)^{25}$	Mali	2012- 2012	UN	PCR	8	1	Medium	High
Crimean-Congo haemorrhagic fever virus	Alam et al. (2013) <sup>59</sup>	Pakistan	2008- 2008	D HEM	PCR, IgM	44	16	High	High

Pathogen	First author, year of	Country	Study Bariad	Study Population	Diagnostics Used	Number	Number	Representativeness Bias	Precision Bigs Coding
	reference		reriou	Classification		Testeu	rositive	Coung	blas Couling
Crimean-Congo	Ali et al. (2007) <sup>60</sup>	Pakistan	2001-	D HEM	PCR	10	3	High	High
haemorrhagic fever			2001						
Crimean-Congo	Bukbuk et al. (2016) <sup>61</sup>	Nigeria	2010-	D SP	PCR	380	1	High	Medium
haemorrhagic fever	( )		2014						
virus									_
Crimean-Congo	Kuchuloria et al. $(2016)^{62}$	Georgia	2008-	UN	lgM	537	3	Medium	Low
virus	(2010)		2011						
Eastern equine encephalitis virus	Aguilar et al. (2007) <sup>63</sup>	Peru	NA-NA	D NEU	ELISA	153	2	High	Medium
Ehrlichia spp.	Chikeka et al. (2016) <sup>64</sup>	Nicaragua	NA-NA	UN	IFA	748	1	Low	Low
Ehrlichia spp.	Ndip et al. (2009) <sup>65</sup>	Cameroon	2003-	UN	PCR	118	12	Medium	High
Hantavirus	Armien et al. (2013) <sup>66</sup>	Panama	2005	D SP	PCR	150	117	High	Medium
Trainia ( II as	· · · · · · · · · · · · · · · · · · ·	1 unumu	2010	2 51	Ton	100	11,		
Hantavirus	Castillo Ore et al.	Peru	2007-	UN	IgM	5174	9	Low	Low
Hentovinus	$(2012)^{67}$	India	2010	DUEM	ELISA	152	22	Link	Madium
Hamavirus	Chandy et al. (2005)	Illula	2002-2003	DIEW	LLISA	152	23	ingn	weatum
Hantavirus	Chandy et al. (2009) <sup>69</sup>	India	2005-	UN	ELISA, IFA, PCR	347	86	Low	Medium
	C1 1 (2017) <sup>70</sup>		2007	1.01	DI IGA	200			
Hantavirus	Chau et al. $(2017)^{10}$	Mozambique	2012-2014	UN	ELISA	200	4	Low	Medium
Hantavirus	Chen et al. (2014) <sup>71</sup>	China	2011-	D HEM	PCR, IFA	85	33	High	High
			2012						
Hantavirus	Chrispal et al. (2010) <sup>72</sup>	India	2007- 2008	UN	ELISA	398	1	Low	Low
Hantavirus	Cruz et al. (2012) <sup>73</sup>	Bolivia	2008-	UN	PCR, IgM	372	9	Low	Medium
		(Plurinational State of)	2009						
Hantavirus	Klempa et al. (2010) <sup>74</sup>	Guinea	2001-	D HEM	ELISA, Neutralization	717	8	High	Low
	1 ( )		2005		test				
Hantavirus	Kuchuloria et al. $(2014)^{75}$	Georgia	2008- 2011	UN	IgM	537	2	Low	Low
Hantavirus	Liu et al. (2007) <sup>76</sup>	China	2002-	UN	IFA, PCR	130	49	Low	High
Hantavirus	Mattar et al. (2017) <sup>39</sup>	Colombia	2004	UN	ELISA	100	4	Medium	High
			2013						
Hantavirus	Suharti et al. (2009) <sup>77</sup>	Indonesia	1995- 1996	D SP	ELISA	60	5	High	High
Hantavirus	Thompson et al. $(2015)^{78}$	Nepal	2008- 2011	UN	IgM	125	2	Low	High
Hantavirus	Zhan et al. (2017) <sup>79</sup>	China	2011-	D SP	IgM, PCR	141	2	High	Medium
			2011						

Pathogen	First author, year of	Country	Study Period	Study Population	Diagnostics Used	Number Tested	Number Positive	Representativeness Bias	Precision Bias Coding
	reference		I tillou	Clussification		resteu	1 USHIVE	couning	Dias Counig
Japanese encephalitis	Anga et al. (2010) <sup>80</sup>	Papua New Guinea	2007-2008	D NEU	IgM	129	2	High	High
Japanese encephalitis	Chatteriee et al. (2004) <sup>81</sup>	India	1996-	D NEU	НІ	72	24	High	High
virus	(-•••)		1999						
Japanese encephalitis virus	Chheng et al. (2013) <sup>82</sup>	Cambodia	2009- 2010	UN	ELISA	107	6	Low	High
Japanese encephalitis	Dias et al. (2018) <sup>83</sup>	India	2014- 2014	UN	RNA sequencing	4	1	Low	High
Japanese encephalitis virus	Ellis et al. (2006) <sup>84</sup>	Thailand	1999- 2002	UN	ELISA	530	1	Low	Low
Japanese encephalitis	Joshi et al. (2013) <sup>85</sup>	India	2007- 2007	D NEU	ELISA	152	4	High	Medium
Japanese encephalitis	Kakoti et al. (2013) <sup>86</sup>	India	2012- 2012	D HEM	IgM	223	49	High	Medium
Japanese encephalitis virus	Kumar et al. (2015) <sup>87</sup>	India	NA-NA	D NEU	IgM	108	54	High	High
Japanese encephalitis virus	Maude et al. (2016) <sup>88</sup>	Bangladesh	2012- 2012	UN	IgM	300	1	Medium	Medium
Japanese encephalitis virus	Medhi et al. (2017) <sup>89</sup>	India	2012- 2014	D NEU	ELISA	1707	601	High	Low
Japanese encephalitis virus	Rasul et al. (2012) <sup>90</sup>	Bangladesh	2007- 2009	D NEU	ELISA	130	2	High	High
Japanese encephalitis virus	Rauf et al. (2018) <sup>91</sup>	India	2014- 2014	D NEU	IgM, PCR	54	8	High	High
Japanese encephalitis virus	Rayamajhi et al. (2006) <sup>92</sup>	Nepal	2000- 2001	D NEU	IgM	117	54	High	High
Japanese encephalitis virus	Rayamajhi et al. (2007) <sup>93</sup>	Nepal	2000- 2001	D NEU	IgM	94	54	High	High
Japanese encephalitis virus	Rayamajhi et al. (2011) <sup>94</sup>	Nepal	2006- 2008	D NEU	IgM	86	9	High	High
Japanese encephalitis virus	Sarkar et al. (2012) <sup>95</sup>	India	2010- 2010	D NEU	IgM	43	23	High	High
Japanese encephalitis virus	Singh et al. (2009) <sup>96</sup>	Nepal	2003- 2004	D NEU	IgM	107	19	High	High
Japanese encephalitis virus	Singh et al. (2014) <sup>97</sup>	India	2008- 2011	D NEU	PCR	1410	10	High	<mark>Low</mark>
Japanese encephalitis virus	Swami et al. (2008) <sup>98</sup>	India	2003- 2005	D NEU	IgM, PCR	40	9	High	High
Japanese encephalitis virus	Taraphdar et al. (2012) <sup>99</sup>	India	2010- 2010	UN	PCR	58	23	Low	High
Lassa virus	Akhuemokhan et al. $(2017)^{100}$	Nigeria	2009- 2010	UN	PCR	243	13	Low	Medium
Lassa virus	Boisen et al. (2015) <sup>101</sup>	Sierra Leone	2012- 2012	D SP	PCR, Antigen detection	53	29	High	High

Pathogen	First author, year of	Country	Study	Study Population	Diagnostics Used	Number	Number	Representativeness Bias	Precision
	reference		Period	Classification		lested	Positive	Coding	Bias Coding
Lassa virus	Ehichioya et al.	Nigeria	2005-	D SP	PCR	451	2	High	Low
	$(2012)^{102}$		2008						
Lassa virus	Schoepp et al. (2014) <sup>103</sup>	Sierra Leone	2006-	D SP	ELISA	253	7	High	Medium
L agaa vimta	Shahu at al $(2018)^{104}$	Niceria	2008	DSD	DCD	24	11		High
Lassa virus	Sileilu et al. (2018)	Nigeria	2010-2016	DSF	FUK	54	11	111gu	mgn
Lassa virus	Stremlau et al. (2015) <sup>105</sup>	Nigeria	NA-NA	D HEM	Sequencing	195	104	High	Medium
Leishmania donovani	Hailu et al. (2006) <sup>106</sup>	Ethiopia	NA-NA	D SP	Microscopy, Culture	103	49	High	High
Leishmania donovani	Joshi et al. (2006) <sup>107</sup>	Nepal	1998-	D SP	Bone marrow	996	284	High	Low
Laighmania donovani	Multhton at al. $(2015)^{108}$	Sudan	2002	DSP	Culture	295	101	Link	Madium
Leisnmania aonovani	Mukiltar et al. (2015)	Sudali	2012-2014	DSF	Culture	285	191	riign	wedium
Leishmania donovani	Rijal et al. (2004) <sup>109</sup>	Nepal	2000-	D SP	Microscopy	261	155	High	Medium
_			2002						
Leptospira spp.	Albuquerque Filho et al. $(2011)^{110}$	Brazıl	2009-2009	UN	Culture	97	56	Low	High
Leptospira spp.	Alia et al. (2019) <sup>111</sup>	Malaysia	2016-	D SP	PCR	50	13	High	High
_			2017						
Leptospira spp.	Barragan et al. (2016) <sup>112</sup>	Ecuador	2013- 2015	UN	PCR	668	100	Low	Low
Leptospira spp.	Biggs et al. (2011) <sup>113</sup>	United Republic	2007-	UN	MAT	831	70	Low	Low
		of Tanzania	2008						
Leptospira spp.	Blacksell et al. (2006) <sup>114</sup>	Lao People's	2001-	UN	MAT	186	5	Medium	Medium
		Democratic	2003						
<b>T</b> , ·	D 1 (1 (2011))]5	Republic	2001	IDI		410	120	No. 11	T
Leptospira spp.	Boonslip et al. (2011)	Inaliand	2001-2002	UN	Culture, PCK	418	120	<u>Iviedium</u>	Low
Leptospira spp.	Chansamouth et al.	Lao People's	2006-	UN	MAT	158	1	Medium	Medium
	$(2016)^{116}$	Democratic	2010						
	× /	Republic							
Leptospira spp.	Chheng et al. (2013) <sup>82</sup>	Cambodia	2009-	UN	Culture, PCR	1179	17	Low	Low
T	Chieffrage et al.	E I.e.	2010	UN	DCD	210	122		Madin
Lepiospira spp.	$(2015)^{117}$	Ecuador	2011-2012	UN	PCK	210	152	Low	Medium
Leptospira spp.	Cohen et al. (2007) <sup>118</sup>	Thailand	2002-	UN	MAT	704	67	Low	Low
			2003						
Leptospira spp.	Crump et al. $(2013)^{33}$	United Republic of Tanzania	2007- 2008	UN	MAT	453	40	Low	Low
Leptospira spp.	Dassanavake et al.	Sri Lanka	2007-	UN	МАТ	123	62	Low	High
20p100p11 4 0pp.	$(2009)^{119}$	STI Bullitu	2008			120	52		<u> </u>
Leptospira spp.	Dittrich et al. (2018) <sup>120</sup>	Lao People's	2014-	D SP	MAT	248	12	High	Medium
		Democratic Republic	2015						

Pathogen	First author, year of	Country	Study Poriod	Study Population	Diagnostics Used	Number Tested	Number Positivo	Representativeness Bias	Precision Bias Coding
	reference		renou	Classification		Testeu	rositive	Counig	Blas Couling
Leptospira spp.	Ellis et al. (2006) <sup>84</sup>	Thailand	1999- 2002	UN	IgM, MAT	613	107	Low	Low
Leptospira spp.	Faruque et al. (2017) <sup>12</sup>	Thailand	2008- 2009	UN	Culture	720	1	Medium	Low
Leptospira spp.	Gasem et al. (2009) <sup>121</sup>	Indonesia	2005- 2006	UN	PCR	137	4	Low	High
Leptospira spp.	Guillebaud et al. $(2018)^{122}$	Madagascar	2014- 2015	UN	PCR	682	1	Low	Low
Leptospira spp.	Hem et al. (2016) <sup>123</sup>	Cambodia	2007- 2009	UN	MAT	2044	17	Low	Low
Leptospira spp.	Hercik et al. (2017) <sup>13</sup>	United Republic of Tanzania	2014- 2015	UN	PCR	842	22	Low	Low
Leptospira spp.	Hercik et al. (2018) <sup>124</sup>	United Republic of Tanzania	2014- 2014	UN	PCR	191	3	Low	Medium
Leptospira spp.	Ismail et al. (2006) <sup>125</sup>	Egypt	1999- 2003	UN	MAT	886	141	Low	Low
Leptospira spp.	Kendall et al. (2010) <sup>126</sup>	Bangladesh	2001- 2001	UN	MAT	78	7	Low	High
Leptospira spp.	Koizumi et al. (2009) <sup>127</sup>	Sri Lanka	2008- 2008	D SP	PCR	107	3	High	High
Leptospira spp.	LaRocque et al. (2005) <sup>128</sup>	Bangladesh	2001- 2001	D SP	PCR	359	63	High	Medium
Leptospira spp.	Libraty et al. (2007) <sup>129</sup>	Thailand	1994- 1999	UN	MAT	812	14	Low	Low
Leptospira spp.	Mattar et al. $(2017)^{39}$	Colombia	2012- 2013	UN	ELISA, MAT	100	27	Medium	High
Leptospira spp.	Matthias et al. (2008) <sup>130</sup>	Peru	2003- 2006	UN	Culture	881	45	Medium	Low
Leptospira spp.	Mayxay et al. (2013) <sup>131</sup>	Lao People's Democratic Republic	2008- 2010	UN	Culture, MAT, PCR	1932	137	Low	Low
Leptospira spp.	Maze et al. $(2016)^{132}$	United Republic of Tanzania	2012- 2014	UN	MAT	1017	19	Low	Low
Leptospira spp.	McGready et al. $(2010)^{133}$	Thailand	2004- 2006	UN	Culture, MAT	203	5	Medium	Medium
Leptospira spp.	Mueller et al. $(2014)^{134}$	Cambodia	2008- 2010	UN	PCR	1193	112	Low	Low
Leptospira spp.	Murdoch et al. (2004) <sup>135</sup>	Nepal	2001- 2001	UN	PCR	26	11	Low	High
Leptospira spp.	Murray et al. (2011) <sup>136</sup>	Egypt	2005- 2007	UN	Culture	2441	47	Low	Low
Leptospira spp.	Natarajaseenivasan et al. (2004) <sup>137</sup>	India	2000- 2000	D SP	MAT, Culture	29	7	High	High

Pathogen	First author, year of publication and	Country	Study Period	Study Population	Diagnostics Used	Number Tested	Number Positive	Representativeness Bias	Precision Bias Coding
	reference		1 criou	Chussineuron		1 corea	1 OSHUTC	coung	Dias counig
Leptospira spp.	Natarajaseenivasan et al. $(2012)^{138}$	India	2009- 2009	D SP	PCR	75	71	High	High
Leptospira spp.	Phimda et al. (2007) <sup>139</sup>	Thailand	2003- 2005	D SP	Culture, MAT	296	55	High	Medium
Leptospira spp.	Rafizah et al. (2013) <sup>140</sup>	Malaysia	NA-NA	UN	MAT	999	53	Medium	Low
Leptospira spp.	Rao et al. (2005) <sup>141</sup>	India	NA-NA	D SP	ELISA	70	2	High	High
Leptospira spp.	Ravindar et al. (2018) <sup>142</sup>	India	2016- 2017	UN	PCR	100	13	Low	High
Leptospira spp.	Reller et al. $(2014)^{143}$	Nicaragua	2008- 2009	UN	PCR	748	17	Low	Low
Leptospira spp.	Ribeiro et al. (2017) <sup>144</sup>	Mozambique	2012- 2015	UN	ELISA, MAT	373	3	Low	Medium
Leptospira spp.	Ricapa-Antay et al. $(2018)^{145}$	Peru	2016- 2016	UN	PCR	139	16	Medium	Medium
Leptospira spp.	Rubbo et al. (2018) <sup>146</sup>	Central African Republic	2012- 2015	UN	MAT	32	2	Medium	High
Leptospira spp.	Sengupta et al. (2017) <sup>147</sup>	India	2012- 2014	UN	PCR	150	5	Medium	Medium
Leptospira spp.	Suttinont et al. (2006) <sup>148</sup>	Thailand	2001-2002	UN	Culture, MAT, IFA	845	293	Medium	Low
Leptospira spp.	Thipmontree et al. $(2014)^{149}$	Thailand	2001- 2012	UN	Culture, IFA, PCR	726	118	Medium	Low
Leptospira spp.	Waggoner et al. $(2017)^{150}$	Kenya	2014- 2015	UN	PCR	385	1	Low	Low
Leptospira spp.	Wuthiekanun et al. $(2007)^{151}$	Thailand	2001- 2002	UN	Culture	989	83	Low	Low
Leptospira spp.	Zida et al. (2018) <sup>152</sup>	Burkina Faso	2014- 2015	UN	PCR	781	1	Low	Low
Listeria spp.	El-Mahallawy et al. $(2005)^{153}$	Egypt	1999- 1999	D COMORBID	Culture	1135	1	High	Low
Nipah virus	Chadha et al. (2006) <sup>154</sup>	India	2001- 2001	D NEU	PCR	6	5	High	High
Orientia tsutsugamushi	Blacksell et al. (2007) <sup>155</sup>	Nepal	2002- 2004	UN	IFA	103	5	Low	High
Orientia tsutsugamushi	Blacksell et al. (2010) <sup>156</sup>	Lao People's Democratic Republic	2003- 2007	D SP	IFA	1030	101	High	Low
Orientia tsutsugamushi	Blacksell et al. (2016) <sup>157</sup>	Thailand	2006- 2007	UN	IFA, PCR, Culture	152	37	Medium	Medium
Orientia tsutsugamushi	Blacksell et al. (2016) <sup>158</sup>	Thailand	2007- 2008	UN	PCR, Culture	135	22	Medium	High
Orientia tsutsugamushi	Chansamouth et al. $(2016)^{116}$	Lao People's Democratic Republic	2006- 2010	UN	IFA, Culture, PCR	217	16	Medium	Medium

Pathogen	First author, year of publication and	Country	Study Period	Study Population Classification	Diagnostics Used	Number Tested	Number Positive	Representativeness Bias Coding	Precision Bias Coding
	reference							8	8
Orientia tsutsugamushi	Chen et al. (2014) <sup>71</sup>	China	2011- 2012	D HEM	PCR	85	1	High	High
Orientia tsutsugamushi	Chheng et al. (2013) <sup>82</sup>	Cambodia	2009-	UN	PCR, IFA	1179	17	Low	Low
Orientia tsutsugamushi	Jung et al. (2015) <sup>159</sup>	Democratic People's Republic of Korea	2009- 2013	UN	IFA	382	3	Low	Medium
Orientia tsutsugamushi	Kingston et al. (2018) <sup>160</sup>	Bangladesh	2014- 2015	UN	PCR	416	45	Low	Low
Orientia tsutsugamushi	Kocher et al. (2017) <sup>161</sup>	Peru	2013- 2013	UN	ELISA	1124	1	Low	Low
Orientia tsutsugamushi	Kumar et al. $(2014)^{162}$	India	2011- 2012	UN	PCR	199	48	Low	Medium
Orientia tsutsugamushi	Liu et al. (2007) <sup>76</sup>	China	2002- 2004	UN	IFA, PCR	130	46	Low	High
Orientia tsutsugamushi	Maude et al. (2015) <sup>163</sup>	Bangladesh	2012- 2012	UN	PCR	300	1	Low	Medium
Orientia tsutsugamushi	Mayxay et al. (2013) <sup>131</sup>	Lao People's Democratic Republic	2008- 2010	UN	Culture, PCR	1871	170	Low	Low
Orientia tsutsugamushi	McGready et al. $(2010)^{133}$	Thailand	2004- 2006	UN	Culture, PCR, IFA	203	11	Medium	Medium
Orientia tsutsugamushi	Mueller et al. (2014) <sup>134</sup>	Cambodia	2008- 2010	UN	PCR	1193	47	Low	Low
Orientia tsutsugamushi	Paris et al. (2011) <sup>164</sup>	Thailand	2007- 2008	UN	IFA, Culture, PCR	138	26	Medium	High
Orientia tsutsugamushi	Phimda et al. (2007) <sup>139</sup>	Thailand	2003- 2005	D SP	IFA	230	34	High	Medium
Orientia tsutsugamushi	Reller et al. (2012) <sup>165</sup>	Sri Lanka	2007- 2007	UN	ELISA	883	17	Low	Low
Orientia tsutsugamushi	Saisongkorh et al. $(2004)^{166}$	Thailand	NA-NA	UN	PCR	36	9	Medium	High
Orientia tsutsugamushi	Sonthayanon et al. $(2006)^{167}$	Thailand	2000- 2001	UN	IFA	722	183	Low	Low
Orientia tsutsugamushi	Srinivasan et al. $(2017)^{168}$	India	2014- 2015	D SP	PCR	68	6	High	High
Orientia tsutsugamushi	Thipmontree et al. $(2016)^{169}$	Thailand	2011- 2012	UN	IFA	495	98	Low	Low
Orientia tsutsugamushi	Tshokey et al. (2018) <sup>170</sup>	Bhutan	2014- 2015	UN	PCR	1044	7	Medium	Low
Pasteurella spp.	Bengre et al. (2012) <sup>171</sup>	India	2009- 2011	D COMORBID	Culture	50	1	High	High
Pasteurella spp.	El-Mahallawy et al. $(2005)^{153}$	Egypt	1999- 1999	D COMORBID	Culture	1135	6	High	Low

