Zoonotic causes of febrile illness in malaria endemic countries

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Zoonotic causes of febrile illness in malaria endemic countries: a systematic review

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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.

Introduction

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

Methods

Search strategy and selection criteria

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

Three search concepts for 'fever,' 'zoonoses,' and 'malaria endemic countries' were constructed. To construct the 'fever' concept the exploded subject heading and keywords were combined using database appropriate syntax (e.g., exp Fever/ OR fever$1.mp. OR 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)[22] and World Organisation of Animal Health (OIE)[23] as well as literature-based searches to identify 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. Additional details of search concept construction are given in the appendix. All pathogens identified through these approaches were mapped to existing subject headings and keywords at the lowest taxonomic level possible, typically genus or species. In instances where pathogen species or serovars within the same genus varied in their zoonotic status, search concepts were constructed to include all zoonotic and non-zoonotic species or serovars and articles relating to non-zoonotic species were excluded at the full text stage. The candidate pathogens were classified to differentiate pathogens 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 the majority of human infections are not acquired through zoonotic transmission. We classified pathogens using the stages in the process towards human endemicity defined in Wolfe et al.[24] Pathogens classified at stages one to three (normatively acquired through zoonotic transmission) were retained (appendix). 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., exp anthrax/ OR anthrax.mp. OR exp Bacillus anthracis/ OR bacillus anthracis.mp.). The list of pathogen or disease specific searches was combined using OR syntax to generate the full 'zoonoses' search concept (appendix). The 'malaria endemic countries' concept was constructed by mapping country names for countries defined as malaria endemic in the WHO global malaria reports for the years 2005 and 2016 to Medline and Embase subject headings.[10,25] Each country was searched for using both the exploded subject heading where possible and keywords in all cases (e.g., exp Kenya/OR Kenya.mp.). The three concepts, fever,' 'zoonoses,' and 'malaria endemic countries' were combined using AND operators and database specific syntax (appendix).

Study selection and validity assessment

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

PubMed, Google and the libraries of the University of Glasgow, Duke University, Washington University in St. Louis, and US Centers for Disease Control and Prevention (US CDC). Articles were excluded if a full text for the citation could not be obtained. Two 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 diagnostic case definitions based on WHO and US CDC guidelines ensured that only studies reporting robust and specific diagnostic methods were retained (table 2). Articles were excluded if they did not meet one or more of the study inclusion criteria or if they did meet at 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 with other reviewers.

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

Pathogen	Species, subspecies, and serovars excluded	Pathogen type[13]
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 spongiform encephalopathy	-	Prion
Brucella spp.	-	Bacteria
Burkholderia spp.	*B. cepacia* complex and *B. pseudomallei* excluded	Bacteria
Campylobacter spp.	-	Bacteria
Chlamydia spp.	All species excluded with the exception of *C. psittaci*	Bacteria
Coxiella burnetii	-	Bacteria
Cryptosporidium 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 *E. coli*	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 *F. tularensis*	Bacteria
Hantavirus	-	Virus
Henipaviruses	-	Virus
Lassa virus	-	Virus
Leishmania spp.	*L. donovani* excluded if detected in India	Protozoa
Leptospira spp.	-	Bacteria
Listeria spp.	-	Bacteria
Lyssavirus	All species excluded with the exception of Rabies virus	Virus
Marburg virus	-	Virus
Mycobacterium	All species excluded with the exception of *M. bovis* and *M. avis*	Bacteria
Nairovirus	All species excluded with the exception of Crimean-Congo haemorrhagic fever virus	Virus
Orientia[1]	-	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
Rickettsia spp.[2]	*R. prowazekii* excluded	Bacteria
Salmonella spp.	All species, subspecies, and serovars excluded with the exception of nontyphoidal *Salmonella* serovars	Bacteria
Schistosoma spp.	*S. haematobium, S. intercalatum,* and *S. mekongi.*excluded	Helminth
Streptobacillus spp.	-	Bacteria
Streptococcus spp.	All species excluded with the exception of *S. canis*, *S. suis*, *S. equi,* and *S. iniae*	Bacteria
Taenia spp.		Helminth
Toxocara		Helminth
Toxoplasma gondii	-	Protozoa
Trichinella spp.	-	Helminth
Trypanosoma spp.	All species excluded with the exception of *T. brucei* rhodesiense and *T. cruzi*	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 *Y. pestis*, *Y. enterocolitica* and *Y. pseudotuberculosis*	Bacteria

[1] *Orientia* was covered by search syntax for *Rickettsia.*

[2] For data extraction, data on *Rickettsia* were classified as *Rickettsia* (SFGR) or *Rickettsia* (TGR) where the data resolution allowed. When details on the species of *Rickettsia* were not given, these data were classified as *Rickettsia* spp.