Pathogen	First author, year of publication and	Country	Study Period	Study Population	Diagnostics Used	Number Tested	Number Positive	Representativeness Bias	Precision Bias Coding
	reference		i citou	Classification		I Cottu	1 Ushtive	County	Dias Counig
Rickettsia (SFGR)	Aarsland et al. $(2012)^{17}$	Ethiopia	2009- 2010	UN	PCR	102	4	Low	High
Rickettsia (SFGR)	Bouchaib et al. (2018) <sup>172</sup>	Algeria	2013- 2015	UN	PCR	166	57	Low	Medium
Rickettsia (SFGR)	Chowdhury et al. $(2017)^{173}$	Bangladesh	2015- 2016	D SP	PCR	414	81	High	Low
Rickettsia (SFGR)	Crump et al. (2013) <sup>33</sup>	United Republic of Tanzania	2007- 2008	UN	IFA	450	36	Low	Low
Rickettsia (SFGR)	dos Santos et al. $(2012)^{174}$	Brazil	2009- 2010	D HEM	PCR	110	36	High	High
Rickettsia (SFGR)	Eremeeva et al. (2013) <sup>175</sup>	Guatemala	2007- 2007	UN	PCR, IFA	17	1	High	High
Rickettsia (SFGR)	Faruque et al. $(2017)^{12}$	Thailand	2008- 2009	UN	PCR	360	1	Medium	Medium
Rickettsia (SFGR)	Gaowa et al. (2018) <sup>176</sup>	China	2015- 2016	UN	PCR	261	6	Medium	Medium
Rickettsia (SFGR)	Hidalgo et al. (2013) <sup>177</sup>	Colombia	2010- 2011	D SP	IFA	26	7	High	High
Rickettsia (SFGR)	Kingston et al. (2018) <sup>160</sup>	Bangladesh	2014- 2015	UN	PCR	416	2	Low	Low
Rickettsia (SFGR)	Kuloglu et al. (2012) <sup>178</sup>	Turkey	2003- 2009	D SP	PCR, IFA	126	97	High	High
Rickettsia (SFGR)	Liu et al. (2016) <sup>179</sup>	China	2014- 2014	D SP	PCR	733	56	High	Low
Rickettsia (SFGR)	Maina et al. (2012) <sup>180</sup>	Kenya	2008- 2010	UN	PCR	699	50	Low	Low
Rickettsia (SFGR)	Manock et al. (2009) <sup>38</sup>	Ecuador	2001- 2004	UN	ELISA	214	6	Medium	Medium
Rickettsia (SFGR)	Mattar et al. (2017) <sup>39</sup>	Colombia	2012- 2013	UN	IFI	100	2	Medium	High
Rickettsia (SFGR)	Mayxay et al. (2013) <sup>131</sup>	Lao People's Democratic Republic	2008- 2010	UN	PCR	1849	2	Low	Low
Rickettsia (SFGR)	Mediannikov et al. $(2010)^{181}$	Senegal	2008- 2009	UN	PCR	204	8	Medium	Medium
Rickettsia (SFGR)	Mediannikov et al. $(2013)^{182}$	No Specific Country	2010- 2012	UN	PCR	2612	321	Low	Low
Rickettsia (SFGR)	Mongkol et al. (2018) <sup>183</sup>	Thailand	2012- 2014	D SP	PCR	168	8	High	Medium
Rickettsia (SFGR)	Mourembou et al. $(2015)^{184}$	Gabon	2011- 2012	UN	PCR	793	8	Low	Low
Rickettsia (SFGR)	Mourembou et al. $(2015)^{185}$	Gabon	2013- 2014	UN	PCR	410	42	Low	Low

Pathogen	First author, year of publication and	Country	Study Period	Study Population Classification	Diagnostics Used	Number Tested	Number Positive	Representativeness Bias Coding	Precision Bias Coding
	reference						_		
Rickettsia (SFGR)	Ndip et al. (2004) <sup>186</sup>	Cameroon	2003- 2003	UN	PCR	118	7	Medium	High
Rickettsia (SFGR)	Prakash et al. (2012) <sup>187</sup>	India	2006-2008	D SP	PCR	58	34	High	High
Rickettsia (SFGR)	Reller et al. (2012) <sup>165</sup>	Sri Lanka	2007- 2007	UN	IFA	883	108	Low	Low
Rickettsia (SFGR)	Reller et al. (2016) <sup>58</sup>	Nicaragua	2008-2009	UN	IFA	748	6	Low	Low
Rickettsia (SFGR)	Richards et al. (2010) <sup>188</sup>	Kenya	2006- 2008	UN	PCR	163	6	Medium	Medium
Rickettsia (SFGR)	Sokhna et al. (2013) <sup>16</sup>	Senegal	2011- 2012	UN	PCR	440	28	Low	Low
Rickettsia (SFGR)	Sothmann et al. $(2017)^{189}$	Ghana	2012- 2012	UN	PCR	431	6	Medium	Low
Rickettsia (TGR)	Blacksell et al. (2007) <sup>155</sup>	Nepal	2002- 2004	UN	IFA	103	9	Low	High
Rickettsia (TGR)	Blacksell et al. (2010) <sup>156</sup>	Lao People's Democratic Republic	2003- 2007	D SP	IFA	1030	183	High	Low
Rickettsia (TGR)	Chansamouth et al. $(2016)^{116}$	Lao People's Democratic Republic	2006- 2010	UN	IFA, Culture, PCR	217	15	Medium	Medium
Rickettsia (TGR)	Chen et al. (2014) <sup>71</sup>	China	2011- 2012	D HEM	IFA	85	1	High	High
Rickettsia (TGR)	Chheng et al. (2013) <sup>82</sup>	Cambodia	2009- 2010	UN	PCR, IFA	1179	5	Low	Low
Rickettsia (TGR)	Chowdhury et al. $(2017)^{173}$	Bangladesh	2015- 2016	D SP	PCR	414	1	High	Low
Rickettsia (TGR)	Crump et al. (2013) <sup>33</sup>	United Republic of Tanzania	2007- 2008	UN	IFA	450	2	Low	Low
Rickettsia (TGR)	Faruque et al. $(2017)^{12}$	Thailand	2008- 2009	UN	PCR	720	1	Medium	Low
Rickettsia (TGR)	Gasem et al. (2009) <sup>121</sup>	Indonesia	2005- 2006	UN	IFA	137	4	Low	High
Rickettsia (TGR)	Hidalgo et al. (2008) <sup>190</sup>	Colombia	2005- 2005	UN	IFA	120	14	Low	High
Rickettsia (TGR)	Hidalgo et al. (2013) <sup>177</sup>	Colombia	2010- 2011	D SP	IFA	26	2	High	High
Rickettsia (TGR)	Kingston et al. (2018) <sup>160</sup>	Bangladesh	2014- 2015	UN	PCR	416	24	Low	Low
Rickettsia (TGR)	Manock et al. (2009) <sup>38</sup>	Ecuador	2001- 2004	UN	ELISA	255	8	Medium	Medium
Rickettsia (TGR)	Maude et al. (2015) <sup>163</sup>	Bangladesh	2012- 2012	UN	PCR	300	2	Low	Medium

Pathogen	First author, year of publication and	Country	Study Period	Study Population Classification	Diagnostics Used	Number Tested	Number Positive	Representativeness Bias Coding	Precision Bias Coding
	reference		1 chiou	Chassinearion		resteu	1 obline	Counig	Dias counig
Rickettsia (TGR)	Mayxay et al. (2013) <sup>131</sup>	Lao People's	2008-	UN	PCR	1849	12	Low	Low
		Democratic	2010						
		Republic							
Rickettsia (TGR)	McGready et al. $(2010)^{133}$	Thailand	2004- 2006	UN	Culture, PCR, IFA	203	14	Medium	Medium
Rickettsia (TGR)	Mongkol et al. (2018) <sup>183</sup>	Thailand	2012- 2014	D SP	PCR	168	3	High	Medium
Rickettsia (TGR)	Pradhan et al. (2012) <sup>191</sup>	Nepal	2006- 2007	UN	PCR	1039	22	Low	Low
Rickettsia (TGR)	Reller et al. (2012) <sup>165</sup>	Sri Lanka	2007-	UN	IFA	883	61	Low	Low
Distantia (TCD)	D-11	NI:	2007	LINI	IE A	749	1	T	T
Rickettsia (IGR)	Keller et al. $(2016)^{50}$	Nicaragua	2008-2009	UN	IFA	/48	1	Low	Low
Rickettsia (TGR)	Thompson et al. $(2015)^{78}$	Nepal	2008- 2011	UN	IFA	125	21	Low	High
Rickettsia (TGR)	Zimmerman et al.	Nepal	2001-	UN	PCR	756	50	Low	Low
,	$(2008)^{192}$	1	2001						
Rickettsia spp.	Hercik et al. (2017) <sup>13</sup>	United Republic	2014-	UN	PCR	842	2	Low	Low
**	· · · ·	of Tanzania	2015						
Rickettsia spp.	Kingston et al. (2018) <sup>160</sup>	Bangladesh	2014- 2015	UN	PCR	416	3	Low	Low
Rickettsia spp.	Mongkol et al. (2018) <sup>183</sup>	Thailand	2012-	D SP	PCR	168	15	High	Medium
11	8		2014				-		
Rickettsia spp.	Mueller et al. (2014) <sup>134</sup>	Cambodia	2008-	UN	PCR	1193	2	Low	Low
**			2010						
Rickettsia spp.	Ricapa-Antay et al.	Peru	2016-	UN	PCR	139	9	Medium	Medium
	$(2018)^{145}$		2016						
Rift Valley fever virus	Baudin et al. (2016) <sup>193</sup>	Sudan	2011-	UN	IgM	130	17	Medium	High
			2012						
Rift Valley fever virus	Guillebaud et al.	Madagascar	2014-	UN	PCR	682	1	Low	Low
D:0 V-11 6	$(2018)^{122}$	Ciama Lasara	2015	D CD	ELICA	252	5	111.1	Madina
Rift valley lever virus	Schoepp et al. (2014)	Sierra Leone	2006-	D SP	ELISA	255	5	nign	Medium
Rift Valley fever virus	Sow et al. (2016) <sup>194</sup>	Senegal	2008	UN	PCR	13845	1	Low	Low
Kint valicy level virus	50w et al. (2010)	Sellegal	2003-	UN	ICK	15045	1	Low	LOW
Salmonella (non-	Akinvemi et al.	Nigeria	2004-	D GI	Culture	235	16	High	Medium
Typhi)	$(2007)^{195}$	8	2005						
Salmonella (non-	Akinyemi et al.	Nigeria	2010-	UN	Culture	135	2	Low	High
Typhi)	$(2015)^{196}$		2011						
Salmonella (non-	Al-Emran et al.	No Specific	2011-	UN	Culture	8161	28	Low	Low
Typhi)	(2016) <sup>197</sup>	Country	2013						<b></b>
Salmonella (non-	Al-Emran et al.	No Specific	NA-NA	UN	Culture	10636	77	Low	Low
Typhi)	(2016)198	Country	1	1	1			1	

Pathogen	First author, year of publication and	Country	Study Period	Study Population Classification	Diagnostics Used	Number Tested	Number Positive	Representativeness Bias Coding	Precision Bias Coding
	reference								
<i>Salmonella</i> (non- Typhi)	Andualem et al. $(2014)^{199}$	Ethiopia	2010- 2011	D SP	Culture	270	7	High	Medium
Salmonella (non-	Bello et al. (2018) <sup>200</sup>	Nigeria	NA-NA	D COMORBID	Culture	225	10	High	Medium
Typhi)	· · ·	-							
<i>Salmonella</i> (non- Typhi)	Biggs et al. (2014) <sup>201</sup>	United Republic of Tanzania	2006- 2008	UN	Culture	4106	163	Low	<mark>Low</mark>
Salmonella (non-	Bilman et al. (2017) <sup>202</sup>	Turkey	2014-	D GI	Culture	48	10	High	High
Typhi)			2014						
Salmonella (non- Typhi)	Brooks et al. $(2005)^{203}$	Bangladesh	2000- 2001	UN	Culture	888	2	Low	Low
Salmonella (non- Typhi)	Brown et al. (2017) <sup>204</sup>	Nigeria	2013- 2014	D COMORBID	Culture	116	1	High	High
Salmonella (non- Typhi)	Chheng et al. (2013) <sup>82</sup>	Cambodia	2009- 2010	UN	Culture	1180	1	Low	Low
Salmonella (non- Typhi)	Crump et al. (2011) <sup>205</sup>	United Republic of Tanzania	2007- 2008	UN	Culture	224	2	Low	Medium
Salmonella (non- Typhi)	Crump et al. (2011) <sup>206</sup>	United Republic of Tanzania	2007- 2008	UN	Culture	139	1	Low	Medium
Salmonella (non- Typhi)	D'Acremont et al. (2014) <sup>207</sup>	United Republic of Tanzania	2008- 2008	UN	Culture	424	1	Low	Low
Salmonella (non- Typhi)	Davies et al. (2016) <sup>208</sup>	Nigeria	NA-NA	UN	Culture	129	15	Low	High
Salmonella (non- Typhi)	Dong et al. (2014) <sup>209</sup>	China	2009- 2011	UN	Culture	2529	3	Low	Low
Salmonella (non- Typhi)	Eibach et al. (2016) <sup>210</sup>	Ghana	2007- 2012	UN	Culture	7172	215	Low	Low
Salmonella (non- Typhi)	Gordon et al. (2010) <sup>211</sup>	Malawi	NA-NA	UN	Culture	355	70	Low	Medium
Salmonella (non- Typhi)	Hercik et al. (2017) <sup>13</sup>	United Republic of Tanzania	2014- 2015	UN	PCR	842	4	Low	Low
Salmonella (non- Typhi)	Hogan et al. (2018) <sup>46</sup>	Ghana	2013- 2015	UN	Culture	1238	28	Low	Low
Salmonella (non- Typhi)	Saha et al. (2017) <sup>212</sup>	Bangladesh	2012- 2016	UN	Culture	5185	1	Medium	Low
Salmonella (non- Typhi)	Jeon et al. (2018) <sup>213</sup>	No Specific Country	2010- 2014	UN	Culture	13431	94	Low	Low
Salmonella (non- Typhi)	Kibuuka et al. (2015) <sup>214</sup>	Uganda	2012- 2012	UN	Culture	250	11	Medium	Medium
Salmonella (non- Typhi)	Kiemde et al. (2018) <sup>215</sup>	Burkina Faso	2015- 2015	UN	Culture	684	31	Low	Low
Salmonella (non- Typhi)	Ley et al. (2009) <sup>216</sup>	United Republic of Tanzania	2008- 2009	UN	Culture	1680	49	Low	Low
Salmonella (non- Typhi)	Mahende et al. (2014) <sup>217</sup>	United Republic of Tanzania	2013- 2013	UN	Culture	808	2	Low	Low

Pathogen	First author, year of publication and	Country	Study Period	Study Population Classification	Diagnostics Used	Number Tested	Number Positive	Representativeness Bias	Precision Bias Coding
	reference		1 thing			1 corea	1 0510110	couning	Dias counig
Salmonella (non-	Marks et al. (2017) <sup>218</sup>	No Specific	2010-	UN	Culture	13431	94	Low	Low
Typhi)		Country	2014						
Salmonella (non-	Meremo et al. $(2012)^{219}$	United Republic	NA-NA	UN	Culture	346	12	Low	Medium
Typhi)		of Tanzania							
<i>Salmonella</i> (non- Typhi)	Moon et al. $(2013)^{220}$	Mozambique	2012- 2012	D COMORBID	Culture	258	28	High	Medium
Salmonella (non- Typhi)	Mourembou et al. $(2016)^{221}$	Gabon	NA-NA	UN	PCR	410	3	Low	Low
Salmonella (non-	Mtove et al. (2010) <sup>222</sup>	United Republic	2008-	UN	Culture	1502	45	Low	Low
Typhi)		of Tanzania	2009				-		
Salmonella (non-	Mtove et al. (2011) <sup>223</sup>	United Republic	2006-	UN	Culture	6836	232	Low	Low
Typhi)		of Tanzania	2010						
Salmonella (non-	Mtove et al. (2011) <sup>224</sup>	United Republic	2009-	UN	Culture	965	1	Medium	Low
Typhi)		of Tanzania	2010						
<i>Salmonella</i> (non- Typhi)	Nadjm et al. (2010) <sup>225</sup>	United Republic of Tanzania	NA-NA	UN	Culture	3639	160	Low	Low
Salmonella (non-	Nadjm et al. (2012) <sup>226</sup>	United Republic	2007-	UN	Culture	198	5	Low	Medium
Typhi)		of Tanzania	2007						
Salmonella (non-	Ochaya et al. (2018) <sup>227</sup>	Uganda	2013-	D COMORBID	Culture	256	3	High	Medium
Typhi)			2013						
Salmonella (non-	Onchiri et al. (2016) <sup>228</sup>	Kenya	2012-	UN	Culture	1496	19	Low	Low
Typhi)			2014						
Salmonella (non-	Onyango et al. (2008) <sup>229</sup>	Kenya	2004-	D GI	Culture	20	18	High	High
Typhi)			2005			1.0			
Salmonella (non-	Onyango et al. $(2009)^{250}$	Kenya	2004-	D GI	Culture	40	20	High	High
Typhi)	P 1 4 1 (201 () <sup>23</sup> ]		2005	TDI	C. I.	12.421	70		
Salmonella (non-	Park et al. $(2016)^{251}$	No Specific	2010-	UN	Culture	13431	73	Low	Low
Typhi)	$P_{\text{otense}} = 1 (2004)^{232}$	Country Malanai	2014	TINI	Caltana	252	4.4	T	Madin
Salmonella (non-	Peters et al. $(2004)^{-1}$	Malawi	2000-	UN	Culture	352	44	Low	Medium
Salmonolla (non	<b>Product at al.</b> $(2012)^{191}$	Nonal	2000	UN	Culture	1020	2	Low	Low
Typhi)	Flauliali et al. (2012)	Nepai	2000-	UN	Culture	1039	2	Low	LOW
Salmonella (non-	Preziosi et al. (2015) <sup>233</sup>	Mozambique	2007	UN	Culture	841	10	Low	Low
Typhi)	1 Teziosi et al. (2013)	Wozamolque	2014	011	Culture	0-11	10	Low	Low
Salmonella (non-	Sothmann et al.	Ghana	2012-	UN	Culture	2306	24	Low	Low
Typhi)	$(2015)^{234}$	Onunu	2012	011	Culture	2000		2011	
Salmonella (non-	Tezcan et al. (2006) <sup>235</sup>	Turkey	1996-	D COMORBID	Culture	621	1	High	Low
Typhi)	( )		2004						
Salmonella (non-	Wiersinga et al.	Gabon	2012-	UN	Culture	941	5	Low	Low
Typhi)	$(2015)^{23\overline{6}}$		2013						
Schistosoma mansoni	Degarege et al. (2012) <sup>237</sup>	Ethiopia	2010-	UN	Microscopy	702	82	Low	Low
		-	2011						_
Streptococcus spp.	Hinjoy et al. (2017) <sup>238</sup>	Thailand	2015-	UN	Culture	70	1	Medium	High
			2015						

Pathogen	First author, year of publication and reference	Country	Study Period	Study Population Classification	Diagnostics Used	Number Tested	Number Positive	Representativeness Bias Coding	Precision Bias Coding
Toxoplasma gondii	Adurthi et al. (2008) <sup>239</sup>	India	NA-NA	D COMORBID	PCR	162	21	High	Medium
Venezuelan Equine Encephalitis virus	Forshey et al. (2010) <sup>240</sup>	No Specific Country	2000- 2007	UN	Culture, PCR, ELISA	13259	250	Low	Low
Venezuelan Equine Encephalitis virus	Kocher et al. (2016) <sup>241</sup>	Peru	2013- 2014	UN	PCR	2054	22	Low	Low
Venezuelan Equine Encephalitis virus	Manock et al. (2009) <sup>38</sup>	Ecuador	2001- 2004	UN	Culture, IgM, IFA, PCR	229	2	Medium	Medium
Venezuelan Equine Encephalitis virus	Morrison et al. (2008) <sup>242</sup>	Peru	2005- 2006	UN	IFA, PCR	1136	34	High	Low
West Nile virus	Boisen et al. (2015) <sup>101</sup>	Sierra Leone	2012- 2012	D SP	PCR	23	4	High	High
West Nile virus	Chinikar et al. (2012) <sup>243</sup>	Iran (Islamic Republic of)	2008- 2009	D NEU	PCR	249	3	High	Medium
West Nile virus	Elyan et al. (2014) <sup>244</sup>	Afghanistan	2008- 2010	UN	PRNT	277	24	Medium	Medium
West Nile virus	Hercik et al. (2017) <sup>13</sup>	United Republic of Tanzania	2014- 2015	UN	PCR	842	1	Low	Low
West Nile virus	Kumar et al. (2014) <sup>245</sup>	India	2009- 2010	UN	PCR	105	27	High	High
West Nile virus	Rutvisuttinunt et al. $(2014)^{246}$	Nepal	2009- 2010	D SP	PCR	14	2	High	High
West Nile virus	Tigoi et al. (2015) <sup>247</sup>	Kenya	2009- 2012	UN	PRNT	379	47	Low	Medium
West Nile virus	Williams et al. (2018) <sup>248</sup>	United Republic of Tanzania	2013- 2014	UN	Sequencing	12	2	Medium	High
Yersinia pestis	Sinyange et al. (2016) <sup>249</sup>	Zambia	2015- 2015	D SP	PCR	12	6	High	High

### Table S7: Summary of number of studies from each global region represented in the study dataset.

WHO Region	Number (%) of malaria endemic countries contributing data	Number (%) of studies contributing data (n=235 <sup>1</sup> )
Africa	21 of 44 (47·7%)	83 (35.3%)
Americas	8 of 23 (34.8%)	21 (8.9%)
Eastern Mediterranean	8 of 14 (57·1%)	22 (9.4%)
Europe	2 of 9 (22·2%)	6 (2.6%)
South-East Asia	8 of 10 (80.0%)	81 (34.5%)
Western Pacific	6 of 10 (60·0%)	22 (9.4%)
<sup>1</sup> Table includes data from 235	of 244 articles included in the review, excluding	9 articles reporting data from

Page 28 of 42

multiple countries excluded for this analysis.

# Figure S1: Barchart showing the number of articles contributing data for each country included in the study, displayed by country and WHO region.



- Figure S2: Barcharts showing number of articles from each global region contributing data for each of 30
- 506 507 508 509 510 zoonoses.
- Plot panels indicate the WHO defined global region and bar colour indicates type of pathogen.



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521	<ul> <li>MITO: ZOOHOSES. 2010. <u>http://www.who.mit/ZOOHOSES/diseases/clip</u> (Accessed 01 June 2010).</li> <li>OIE OIE Listed diseases infections and infectations in force in 2016. 2016. <u>http://www.vio.int/animal.</u></li> </ul>
522	4. OIL. OIL-Listed diseases, infections and infestations in force in 2010. 2010. <u>http://www.oic.int/animal-</u> health in the world/oie listed diseases 2016/ (Accessed 01 Jun 2016)
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# Dear editor

We would like to thank the three anonymous reviewers and the editor for their comments on this manuscript, and the opportunity to resubmit this revision of our paper. We have worked through and documented our point-by-point responses (shown in italics) to all of the comments made and these are detailed in the text below. The principal update made is to rerun the searches at the start of 2019 to bring this review fully up to date. We hope that this update and our responses to the other points raised will provide all of the information needed for resubmission.

Best wishes Jo Halliday

# Notes from the editor (general editorial points follow the reviewers' comments):

\* When revising your manuscript in response to the comments below, please ensure that you do not exceed the limits of 4500 words and 150 references (for detailed guidance see our instructions for authors<u>https://www.thelancet.com/pb/assets/raw/Lancet/authors/tlid-info-for-authors.pdf</u>)

In correspondence with the deputy editor Dr Sekkides on 25 March 2019 it was advised that we include details of the references that are only cited in the appendix table (that provides details of all articles included in the review), in the appendix. We count the article length as 4420 words and 47 references in the main file.

\* It is essential that you bring your search up to date

We have updated the review to include all references documented before 03 January 2019 when the update searches for this resubmission were run. This date is included in the revised submission (line 106)

\* Owing to the limited space available we only allow seven non-text items. I suggest that you move tables 1 and 3 to your appendix and any other two tables, figures, or both (maybe figures 3 and 4). Given table 1 is largely the same as the one in your appendix, retain the version you had in the manuscript, as this contains more information

We have updated the paper and retained only 7 non-text items in the main text file. These are included as follows:

1 – Table 1 - Pathogens included in the study – this combines the content from the main file and appendix, and the redundant version in the appendix has been dropped
2 – Table 2 – Inclusion and exclusion criteria – retained in the main text
(NB – to ensure that the references included in the figures compile into the reference list in the appropriate order we have retained the tables in the main text file).

3 - Figure 1: Flow diagram of records and articles assessed for the review

4 - Figure 2: Map illustrating the malaria-endemic countries included in the study and number of articles contributing data for each country.

5 - Figure 3: Barchart showing number of articles where each pathogen was looked for diagnosed and had data extracted

6 - Figure 4: Proportion of fevers attributed to each zoonosis.

7 - Figure 5: Venn diagram illustrating the associations between febrile population clinical presentation and pathogens identified.

The remaining tables and figures are now either omitted from the revision or included in the in appendix file.

The table giving details of all of the studies included in the review is now included (with its own standalone bibliography in the appendix – table S6). The appendix file also includes a link to a DOI where an excel format version of the table can be accessed (this will be activated as/when the paper is ready for publication)

\* A paper of this type does not require a research in context panel. Move this into the main text or omit entirely if this information is already presented *This section has been removed from the revised submission* 

\* Please submit ICMJE forms completed by all authors(<u>https://www.thelancet.com/pb/assets/raw/Lancet/authors/icmje-coi-form.zip</u>) *We have uploaded ICMJE forms for all authors* 

Reviewers' comments:

Reviewer #1:

1. The authors mention co-endemicity but there is no mention of co-infection and that the possibility of co-infection with malaria and another pathogen is real and what the probability of this could be

We have updated the manuscript to include data on the number of studies that reported exclusion of some pathogens/syndromes and malaria specifically. We have also added some additional results on the number of zoonotic pathogens that the studies looked for, diagnosed and contributed data for. Lines 396-300 now read:

"Of the 244 studies, twelve (4.9%) described a demographically restricted population, 55 (22.5%) reported some exclusions from the population, and 32 (13.1%) mentioned exclusion of malaria-infected individuals specifically (appendix table S6). Of the 244 studies, 73 (29.9%) reported looking for more than one zoonosis, 43 (17.6%) diagnosing more than one zoonosis and 37 (15.2%) contributing data on more than one zoonosis."

We have also added content on this point to the discussion (lines 432-435), which now reads:

"The design of this review did not allow explicit investigation of co-infections, either of zoonoses with malaria or of multiple zoonoses. Co-infections are likely to be an important factor underlying both the distribution and prevalence of some zoonotic pathogens, including for example nontyphoidal Salmonella serovars.[1]

2. This paper describes how in many malaria endemic settings; differential diagnosis of zoonotic pathogens is under-recognized/diagnosed. It is a shame that such a piece of in depth research did not include other languages besides English e.g. Russia. When one looks at the map of distribution it is also clear that there is research bias for examples with countries that have many research projects like Tanzania featuring high. There is also no real discussion about zoonoses often not being a blanket problem but a problem in high risk areas/ populations. This would enhance the paper.

With the exception of the franco-phone in West Africa, for most malariaendemic countries, English is the primary language for biomedical science. However, we do agree with the limitations identified by the reviewer here and have addressed some of these points in the discussion content and limitations paragraph specifically as follows:

Lines 404:407

"The restriction of this review to English language texts will have reduced the probability that studies from French and Spanish speaking countries were included and may partially account for some gaps, such as the 23 countries in Africa and 15 in the Americas for which no eligible studies were identified."

We have added a comment in the discussion to clarify the point about the dominance of a small number of countries in the data set (lines 337-345), that read:

"The geographic variation in the distribution of studies by country (figure 2) and region (appendix table S7, figure S2) is likely to be strongly influenced by variation in research and publication effort. There is noticeable geographic segregation for some zoonoses, with NTS and SFGR reported more frequently in Africa, and Leptospira spp., Orientia tsutsugamushi, and typhus-group rickettsioses (TGR) reported more frequently in South-East Asia and Western Pacific regions (appendix figure S2). For viruses, Lassa virus was reported only in Africa and JEV predominantly in South-East Asia. The distribution of studies cannot be interpreted as an accurate reflection of the underlying distribution of zoonotic pathogens, their prevalence or clinical importance.."

We have also added more detail to the flowchart (Figure 1) to clearly show the number of abstracts and full texts excluded on the basis of language in the figure (n=48 of 13,321 records) and we give the breakdown of articles by language excluded in the figure caption. To address the comment about zoonoses not being a blanket problem we have added the following content in the discussion (lines 396-400):

"Within populations at risk, it is important that aetiologic studies are followed by epidemiologic risk factor studies to determine whether certain sub-groups are at higher risk for specific zoonotic diseases. Robust febrile illness surveillance systems help inform local epidemiology and febrile illness management, and are also essential for detection of disease outbreaks.[2]."

3. Results highlight (line 353...) It is not about patient awareness only and about early seeking and diagnosis but also about awareness in populations at risk (occupations, communities, geographical high risk areas etc.), behavior change, prevention in Animals and relation to WASH.. This could be addressed a little in discussion.

We have address this point in two locations.

Lines 347-349 have been updated and these now read:

"Once pathogens are identified in any location there will likely be increased clinical, patient, and community awareness of those pathogens, as well as improved diagnostic capacity to detect them"

Later in the discussion we have update content on actions that can be taken to tackle and reduced the burden of zoonotic diseases. Lines 460-466 now read:

"One Health efforts to share data and knowledge between animal and human health sectors could help raise clinician awareness of locally relevant zoonoses, inform history taking, and guide diagnostic and management decision making. Control of disease in animal populations and prevention of transmission from animals to humans are likely to be the most effective ways to reduce human disease risk with many zoonoses, necessitating active engagement with populations at risk to develop sustainable disease control interventions."

4. In discussion: POC test are expensive and scarce, these should include pathogen panels in the future. There is a need for Target product profiles to guide diagnostic developers. *We agree that accurate POC tests are scarce, and that etiologic research can and should inform diagnostic developers. Accordingly we have added to the (lines 454-458):* 

"Continued efforts are needed to develop multi-pathogen diagnostics, ideally with formats appropriate for point of care use. To avoid perpetuation of self-fulfilling prophesies that can arise when only pathogens tested for (and detected) are assumed to be present, the development and evaluation of such diagnostics should be informed by data describing the pathogens present in specific settings and also the wider context."

5. In discussion some space should be given to the argument that strong systems detecting febrile illness could bolster detection of epidemic of unknown origin or other causes. We have updated the discussion to include a point addressing this comment. Lines 396 to 400 now read:

"Within populations at risk, it is important that aetiologic studies are followed by epidemiologic risk factor studies to determine whether certain sub-groups are at higher risk for specific zoonotic diseases. Robust febrile illness surveillance systems help inform local epidemiology and febrile illness management, and are also essential for detection of disease outbreaks.[2]."

6. The last search was conducted in Aug 2016, 2 years ago, in the meantime there are more publications that would potentially reinforce the strength of the paper. This should be assessed by authors to identify whether worth updating the study.

We have updated the review to include all references documented before 03 January 2019 when the update searches for this resubmission were run.

Some text editing may improve readibility on phrase : 190-2, 266-8, 288, etc

We have updated the text in these identified locations as follows: 190-192 (now lines 202-205) now reads:

"To extract data on zoonotic pathogens, every article was classified to record if the study reported looking for or diagnosing one or more febrile individuals with any of the zoonotic pathogens included in the study reference list (table 1), irrespective of the diagnostics used"

266-268 (now lines 302-306) now reads:

"Among the 75 differentiated populations, 36 (48.0%) had specific febrile aetiologies suspected, 17 (22.7%) were classified as febrile neurological, eight (10.7%) as comorbid populations, eight (10.7%) as febrile haemorrhagic, five (6.7%) as febrile gastrointestinal and one (1.3%) as febrile respiratory"

288-289 (now lines 285-286) now reads: "The proportion of fevers attributed to each pathogen reported ranged from <1.0% to 95.0% (figure 4)"

Reviewer #3: This is a high quality systematic review on globally important clinical problem: In malaria-endemic countries, febrile patients receive frequently empiric-malaria treatment or empiric antibiotics -mostly beta-lactams- against typical bacterial pathogens. Both are usually not active against many zoonosis (e.g. coxiella, brucella etc) - resulting in a high proportion in inadequate empiric treatment in regions where zoonoses are frequent. This article summaries the augilable avidence in a year structured, commerchensive and

This article summaries the available evidence in a very structured, comprehensive and systematic way. These data will be extremely helpful to design e.g. molecular POCT panels for certain regions. I am very enthusiastic about the research question and the approach, and I was indeed looking for an article like this but did not found it yet. There are only minor issues:

1. Table 3: please add the used diagnostics approaches and the enrolled syndromes (gastrointestinal, neurological et.c) (you can use the coding from the inclusion criteria)
We have added information on the febrile population classification and diagnostic tests used to the summary table which is now Table S6 in the appendix material. The bias coding of each population has also been included in the update.

In addition, we will make a search and sortable excel copy of the full dataset accessible via a DOI (included in the appendix file) at Glasgow University that can be linked to the publication and made public on acceptance.

2. Sort table 3 by pathogen or provide an interactive table online that allows the reader to sort by region, pathogen, syndrome, year etc.

The Table S6 in the appendix material is now sorted by pathogen (then Author last name). In addition, we will make a search and sortable excel copy of the full dataset accessible.

3. Please mention, how many papers you omitted because of language reasons - this may be critical, since Spanish and French is frequently the main language in many of the addressed countries.

Two abstracts and 46 full texts were excluded on the basis of language. These numbers are now clearly shown in figure 1.

4. How many articles do you omit because no full text was available? *Twenty-six articles were omitted because pdfs could not be obtained through the searches and library systems searched.* 

To address these two points, we have updated figure 1 to clearly show the number of abstracts and full text excluded on the grounds of language and PDF availability. The breakdown of number of excluded references written in different languages is given in the caption for the figure.

5. Why did you stop you research in 2016? This is 2 years ago? We have updated the review to include all references documented before 03 January 2019 when the update searches for this resubmission were run.

Reviewer #5: Overview and general recommendation:

The present study makes a valuable contribution to the knowledge about the main zoonoses that may be explaining the causes of febrile syndromes in non-malarial patients from endemic areas for several infectious diseases. Likewise, the importance of overcoming the challenge of malaria overdiagnosis in febrile patients is highlighted, as documenting the presence of other etiological agents leads to a targeted treatment preventing complications and deaths. Similarly, the contribution of elements for the construction of diagnostic and treatment algorithms for febrile syndromes would reduce the burden of infant mortality in these endemic areas for malaria. I also emphasize the good writing, the scientific rigor and the proper use of the bibliographical references, nevertheless, some suggestions are made on some aspects of the manuscript.

Minor comments:

### Abstract

Is complete; It has an introduction, objectives, methods, results and conclusions.

### Introduction

It is well elaborated, it is pertinent, accurate and well documented bibliographically.

### Methodology Results and Discussion

The study is well planned as a systematic review, very detailed in terms of trying to capture all peer-reviewed articles, written in English and visible in the databases that they consulted. However, there are some observations related to the following aspects:

I suggest a better clarification of how they analyzed the risks of biases, because what's reported (lines: 211-214) is not systematic in this.

We have substantially updated the content on bias assessment in the manuscript. This is done in a revised section now titled "Data extraction and bias assessment" (Pg 8), with specific additional content on the methods used in lines 216-236. This content reads:

"The principal source of potential bias affecting the interpretation of the findings of this study is the lack of standardization of the febrile populations included in different studies. Criteria were defined to classify potential bias in study representativeness and prevalence estimate precision (appendix table S5).[3-5] The representativeness bias criterion was designed to classify the representativeness of the study population, relative to the general population where the study was conducted. This was based on the description of the febrile population, the restriction (if any) of the study sample to specific clinical or demographic sub-populations and the reporting of disease outbreaks at the time of data collection. Each population was classified as follows: i) populations classified as undifferentiated febrile with no demographic restriction and no clinical aetiologies excluded were classified as low risk; *ii)* populations classified as undifferentiated febrile with demographic restriction and/or reporting exclusion of specific aetiologies or syndromes were classified as medium risk; iii) differentiated febrile populations and those from studies reporting disease outbreaks at the time of data collection were classified as high risk. The second, outcome-level, bias criterion was designed to classify risk of bias in the estimated precision of the proportion of fevers attributed to each pathogen. Thresholds used for this criterion are the sample sizes needed to estimate proportions of 50% and 10% with 95% confidence and 0.05 precision respectively, assuming an infinite population size. Each population was classified as follows: i) proportion estimates based on a sample size of greater than or equal to 385 were classified as low risk; *ii)* proportion estimates based on a sample size of greater than 385 but less than 139 were classified as medium risk; iii) proportion estimates based on a sample size of less than 139 were classified as high risk."

We have revised the lines referred to here to retain the point made but clearly distinguish this from more formal bias assessment steps. This content is now included in lines 235-243 which now read:

"Additional potential sources of bias included variation in the pathogens tested for, and variation in the diagnostic approaches applied. For included studies, data on the pathogens tested for (with any diagnostic approach) were summarized alongside pathogens for which diagnostic test criteria were met to qualitatively evaluate the biases introduced by only extracting data on pathogens diagnosed using methods meeting study inclusion criteria."

The results of this bias coding are summarised in the results section (lines 286-288 and 307-309). The bias coding (representativeness and precision) of all studies and prevalence estimates are shown in appendix table S6. The representativeness bias coding of all prevalence estimates obtained from extracted data is shown in the revision of figure 4 and interpretation of the influence of these biases upon the key study findings is given in the discussion in lines 416 to 426.

I suggest to detail more accurately the risk assessment of bias in the individual studies; and to deepen the explanation of Figure 7 considering that and the characteristics of each study, which is currently very focused on the bibliometric analysis.

We have revised and updated Figure 7 (now Figure 4) to include representation of the representativeness bias assessment for each data point. The bias coding for all study populations included in the review are also show in the appendix Table S6 and these data are summarised in the results section (lines 286-288 and 307-309) and discussion sections (lines 416 to 426).

There is a bias in the selection of studies for restricting the language, which is enunciated by the authors.

There is a good bibliometric analysis (analysis of the publications) of Table 4 and of Figures 2, 3, 4 and 5, which is important to understand the dynamics of publication in an area. However, it would also be important to inform a little more about the occurrence or distribution of the causes of febrile illness. This way, it wouldn't be interpreted as a selection bias due to language restriction.

Due to limitations on the number of tables and figures that can be included in the main manuscript file (7 in total) Table 4 (now Table S7 in the appendix) and Figure 2 (now Figure S1 in the appendix) have been moved to the appendix content.

Due to the biases inherent in this dataset we are reluctant to over-interpret these data and feel that graphical representation of the data extracted in these figures and discussion of these patterns in the text is appropriate. In the discussion text we do refer to the geographical variation in number of studies on different pathogens (lines 337-345):

"The geographic variation in the distribution of studies by country (figure 2) and region (appendix table S7, figure S2) is likely to be strongly influenced by variation in research and publication effort. There is noticeable geographic segregation for some zoonoses, with NTS and SFGR reported more frequently in Africa, and Leptospira spp., Orientia tsutsugamushi, and typhus-group rickettsioses (TGR) reported more frequently in South-East Asia and Western Pacific regions (appendix figure S2). For viruses, Lassa virus was reported only in Africa and JEV predominantly in South-East Asia. The distribution of studies cannot be interpreted as an accurate reflection of the underlying distribution of zoonotic pathogens, their prevalence or clinical importance."

We hope that the update of figure 4 to include separate panels for different WHO regions and provision of the study dataset in excel format will enable further investigation of these patterns by readers interested in specific regions.

The mean and median of the proportions reported in the included studies could make some untrained readers think that this is a measure of synthesis.

We have removed this quantitative summary of the proportion data from the results section (lines 285-286) which now includes only the description of the range and reads: "The proportion of fevers attributed to each pathogen reported ranged from <1.0% to 95.0% (figure 4)."

In addition, we have included content in the discussion (lines 416-422) to highlight the caution needed in interpreting these data 'quantitatively' as follows:

"The bias assessments for study representativeness and precision in the estimates of proportion of fevers attributable to a given pathogen both reveal that the majority of data points had medium or high risk of one or both types of bias. This emphasizes the need for cautious and essentially non-quantitative interpretation of the data extracted from these studies. Many studies with risk of precision bias due to smaller sample size tended to report the highest prevalences of disease attribution to a given pathogen (figure 5); and, interestingly, these studies were often also classified as high risk for representativeness bias."

The results are consistent with the objectives of the proposal and they explain the frequency of 29 zoonoses, prioritized according to the review of articles that met selection criteria. The discussion is well posed, and it reveals the diagnostic difficulty for some pathologies such as leptospirosis and the diagnostic limitations within the scope of the first levels of care. The limitations of the study are adequately described. A complete review of the selected articles was made and fidelity was verified with the definition of infection by zoonotic pathogens.

Conclusion

It is consistent with the purpose of the study.

# References, Tables and figures

There is a good handling of the references; All references are cited within the manuscript and are relevant to support the different statements, purposes or citations. Regarding the figures, some data on hemorrhagic fevers and some numbers that should coincide with the text of the manuscript should be unified.

Apologies for these errors in the previous figure and text versions – see below for our responses to each specific point identified

## Page 3, row 68

...human pathogens cause zoonoses.... They are not zoonoses We have updated this so that the revised content (lines 65-66) now reads: "Fever is one of the most common reasons for healthcare seeking globally and the majority of human pathogens are zoonotic"

Page 3, row 82 Fever is not a syndrome, but a symptom We have updated this so that the revised content (line 78) now reads: "Fever is one of the most common symptoms prompting healthcare seeking globally [6-8]."

Page 5, row 256

These 29 pathogens as they state are not in figures 5 and 7. Apologies for these errors in the previous figure and text versions – we have updated figures 5 and 7 (now Figure S2 and Figure 4) to resolve these inconsistencies. Figure 3 includes all of the named pathogens looked for (n=40), diagnosed (n=31) and for which data were extracted (n=30). This is now clarified in the update legend for the figure:

"Figure 3: Barchart showing the number of articles that looked for, reported diagnosis of and contributed data for each of 40, 31 and 30 zoonoses respectively. These data were tabulated for all zoonoses (n=40) and articles included in the review (n=244). Bar colour indicates pathogen type and shading differentiates studies that i) contribute data meeting study diagnostic criteria (left hand bar sections with darkest shading, n=30 pathogens indicated by \*), ii) report diagnosis with approaches that do not meet study diagnostic criteria (central bar sections with lighter shading, n=31 pathogens that comprised the 30 with extracted data and Escherichia coli), iii) report looking for but not diagnosing a zoonosis (right hand bar section with lightest shading, n=40 pathogens, also including Burkholderia spp. Tick borne encephalitis virus, Marburg virus, Rabies virus, Newcastle Disease virus, Mycobacterium bovis, Francisella tularensis, Ebola virus and Cryptosporidium parvum). "

Figure S2 includes data for the n=30 pathogens with extracted data. This is now updated in the figure legend which reads:

*"Figure S2: Barcharts showing number of articles from each global region contributing data for each of 30 zoonoses.*"

*Plot panels indicate the WHO defined global region and bar colour indicates type of pathogen.*"

At least the 3 protozoa mentioned in this page are not contemplated in the figures mentioned, because only Leishmaniasis and Toxoplasmosis but not Cryptosporidium parvum that is contemplated within the 36 pathogens of figure 4.

This query arises from ambiguity between the list of pathogens summarised at different points. The figure 4 referred to is now Figure 3 in the revision and this includes all 40 pathogens looked for. The summary of the number of pathogens that are bacteria, viruses, protozoa and helminths refers to the subset of 30 pathogens for which data were extracted.