Table 2: Inclusion and exclusion criteria for full text review

Outcome	Criterion
Inclusion:	• Febrile population (≥ 2 people with a fever, defined as body temperature ≥ 38·0°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 iii) Serological diagnosis of acute infection based on testing of both acute and convalescent phase serum samples and demonstration of seroconversion 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[1] v) IgM detection in cerebrospinal fluid (CSF) for selected pathogens for which widely accepted case definitions include IgM detection in CSF[2]
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 ≥ 2 people principally classified based on a shared (100% frequency) aetiological diagnosis. • Review

[1]The following met study criteria for valid diagnostics for pathogen detection based on single sera only: *Leptospira* spp. agglutination titer of ≥ 800 by microscopic agglutination test in one serum specimen [26]; detection of Hantavirus-specific IgM in a serum sample [27]; detection of virus-specific IgM antibodies in serum with confirmatory virus-specific neutralizing antibodies for Eastern equine encephalitis virus (EEEV), West Nile virus (WNV), Western equine encephalitis virus (WEEV), and Venezuelan equine encephalitis virus (VEEV) [28]; identification of lyssavirus specific antibody by indirect fluorescent antibody test or complete rabies virus neutralization at 1:5 dilution in the serum of an unvaccinated person [29]; detection of viral antigens in blood by enzyme-linked immunosorbent assay for Ebola [30,31], Marburg [31,32], Lassa [31,33], and Crimean-Congo haemorrhagic fever viruses [31]; detection of Rift Valley fever antigens or IgM in blood by enzyme-linked Immunosorbent assay [34]; and

[2] IgM detection in CSF was considered a valid diagnostic for EEEV, Japanese encephalitis virus (JEV), rabies virus, WEEV, WNV and VEEV [28,29,35].

Data extraction and bias assessment

Data extraction was conducted independently by one of two reviewers (JEBH and MC). Article-level data were extracted on the location (country and WHO regional classification), [36] study period (start and end year of data collection), and eligibility criteria used in the study. Each population was classified according to the clinical presentation as undifferentiated or differentiated. Differentiated febrile populations were further classified as: i) febrile neurologic; ii) febrile haemorrhagic; iii) febrile gastrointestinal; iv) febrile respiratory; v) specific febrile aetiology suspected; vi) febrile co-morbid group (i.e., malignancy, immunocompromise).[37-39] Data extracted on each population included any demographic restriction of the study population, the age range of the study participants, whether the population was described as inpatient or outpatient, urban or rural, and whether data were collected during a reported disease outbreak or not. 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. Additional data were extracted when the article reported application of a diagnostic approach that met study validity criteria. For each combination of article and pathogen, details of the valid diagnostic methods used, the type and number of samples tested, and the number of positive samples were recorded (appendix table S3, S4). In instances where more than one valid diagnostic method was used in the same study for a given pathogen (e.g., culture-based and serologic case definitions), data on the total number of individuals tested and positive for each pathogen using valid methods were aggregated. Some articles contributed data on more than one pathogen but no data on participant numbers were extracted for pathogens not identified using diagnostic approaches that met study inclusion criteria.

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).[40-42] 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.

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.

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.[43]

Role of the funding source

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 to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Database searches yielded a total of 16,332 and 10,574 records through Embase and Medline, respectively, resulting in a total of 17,852 unique records following de-duplication (figure 1). A total of 4,531 (25·4%) records were excluded during pre-screening, 13,321 (74·6%) records were screened and 962 (7·2%) of these were retained after title and abstract review. In total, 718 (74·6%) articles were excluded during full text review and 244 (25·4%) articles met all study inclusion criteria and were included (figure 1, appendix table S6).

Articles included in the review yielded data from 53 (48·2%) of the 110 malaria endemic countries (figure 2). The majority of articles with a single country origin (n=235) reported data from Africa (83 of 235 articles, 35·3%) or South-East Asia (81 of 235 articles, 34·5%) (appendix table S7, figure S1). One hundred and six (45·1%) of the 235 articles with a single country origin were conducted in one of six dominant countries: India (n=31), United Republic of Tanzania (n=22), Thailand, (n=20), Nepal (n=12), Bangladesh (n=11), and Nigeria (n=10). The data reported in the review were gathered between 1994 and 2017 inclusive.

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).

The number of febrile individuals included in each study population ranged from 4 to 13,845, with a median of 300 (IQR: 120 – 812). In total, 309 records of zoonotic pathogens causing

fever were extracted from the 244 articles. The proportion of fevers attributed to each pathogen reported ranged from <1·0% to 95·0% (figure 4). The risk of bias classification in the precision of the proportion of fevers attributed to each zoonosis was 136 (44·0%) of 309 low risk, 79 (25·6%) of 309 medium risk, and 94 (30·4%) of 309 high risk.

Of the 244 studies, 87 (35·7%) described the clinical setting as inpatient, 36 (14·8%) as outpatient, 39 (16·0%) as mixed, and 82 (33·6%) gave no clear classification of the clinical setting. Thirty (12·3%) studies described the study area as urban, 59 (24·2%) as rural, 45 (18·4%) mixed or both, and 110 (45·1%) gave no clear classification of the study area. Eighteen (7·4%) studies included adult participants, 43 (17·6%) included children, 153 (62·7%) included both adults and children and 30 (12·3%) gave no clear classification of the ages included. 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. Of the 244 studies, 10 (4·1%) were described as outbreak investigations and 169 (69·3%) populations were classified as undifferentiated febrile populations. 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. The associations between clinical presentation of febrile populations and the subset of 25 pathogens identified in the differentiated populations are shown in figure 5. The risk of bias classification in the representativeness of febrile populations was 121 (49·6%,) of 244 low risk, 45 (18·4%,) of 244 medium risk, and 78 (32·0%,) of 244 high risk.

Discussion

This systematic review reveals diverse zoonoses causing febrile illness within multiple malaria-endemic countries, often at high prevalence. However, sparse and patchy reporting suggests that the prevalence of zoonoses is widely under-estimated. Knowledge of probable infecting pathogen is crucial to inform clinical management of febrile illness and there is a clear need for further investigation of the zoonotic causes of febrile illness to generate data relevant to clinicians, epidemiologists, and health policy makers globally. This study should generate greater awareness of the clinical importance of zoonoses and provide a pragmatic starting point for actions to better manage these diseases, for example through improved diagnostic and clinical treatment algorithms. These findings demonstrate the need for enhanced epidemiological understanding of multiple zoonoses to inform disease prevention.

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). There are multiple steps and biases in the processes from a patient seeking care with febrile illness to the publication of an English language scientific paper on the occurrence and prevalence of a specific zoonosis that could be included in this review. The underlying distribution and relative clinical importance of individual pathogens varies, as do patient healthcare seeking behaviour, clinical, and patient awareness of different pathogens, diagnostic capacities, and probability of publication. It is therefore not plausible to expect this review to yield data on all zoonoses in all countries. However, considering the inclusion of

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

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. The pathogens that are looked for depend on factors such as the diagnostic capacity available, existing data, and local assessment of the likely causes of febrile illness in a specific location. 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. In this way, dogma about the 'known' important causes of febrile illness in specific locations can arise and contribute to the neglect of other pathogens. The findings of this review may help indicate potential gaps in what is looked for and can highlight pathogens and locations where these dogmas should be questioned.

The majority of the 30 zoonotic causes of fever contributing data for this review were bacteria (56·7%). This proportion is greater than expected from the taxonomic distribution of all zoonotic pathogens, which comprise 30·1% bacteria[44] and also contrasts with the taxonomic distribution of emerging zoonoses, which are dominated by viruses.[13] This finding reinforces the clinical importance of endemic bacterial zoonoses. The comparisons between the number of articles that looked for, diagnosed, and contributed data for each of 40 zoonoses reveals the range of zoonotic pathogens investigated and indicates the relative investigative effort used for each pathogen (figure 3). However, the figures for number of articles where a pathogen was looked for but not identified must be interpreted with caution given the high probability of reporting bias and how rarely negative results are reported. For several pathogens, the number and proportion of articles that reported a zoonotic diagnosis but did not contribute further data for analysis (because the diagnostic approaches described did not meet study quality criteria) are substantial (figure 3). This demonstrates that for many, predominantly bacterial pathogens, suboptimal diagnostic tests or imprecise case definitions are in widespread use, highlighting the challenges of accurately quantifying disease prevalence and comparing studies.