We hope that changes made to the legends of the relevant figures and the results text (see below) address and resolve this source of confusion:

*The relevant part of the results section has been reordered, with additional references to figures – lines 274-281:* 

"The 244 articles included for data extraction reported looking for and diagnosing 40 and 31 zoonoses, respectively, in these populations (figure 3). The number of included zoonoses was reduced to 30 after the criteria for diagnostic testing approach were applied. The 244 articles yielded data that met diagnostic test criteria for 30 zoonoses that included 17 bacterial pathogens (56.7%), nine viruses (30.0%), three protozoa (10.0%), and one helminth (3.3%). Leptospira spp., nontyphoidal Salmonella serovars (NTS) and rickettsioses were the most frequently reported bacteria, while Japanese encephalitis virus (JEV), Hantavirus, and West Nile virus (WNV) dominated among reported viruses (figures 3, 4)."

Page 5, row 256

In figure 4 the authors state 36 pathogens but not 29. In figures 5 and 7, 29 pathogens are mentioned.

See explanation for related query above.

Page 6, row 271

In Figure 6, 6 pathogens are not listed, but 5 considering Rickettsia (SFGR) and Rickettsia (TGR) as separate zoonoses; and 4 pathogens if they include both rickettsioses as a single zoonosis, as stated in the description of figure 6 (page 48).

Apologies for the errors in the previous version of this figure. In the revised version (Figure 5), the distinction between Rickettsia (SFGR), Rickettsia (TGR) and Rickettsia spp. is made here as elsewhere in the text, with all three now included in the figure labelling. The explanation of these grouping is also now included in a footnote to Table 1. We have also included the details of the 5 pathogens not shown in the figure, with explanation, in the revised figure legend:

*"Figure 5: Venn diagram illustrating the associations between febrile population clinical presentation and pathogens identified.* 

Circles are scaled to the number of pathogens detected in each type of febrile population. Undifferentiated, shown in green, 23 pathogens (including pathogens also seen in other populations); febrile neurological, shown in red, four pathogens; febrile gastrointestinal, shown in blue, two pathogens; febrile respiratory, shown in purple, one pathogen, febrile haemorrhagic, shown in yellow, seven pathogens. Five pathogens are not represented in the figure as they were only detected in febrile populations classified as co-morbid (Listeria spp., Pasteurella spp. and Toxoplasma gondii) or in febrile populations with a specific febrile aetiology suspected (Leishmania donavani, and Yersinia pestis). "

Page 48, Paragraph corresponding to Figure 5, Line 1226

The authors count 29 zoonoses considering Rickettsia (SFGR) and Rickettsia (TGR) as different zoonoses. However in figure 6 they include Rickettsia (SFGR) and Ricketts TGR) as a single because they speak of 4 hemorrhagic zoonoses in the description of the figure: .....

"febrile haemmorhagic, shown in orange, 4 pathogens" .... In figure 7 they also graph both rickettsiosis separately. zoonoses should always be counted in the same way throughout the manuscript.

See responses to the linked points above.

Page 48, Paragraph corresponding to Figure 6, Line 1233 If they talk about 4 hemorrhagic pathogens they would not be undifferentiated 22 but 21. If

they are 5 hemorrhagic, it is good to talk about 22 undifferentiated

We have updated the legend of the figure (now Figure 4) which now reads:

*"Figure 5: Venn diagram illustrating the associations between febrile population clinical presentation and pathogens identified.* 

Circles are scaled to the number of pathogens detected in each type of febrile population. Undifferentiated, shown in green, 23 pathogens (including pathogens also seen in other populations); febrile neurological, shown in red, four pathogens; febrile gastrointestinal, shown in blue, two pathogens; febrile respiratory, shown in purple, one pathogen, febrile haemorrhagic, shown in yellow, seven pathogens. Five pathogens are not represented in the figure as they were only detected in febrile populations classified as co-morbid (Listeria spp., Pasteurella spp. and Toxoplasma gondii) or in febrile populations with a specific febrile aetiology suspected (Leishmania donavani, and Yersinia pestis). "

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We originally included this panel but were advised (in above email) that a paper of this type does not require this panel so have omitted this

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Yours sincerely,

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### 66

#### 67 Abstract

68 Fever is one of the most common reasons for healthcare seeking globally and the

- 69 majority of human pathogens are <del>zoonoses</del>zoonotic. We conducted a systematic
- 70 review to describe the occurrence and distribution of zoonotic causes of human febrile
- 71 illness reported in malaria endemic countries. Articles included in the review yielded
- 72 data from 46 (41-853 (48.2%) of the 110 malaria endemic countries included in
- 73 searches. The 181244 articles included described diagnosis of 2930 zoonoses in
- 74 febrile people from 46 countries. The majority of zoonoses were bacterial (n=1617),
- 75 with viruses (n=9), protozoa (n=3) and helminths (n=1) also identified. Leptospira
- 76 spp. and nontyphoidal Salmonella serovars were the most frequently reported 77
- pathogens. Despite evidence of profound data gaps, this review reveals widespread 78
- distribution of a diverse range of zoonotic causes of febrile illness. ImprovedGreater 79 understanding of the epidemiology of zoonoses in different settings is needed to
- 80 improve awareness and management of the multiple zoonotic causes of febrile illness.
- 81

#### 82 Introduction

- 83 Fever is one of the most common syndromessymptoms prompting healthcare seeking 84 globally (1-3).<sup>1-3</sup> Fever has myriad causes and thetheir non-specific clinical 85 presentation means that clinical history and physical examination are often unableinsufficient to accurately suggest theidentify causal pathogen (1).pathogens.<sup>1</sup> 86 87 Limitations in laboratory services and available diagnostic tools further contribute to diagnostic challenges (4). In malaria-endemic countries, fever is often assumed to be 88 89 due to malaria  $\frac{(5)}{1}$ .<sup>5</sup> The mortality and morbidity attributable to malaria remains 90 considerable, but there is also evidence of widespread over-diagnosis (6,7) and indeed globally-within malaria-endemic areas (8)...<sup>6-8</sup> The recognized over-diagnosis of 91 malaria together with declines in malaria incidence since the peak in global malaria 92 deaths in 2004 + (9,10) have prompted attention to non-malaria causes of fever in these 93 mala<u>ria-endemic</u> areas- $(1^{1,12})$ . Zoonotic pathogens are likely to play a substantial role 94 95 globally as causes of fever globally. Almost two-thirds of all human pathogens are zoonotic (13),<sup>13</sup> and there is growing evidence that many zoonoses cause more cases 96 of human febrile illness than previously appreciated  $\underline{-(^{12,14-20})}$ . Improved 97 98 understanding of the impacts and burdens of zoonotic causes of fever in malaria-99 endemic countries would provide the epidemiological evidence base to enable for 100 disease control program development and also influence diagnostic and treatment 101 algorithms for fever, with the potential to improve clinical outcomes. The aim of this 102 study was to systematically review the published literature to describe the occurrence
- 103 and distribution of reported zoonotic causes of human febrile illness in countries 104 where malaria is endemic.
- 105

#### 106 **Methods**

#### 107 Search strategy and selection criteria

108 The target literature for this systematic review was peer-reviewed published articles 109 that described the testing of one or more febrile peopleperson from malaria-endemic 110 countries for one or more zoonotic pathogenspathogen using robust diagnostic testing 111 criteria to demonstrate acute infection. Literature searches of the Medline and Embase

- 112 databases were run using the OvidSP gateway. Searches were limited to English
- 113 language articles published in the period 2004 to <del>2016</del>2019 inclusive, to span the 114
- period from the described peak of global malaria mortality in 2004 (9).to present.<sup>9</sup>
- The searches were last executed on <del>26 August 2016.03</del> January 2019. Outputs of 115

database searches were combined and de-duplicated in R (21). Fullusing R.<sup>21</sup>
 Additional details of searches, screening, review, and data extraction processes are
 given in the Supplementary Information (SI).appendix.

118 119

120 We constructed three Three search concepts for 'Fever', 'Zoonoses', and 'Malaria Endemic Countries' fever,' 'zoonoses,' and 'malaria endemic countries' were 121 constructed. To construct the 'Fever' fever' concept the exploded subject heading and 122 123 keywords were combined using database appropriate syntax (e.g-., exp Fever/ OR 124 fever\$1.mp. OR febrile.mp.). For the 'Zoonoses' concept, a reference list of 125 eligible zoonotic pathogens was compiled using lists of zoonotic diseases from the 126 World Health Organization (WHO) (22) and World Organisation of Animal Health (OIE) (23))<sup>22</sup> and World Organisation of Animal Health (OIE)<sup>23</sup> as well as literature-127 based searches to identify frequently reported zoonotic causes of human fever. We 128 129 conducted preliminary searches of Medline and Embase using the search syntax '(exp 130 Fever/ OR fever.mp.) AND (exp Zoonoses/ OR zoonoses.mp OR zoonosis.mp)' 131 limited to humans. FullAdditional details of these three preliminary searchessearch 132 concept construction are given in the SI appendix. All pathogens identified through 133 these approaches were mapped to existing subject headings and keywords at the 134 lowest appropriate taxonomic level possible, typically genus or species. In instances 135 where pathogen species or serovars within the same genus varied in their zoonotic 136 status, search concepts were constructed to include all zoonotic and non-zoonotic 137 species or serovars and articles relating to non-zoonotic species were excluded at the 138 full text stage. The candidate pathogens were classified to differentiate pathogens 139 normatively acquired by people through direct or indirect transmission from 140 vertebrate animals to humans, as compared to pathogens where zoonotic transmission 141 has been recorded but where the majority of human infections are not acquired 142 through zoonotic transmission. We classified pathogens using the stages in the process towards human endemicity defined in Wolfe et al (24). Pathogens classified 143 as stages 1 to 3 were retained and full details are given in the SL.<sup>24</sup> Pathogens 144 145 classified at stages one to three (normatively acquired through zoonotic transmission) 146 were retained (appendix). The search concept for each pathogen or disease included 147 exploded subject headings for both the pathogen and the diseases caused in humans 148 and terms for both pathogen and disease were also included as keywords (e.g., exp 149 anthrax/ OR anthrax.mp. OR exp Bacillus anthracis/ OR bacillus anthracis.mp.). The 150 list of pathogen- or disease- specific searches was combined using OR syntax to 151 generate the full 'zoonoses' search concept (Table 1 & SIappendix). The 'Malaria 152 Endemic Countries' malaria endemic countries' concept was constructed by mapping 153 country names for countries defined as malaria endemic in the WHO global malaria 154 reports for the years 2005 and 2016 to Medline and Embase subject headings (10,25). 155 Each country was searched for using both the exploded subject heading where 156 available and keywords in all cases (e.g., exp Kenya/OR Kenya.mp.). All three concepts, Fever', 'Zoonoses', and 'Malaria Endemic Countries' were combined using 157 AND operators and database specific syntax gateway (SI).<sup>10,25</sup> Each country was 158 159 searched for using both the exploded subject heading where possible and keywords in all cases (e.g., exp Kenva/OR Kenva.mp.). The three concepts, fever, ' 'zoonoses,' and 160 'malaria endemic countries' were combined using AND operators and database 161 162 specific syntax (appendix).

163

## 164 Study selection and validity assessment

165	Articles that reported the diagnosis of a zoonotic pathogen in a population from a
166	malaria endemic country defined principally on the basis of febrile illness were
167	selected for full-text review. <u>Conference proceedings and records that did not include</u>
168	any abstract text or an abstract in English were excluded. Abstracts and titles were
169	screened by two independent reviewers (two of DVH, GL, MC, and MES, KJA,
170	GAFL, DVH, JAC, SC and MPR) using pre-defined criteria (SI Table S2 appendix
171	table S1). Articles were selected for inclusion if the abstract or title described clinical
172	and/or laboratory evaluation of a group of $\geq 2$ people with a <u>all of whom had</u> fever and
173	diagnosissome of whom were diagnosed of one or more pathogens from the reference
174	list of zoonotic pathogens (Tabletable 1). Abstracts referring to the use of blood
175	culture were also retained at this stage even if a zoonosis was not explicitly mentioned
176	in the abstract (SI Table S2). Conference proceedings were excluded.appendix table
177	<u>S1).</u> When two reviewers disagreed on article classification, a third independent
178	reviewer ( <del>DVH, GLone of JEBH</del> , MC, MES, GAFL, DVH or MPR) resolved the
179	tiebreak. Full text articles were sought for all articles not excluded at the screening
180	stepduring abstract review steps. All articles were searched for using PubMed, Google
181	and the libraries of the University of Glasgow, Duke University, Washington
182	University in St. Louis, and US Centers for Disease Control and Prevention (US
183	CDC). Articles were excluded if a full-text for the citation could not be obtained.
184	Two independent reviewers (two of, JEBH, MPR, JBMC, MES, JB and MCMPR)
185	evaluated full text articles using pre-defined inclusion and exclusion criteria
186	(Tabletable 2)., appendix table S2). Strict diagnostic case definitions were used based
187	on WHO and <u>US</u> CDC guidelines to ensure <u>ensured</u> that only studies reporting robust
188	and specific diagnostic methods were retained (Table 12). Articles were excluded
189	if they met <u>did not meet</u> one or more of the study exclusion <u>inclusion</u> criteria or failed
190	to <u>if they did</u> meet at least one <u>of the</u> study inclusion criterion (Table <u>exclusion criteria</u>
191	(table 2). In cases where reviewers disagreed on article classification, discrepancies
192	were checked and resolved by JEBH in discussion with other reviewers.

193

194 Table 1. Zoonoses included in the review, with details of species and serovars
 195 excluded where appropriate.

Pathogen	Species, subspecies, and serovars excluded	Pathogen
		type
<u>Alphaviruses</u>	All species excluded with the exception of	<u>Virus</u>
	Eastern equine encephalitis virus (EEEV)	
	complex, Venezuelan equine encephalitis (VEEV)	
	complex, and Western equine encephalitis	
	(WEEV) complex	
<u>Anaplasma spp.</u>	-	Bacteria
<b>Aphthoviruses</b>	All species excluded with the exception of Foot-	<u>Virus</u>
	and-mouth disease virus	
Avulaviruses	All species excluded with the exception of	Virus
	Newcastle disease virus	
<u>Babesia spp.</u>	-	Protozoa
<u>Bacillus</u>	-	<b>Bacteria</b>
antrhracis		
Bartonella spp.	B. bacilliformis and B. quintana excluded	Bacteria
Borrelia spp.	B. recurrentis excluded	<u>Bacteria</u>
Bovine	-	Prion
<u>spongiform</u>		

encephalopathy		
Brucella spp.	_	Bacteria
Burkholderia	<i>B. cepacia</i> complex and <i>B. pseudomallei</i> excluded	Bacteria
spp.		
<i>Campylobacter</i>	-	Bacteria
spp.		
Chlamydia spp.	All species excluded with the exception of C.	Bacteria
	<u>psittaci</u>	
Coxiella burnetii		Bacteria
Cryptosporidium	C. hominis excluded	Protozoa
spp.		
Ebolavirus	-	Virus
Echinococcus	-	Helminth
spp.		
Ehrlichia spp.	-	<b>Bacteria</b>
Enteroviruses	All species excluded with the exception of Swine	Virus
	vesicular disease virus	
Escherichia spp.	All species excluded with the exception of Shiga-	<b>Bacteria</b>
	toxin producing E. coli	
Flaviviruses	All species excluded with the exception of	Virus
	Japanese encephalitis virus (JEV), West Nile	
	virus (WNV), and Tick-borne-encephalitis virus.	
Francisella spp.	All species excluded with the exception of <i>F</i> .	Bacteria
	tularensis	
Hantavirus	-	Virus
Henipaviruses	-	Virus
Lassa virus	-	Virus
Leishmania spp.	L. donovani excluded if detected in India	Protozoa
Leptospira spp.	-	Bacteria
Listeria spp.	2	Bacteria
Lyssavirus	All species excluded with the exception of Rabies	Virus
	virus	
Marburg virus	2	Virus
<u>Mycobacterium</u>	All species excluded with the exception of <i>M</i> .	Bacteria
	bovis and M. avis	
Nairovirus	All species excluded with the exception of	Virus
	Crimean-Congo haemorrhagic fever virus	
<u>Orientia<sup>1</sup></u>	<u>-                                     </u>	Bacteria
Orthopox viruses	All species excluded with the exception of	Virus
	Cowpox virus, Monkeypox virus, and Vaccinia	
	virus	
Pasteurella spp.	<u> </u>	<u>Bacteria</u>
Phleboviruses	All species excluded with the exception of Rift	Virus
	Valley fever (RVF) virus	
<u>Rickettsia spp.<sup>2</sup></u>	<u>R. prowazekii excluded</u>	Bacteria
Salmonella spp.	All species, subspecies, and serovars excluded	Bacteria
	with the exception of nontyphoidal Salmonella	
	serovars	
Schistosoma spp.	S. haematobium, S. intercalatum, and S.	Helminth

		<i>mekongi</i> .excluded	
	<u>Streptobacillus</u>		Bacteria
	<u>spp.</u>		
	<u>Streptococcus</u>	All species excluded with the exception of S.	Bacteria
	<u>spp.</u>	canis, S. suis, S. equi, and S. iniae	
	<u>Taenia spp.</u>		Helminth
	<u>Toxocara</u>		<u>Helminth</u>
	<u>Toxoplasma</u> gondii	=	Protozoa
	<i>Trichinella</i> spp.	-	Helminth
	Trypanosoma	All species excluded with the exception of <i>T</i> .	Protozoa
	spp.	brucei rhodesiense and T. cruzi	
	Varicelloviruses	<u>All species excluded with the exception of</u> Pseudorabies virus	<u>Virus</u>
	Vesiculoviruses	All species excluded with the exception of	Virus
	<u>v esteuto viruses</u>	Vesicular Stomatitis virus	<u>viius</u>
	Yersinia spp	All species excluded with the exception of Y	Bacteria
	<u>10.80000 5000</u>	pestis. Y. enterocolitica and Y. pseudotuberculosis	Duotonu
196	<sup>1</sup> Orientia was c	covered by search syntax for <i>Rickettsia</i> .	<u> </u>
197	$^{2}$ For data extrac	ction, data on <i>Rickettsia</i> were classified as <i>Rickettsia</i> (SI	FGR) or
198	Rickettsia (TGR	) where the data resolution allowed. When details on th	e species of
199	Rickettsia were	not given, these data were classified as <i>Rickettsia</i> spp.	<u> </u>
200			
201	Table 2: Inclusi	on and exclusion criteria for full text review	
	Outcome C	Criterion	
	Inclusion:	Febrile population ( $\geq 2$ people with a fever, defined a	is body
		<u>temperature <math>\geq</math> 38.0°C)</u>	
	•	Diagnosis of one or more zoonotic pathogens from pathogens	re-defined
		reference list of eligible aetiological agents (table 1)	
	•	Diagnostic test criteria:	
	i	Culture of the pathogen from sample(s) collected from	<u>m a febrile</u>
		person	
	<u>ii</u>	) Direct detection of the pathogen (e.g., by PCR based	techniques)
		from sample(s) collected from a febrile person	
	<u>ii</u>	i) Serological diagnosis of acute infection based on test	ing of both
		acute and convalescent phase serum samples and der	nonstration of
		seroconversion	
	<u>i</u>	v) Diagnosis of acute infection based on detection of pa	thogen-
		specific antibody or antigens in a single serum sampl	<u>e only for</u>
		selected pathogens, for which widely accepted case c	lefinitions
		deemed pathogen-specific antibody or antigen detect	<u>10n</u>
		sufficiently accurate	- <b>1</b> 41
	<u>v</u>	<u>) Igwi detection in cerebrospinal fluid (USF) for selection which widely occurred accurate for the selection in the last second second</u>	ed pathogens
		$\frac{100 \text{ which widely accepted case definitions include Ig}}{CSE^2}$	givi detection in
		<u>Lor</u>	

	Exclusion: • Failure to meet inclusion criteria described above
	• Lack of study detail e.g., number of people tested for each
	pathogen
	• Negative diagnostic test results in all patients
	• Study designed to evaluate diagnostic test and/or vaccine
	performance without presenting novel data on number or
	proportion of patients diagnosed with a study pathogen from a
	previously described population of febrile people.
	• Study described as a group of $\geq 2$ people principally classified
	based on a shared (100% frequency) aetiological diagnosis
	Review
202	<sup>1</sup> The following met study criteria for valid diagnostics for nathogen detection based
202	on single sera only. Lentospira spin agglutination titer of $> 800$ by microscopic
203	agglutination test in one serum specimen <sup>26</sup> detection of Hantavirus-specific IoM in a
205	serum sample <sup>27</sup> : detection of virus-specific IgM antibodies in serum with
205	confirmatory virus-specific neutralizing antibodies for Eastern equine encephalitis
207	virus (EEEV). West Nile virus (WNV). Western equine encephalitis virus (WEEV)
208	and Venezuelan equine encephalitis virus (VEEV) $^{28}$ ; identification of lyssavirus
209	specific antibody by indirect fluorescent antibody test or complete rabies virus
210	neutralization at 1:5 dilution in the serum of an unvaccinated person $^{29}$ : detection of
211	viral antigens in blood by enzyme-linked immunosorbent assay for Ebola <sup>30,31</sup> .
212	Marburg <sup>31,32</sup> , Lassa <sup>31,33</sup> , and Crimean-Congo haemorrhagic fever viruses <sup>31</sup> .
213	detection of Rift Valley fever antigens or IgM in blood by enzyme-linked
214	Immunosorbent assay <sup>34</sup> ; and
215	$^{2}$ IgM detection in CSF was considered a valid diagnostic for EEEV, Japanese
216	encephalitis virus (JEV), rabies virus, WEEV, WNV and VEEV <sup>28,29,35</sup> .
217	
218	Data extraction and bias assessment
219	Data extraction was conducted independently by one of two reviewers (JEBH and
220	MC). Article-level data were extracted on the location (country and WHO regional
221	classification (26)), <sup>36</sup> study period (start and end year of data collection), and
222	eligibility criteria used in the study. Data extracted on the study population included
223	whether the population was described inpatient or outpatient and urban or rural. Each
224	population reported was classified according to the clinical presentation as
225	undifferentiated febrile or differentiated febrile. Differentiated febrile populations
226	were further classified as: i) febrile neurologic; ii) febrile hemorrhagichaemorrhagic;
227	iii) febrile gastrointestinal; iv) febrile respiratory; v) specific febrile aetiology
228	suspected (27-29). Articles were also classified to record if the; vi) febrile co-morbid
229	group (i.e., malignancy, immunocompromise). <sup>37-39</sup> Data extracted on each population
230	included any demographic restriction of the study population, the age range of the
231	study participants, whether the population was described as inpatient or outpatient,
232	urban or rural, and whether data were collected during a reported disease outbreak or
233	not. To extract data on the zoonotic pathogens included in each study, every included
234	article was first classified to record if the study reported looking for diagnosedor
235	diagnosing one or more febrile individuals with eachany of the zoonotic pathogens
236	included in the study reference list (Tabletable 1), irrespective of the diagnostics used.
237	Second, forAdditional data were extracted when the article reported application of a
238	diagnostic approach that met study validity criteria. For each combination of article
239	and pathogen, details of the valid diagnostic methods used, <u>the</u> type and number of
240	samples tested, and the number of positive samples were recorded. (appendix table