Persistent challenges in the diagnosis of febrile patients include limited laboratory capacity, reliance on demonstration of seroconversion for confirmed diagnosis of many pathogens, unsustainable costs associated with more advanced diagnostic technologies, and lack of simple and affordable tests for the accurate and timely diagnosis of several zoonotic pathogens. In addition, the delays in patient presentation that are typical in many resource limited settings, low magnitude bacteraemia at presentation and, presentation of patients during the immune phase of illness, all limit the sensitivity of culture or PCR-based

diagnostic approaches when available. These challenges necessitate syndromic approaches to patient management and broad-spectrum treatment. One specific issue relates to tetracycline use. This study identified rickettsioses and *O. tsutsugamushi* as common causes of fever. 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 shock and severe respiratory distress without shock.[45] In light of the extensive contribution of tetracycline-responsive infections to fever in malaria-endemic countries, revisions to clinical guidelines may be warranted to suggest the empirical use of tetracyclines in addition to beta-lactams in scenarios where the infection with tetracycline-responsive pathogens cannot be excluded.

The findings of this review show that one or more zoonotic causes of fever are likely to present a threat to health in all of the countries included in this review. Only a small proportion of the febrile populations included in the study were defined as demographically restricted and most were not clinically differentiated. Even zoonoses commonly linked with specific syndromes (e.g., Crimean-Congo haemorrhagic fever virus and JEV) were diagnosed in undifferentiated populations and should thus be considered in the differential diagnosis of undifferentiated febrile illness. 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.[46]

There are several important limitations to this study. We examined the contribution of zoonotic pathogens to febrile illness only in malaria-endemic countries and excluded articles not available in English from our analysis. 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. Studies reporting all negative test results were excluded. This strategy was motivated by the inevitable influence of publication bias and challenges of systematically quantifying the non-reporting of either diagnostic test performance or the non-detection of specific pathogens. Biases in testing practices for different pathogens in different locations and with different clinical febrile presentations will influence the pathogens looked for, detected and reported. The application of diagnostic criteria that are strictly comparable across pathogens is not feasible. In this study, strict diagnostic criteria were applied, preferentially including diagnostic approaches with a high specificity, to minimize the influence of false positives within the analyses. 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. Figure 5 shows clear variation in risk of representativeness bias across pathogens, potentially linked to variation in clinical presentation. For example, the majority of data points for *Japanese encephalitis virus* and indeed all data points for *Leishmania donovanii* are

classified as high risk of representativeness bias. This review focused on studies reporting diagnostic investigation of patient populations that were principally defined by fever and populations principally 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). This review therefore had an inherently low sensitivity for studies describing disease outbreaks. This focus explains, for example, the absence of studies describing the 2014-2016 Ebola West Africa outbreak. 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.[47] Serological diagnosis of acute infection based on testing of both acute and convalescent phase sera is central to the confirmed diagnosis of multiple pathogens included in the study. As a consequence, individuals who die prior to the collection of convalescent samples are unlikely to contribute data (in the absence of other valid test options) and the proportions of fevers attributable to pathogens with high probability of acute fatality will be under-estimated. Furthermore, no validity criteria regarding the timing of sample collection for acute and convalescent samples were imposed, leading potentially to false negative results (e.g., seroconversion not detected because of premature convalescent sampling). For these reasons, our findings are unlikely to capture the full extent of morbidity and mortality attributable to zoonoses.

The data compiled in this review demonstrate the need to consider multiple zoonoses among the potential causes of febrile illnesses in malaria-endemic countries. Different zoonoses are likely to be important in different settings. Our study provides a starting point for improving awareness of first the zoonoses that are known to contribute to febrile illness in different malaria-endemic regions and second the fever-causing zoonoses with widespread distribution that should be considered in patient evaluation. The demonstration of major data gaps should encourage a more open-minded approach when considering zoonoses as a potential cause of febrile illness. 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. Untapped sources of information on the distribution and occurrence of fever-causing zoonoses almost certainly exist, particularly in the animal health sector. 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. There are substantial challenges to clinicians and 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 pathogens necessitate efforts to overcome these challenges and translate findings into important public health gains.

Contributors

The author contributions are as follows. Study design: JEBH, KJA, JAC, SC, and MPR. Searches, screening and article review: JEBH, 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, and MPR.

Declaration of interests

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 reports grants from United States National Institute for Allergy and Infectious Diseases and contracted research with BioFire Defense, LLC, outside the submitted work. Other authors declare they have no conflicts of interest.

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Figures

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).

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).

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 4: Proportion of fevers attributed to each zoonosis.
The plot includes one data point per study and pathogen combination. The different panels 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 overlapping points.

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*).