- 241 S3, S4). In instances where more than one valid diagnostic method was used in the 242 same study for a given pathogen (e.g-,, culture-based and serologic case definitions), 243 data on the total number of individuals tested and positive for each pathogen were 244 aggregated. Data on the number of individuals tested and number positive were only 245 extracted for zoonotic pathogens diagnosed using methods that met study inclusion 246 eriteria.using valid methods were aggregated. Some articles contributed data on more 247 than one pathogen but no data on participant numbers were extracted for pathogens 248 not identified using diagnostic approaches that met study inclusion criteria.
- 249

250 The principal source of potential bias affecting the interpretation of the findings of 251 this study is the lack of standardization of the febrile populations included in different 252 studies. Criteria were defined to classify potential bias in study representativeness and prevalence estimate precision (appendix table S5).<sup>40-42</sup> The representativeness bias 253 254 criterion was designed to classify the representativeness of the study population, 255 relative to the general population where the study was conducted. This was based on 256 the description of the febrile population, the restriction (if any) of the study sample to specific clinical or demographic sub-populations and the reporting of disease 257 258 outbreaks at the time of data collection. Each population was classified as follows: i) 259 populations classified as undifferentiated febrile with no demographic restriction and no clinical aetiologies excluded were classified as low risk; ii) populations classified 260 261 as undifferentiated febrile with demographic restriction and/or reporting exclusion of 262 specific aetiologies or syndromes were classified as medium risk; iii) differentiated 263 febrile populations and those from studies reporting disease outbreaks at the time of 264 data collection were classified as high risk. The second, outcome-level, bias criterion 265 was designed to classify risk of bias in the estimated precision of the proportion of fevers attributed to each pathogen. Thresholds used for this criterion are the sample 266 267 sizes needed to estimate proportions of 50% and 10% with 95% confidence and 0.05 268 precision respectively, assuming an infinite population size. Each population was 269 classified as follows: i) proportion estimates based on a sample size of greater than or 270 equal to 385 were classified as low risk; ii) proportion estimates based on a sample 271 size of greater than 385 but less than 139 were classified as medium risk; iii) 272 proportion estimates based on a sample size of less than 139 were classified as high 273 risk. 274

Additional potential sources of bias included variation in the pathogens tested for, and variation in the diagnostic approaches applied. For included studies, data on the pathogens tested for (with any diagnostic approach) were summarized alongside
 pathogens for which diagnostic test criteria were met to qualitatively evaluate the biases introduced by only extracting data on pathogens diagnosed using methods meeting study inclusion criteria.

# 282 **Data analysis**

Extracted data on the zoonotic pathogens diagnosed using valid methods, number of
individuals tested for each pathogen, and number of individuals positive for each
pathogen were used to estimate the proportion of fevers attributable to each pathogen
for each unique pathogen and study combination. All analyses were conducted in R
(21) and plots were made using the package ggplot2 (30).<sup>21</sup> and plots were made
using the package ggplot2.<sup>43</sup>

289

290Role of the funding source

291 The funders of the study had no role in study design, data collection, data analysis,
 292 data interpretation, or writing of the report. The corresponding author had full access
 293 to all the data in the study and had final responsibility for the decision to submit for
 294 publication.
 295

296 The principal sources of potential bias identified in the course of this study are the 297 lack of standardization of the febrile populations included in different studies, variation in the pathogens tested for, and variation in the diagnostic approaches 298 299 applied. Data enabling the characterization of study populations (e.g. location, 300 outbreak or not, inpatient or outpatient, rural or urban etc.) were collected to enable 301 assessment of the influence of these factors on reported outcomes. Data on the pathogens looked for in included studies with any diagnostic approach were 302 303 summarized alongside pathogens for which diagnostic test criteria were met to 304 qualitatively evaluate the biases introduced by only extracting data on pathogens 305 diagnosed using methods meeting study inclusion criteria. Publication bias is likely to 306 strongly influence the outputs from this review, but it was not possible to 307 systematically evaluate this as publication of negative findings is rare, diagnostic 308 practices are highly variable and no robust methodology exists to estimate the 309 expected occurrence of the multiple pathogens included in this review. The review was designed to document only data on the reported presence of zoonotic causes of 310 311 febrile illness in populations that were principally defined by the presence of fever-312 The application of diagnostic criteria that are strictly comparable across pathogens is 313 not feasible. We applied strict diagnostic criteria, erring towards high specificity but 314 reduced sensitivity to minimize the influence of this source of bias. The implications 315 of these likely biases for the interpretation of study data are discussed. 316

# Results

317

318 Database searches yielded a total of 12,27716,332 and 8,06510,574 records through Embase and Medline, respectively, resulting in a total of  $\frac{12,92717,852}{12,92717,852}$  unique records 319 following de-duplication (Figure figure 1). English language abstracts were available 320 321 for 10,927A total of 4,531 (25.4%) records and 687 were excluded during pre-322 screening, 13,321 (74.6%) records were screened and 962 (7.2%) of these were 323 retained after title and abstract review. In total,  $\frac{506718}{74.6\%}$  articles were 324 excluded during full text review (Figure 1). Finally, 181 and 244 (25.4%) articles met 325 all study inclusion criteria and were included in this review (Figure 1 and Table 3). 326 (figure 1, appendix table S6). 327

328 Articles included in the review yielded data from  $\frac{46}{41-853}$  (48.2%) of the 110 329 malaria endemic countries included in searches. Seven (figure 2). The majority of 330 articles with a single country origin (n=235) reported data from multiple countries. 331 The distribution Africa (83 of the remaining 174235 articles by country and WHO 332 region is shown in Figures 2 and 3, and Table 4. Sixty-seven (37.0%) of the 181 333 studies included in the review, 35.3%) or South-East Asia (81 of 235 articles, 34.5%) 334 (appendix table S7, figure S1). One hundred and six (45.1%) of the 235 articles with a 335 single country origin were conducted in one of foursix dominant countries: India 336 (n=23), Thailand, (n=1731), United Republic of Tanzania (n=15), and 22), Thailand, 337 (n=20), Nepal (n=12). Bangladesh (n=11), and Nigeria (n=10). The data reported in 338 included studies the review were gathered from between 1994 to 2015 and 2017 339 inclusive.

340

341	The 181 The 244 articles included for data extraction reported looking for and
342	diagnosing 40 and 31 zoonoses, respectively, in these populations (figure 3). The
343	number of included zoonoses was reduced to 30 after the criteria for diagnostic testing
344	approach were applied. The 244 articles yielded data that met diagnostic test criteria
345	for a total of 2930 zoonoses. The 29 pathogens for which diagnostic data were
346	extracted that included $\frac{16}{17}$ bacterial pathogens ( $\frac{55 \cdot 2\%}{9}$ , $\frac{9}{56} \cdot 7\%$ ), nine viruses
347	(3130.0%), 3 three protozoa $(10.30%)$ , and 1 one helminth $(3.4%)$ . Nontyphoidal 3%).
348	Leptospira spp., nontyphoidal Salmonella serovars (NTS), Leptospira spp.) and
349	rickettsioses were the most frequently reported bacteria, while Japanese encephalitis
350	virus (JEV). Hantavirus, and West Nile virus (WNV) dominated among viruses
351	(Figures 4, 5 and 7). Before applying diagnostic test validity criteria, the 181 articles
352	reported looking for and diagnosing 36 and 35 zoonoses respectively in these
353	populations. This list of zoonoses was reduced to 29 after the criteria for diagnostic
354	testing approach were applied (Figure 4). The breakdown of articles contributing data
355	on different pathogens in different WHO regions is shown in Figure 5 reported
356	viruses (figures 3 4)
350	<u>viruses (figures 5, 4).</u>
358	The number of febrile individuals included in each study population ranged from 4 to
359	13.845 with a median of 300 (IOR: $120 - 812$ ). In total, 309 records of zoonotic
360	nathogens causing fever were extracted from the 244 articles. The proportion of
361	fevers attributed to each pathogen reported ranged from $<1.0\%$ to $95.0\%$ (figure 4)
362	The risk of bias classification in the precision of the proportion of fevers attributed to
363	each zoonosis was 136 (44.0%) of 309 low risk, 79 (25.6%) of 309 medium risk, and
364	94 (30.4%) of 309 high risk.
365	
366	Of the $\frac{181244}{181244}$ studies, $\frac{75}{41487}$ ( $\frac{35}{7}$ ) described the clinical setting as inpatient,
367	$\frac{28(15\cdot536(14\cdot8\%))}{28(15\cdot536(14\cdot8\%))}$ as outpatient, $\frac{22(12\cdot239(16\cdot0\%))}{28(12\cdot239(16\cdot0\%))}$ as mixed, and for 56
368	$(30.9\%)$ , $\overline{82}$ (33.6%) gave no clear classification of the clinical setting was given.
369	Twenty-five (13.8%). Thirty (12.3%) studies described the study area as urban, $43$
370	(23-859) (24.2%) as rural, $24$ (13-345 (18.4%) mixed or both, and for 89 (49-2%) 110
371	(45.1%) gave no clear classification of the study area was given. Of the 181 febrile
372	study. Eighteen $(7.4\%)$ studies included adult participants, 43 $(17.6\%)$ included
373	children, 153 (62.7%) included both adults and children and 30 (12.3%) gave no clear
374	classification of the ages included. Of the 244 studies, twelve (4.9%) described a
375	demographically restricted population, 55 ( $22.5\%$ ) reported some exclusions from the
376	population, and 32 (13.1%) mentioned exclusion of malaria-infected individuals
377	specifically (appendix table S6). Of the 244 studies, 73 (29.9%) reported looking for
378	more than one zoonosis, 43 ( $17.6\%$ ) diagnosing more than one zoonosis and 37
379	(15.2%) contributing data on more than one zoonosis. Of the 244 studies, $10 (4.1%)$
380	were described as outbreak investigations and 169 (69.3%) populations, 41 were
381	classified as undifferentiated febrile populations. Among the 75 differentiated
382	populations, 36 (48.0%) had specific febrile aetiologies suspected, 17 (22.7%) were
383	classified as differentiated, 95 (52-5 febrile neurological, eight (10-7%) as
384	undifferentiated, and 45 (24-9%) were mixed. Among the differentiated comorbid
385	populations 4 (9.8%) were, eight (10.7%) as febrile haemorrhagic, five (6.7%) as
386	febrile gastrointestinal <del>, 5 (12-2%) febrile haemorrhagic, 17 (41-5%) febrile</del>
387	neurological, 12 (29-3%) had specific febrile aetiologies suspected, and the remaining
388	$3 (7 \cdot and one (1 \cdot 3\%))$ were mixed populations (including patients with as febrile
389	respiratory symptoms) The associations between clinical presentation of febrile
200	populations and the 29subset of 25 pathogens identified in the different groups

391 differentiated populations are shown in Figure 6. All 6 pathogens identified in febrile 392 haemorrhagic populations were also detected in undifferentiated patient groups. 393 Eastern Equine Encephalitis virus (EEEV) and Nipah virus were only detected figure 394 5. The risk of bias classification in febrile neurological populations and 395 *Campylobacter* spp. was only detected in athe representativeness of febrile 396 gastrointestinal population (Figure 6). 397 398 In total, 9 (5-0%) of 181 studies included were described as outbreak investigations. 399 These 9 studies included data from 7 countries and 8 pathogens, describing outbreaks of Crimean-Congo Haemorrhagic Fever (CCHF) virus in Pakistan, JEV in Thailand, 400 401 Leptospira spp. in Bangladesh and Thailand, Nipah virus in India, spotted-fever group rickettsioses (SFGR) in Guatemala, Venezuelan Equine Encephalitis virus (VEEV) in 402 403 Peru, WNV in India (2 studies), and Yersinia pestis in Zambia. 404 405 The number of febrile individuals included in each study population ranged from 6 to 406 13,840 individuals, with a median of 291 populations was 121 (49.6%,) of 244 low risk, 45 (18.4%,) of 244 medium risk, and mean of 922. In total, 226 records of 407 408 zoonotic pathogens causing fever were extracted from the 181 articles. Figure 7 plots 409 the proportion of fevers attributed to each pathogen reported in the included studies. The proportion of fevers attributed of a given pathogen ranged from <1% to 95%, 410 411 median 5.5% and mean 13.5%.78 (32.0%,) of 244 high risk. 412 413 Discussion 414 The findings of this This systematic review reveal areveals diverse group of zoonoses 415 causing febrile illness within multiple malaria-endemic countries, often at high 416 prevalence. Zoonoses are documented as a cause of fever in all regions included in this study and many different zoonoses contribute to clinical burdens. However, 417 418 sparse and patchy reporting suggests that the <del>clinical burden</del>prevalence of zoonoses is 419 likely to be widely under-estimated. As knowledge Knowledge of probable infecting 420 pathogen is paramount crucial to inform the clinical management and prevention of 421 febrile illness, and there is a clear need for further investigation of the zoonotic causes 422 of febrile illness globally to generate data relevant to clinicians, epidemiologists, and 423 health policy makers. Our study highlights the clinical importance of several 424 pathogens, including some that occur across a wide range of areas and at high 425 prevalence. The globally. This study should generate greater awareness about of the 426 clinical importance of <del>zoonotic pathogens</del>zoonoses and provide a pragmatic starting 427 point for actions to better manage these diseases, for example through improved 428 diagnostic and clinical treatment algorithms, as well as. These findings demonstrate 429 the need for enhanced epidemiological understanding that is needed of multiple 430 zoonoses to inform disease prevention. 431 432 This review reveals substantial gaps in the evidence base, including a complete 433 absence of eligible studies from more than half of the majority, 64 (58-2%) of 110 434 countries, included in the review (Figure figure 2). There are multiple steps and biases in the processes from a patient seeking care with febrile illness to the publication of 435 436 an English language scientific paper on the occurrence and prevalence of a specific 437 zoonosis that could be included in this review. The underlying distribution and 438 relative clinical importance of individual pathogens will varyvaries, as well asdo 439 patient healthcare seeking behavior behaviour, clinical, and patient awareness of 440 different pathogens, diagnostic capacities, and probability of publication. It is

441 therefore not plausible to expect this review to yield data on each zoonosisall 442 zoonoses in all countries. However, considering the inclusion of 110 countries and 443 construction of searches for 4850 pathogens or pathogen groups, the identification of 444 just 181244 eligible studies underscores the profound overall shortage of robust quantitative data describing the role of any zoonoses as causes of fever in most 445 446 malaria-endemic countries. The geographic variation in the distribution of studies by country and region (Table 4) is likely to be strongly influenced by variation in 447 448 research and publication effort on the topic of non-malaria febrile illness and cannot 449 be interpreted as an accurate reflection of the underlying distribution of zoonotic pathogens or their clinical importance. The restriction of this review to English 450 451 language texts will also have reduced the probability that studies from French and 452 Spanish speaking countries were included and may partially account for some specific 453 gaps, such as the 27 countries in Africa and 15 in the Americas for which no eligible 454 studies were identified (Figure 2, Table 4). 455

456 We extracted data on 29 zoonotic causes of fever in malaria endemic countries. Among these, the majority (55-2%) were bacteria. The proportion of bacteria is 457 458 significantly greater than expected from the taxonomic distribution of all zoonotic 459 pathogens, which comprise 30.1% bacteria ( $\gamma^2 = 26.4$ , d.f. = 1, p<0.001, data from (31)) and also contrasts with the taxonomic distribution of emerging zoonoses, which 460 461 are dominated by viruses (13). While this study is unlikely to accurately reflect the 462 true taxonomic distribution of all fever causing zoonoses, this finding does reinforce 463 the clinical importance of endemic bacterial zoonoses and need for greater awareness 464 of these zoonoses, particularly given the availability of effective treatments that could substantially mitigate these disease burdens. 465 466

467 The geographic variation in the distribution of studies by country (figure 2) and region (appendix table S7, figure S2) is likely to be strongly influenced by variation in 468 469 research and publication effort. There is noticeable geographic segregation for some 470 zoonoses, with NTS and SFGR reported more frequently in Africa, and Leptospira 471 spp., *Orientia tsutsugamushi*, and typhus-group rickettsioses (TGR) reported more frequently in South-East Asia (Figure 5).and Western Pacific regions 472 473 (appendix figure S2). For viruses, Lassa virus was reported only in Africa and JEV 474 onlypredominantly in South-East Asia. These geographic differences in the reporting 475 patterns will only partially reflect the true. The distribution of studies cannot be interpreted as an accurate reflection of the underlying distribution andof zoonotic 476 477 pathogens, their prevalence of each pathogen. Diagnostic testing behavior is not 478 uniform and theor clinical importance. The pathogens that are looked for also 479 dependsdepend on factors such as the diagnostic capacity available, existing data, and local assessment of the likely causes of febrile illness in a specific location. The data 480 481 generated in this review cannot be used to formally quantify the under or over 482 representation of different pathogens in different countries but may help indicate 483 potential gaps in what is looked for. Once specificOnce pathogens are identified in 484 specific locations, any location there will likely be improved increased clinical and, 485 patient, and community awareness of those pathogens, as well as improved diagnostic capacity to detect them. In this way, dogma about the 'known' important causes of 486 487 febrile illness in specific locations can arise and contribute to the neglect of other 488 pathogens. The findings of this review can highlight pathogens and locations where 489 these dogmas should be questioned. The relative lack of studies reporting robust 490 diagnoses of illness caused by Leptospira spp. in Africa, for example, is likely to

- 491 reflect a lack of research effort and limited diagnostic capacity rather than a relative 492 absence of clinical leptospirosis in the region (14). Similarly, recent studies indicate 493 that the lack of studies investigating *O. tsutsugamushi* in Africa may be a reflection of 494 a presumed absence of scrub typhus in Africa and a consequent failure to test for 495 *Orientia*, rather than an absence of the pathogen itself, potentially allowing a 496 substantial incidence of scrub typhus to go unrecognized (32,33). The findings of this 497 review may help indicate potential gaps in what is looked for and can highlight 498 pathogens and locations where these dogmas should be questioned. 499
- 500 Figure 4 shows The majority of the comparison 30 zoonotic causes of fever 501 contributing data for this review were bacteria (56.7%). This proportion is greater 502 than expected from the taxonomic distribution of all zoonotic pathogens, which 503 comprise 30.1% bacteria<sup>44</sup> and also contrasts with the taxonomic distribution of emerging zoonoses, which are dominated by viruses.<sup>13</sup> This finding reinforces the 504 clinical importance of endemic bacterial zoonoses. The comparisons between the 505 506 number of articles that looked for, diagnosed, and contributed data for each of  $\frac{36}{36}$ zoonoses mentioned in the 181 articles analyzed. These three metrics and their 507 508 comparison provide several insights. First, revealing40 zoonoses reveals the range of 509 zoonotic pathogens investigated and providing an indication of indicates the relative investigative effort used for each pathogen. The (figure 3). However, the figures for 510 511 number of articles where a pathogen was looked for but not identified must be 512 interpreted with caution given the high probability of reporting bias and likelihood 513 that studies often omit mention of investigations for pathogens that are not subsequently found. Finally, forhow rarely negative results are reported. For several 514 515 pathogens, the number (and/or proportion) of articles that reported a zoonotic 516 diagnosis of a zoonoses but did not contribute further data for this are non trivial. 517 These articles report diagnosis of zoonoses but data were not extracted as analysis 518 (because the diagnostic approaches described dodid not meet study quality criteria-519 These results demonstrate) are substantial (figure 3). This demonstrates that for many, 520 predominantly bacterial pathogens, suboptimal and/or non-standardized diagnostic 521 tests or imprecise case definitions are in widespread use, highlighthighlighting the 522 challenges of accurately quantifying disease prevalence and comparing studies. 523
- 524 Unfortunately, several factors contribute to the ongoing Persistent challenges of in the 525 diagnosis of febrile patients. These include limited laboratory capacity, reliance on 526 demonstration of seroconversion for confirmed diagnosis of many pathogens (with 527 limited utility for management of acute cases), non sustainable, unsustainable costs 528 associated with more advanced diagnostics diagnostic technologies, and lack of simple 529 and affordable tests for the accurate and timely diagnosis of several zoonotic 530 pathogens. Linked to this In addition, the delays in patient presentation that are typical 531 in many resource limited settings, lead to low magnitude bacteremiabacteraemia at 532 presentation or patients during the immune phase of illness, 533 factors that furtherall limit the sensitivity of culture or PCR-based diagnostic 534 approaches when available. These challenges necessitate syndromic approaches to 535 patient management and broad-spectrum treatment. One specific issue relates to 536 tetracycline use. O. tsutsugamushi and rickettsioses, which this This study identified 537 rickettsioses and O. tsutsugamushi as common causes of fever,. These would both 538 benefit from treatment with tetracyclines, which are not currently included in the 539 Integrated Management of Adolescent and Adult Illness (IMAI) algorithms for septic shock and severe respiratory distress without shock (34).<sup>45</sup> In light of the extensive 540

- 541 contribution of tetracycline-responsive infections to fever in malaria-endemic
  542 countries, revisions to clinical guidelines may be warranted to suggest the empirical
  543 use of tetracyclines in addition to beta-lactams in those scenarios where the infection
  544 with tetracycline-responsive pathogens could notcannot be excluded.
- 545

554

546 The diversity of pathogens identified in this review add to the existing diagnostic 547 challenges facing clinicians, laboratories, and health systems. To some extent, findings from existing actiology studies can be extrapolated to inform practice in 548 549 other similar countries and settings. This approach may be most valuable for pathogens with well described and stable epidemiology. However, where pathogens 550 show wide spatial and temporal variability in incidence, more locally-specific 551 research efforts will be needed to assess the relative contribution of different zoonoses 552 553 to fever in different settings.

The most common patient population in this review comprised people with 555 556 undifferentiated febrile illness. Figure 6 illustrates the associations between different zoonoses and different clinical presentations. While some zoonotic pathogens were 557 558 associated with specific clinical presentations in addition to fever (e.g. neurological, 559 gastrointestinal, haemorrhagic clinical presentation) in some reports, almost all 560 pathogens were also detected in undifferentiated populations. This suggests that 561 zoonoses commonly linked with specific syndromes (e.g. Crimean Congo 562 haemorrhagic syndrome and JEV) still need to be considered in the differential 563 diagnosis of undifferentiated fever, even in the absence of other specific clinical 564 features. While documented associations between pathogens and specific clinical 565 presentations may assist clinicians in the differential diagnosis of febrile illnesses, the 566 impact of variation in when specific pathogens are tested for must also be remembered when interpreting these data. 567

The findings of this review show that one or more zoonotic causes of fever are likely 568 569 to present a threat to health in all of the countries included in this review. Only a 570 small proportion of the febrile populations included in the study were defined as 571 demographically restricted and most were not clinically differentiated. Even zoonoses 572 commonly linked with specific syndromes (e.g., Crimean-Congo haemorrhagic fever 573 virus and JEV) were diagnosed in undifferentiated populations and should thus be 574 considered in the differential diagnosis of undifferentiated febrile illness. Within 575 populations at risk, it is important that aetiologic studies are followed by 576 epidemiologic risk factor studies to determine whether certain sub-groups are at 577 higher risk for specific zoonotic diseases. Robust febrile illness surveillance systems 578 help inform local epidemiology and febrile illness management, and are also essential 579 for detection of disease outbreaks.<sup>46</sup>

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581 There are several important limitations to this study. We examined the contribution of 582 zoonotic pathogens to febrile illness only in malaria-endemic countries and excluded 583 articles not available in English from our analysis. Articles The restriction of this 584 review to English language texts will have reduced the probability that studies from 585 French and Spanish speaking countries were only included and may partially account 586 for some gaps, such as the 23 countries in the review if they included valid data on 587 diagnosis of one or more zoonoses. Africa and 15 in the Americas for which no 588 eligible studies were identified. Studies reporting the performance of tests resulting 589 in all negative test results were thus excluded from the analysis. This selection 590 strategy was motivated by the inevitable influence of publication bias and

591 complexities inchallenges of systematically quantifying the non-reporting of either 592 diagnostic test performance or the non-detection of specific pathogens. The findings 593 of this study thus include only populations where zoonoses were identified. 594 Biases in testing practices for different pathogens in different locations and with 595 different clinical febrile presentations will influence the pathogens looked for, 596 detected and reported. The application of diagnostic criteria that are strictly 597 comparable across pathogens is not feasible. in this study. The proportions of 598 febrile illnesses attributable to each zoonotic pathogen (Figure 7) thus apply 599 only for populations where the pathogen is known to be present. In this study, 600 strict diagnostic criteria were applied, preferentially including diagnostic approaches 601 with a high specificity, to minimize the influence of false positives within the analyses. The bias assessments for study representativeness and precision in the 602 603 estimates of proportion of fevers attributable to a given pathogen both reveal that the 604 majority of data points had medium or high risk of one or both types of bias. This 605 emphasizes the need for cautious and essentially non-quantitative interpretation of the 606 data extracted from these studies. Many studies with risk of precision bias due to 607 smaller sample size tended to report the highest prevalences of disease attribution to a given pathogen (figure 5); and, interestingly, these studies were often also classified 608 609 as high risk for representativeness bias. Figure 5 shows clear variation in risk of 610 representativeness bias across pathogens, potentially linked to variation in clinical presentation. For example, the majority of data points for Japanese encephalitis virus 611 and indeed all data points for Leishmania donovanii are classified as high risk of 612 613 representativeness bias. This review focused on studies reporting diagnostic 614 investigation of patient populations that were principally defined by fever (e.g. febrile populations some of whom had one or more zoonoses) and populations principally 615 616 defined by a common aetiological diagnosis were excluded (e.g., populations defined by presence or suspicion of one or more zoonosis, some of whom were febrile). As a 617 618 consequence, this systematic This review therefore had relatively an inherently low sensitivity for studies describing outbreaks, with just 9 included studies described 619 as documenting disease outbreaks (but meeting all study criteria and thus 620 retained). This focus explains, for example, the absence of studies describing the 621 622 2014-2016 Ebola West Africa outbreak-amongst others. Our findings are therefore 623 unlikely to capture the full extent. The design of this review did not allow explicit investigation of morbidity and mortality attributable to co-infections, either of 624 zoonoses with malaria or of multiple zoonoses that cause outbreaks. Co-infections 625 626 are likely to be an important factor underlying both the distribution and prevalence of some zoonotic pathogens, including for example nontyphoidal Salmonella serovars.<sup>4</sup> 627 628 Serological diagnosis of acute infection based on testing of both acute and 629 convalescent phase serum samples sera is central to the confirmed diagnosis of 630 multiple pathogens included in the study: as. As a consequence, individuals who die prior to the collection of convalescent samples are unlikely to contribute data (in the 631 632 absence of other valid confirmatory test options) and the proportion proportions of 633 fevers attributable to pathogens with high probability of acute fatality will be under-634 estimated and our findings may not fully capture the contribution of zoonoses in 635 lethal febrile illnesses. Furthermore, no validity criteria regarding the timing of 636 sample collection for acute and convalescent samples were imposed, leading potentially to false negative results (e.g., seroconversion not detected because of 637 638 premature convalescent sampling). For these reasons, our findings are unlikely to 639 capture the full extent of morbidity and mortality attributable to zoonoses. 640

641 The data compiled in this review demonstrate the need to consider multiple zoonoses 642 among the potential causes of febrile illnesses in malaria-endemic countries. The 643 diversity of pathogens identified and the geographic variation in their distribution 644 indicates that different Different zoonoses are likely to be important in different settings. Nonetheless, our Our study provides a starting point for improving awareness 645 of first the zoonoses that are known to contribute to febrile illness in different 646 647 malaria-endemic regions and second the fever-causing zoonoses with widespread 648 distribution that should also be considered in patient evaluation. The demonstration of 649 major data gaps should also encourage a more open-minded approach when 650 considering zoonoses as a potential cause of febrile illness. 651 652 Greater research effort is needed to overcome the current paucity of evidence. In 653 addition, untapped Continued efforts are needed to develop multi-pathogen 654 diagnostics, ideally with formats appropriate for point of care use. To avoid 655 perpetuation of self-fulfilling prophesies that can arise when only pathogens tested for 656 (and detected) are assumed to be present, the development and evaluation of such diagnostics should be informed by data describing the pathogens present in specific 657 658 settings and also the wider context. Untapped sources of information on the 659 distribution and occurrence of fever-causing zoonoses almost certainly also exist, particularly in the animal health sector, and. One Health efforts to share data and 660 661 knowledge between animal and human health sectors could help raise clinician 662 awareness of locally-relevant zoonoses, inform history taking, and guide diagnostic 663 and management decision making. Given the diversity Control of pathogens, 664 continued efforts disease in animal populations and prevention of transmission from 665 animals to humans are also neededlikely to be the most effective ways to reduce 666 human disease risk with many zoonoses, necessitating active engagement with 667 populations at risk to develop multi-pathogen diagnostics. This is also important to avoid perpetuation of self-fulfilling prophesies that can arise when only pathogens 668 tested for (and hence detected) are assumed to be present. While there sustainable 669 disease control interventions. There are substantial challenges to clinicians and 670 671 epidemiologists in revealing the true impacts of many zoonoses, the. The enormous 672 global burden of febrile illness and scope for improvements in the diagnosis and treatment of zoonotic pathogens necessitates necessitate efforts to overcome these 673 674 challenges and translate findings into important public health gains. 675

677	<b>Research in Context</b>

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## 678 **Evidence before this study**

Fever is one of the most common drivers of healthcare seeking globally and there is
growing awareness of the clinical importance of multiple causes of febrile illness.
Zoonoses are known to be important, but many zoonoses remain systematically
under-reported and there are large and persistent gaps in our understanding of the
human health impacts of zoonoses globally. We conducted a systematic review to
describe the occurrence and distribution of reported zoonotic causes of human febrile
illness in malaria endemic countries.

- 686 We reviewed studies identified in Medline and Embase databases that described
  687 testing of febrile populations for zoonotic pathogens, using a pre-defined list of
  688 eligible zoonotic pathogens and applying quality criteria for diagnostic tests.
  689 Literature searches were run using the OvidSP gateway and were limited to peer-
- 690 reviewed English language articles published in the period 2004 to 2016 inclusive, to
   691 span the period from the described peak of global malaria mortality in 2004 to
- 692 present. The searches were last executed on 26 August 2016.

## 693 **Added value of this study**

694 This review reveals the widespread occurrence of zoonotic causes of febrile illness,
 695 with a diverse range of pathogens identified. Data were extracted on the zoonotic
 696 pathogens detected and the number of individuals tested and positive for each
 697 pathogen using diagnostics that met study inclusion criteria. We identified 181

- 697 pathogen using diagnostics that met study inclusion criteria. We identified 181
  698 articles, from 46 countries and 7 WHO regions that described diagnosis of 29
  699 zoonoses in febrile people. The majority of zoonoses were bacterial. Our data identify
  700 substantial gaps in the current evidence base and highlight areas for future research
- 701 investment.

## 702 Implications of all the available evidence

The principal implications of the study findings are that zoonotic pathogens are
ubiquitous but sparsely reported and that many different zoonoses are likely to
contribute to substantial under-documented clinical burdens across the regions
included in this study. Given the crucial importance of knowledge of probable
infecting pathogen to inform clinical management of febrile illness there is a clear
need for further investigation of the zoonotic causes of febrile illness globally to
generate data relevant to clinicians, epidemiologists and health policy makers.

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# 713 **Contributors**

The author contributions are as follows. Study design: JEBH, MPRKJA, JAC, SC,
KJA-and JACMPR. Searches, screening and article review: JEBH, PH, DVH, GL,
MC, MES, KJA, JB, GAFL, DVH, PH, JAC, SC, and MPR. Data extraction: JEBH
and MC. Data analysis: JEBH. Manuscript writing: JEBH, MC, MES, KJA, JAC, SC,
KJA and MPR.

# 720 **Declaration of interests**

We declare no competing interest. JEBH reports grants from the Biotechnology and
Biological Sciences Research Council, UK, and collaboration with Arbor biosciences
outside the submitted work. JAC reports grants from United States National Institutes
of Health and Biotechnology and Biological Sciences Research Council, UK. MPR
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Diseases and contracted research with BioFire Defense, LLC, outside the submitted
work. Other authors declare they have no conflicts of interest.

The funders of the study had no role in study design, data collection, data analysis,
data interpretation, or writing of the report. The corresponding author had full access
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1410	

## 1411 **Tables**

1412

1413Table 1. Zoonoses included in the review, with details of species and serovars where

1414 appropriate.

Dethogen	Species subspecies and sevenars evaluated	Dethegen
Pathogen	<del>species, subspecies, and serovars excluded</del>	Pathogen
		type (13)
Alphaviruses	All species excluded with the exception of	<del>Virus</del>
	Eastern equine encephalitis virus (EEEV)	
	complex, Venezuelan equine encephalitis (VEEV)	
	complex, and Western equine encephalitis virus	
	(WFFV) complex	
Angelaguagen	(WEEV) complex	Destario
Anapiasma spp.		Dacteria
Aphthoviruses	All species excluded with the exception of Foot	<del>V Irus</del>
	and-mouth disease virus	
Avulaviruses	All species excluded with the exception of	<del>Virus</del>
	Newcastle disease virus	
Babesia spp.	-	Protozoa
Bacillus	_	Bacteria
antrhracis		Buetena
Rartonella spp	R hacilliformis and R quintana	Rectoria
Borralia app.	D. bacurgorinis and D. quintand	Bactoria
<del>borrena spp.</del>	D. ICCUITCINIS	Diciella
Bovine	-	Prion
spongiform		
encephalopathy		
<del>Brucella spp.</del>	-	<b>Bacteria</b>
Burkholderia	B. cepacia complex and B. psuedomallei	<b>Bacteria</b>
<del>SDD.</del>		
<i>Campylohaeter</i>	-	Bacteria
ennpytooueter		Ductoriu
Chlamudia opp	All spacing avaluded with the exception of $C$	Pactoria
<del>Cnumyuu spp.</del>	rait species excluded with the exception of e.	Dacteria
	psinaci	D
Coxiella burnetu		Bacteria
<i>Cryptosporidium</i>	<del>C. hominis</del>	Protozoa
<del>spp.</del>		
<i>Ebolavirus</i>	-	<del>Virus</del>
<i>Echinococcus</i>	-	Helminth
snn-		
Ehrlichia spp.	_	Bacteria
Enterovirusos	All species excluded with the exception of Swine	Virus
Enteroviruses	rin species exeruded with the exception of Swille	<del>-v 11 uS</del>
<b></b>	Vesicular alsease virus	<b>D</b>
Escherichia spp.	All species excluded with the exception of Shiga-	Bacteria
	toxin producing <i>E. coli</i>	
Flaviviruses	All species excluded with the exception of	<del>Virus</del>
	Japanese encephalitis virus (JEV), West Nile	
	virus (WNV), and Tick-borne encephalitis	
	viruses	
Francisalla	$\begin{array}{c} \text{All spacing evaluated with the evacation of } E \end{array}$	Bactoria
<del>- ranciseita spp.</del>	tularania	Dacteria
TT	tuarensis	* 7*
Hantavirus	-	<del>Virus</del>

Henipaviruses	-	<del>Virus</del>
Lassa virus	-	<del>Virus</del>
<i>Leishmania</i> spp.	L. donovani if detected in India	Protozoa
Leptospira spp.	-	Bacteria
Listeria spp.	-	Bacteria
Lyssavirus	All species excluded with the exception of rabies	<del>Virus</del>
Marburg virus	-	<del>Virus</del>
<i>Mycobacterium</i>	All species excluded with the exception of <i>M</i> .	Bacteria
Noinessimo	<i>Dovis</i> and <i>M. avis</i>	Vima
INAIFOVIFUS	An species excluded with the exception of	- <del>v irus</del>
Orthonormi	Crimean-Congo nemorrhagic jever virus	X7:
<del>Orthopox viruses</del>	All species excluded with the exception of	<del>V Irus</del>
	<del>Cowpox virus, Monkeypox virus, and Vaccinia</del>	
<i>Pasteurella</i> spp.	-	Bacteria
Phleboviruses	All species excluded with the exception of <i>Rift</i> Valley Fever virus	Virus
Rickettsia spp.	All species excluded with the exception of <i>R</i> .	Bacteria
<del>Salmonella spp.</del>	All species, subspecies, and serovars excluded with the exception of nontyphoidal Salmonella serovars	Bacteria
Schistosoma spp.	S. haematobium, S. intercalatum, and S. mekongi.	Helminth
Streptobacillus	-	Bacteria
<del>spp.</del>		D (
<del>Streptococcus</del> SDD:	All species excluded with the exception of 5. canis, S. suis, S. caui, and S. iniae	Bacteria
Taenia spp.	-	Helminth
Toxocara	-	Helminth
<del>Toxoplasma</del> sondii	-	Protozoa
Trichinella spp	-	Helminth
Trypanosoma	All species excluded with the exception of T	Protozoa
<del>Spp.</del>	brucei rhodesiense and T. cruzi	11000200
Varicelloviruses	All species excluded with the exception of	Virus
	Pseudorabies virus	
Vesiculoviruses	All species excluded with the exception of	Virus
	Vesicular stomatitis virus	
<del>Yersinia spp.</del>	All species excluded with the exception of <i>Y</i> .	Bacteria
	pesns, 1. enteroconnica and 1. pseudonaberculosis	

## 1417 | Table 2: Inclusion and exclusion criteria for full text review

<u>Outcome</u> <u>Criterion</u>						
	Inclusion	Enterior				
	menusion.	• Februe population ( $\geq 2$ people with a lever, defined as body				
		$\frac{\text{temperature} \geq 38.0^{\circ}\text{C}}{2}$				
		Diagnosis of one or more zoonotic pathogens from pre-				
		defined reference list of eligible aetiological agents (Table 1)				
		Diagnostic test criteria:				
		i) Culture of the pathogen from sample(s) collected from an				
		febrile person				
		ii) Direct detection of the pathogen (e.g. by PCR based				
		techniques) from sample(s) collected from a febrile person				
		iii) Secological diagnosis of acute infection based on testing of				
		hoth soute and convalescent phase serum samples and				
		demonstration of sereconversion				
		iv) Diagnosis of south infection based on detection of nother				
		iv) Diagnosis of acute infection based on detection of pathogen-				
		specific lgM or antigens in a single serum sample only for				
		selected pathogens, for which widely accepted case				
		definitions deemed pathogen specific IgM or antigens				
		detection sufficiently accurate (see footnote <sup>+</sup> )				
		v) IgM detection in CSF (e.g. for JEV and WNV)				
	Exclusion	Eailure to meet inclusion criteria described above				
	Exclusion.	<ul> <li>Lack of study detail a g, number of people tested for each</li> </ul>				
		• Lack of study detail e.g. number of people tested for each				
		patnogen				
		Negative diagnostic test results in all patients				
		<ul> <li>Study designed to evaluate diagnostic test and/or vaccine</li> </ul>				
		performance without presenting novel data on number or				
		proportion of patients diagnosed with a study pathogen from				
		a previously described population of febrile people.				
		• Study described as a group of > 2 people principally				
		classified based on a shared (100% frequency) actiological				
		diagnosis				
		Deview				
1/10	<sup>1</sup> The fellowin	- Review				
1410	200 hy miana	is were considered valid tests: <i>Leptospira</i> spp. aggridination ther of $\leq$				
1419	<del>800 by micro</del>	scopic aggrutination test in one serum specimen (55); detection of				
1420	Hantavirus sj	pecific IgM in a serum sample (36); detection of virus specific IgM				
1421	antibodies in	serum with confirmatory virus specific neutralizing antibodies for				
1422	Eastern equit	ie encephalitis virus (EEEV), West Nile virus (WNV), Western equine				
1423	encephalitis v	virus (WEEV), and Venezuelan equine encephalitis virus (VEEV) (37);				
1424	identification	of lyssavirus specific antibody by indirect fluorescent antibody test or				
1425	complete rab	ies virus neutralization at 1:5 dilution in the serum of an unvaccinated				
1426	<del>person (38); (</del>	detection of viral antigens in blood by enzyme-linked immunosorbent				
1427	assay for Ebc	ala (39,40), Marburg (40,41), Lassa (40,42), and Crimean-Congo				
1428	hemorrhagic-	fever viruses (40); detection of Rift Valley fever antigens or IgM in				
1429	blood by enzy	yme-linked Immunosorbent assay (43); and IgM detection in CSF for				
1430	EEEV, Japar	uese encephalitis virus (JEV), rabies virus, WEEV, WNV and VEEV				
1431	(37,38.44).					
1432	<u></u>					
1433						
1.00						

Table 3: Characteristics and summary of extracted data for the 181 articles included in the review.