Figure 1

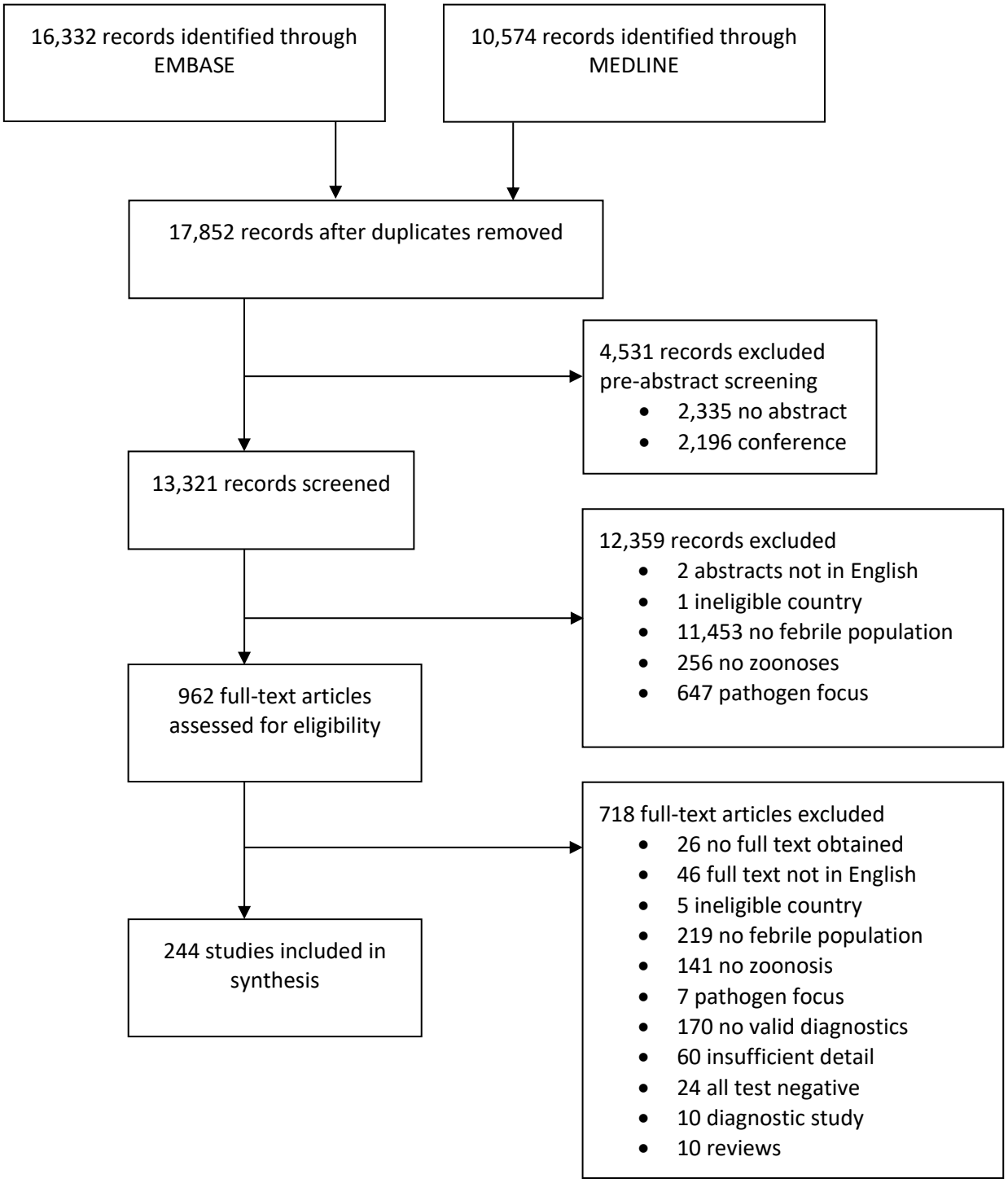

16,332 records identified through EMBASE
10,574 records identified through MEDLINE
17,852 records after duplicates removed
4,531 records excluded pre-abstract screening
• 2,335 no abstract
• 2,196 conference
13,321 records screened
12,359 records excluded
• 2 abstracts not in English
• 1 ineligible country
• 11,453 no febrile population
• 256 no zoonoses
• 647 pathogen focus
962 full-text articles assessed for eligibility
718 full-text articles excluded
• 26 no full text obtained
• 46 full text not in English
• 5 ineligible country
• 219 no febrile population
• 141 no zoonosis
• 7 pathogen focus
• 170 no valid diagnostics
• 60 insufficient detail
• 24 all test negative
• 10 diagnostic study
• 10 reviews
244 studies included in synthesis

Figure 2

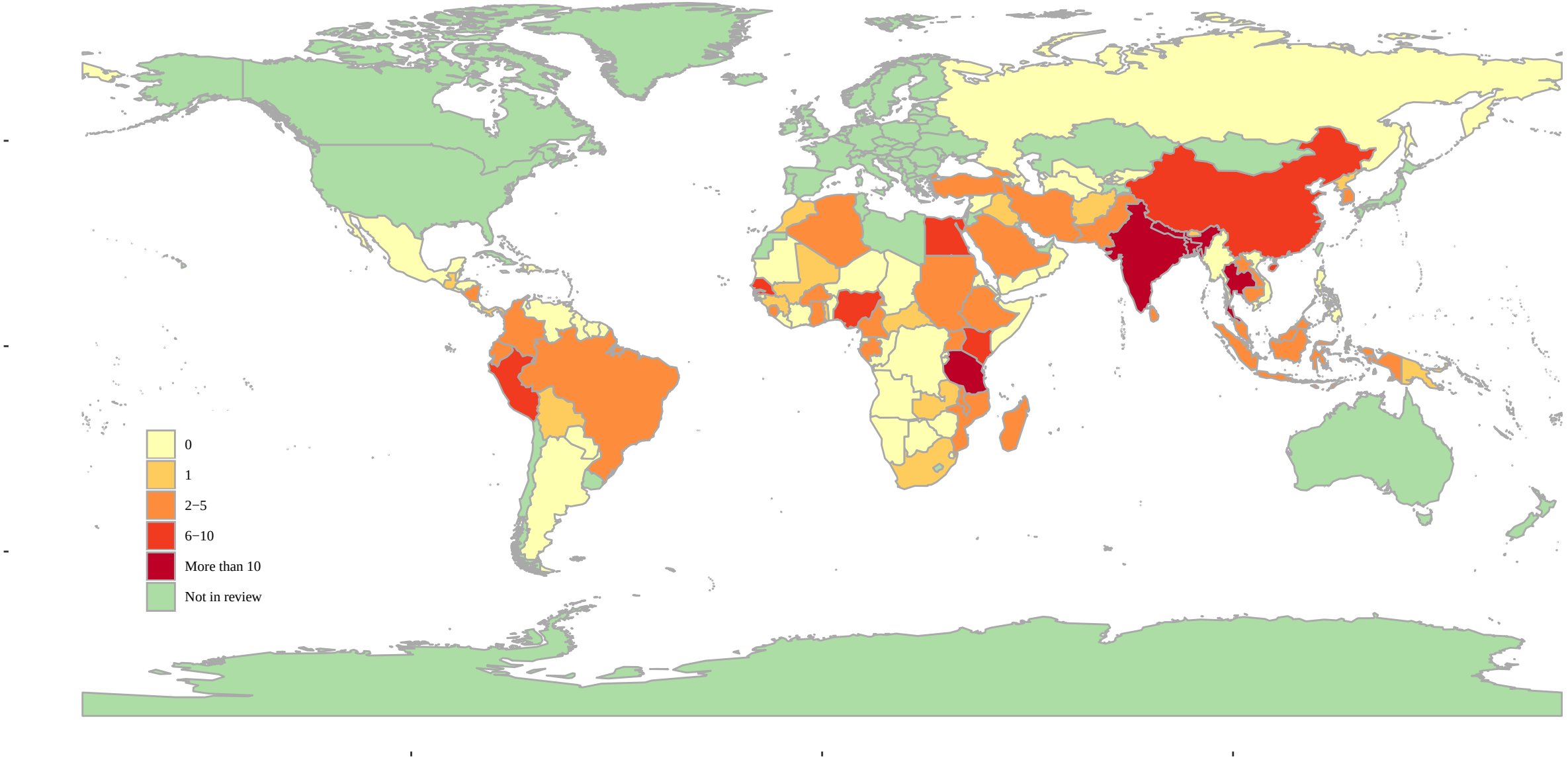


Figure 3