First author, year of		<b>Study</b>		Number of	Number of
publication and reference	<b>Country</b>	Period	Pathogen	<b>Individuals Tested</b>	<b>Individuals Positive</b>
		<del>2009-</del>			
Aarsland et al (2012)(45)	<b>Ethiopia</b>	<del>2010</del>	<del>Borrelia spp.</del>	<del>102</del>	2
		<del>2009-</del>			
Aarsland et al (2012)(45)	<b>Ethiopia</b>	<del>2010</del>	Rickettsia (SFGR)	<del>102</del>	4
Adurthi et al (2008)(46)	India	-	<del>Toxoplasma gondii</del>	<del>162</del>	<del>21</del>
		<del>1999-</del>			
Afifi et al (2005)(47)	Egypt	<del>2003</del>	<i>Brucella</i> spp.	<del>9883</del>	<del>275</del>
			Eastern equine		
Aguilar et al (2007)(48)	Peru	-	encephalitis virus	<del>153</del>	2
		2004-	<i>Salmonella</i> (non-Typhi)		
Akinyemi et al (2007)(49)	Nigeria	<del>2005</del>	serovars	<del>235</del>	<del>16</del>
		<del>2010-</del>	<i>Salmonella</i> (non-Typhi)		
Akinyemi et al (2015)(50)	Nigeria	<del>2011</del>	serovars	<del>135</del>	2
		<del>2008-</del>	Crimean-Congo		
Alam et al (2013)(51)	Pakistan	<del>2008</del>	haemorrhagic fever virus	44	<del>16</del>
Albuquerque Filho et al		<del>2009</del> -			
(2011)(52)	Brazil	<del>2009</del>	<i>Leptospira</i> spp.	<del>97</del>	<del>56</del>
			<del>Salmonella (non-Typhi)</del>		
Al-Emran et al (2016)(53)	No Single Country	-	serovars	<del>10636</del>	77
		<del>2011</del> -	<i>Salmonella</i> (non-Typhi)		
Al-Emran et al (2016)(54)	No Single Country	<del>2013</del>	serovars	<del>8161</del>	28
		2001-	Crimean-Congo		
Ali et al (2007)(55)	Pakistan	2001	haemorrhagic fever virus	10	3
Andualem et al (2014)(56)	<b>Ethiopia</b>	<del>2010-</del>	<del>Salmonella (non-Typhi)</del>	<del>270</del>	7

First author, year of		<b>Study</b>		Number of	Number of
publication and reference	<b>Country</b>	Period	<b>Pathogen</b>	<b>Individuals Tested</b>	<b>Individuals Positive</b>
		<del>2011</del>	serovars		
		2007-	Japanese encephalitis		
Anga et al (2010)(57)	Papua New Guinea	<del>2008</del>	<del>virus</del>	<del>129</del>	2
		<del>2008-</del>			
Angelakis et al (2014)(58)	No Single Country	<del>2012</del>	Coxiella burnetii	<del>1888</del>	7
		<del>2006 -</del>			
Armien et al (2013)(59)	Panama	<del>2010</del>	Hantavirus	<del>150</del>	<del>117</del>
		<del>2010-</del>			
Barua et al (2016)(60)	India	<del>2012</del>	<del>Brucella spp.</del>	<del>102</del>	<del>18</del>
		<del>2009-</del>			
Bengre et al (2012)(61)	India	<del>2011</del>	Pasteurella spp.	<del>50</del>	1
	United Republic of	<del>2007-</del>			
Biggs et al (2011)(62)	<del>Tanzania</del>	<del>2008</del>	<i>Leptospira</i> spp.	<del>831</del>	<del>70</del>
	United Republic of	<del>2006-</del>	<del>Salmonella (non-Typhi)</del>		
Biggs et al (2014)(63)	<del>Tanzania</del>	<del>2008</del>	serovars	<del>4106</del>	<del>163</del>
	Lao People's	<del>2001-</del>			
Blacksell et al (2006)(64)	Democratic Republic	<del>2003</del>	<i>Leptospira</i> spp.	<del>186</del>	5
		<del>2002-</del>			
Blacksell et al (2007)(65)	Nepal	<del>2004</del>	Orientia tsutsugamushi	<del>103</del>	5
		<del>2002-</del>			
Blacksell et al (2007)(65)	Nepal	<del>2004</del>	Rickettsia (TGR)	<del>103</del>	9
	Lao People's	<del>2003-</del>			
Blacksell et al (2010)(66)	Democratic Republic	<del>2007</del>	Orientia tsutsugamushi	<del>1030</del>	<del>101</del>
	Lao People's	<del>2003-</del>			
Blacksell et al (2010)(66)	Democratic Republic	2007	Rickettsia (TGR)	<del>1030</del>	<del>183</del>
		<del>2007-</del>			
Blacksell et al (2016)(67)	<del>Thailand</del>	<del>2008</del>	<del>Orientia tsutsugamushi</del>	<del>135</del>	<del>22</del>

First author, year of		<b>Study</b>		Number of	Number of
publication and reference	<b>Country</b>	Period	Pathogen	<b>Individuals Tested</b>	<b>Individuals Positive</b>
		<del>2006-</del>			
Blacksell et al (2016)(68)	<b>Thailand</b>	<del>2007</del>	<del>Orientia tsutsugamushi</del>	<del>152</del>	<del>37</del>
		<del>2012-</del>			
Boisen et al (2015)(69)	Sierra Leone	<del>2012</del>	<del>Lassa virus</del>	<del>53</del>	<del>29</del>
		<del>2012 -</del>			
Boisen et al (2015)(69)	Sierra Leone	<del>2012</del>	West Nile virus	<del>23</del>	4
		<del>2001-</del>			
Boonsilp et al (2011)(70)	<b>Thailand</b>	<del>2002</del>	<i>Leptospira</i> spp.	<del>418</del>	<del>120</del>
		<del>2000-</del>			
Bottieau et al (2011)(71)	No Single Country	<del>2006</del>	Campylobacter spp.	<del>512</del>	<del>47</del>
		<del>2000-</del>	<del>Salmonella (non-Typhi)</del>		
Brooks et al (2005)(72)	Bangladesh	<del>2001</del>	serovars	<del>888</del>	2
		<del>2007-</del>			
Castillo Ore et al (2012)(73)	Peru	<del>2010</del>	Hantavirus	<del>5174</del>	9
		<del>2001-</del>			
Chadha et al (2006)(74)	India	<del>2001</del>	Nipah virus	<del>6</del>	<del>5</del>
		<del>2002-</del>			
Chandy et al (2005)(75)	India	<del>2003</del>	Hantavirus	<del>152</del>	23
		<del>2005-</del>			
Chandy et al (2009)(76)	India	<del>2007</del>	Hantavirus	<del>347</del>	<del>86</del>
	Lao People's	<del>2006-</del>			
Chansamouth et al (2016)(77)	Democratic Republic	<del>2010</del>	<i>Leptospira</i> spp.	<del>158</del>	4
	Lao People's	<del>2006-</del>			
Chansamouth et al (2016)(77)	Democratic Republic	2010	<del>Orientia tsutsugamushi</del>	217	<del>16</del>
	Lao People's	<del>2006-</del>			
Chansamouth et al (2016)(77)	Democratic Republic	2010	Rickettsia (TGR)	217	<del>15</del>
Chatterjee et al (2004)(78)	India	<del>1996-</del>	Japanese encephalitis	72	24

First author, year of		Study		Number of	Number of
publication and reference	<b>Country</b>	Period	<b>Pathogen</b>	<b>Individuals Tested</b>	<b>Individuals Positive</b>
		<del>1999</del>	<del>virus</del>		
		2011-			
Chen et al (2014)(79)	<b>China</b>	<del>2012</del>	Hantavirus	<del>85</del>	<del>33</del>
		<del>2011-</del>			
Chen et al (2014)(79)	<del>China</del>	<del>2012</del>	Orientia tsutsugamushi	<del>85</del>	4
		<del>2011-</del>			
Chen et al (2014)(79)	<del>China</del>	2012	Rickettsia (TGR)	<del>85</del>	1
		<del>2009-</del>	Japanese encephalitis		
Chheng et al (2013)(80)	<b>Cambodia</b>	2010	<del>virus</del>	<del>107</del>	<del>6</del>
		<del>2009-</del>			
Chheng et al (2013)(80)	<b>Cambodia</b>	<del>2010</del>	<i>Leptospira</i> spp.	<del>1179</del>	<del>17</del>
		<del>2009-</del>			
Chheng et al (2013)(80)	Cambodia	2010	Orientia tsutsugamushi	<del>1179</del>	<del>17</del>
		<del>2009-</del>			
Chheng et al (2013)(80)	<b>Cambodia</b>	<del>2010</del>	Rickettsia (TGR)	<del>1179</del>	5
		<del>2009</del> -	<del>Salmonella (non-Typhi)</del>		
Chheng et al (2013)(80)	Cambodia	<del>2010</del>	serovars	<del>1180</del>	1
Chikeka et al (2016)(81)	Nicaragua	-	<del>Ehrlichia spp.</del>	<del>748</del>	4
	Iran (Islamic Republic	2008-			
Chinikar et al (2012)(82)	<del>of)</del>	<del>2009</del>	West Nile virus	<del>249</del>	3
		2011-			
Chiriboga et al (2015)(83)	Ecuador	<del>2012</del>	<i>Leptospira</i> spp.	<del>210</del>	<del>132</del>
		2007-			
Chrispal et al (2010)(84)	India	<del>2008</del>	Hantavirus	<del>398</del>	1
		2003-			
Ciftdogan et al (2011)(85)	<del>Turkey</del>	<del>2008</del>	Brucella spp.	<del>92</del>	3

First author, year of		<b>Study</b>		Number of	Number of
publication and reference	<b>Country</b>	Period	<b>Pathogen</b>	<b>Individuals Tested</b>	<b>Individuals Positive</b>
		2002-			
Cohen et al (2007)(86)	<b>Thailand</b>	<del>2003</del>	<i>Leptospira</i> spp.	<del>704</del>	<del>67</del>
	United Republic of	<del>2007-</del>	Salmonella (non-Typhi)		
Crump et al (2011)(5)	<del>Tanzania</del>	<del>2008</del>	serovars	<del>224</del>	2
	United Republic of	<del>2007-</del>	Salmonella (non-Typhi)		
Crump et al (2011)(87)	<del>Tanzania</del>	<del>2008</del>	serovars	<del>139</del>	1
	United Republic of	2007-			
Crump et al (2013)(12)	<del>Tanzania</del>	<del>2008</del>	<i>Brucella</i> spp.	<del>453</del>	<del>16</del>
	United Republic of	2007-			
Crump et al (2013)(12)	Tanzania	<del>2008</del>	Coxiella burnetii	<del>482</del>	<del>24</del>
	United Republic of	<del>2007-</del>			
Crump et al (2013)(12)	<del>Tanzania</del>	<del>2008</del>	<i>Leptospira</i> spp.	<del>453</del>	<del>40</del>
	United Republic of	<del>2007-</del>			
Crump et al (2013)(12)	<del>Tanzania</del>	<del>2008</del>	Rickettsia (SFGR)	<del>450</del>	<del>36</del>
	United Republic of	<del>2007-</del>			
Crump et al (2013)(12)	<del>Tanzania</del>	<del>2008</del>	Rickettsia (TGR)	<del>450</del>	2
	Bolivia (Plurinational	<del>2008-</del>			
Cruz et al (2012)(88)	State of)	<del>2009</del>	Hantavirus	<del>372</del>	<del>9</del>
	United Republic of	<del>2008-</del>	<i>Salmonella</i> (non-Typhi)		
D'Acremont et al (2014)(28)	<del>Tanzania</del>	<del>2008</del>	serovars	<del>424</del>	4
		<del>2007-</del>			
Dassanayake et al (2009)(89)	<del>Sri Lanka</del>	<del>2008</del>	<i>Leptospira</i> spp.	<del>123</del>	<del>62</del>
			Salmonella (non-Typhi)		
Davies et al (2016)(90)	Nigeria	-	serovars	<del>129</del>	<del>15</del>
		2010-			
Degarege et al (2012)(91)	Ethiopia	<del>2011</del>	Schistosoma mansoni	<del>702</del>	<del>82</del>
Dong et al (2014)(92)	China	<del>2009-</del>	<del>Salmonella (non-Typhi)</del>	<del>2529</del>	3

First author, year of		Study		Number of	Number of
publication and reference	<b>Country</b>	<b>Period</b>	Pathogen	<b>Individuals Tested</b>	<b>Individuals Positive</b>
		<del>2011</del>	serovars		
		2009-			
dos Santos et al (2012)(93)	Brazil	<del>2010</del>	Rickettsia (SFGR)	<del>110</del>	<del>36</del>
		2005-			
Ehichioya et al (2012)(94)	Nigeria	<del>2008</del>	<del>Lassa virus</del>	4 <del>51</del>	2
		<del>2007-</del>	<del>Salmonella (non-Typhi)</del>		
Eibach et al (2016)(95)	<del>Ghana</del>	<del>2012</del>	serovars	<del>7172</del>	<del>215</del>
		<del>1999 -</del>			
El-Mahallawy et al (2005)(96)	<del>Egypt</del>	<del>1999</del>	<i>Listeria</i> spp.	<del>1135</del>	1
		<del>1999-</del>			
El-Mahallawy et al (2005)(96)	<del>Egypt</del>	<del>1999</del>	Pasteurella spp.	<del>1135</del>	<del>6</del>
		<del>2008-</del>			
Elhelw et al (2014)(97)	Egypt	<del>2009</del>	Borrelia spp.	<del>15</del>	4
		<del>1999-</del>	Japanese encephalitis		
Ellis et al (2006)(98)	<del>Thailand</del>	<del>2002</del>	<del>virus</del>	<del>530</del>	1
		<del>1999 -</del>			
Ellis et al (2006)(98)	<del>Thailand</del>	<del>2002</del>	<i>Leptospira</i> spp.	<del>613</del>	<del>107</del>
		<del>2008-</del>			
Elyan et al (2014)(99)	Afghanistan	<del>2010</del>	West Nile virus	<del>277</del>	<del>24</del>
		<del>2007-</del>			
Eremeeva et al (2013)(100)	<del>Guatemala</del>	<del>2007</del>	Rickettsia (SFGR)	<del>17</del>	4
		<del>1999-</del>			
Fadeel et al (2006)(101)	<del>Egypt</del>	<del>2003</del>	Brucella spp.	<del>1177</del>	<del>202</del>
		<del>2000-</del>	Venezuelan equine		
Forshey et al (2010)(102)	No Single Country	<del>2007</del>	encephalitis virus	<del>13259</del>	<del>250</del>
		<del>2012-</del>			
Fotso Fotso et al (2015)(103)	Algeria	<del>2012</del>	<del>Borrelia spp.</del>	<del>257</del>	4

First author, year of		Study		Number of	Number of
publication and reference	<b>Country</b>	Period	Pathogen	<b>Individuals Tested</b>	<b>Individuals Positive</b>
		<del>2005</del> -			
Gasem et al (2009)(104)	Indonesia	<del>2006</del>	<i>Leptospira</i> spp.	<del>137</del>	4
		<del>2005-</del>			
Gasem et al (2009)(104)	Indonesia	<del>2006</del>	Rickettsia (TGR)	<del>137</del>	4
			<i>Salmonella</i> (non-Typhi)		
Gordon et al (2010)(105)	<del>Malawi</del>	_	serovars	<del>355</del>	<del>70</del>
Hailu et al (2006)(106)	<b>Ethiopia</b>	-	<del>Leishmania donovani</del>	<del>103</del>	<del>49</del>
		2008-			
Hamilton et al (2011)(107)	Iraq	<del>2008</del>	Coxiella burnetii	<del>18</del>	8
		<del>2007-</del>			
Hem et al (2016)(108)	<b>Cambodia</b>	<del>2009</del>	<i>Leptospira</i> spp.	<del>2044</del>	<del>17</del>
		<del>2005-</del>			
Hidalgo et al (2008)(109)	Colombia	<del>2005</del>	Rickettsia (TGR)	<del>120</del>	14
		<del>2010-</del>			
Hidalgo et al (2013)(110)	<b>Colombia</b>	<del>2011</del>	Rickettsia (SFGR)	<del>26</del>	7
		<del>2010-</del>			
Hidalgo et al (2013)(110)	<b>Colombia</b>	<del>2011</del>	Rickettsia (TGR)	<del>26</del>	2
		<del>1999-</del>			
Ismail et al (2006)(111)	<del>Egypt</del>	<del>2003</del>	<i>Leptospira</i> spp.	<del>886</del>	<del>141</del>
		<del>2002-</del>			
Jennings et al (2007)(112)	Egypt	<del>2003</del>	Brucella spp.	<del>4490</del>	<del>115</del>
		<del>1998-</del>			
Joshi et al (2006)(113)	Nepal	<del>2002</del>	Leishmania donovani	<del>996</del>	<del>284</del>
		<del>2007-</del>	Japanese encephalitis		
Joshi et al (2013)(114)	India	<del>2007</del>	<del>virus</del>	<del>152</del>	4
		<del>2009-</del>			
Jung et al (2015)(115)	Republic of Korea	<del>2013</del>	<del>Orientia tsutsugamushi</del>	<del>382</del>	3

First author, year of		Study		Number of	Number of
publication and reference	<b>Country</b>	Period	<b>Pathogen</b>	<b>Individuals Tested</b>	<b>Individuals Positive</b>
		<del>2012-</del>	Japanese encephalitis		
Kakoti et al (2013)(116)	India	<del>2012</del>	<del>virus</del>	<del>223</del>	<del>49</del>
		<del>2009-</del>			
Kamal et al (2013)(117)	Saudi Arabia	<del>2011</del>	Brucella spp.	<del>101</del>	<del>50</del>
		2001-			
Kendall et al (2010)(118)	Bangladesh	<del>2001</del>	<i>Leptospira</i> spp.	<del>78</del>	7
		2012-	Salmonella (non-Typhi)		
Kibuuka et al (2015)(119)	<del>Uganda</del>	<del>2012</del>	serovars	<del>250</del>	<del>11</del>
		<del>2001</del>			
Klempa et al (2010)(120)	Guinea	<del>2005</del>	Hantavirus	717	8
		<del>2013-</del>	Venezuelan equine		
Kocher et al (2016)(121)	Peru	<del>2014</del>	encephalitis virus	<del>2054</del>	<del>22</del>
		<del>2008-</del>			
Koizumi et al (2009)(122)	<del>Sri Lanka</del>	<del>2008</del>	<i>Leptospira</i> spp.	<del>107</del>	3
		<del>2002-</del>			
Kosoy et al (2010)(123)	<b>Thailand</b>	<del>2003</del>	Bartonella spp.	<del>261</del>	<del>14</del>
		<del>2008-</del>	Crimean-Congo		
Kuchuloria et al (2014)(124)	Georgia	<del>2011</del>	haemorrhagic fever virus	<del>537</del>	3
		<del>2008-</del>			
Kuchuloria et al (2014)(124)	Georgia	<del>2011</del>	Hantavirus	<del>537</del>	2
		<del>2008-</del>	Crimean-Congo		
Kuchuloria et al (2016)(125)	Georgia	<del>2011</del>	haemorrhagic fever virus	<del>537</del>	3
	-	<del>2008-</del>	_		
Kuchuloria et al (2016)(125)	Georgia	<del>2011</del>	Hantavirus	<del>537</del>	2
		<del>2003-</del>			
Kuloglu et al (2012)(126)	<del>Turkey</del>	<del>2009</del>	Rickettsia (SFGR)	<del>126</del>	<del>97</del>
Kumar et al (2014)(127)	India	<del>2011-</del>	<del>Orientia tsutsugamushi</del>	<del>199</del>	<del>48</del>

First author, year of		<b>Study</b>		Number of	Number of
publication and reference	<b>Country</b>	Period	<b>Pathogen</b>	<b>Individuals Tested</b>	<b>Individuals Positive</b>
		<del>2012</del>			
		2009			
Kumar et al (2014)(128)	India	<del>2010</del>	<del>West Nile virus</del>	<del>105</del>	27
			Japanese encephalitis		
Kumar et al (2015)(129)	India	-	virus	<del>108</del>	<del>5</del> 4
		2001-			
LaRocque et al (2005)(130)	Bangladesh	<del>2001</del>	<i>Leptospira</i> spp.	<del>359</del>	<del>63</del>
	United Republic of	<del>2008-</del>	Salmonella (non-Typhi)		
Ley et al (2009)(131)	<del>Tanzania</del>	<del>2009</del>	serovars	<del>1680</del>	<del>49</del>
		<del>1994 -</del>			
Libraty et al (2007)(132)	Thailand	<del>1999</del>	<i>Leptospira</i> spp.	<del>812</del>	<del>14</del>
		<del>2002</del> -			
Liu et al (2007)(133)	<del>China</del>	<del>2004</del>	Hantavirus	<del>130</del>	<del>49</del>
		<del>2002</del> -			
Liu et al (2007)(133)	<del>China</del>	<del>2004</del>	Orientia tsutsugamushi	<del>130</del>	<del>46</del>
		<del>2014 -</del>			
Liu et al (2016)(134)	<del>China</del>	<del>2014</del>	Rickettsia (SFGR)	<del>733</del>	<del>56</del>
	United Republic of	<del>2013-</del>	<del>Salmonella (non-Typhi)</del>		
Mahende et al (2014)(135)	<del>Tanzania</del>	<del>2013</del>	serovars	<del>808</del>	2
		<del>2008-</del>			
Maina et al (2012)(136)	<del>Kenya</del>	<del>2010</del>	Rickettsia (SFGR)	<del>699</del>	<del>50</del>
		<del>2001-</del>			
Manock et al (2009)(137)	Ecuador	<del>2004</del>	Brucella spp.	<del>275</del>	4
		<del>2001-</del>			
Manock et al (2009)(137)	Ecuador	<del>2004</del>	Coxiella burnetii	<del>33</del>	<del>15</del>
		<del>2001-</del>			
Manock et al (2009)(137)	Ecuador	<del>2004</del>	Rickettsia (SFGR)	<del>214</del>	<del>6</del>

First author, year of		<b>Study</b>		Number of	Number of
publication and reference	<b>Country</b>	Period	Pathogen	Individuals Tested	<b>Individuals Positive</b>
		2001-			
Manock et al (2009)(137)	Ecuador	<del>2004</del>	Rickettsia (TGR)	<del>255</del>	8
		<del>2001-</del>	Venezuelan equine		
Manock et al (2009)(137)	Ecuador	<del>2004</del>	encephalitis virus	<del>229</del>	2
		<del>2003 -</del>			
Matthias et al (2008)(138)	Peru	2006	<i>Leptospira</i> spp.	<del>881</del>	4 <del>5</del>
		<del>2012-</del>			
Maude et al (2015)(139)	Bangladesh	<del>2012</del>	<del>Orientia tsutsugamushi</del>	<del>300</del>	1
		<del>2012-</del>			
Maude et al (2015)(139)	Bangladesh	<del>2012</del>	Rickettsia (TGR)	<del>300</del>	2
	Lao People's	<del>2008-</del>			
Mayxay et al (2013)(140)	<b>Democratic Republic</b>	<del>2010</del>	<i>Leptospira</i> spp.	<del>1932</del>	<del>137</del>
	Lao People's	<del>2008-</del>			
Mayxay et al (2013)(140)	Democratic Republic	<del>2010</del>	<del>Orientia tsutsugamushi</del>	<del>1871</del>	<del>170</del>
	Lao People's	<del>2008-</del>			
Mayxay et al (2013)(140)	Democratic Republic	<del>2010</del>	Rickettsia (SFGR)	<del>1849</del>	2
	Lao People's	<del>2008-</del>			
Mayxay et al (2013)(140)	Democratic Republic	<del>2010</del>	Rickettsia (TGR)	<del>1849</del>	<del>12</del>
		<del>2006-</del>			
Mazyad et al (2007)(141)	<del>Egypt</del>	<del>2006</del>	Coxiella burnetii	<del>150</del>	5
		<del>2004-</del>			
McGready et al (2010)(142)	<del>Thailand</del>	<del>2006</del>	<i>Leptospira</i> spp.	203	5
		<del>2004-</del>			
McGready et al (2010)(142)	Thailand	2006	<del>Orientia tsutsugamushi</del>	<del>203</del>	44
		<del>2004-</del>			
McGready et al (2010)(142)	Thailand	<del>2006</del>	Rickettsia (TGR)	<del>203</del>	-14
Mediannikov et al (2010)(143)	Senegal	<del>2008-</del>	Rickettsia (SFGR)	<del>204</del>	8