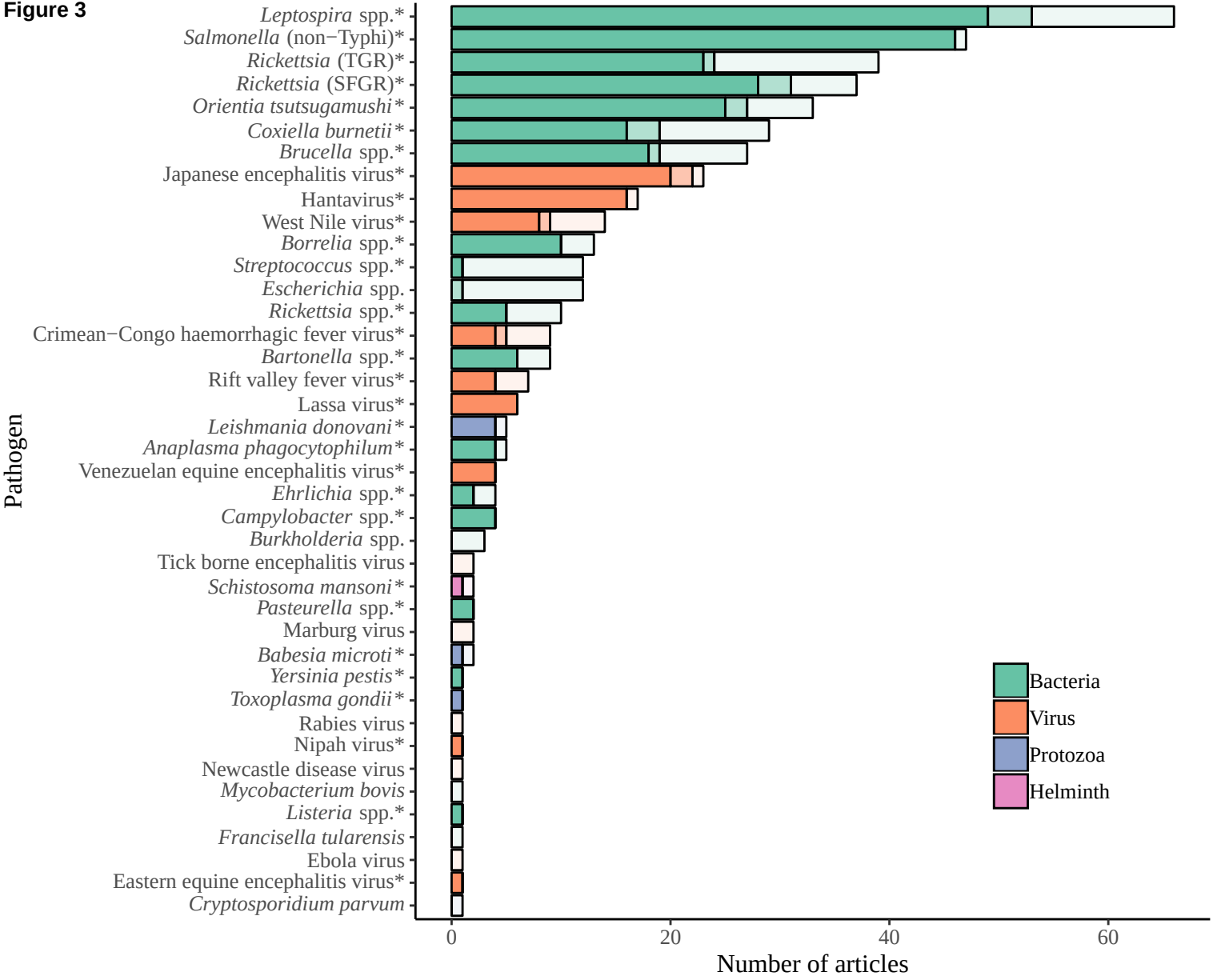
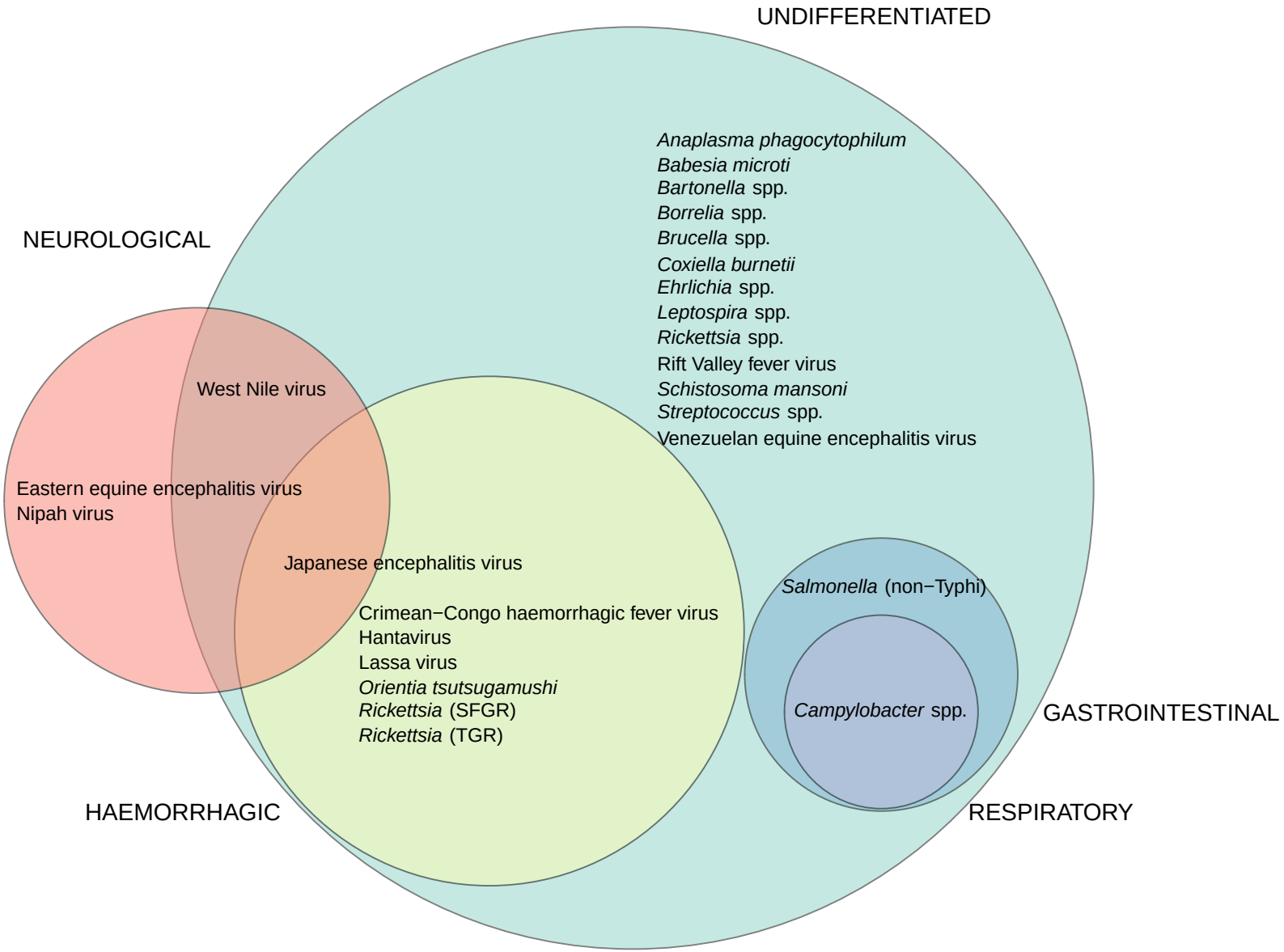