First author, year of		Study		Number of	Number of
publication and reference	<b>Country</b>	Period	<b>Pathogen</b>	<b>Individuals Tested</b>	<b>Individuals Positive</b>
		<del>2009</del>			
		2010-			
Mediannikov et al (2013)(144)	No Single Country	2012	Rickettsia (SFGR)	<del>2612</del>	<del>321</del>
		2010-			
Mediannikov et al (2014)(145)	Senegal	<del>2011</del>	<del>Borrelia spp.</del>	<del>1566</del>	<del>115</del>
	United Republic of		Salmonella (non-Typhi)		
Meremo et al (2012)(146)	<del>Tanzania</del>	-	serovars	<del>346</del>	<del>12</del>
	Iran (Islamic Republic	<del>2011-</del>			
Metanat et al (2014)(147)	<del>of)</del>	<del>2011</del>	Coxiella burnetii	<del>105</del>	<del>23</del>
		<del>2012-</del>	<del>Salmonella (non-Typhi)</del>		
Moon et al (2013)(148)	Mozambique	<del>2012</del>	serovars	<del>258</del>	<del>28</del>
		<del>2005-</del>	Venezuelan equine		
Morrison et al (2008)(149)	Peru	2006	encephalitis virus	<del>1136</del>	<del>3</del> 4
		<del>2011-</del>			
Mourembou et al (2015)(150)	Gabon	<del>2012</del>	Rickettsia (SFGR)	<del>793</del>	8
		<del>2013-</del>			
Mourembou et al (2015)(151)	Gabon	<del>2014</del>	Rickettsia (SFGR)	<del>410</del>	<del>42</del>
			<del>Salmonella (non-Typhi)</del>		
Mourembou et al (2016)(152)	<del>Gabon</del>	-	<del>serovars</del>	<del>410</del>	3
	United Republic of	<del>2008-</del>	<del>Salmonella (non-Typhi)</del>		
Mtove et al (2010)(153)	<del>Tanzania</del>	<del>2009</del>	<del>serovars</del>	<del>1502</del>	<del>45</del>
	United Republic of	<del>2006-</del>	<del>Salmonella (non-Typhi)</del>		
Mtove et al (2011)(154)	<del>Tanzania</del>	<del>2010</del>	<del>serovars</del>	<del>6836</del>	<del>232</del>
	United Republic of	<del>2009-</del>	<del>Salmonella (non-Typhi)</del>		
Mtove et al (2011)(155)	<del>Tanzania</del>	<del>2010</del>	serovars	<del>965</del>	1
		<del>2008-</del>			
Mueller et al (2014)(156)	Cambodia	<del>2010</del>	<i>Leptospira</i> spp.	<del>1193</del>	<del>112</del>

First author, year of		<b>Study</b>		Number of	Number of
publication and reference	<b>Country</b>	<b>Period</b>	Pathogen	Individuals Tested	<b>Individuals Positive</b>
		<del>2008  </del>			
Mueller et al (2014)(156)	<b>Cambodia</b>	<del>2010</del>	Orientia tsutsugamushi	<del>1193</del>	<del>47</del>
		<del>2008-</del>			
Mueller et al (2014)(156)	<b>Cambodia</b>	<del>2010</del>	<i>Rickettsia</i> spp.	<del>1193</del>	2
		<del>2012  </del>			
Mukhtar et al (2015)(157)	Sudan	<del>2014</del>	Leishmania donovani	<del>285</del>	<del>191</del>
		<del>2001 -</del>			
Murdoch et al (2004)(158)	<del>Nepal</del>	<del>2001</del>	<i>Leptospira</i> spp.	<del>26</del>	<del>11</del>
		<del>2005</del> -			
Murray et al (2011)(159)	<del>Egypt</del>	<del>2007</del>	<i>Leptospira</i> spp.	<del>2441</del>	<del>47</del>
	United Republic of		<del>Salmonella (non-Typhi)</del>		
Nadjm et al (2010)(160)	<del>Tanzania</del>	-	serovars	<del>3639</del>	<del>160</del>
	United Republic of	<del>2007-</del>	<i>Salmonella</i> (non-Typhi)		
Nadjm et al (2012)(161)	<del>Tanzania</del>	<del>2007</del>	serovars	<del>198</del>	5
		<del>2003-</del>			
Naheed et al (2008)(162)	Bangladesh	<del>2004</del>	Campylobacter spp.	<del>867</del>	1
		<del>2008-</del>			
Nandagopal et al (2012)(163)	India	<del>2009</del>	<i>Brucella</i> spp.	<del>301</del>	3
Natarajaseenivasan et al		<del>2000-</del>			
<del>(2004)(164)</del>	India	<del>2000</del>	<i>Leptospira</i> spp.	<del>29</del>	7
Natarajaseenivasan et al		<del>2009-</del>			
<del>(2012)(165)</del>	India	<del>2009</del>	<i>Leptospira</i> spp.	<del>75</del>	71
		<del>2003-</del>			
Ndip et al (2004)(166)	Cameroon	<del>2003</del>	Rickettsia (SFGR)	<del>118</del>	7
		<del>2003-</del>			
Ndip et al (2009)(167)	Cameroon	<del>2003</del>	<i>Ehrlichia</i> spp.	<del>118</del>	<del>12</del>
Njeru et al (2016)(168)	Kenya	<del>2014-</del>	Coxiella burnetii	448	<del>10</del>

First author, year of		<b>Study</b>		Number of	Number of
publication and reference	<b>Country</b>	Period	Pathogen	Individuals Tested	<b>Individuals Positive</b>
		<del>2015</del>			
		2002-			
Nordstrand et al (2007)(169)	Togo	<del>2004</del>	<del>Borrelia spp.</del>	237	21
		2004-	Salmonella (non-Typhi)		
<del>Onyango et al (2008)(170)</del>	<del>Kenya</del>	<del>2005</del>	serovars	<del>20</del>	<del>18</del>
		<del>2004</del>	Salmonella (non-Typhi)		
Onyango et al (2009)(171)	<del>Kenya</del>	<del>2005</del>	serovars	<del>40</del>	<del>20</del>
		<del>2007-</del>			
Paris et al (2011)(172)	<b>Thailand</b>	<del>2008</del>	Orientia tsutsugamushi	<del>138</del>	<del>26</del>
		<del>2010-</del>	<del>Salmonella (non-Typhi)</del>		
Park et al (2016)(173)	No Single Country	<del>2014</del>	serovars	<del>13431</del>	73
		<del>2008-</del>			
Parola et al (2011)(174)	Senegal	<del>2009</del>	Borrelia spp.	206	27
		<del>2000-</del>	<del>Salmonella (non-Typhi)</del>		
Peters et al (2004)(175)	<del>Malawi</del>	<del>2000</del>	serovars	<del>352</del>	44
		<del>2003-</del>			
Phimda et al (2007)(176)	Thailand	<del>2005</del>	<i>Leptospira</i> spp.	<del>296</del>	<del>55</del>
		<del>2003-</del>			
Phimda et al (2007)(176)	<del>Thailand</del>	2005	Orientia tsutsugamushi	<del>230</del>	<del>34</del>
		<del>2006-</del>			
Pradhan et al (2012)(177)	Nepal	<del>2007</del>	Rickettsia (TGR)	<del>1039</del>	22
		<del>2006-</del>	<del>Salmonella (non-Typhi)</del>		
Pradhan et al (2012)(177)	Nepal	<del>2007</del>	serovars	<del>1039</del>	2
		<del>2006-</del>			
Prakash et al (2012)(178)	India	<del>2008</del>	Rickettsia (SFGR)	<del>58</del>	<del>34</del>
		<del>2011-</del>	<del>Salmonella (non-Typhi)</del>		
Preziosi et al (2015)(179)	Mozambique	<del>2014</del>	serovars	<del>841</del>	<del>10</del>

First author, year of		<b>Study</b>		Number of	Number of
publication and reference	<b>Country</b>	<b>Period</b>	Pathogen	Individuals Tested	<b>Individuals Positive</b>
Rafizah et al (2013)(180)	<b>Malaysia</b>	-	<i>Leptospira</i> spp.	<del>999</del>	<del>53</del>
Rao et al (2005)(181)	India	-	<i>Leptospira</i> spp.	<del>70</del>	2
		<del>2007-</del>	Japanese encephalitis		
Rasul et al (2012)(182)	Bangladesh	<del>2009</del>	<del>virus</del>	<del>130</del>	2
		2008-			
Ratmanov et al (2013)(183)	Senegal	<del>2011</del>	<del>Coxiella burnetii</del>	<del>874</del>	4
		<del>2000-</del>	Japanese encephalitis		
Rayamajhi et al (2006)(184)	Nepal	<del>2001</del>	<del>virus</del>	<del>117</del>	<del>54</del>
		<del>2000-</del>	Japanese encephalitis		
<del>Rayamajhi et al (2007)(185)</del>	Nepal	<del>2001</del>	<del>virus</del>	<del>94</del>	<del>54</del>
		<del>2006 -</del>	Japanese encephalitis		
<del>Rayamajhi et al (2011)(186)</del>	Nepal	<del>2008</del>	<del>virus</del>	<del>86</del>	<del>19</del>
	United Republic of				
Reller et al (2011)(187)	<del>Tanzania</del>	-	<del>Borrelia spp.</del>	<del>310</del>	<del>13</del>
		<del>2007-</del>			
Reller et al (2012)(188)	<del>Sri Lanka</del>	<del>2007</del>	Orientia tsutsugamushi	<del>883</del>	<del>17</del>
		<del>2007-</del>			
Reller et al (2012)(188)	<del>Sri Lanka</del>	<del>2007</del>	Rickettsia (SFGR)	<del>883</del>	<del>108</del>
		<del>2007-</del>			
Reller et al (2012)(188)	<del>Sri Lanka</del>	<del>2007</del>	Rickettsia (TGR)	<del>883</del>	<del>61</del>
		<del>2008</del> -			
Reller et al (2014) (189)	Nicaragua	<del>2009</del>	<i>Leptospira</i> spp.	<del>748</del>	<del>17</del>
		<del>2006-</del>			
Richards et al (2010)(190)	<del>Kenya</del>	<del>2008</del>	Rickettsia (SFGR)	<del>163</del>	6
		<del>2000-</del>			
Rijal et al (2004)(191)	Nepal	<del>2002</del>	<del>Leishmania donovani</del>	<del>261</del>	<del>155</del>

First author, year of		<b>Study</b>		Number of	Number of
publication and reference	<b>Country</b>	<b>Period</b>	Pathogen	<b>Individuals Tested</b>	<b>Individuals Positive</b>
		<del>2009  </del>			
Rutvisuttinunt et al (2014)(192)	Nepal	<del>2010</del>	West Nile virus	<del>2046</del>	<del>14</del>
Saisongkorh et al (2004)(193)	<b>Thailand</b>	-	Orientia tsutsugamushi	<del>36</del>	<del>9</del>
		2005-			
Sarih et al (2009)(194)	Morocco	<del>2006</del>	<del>Borrelia spp.</del>	<del>127</del>	23
		<del>2010-</del>	Japanese encephalitis		
Sarkar et al (2012)(195)	India	<del>2010</del>	<del>virus</del>	<del>135</del>	<del>36</del>
		<del>2006-</del>			
Schoepp et al (2014)(196)	Sierra Leone	<del>2008</del>	Lassa virus	<del>253</del>	7
		<del>2006-</del>			
Schoepp et al (2014)(196)	Sierra Leone	<del>2008</del>	Rift Valley fever virus	<del>253</del>	5
		<del>2009</del> -			
Shukla et al (2012)(197)	India	<del>2010</del>	West Nile virus	<del>105</del>	27
		<del>2003</del> -	Japanese encephalitis		
Singh et al (2009)(198)	Nepal	<del>2004</del>	<del>virus</del>	<del>107</del>	<del>19</del>
		<del>2008-</del>	Japanese encephalitis		
Singh et al (2014)(199)	India	<del>2011</del>	<del>virus</del>	<del>1410</del>	<del>10</del>
		<del>2015-</del>			
Sinyange et al (2016)(200)	Zambia	<del>2015</del>	Yersinia pestis	<del>12</del>	<del>6</del>
		<del>2008-</del>			
Socolovschi et al (2010)(201)	Senegal	<del>2009</del>	Rickettsia (SFGR)	<del>134</del>	8
		<del>2011-</del>			
Sokhna et al (2013)(202)	Senegal	<del>2012</del>	Bartonella spp.	440	<del>23</del>
		<del>2011-</del>			
Sokhna et al (2013)(202)	Senegal	<del>2012</del>	<del>Borrelia spp.</del>	440	<del>35</del>
		<del>2011-</del>			
Sokhna et al (2013)(202)	Senegal	<del>2012</del>	<del>Coxiella burnetii</del>	<del>440</del>	2

First author, year of		<b>Study</b>		Number of	Number of
publication and reference	Country	Period	Pathogen	<b>Individuals Tested</b>	<b>Individuals Positive</b>
		<del>2011-</del>			
Sokhna et al (2013)(202)	Senegal	<del>2012</del>	Rickettsia (SFGR)	<u>440</u>	<del>28</del>
		<del>2000-</del>			
Sonthayanon et al (2006)(203)	<b>Thailand</b>	<del>2001</del>	Orientia tsutsugamushi	722	<del>183</del>
		2012-	Salmonella (non-Typhi)		
Sothmann et al (2015)(204)	<b>Ghana</b>	<del>2012</del>	serovars	<del>2306</del>	24
		2009-			
Sow et al (2016)(205)	Senegal	<del>2013</del>	Rift Valley fever virus	<del>13845</del>	1
Stremlau et al (2015)(206)	Nigeria	-	Lassa virus	<del>195</del>	104
	<u> </u>	<del>1995-</del>			
Suharti et al (2009)(207)	Indonesia	<del>1996</del>	Hantavirus	<del>60</del>	5
Suputtamongkol et al		2000-			
<del>(2009)(208)</del>	<b>Thailand</b>	2003	Orientia tsutsugamushi	<del>1663</del>	<del>192</del>
Suputtamongkol et al		2000-			
<del>(2009)(208)</del>	<b>Thailand</b>	<del>2003</del>	Rickettsia (TGR)	<del>1663</del>	<del>18</del>
Suputthamongkol et al		<del>1999-</del>			
<del>(2005)(209)</del>	<b>Thailand</b>	<del>2000</del>	Hantavirus	<del>115</del>	8
		<del>2001-</del>			
Suttinont et al (2006)(210)	<b>Thailand</b>	<del>2002</del>	<i>Leptospira</i> spp.	<del>845</del>	<del>293</del>
		<del>2003-</del>	Japanese encephalitis		
<del>Swami et al (2008)(211)</del>	<del>India</del>	<del>2005</del>	<del>virus</del>	<del>40</del>	9
		<del>2010-</del>	Japanese encephalitis		
Taraphdar et al (2012)(212)	<del>India</del>	<del>2010</del>	<del>virus</del>	<del>58</del>	<del>23</del>
		<del>1996-</del>	<i>Salmonella</i> (non-Typhi)		
<del>Tezcan et al (2006)(213)</del>	<del>Turkey</del>	<del>2004</del>	serovars	<del>621</del>	1
		<del>2001-</del>			
Thipmontree et al (2014)(214)	<b>Thailand</b>	<del>2012</del>	Leptospira spp.	<del>726</del>	<del>118</del>

First author, year of		<b>Study</b>		Number of	Number of
publication and reference	<b>Country</b>	Period	Pathogen	<b>Individuals Tested</b>	<b>Individuals Positive</b>
		<del>2008-</del>			
Thompson et al (2015)(215)	Nepal	<del>2011</del>	Hantavirus	<del>125</del>	2
		<del>2008-</del>			
Thompson et al (2015)(215)	Nepal	<del>2011</del>	Rickettsia (TGR)	<del>125</del>	21
		<del>2009-</del>			
<del>Tigoi et al (2015)(216)</del>	<del>Kenya</del>	2012	West Nile virus	<del>379</del>	47
		2012-	Salmonella (non-Typhi)		
Wiersinga et al (2015)(217)	Gabon	<del>2013</del>	serovars	<del>941</del>	5
		2001-			
Wuthiekanun et al (2007)(218)	<b>Thailand</b>	<del>2002</del>	<i>Leptospira</i> spp.	<del>989</del>	<del>83</del>
		<del>2004-</del>	Anaplasma		
<del>Zhang et al (2011)(219)</del>	<del>China</del>	<del>2006</del>	phagocytophilum	<del>26</del>	8
		<del>2009-</del>	Anaplasma		
Zhang et al (2013)(220)	<del>China</del>	<del>2010</del>	phagocytophilum	<del>421</del>	<del>46</del>
		<del>2012-</del>			
<del>Zhou et al (2013)(221)</del>	<del>China</del>	<del>2013</del>	<del>Babesia microti</del>	<del>449</del>	<del>10</del>
		2001-			
Zimmerman et al (2008)(222)	Nepal	<del>2001</del>	Rickettsia (TGR)	<del>756</del>	<del>50</del>

# 1440 Table 4: Summary of number of studies from each global region represented in the study 1441 dataset

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WHO Region	Number (%) of malaria endemic countries contributing data	Number (%) of studies contributing data (n=174 <sup>1</sup> )
Africa	<del>17 of</del> 44 <del>(38·6%)</del>	<del>56</del> <del>(32·2%)</del>
Americas	<del>8 of 23 (34.8%)</del>	<del>16</del> <del>(9·2%)</del>
Eastern Mediterranean	<del>8 of</del> 14 (57%)	<del>17</del> <del>(9-8%)</del>
Europe	<del>2 of</del> 9 <del>(22-2%)</del>	<del>5</del> <del>(2.9%)</del>
South-East Asia	<del>6 of 10 (60.0%)</del>	<del>63</del> ( <del>36·2%)</del>
Western Pacific	<del>6 of 10 (60.0%)</del>	<del>17 (9·8%)</del>

1443 <sup>1</sup>Table includes data from 174 of 181 articles included in the review, excluding 7 articles

1444 reporting data from multiple countries excluded for this analysis.

1447 1448	Figures
1449 1450 1451 1452 1453 1454	Figure 1: Flow diagram of records and articles assessed for the review. Among the 46 articles excluded because the full text was not accessible in English, the breakdown of languages was as follows: French (13 articles); Spanish (11 articles); Turkish (9 articles); Mandarin (6 articles); Portuguese (2 articles); Hebrew (2 articles); Arabic (1 article); Danish (1 article) and Russian (1 article).
1455 1456	Figure 2: Map illustrating the malaria-endemic countries included in the study and number of articles contributing data for each country. (indicated by colour shading).
1457 1458 1459 1460	Figure 3: Barchart showing the number of articles contributing data for each country included in the study, displayed by country and WHO region.
1460 1461 1462 1463	Figure 4 <u>Figure 3</u> : Barchart showing the number of articles that looked for, reported diagnosis of and contributed data for each <del>zoonosis. of 40, 31 and 30 zoonoses respectively.</del> These data were tabulated for all <del>pathogenszoonoses (n=40)</del> and articles included in the
1464 1465 1466	review: (n=244). Bar colour indicates pathogen type and shading differentiates studies that i) contribute data meeting study diagnostic criteria (left hand bar sections with darkest shading); n=30 pathogens indicated by *), ii) report diagnosis with approaches that do not
1467 1468 1469	meet study diagnostic criteria (central bar sections with <u>partial shadinglighter shading, n=31</u> <u>pathogens that comprised the 30 with extracted data and <i>Escherichia coli</i>), iii) report looking for but not diagnosing a zoonosis (right hand bar section with lightest shading, n=40</u>
1470 1471 1472	pathogens, also including Burkholderia spp. Tick borne encephalitis virus, Marburg virus, Rabies virus, Newcastle Disease virus, Mycobacterium bovis, Francisella tularensis, Ebola virus and Cryptosporidium parvum).
1473 1474 1475 1476	Figure 4: Proportion of fevers attributed to each zoonosis. <u>The plot includes one data point per study and pathogen combination</u> . <u>The different panels</u> include data from different WHO regions. Point colour indicates the coding for the risk of
1477 1478 1479	bias for the representativeness of the febrile population and point size is proportional to the number of individuals tested. Points are jittered on the x axis and shaded to visualize overlapping points
1480 1481 1482	Figure 5: Barchart showing number of articles from each global region contributing data for each of 29 zoonoses. Plot papels indicate the WHO defined global region and bar colour indicates type of pathogen
1483 1484 1485	Figure 6 Figure 5: Venn diagram illustrating the associations between febrile population clinical
1485 1486 1487	presentation and pathogens identified. Circles are scaled to the number of pathogens detected in each type of patient population. Undifferentiated, shown in green, 22 pathogens; febrile
1489 1490 1491 1492	pathogens; febrile haemmorhagic, shown in orange, 4 pathogens, <i>Leishmania donavanii</i> , <i>Toxoplasma gondii, Rickettsia</i> spp., and <i>Yersinia pestis</i> are not represented as they were only detected in febrile populations classified as mixed.

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1493	Figure 7: Proportion of fevers attributed to each zoonosis. Circles are scaled to the number of
1494	pathogens detected in each type of febrile population. Undifferentiated, shown in green, 23
1495	pathogens (including pathogens also seen in other populations); febrile neurological, shown
1496	in red, four pathogens; febrile gastrointestinal, shown in blue, two pathogens; febrile
1497	respiratory, shown in purple, one pathogen, febrile haemorrhagic, shown in yellow, seven
1498	pathogens. Five pathogens are not represented in the figure as they were only detected in
1499	febrile populations classified as co-morbid (Listeria spp., Pasteurella spp. and Toxoplasma
1500	gondii) or in febrile populations with a specific febrile aetiology suspected (Leishmania
1501	donavani, and Yersinia pestis).
1502	
1503	The plot includes one data point per study and pathogen combination. Point colour indicates
1504	pathogen type and point size is proportional to the number of individuals tested. Points are
1505	jittered on the x axis and shaded to visualize overlapping points.
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