Leptospira spp.*
Salmonella (non−Typhi)*
Rickettsia (TGR)*
Rickettsia (SFGR)*
Orientia tsutsugamushi*
Coxiella burnetii*
Brucella spp.*
Japanese encephalitis virus*
Hantavirus*
West Nile virus*
Borrelia spp.*
Streptococcus spp.*
Escherichia spp.
Rickettsia spp.*
Crimean−Congo haemorrhagic fever virus*
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
0
20
40
60
Number of articles
Bacteria
Virus
Protozoa
Helminth

Figure 4

Proportion fevers attributed to pathogen
0
25
50
75
Africa
Eastern Mediterranean
Europe
South−East Asia
The Americas
Western Pacific
5000
10000
Low
Medium
High
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.
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.
Schistosoma mansoni
Pasteurella spp.
Babesia microti
Yersinia pestis
Toxoplasma gondii
Nipah virus
Listeria spp.
Eastern equine encephalitis virus
Pathogen

Figure 5


UNDIFFERENTIATED
Anaplasma phagocytophilum
Babesia microti
Bartonella spp.
Borrelia spp.
Brucella spp.
Coxiella burnetii
Ehrlichia spp.
Leptospira spp.
Rickettsia spp.
Rift Valley fever virus
Schistosoma mansoni
Streptococcus spp.
Venezuelan equine encephalitis virus
NEUROLOGICAL
West Nile virus
Eastern equine encephalitis virus
Nipah virus
Japanese encephalitis virus
Crimean−Congo haemorrhagic fever virus
Hantavirus
Lassa virus
Orientia tsutsugamushi
Rickettsia (SFGR)
Rickettsia (TGR)
Salmonella (non−Typhi)
Campylobacter spp.
GASTROINTESTINAL
HAEMORRHAGIC
RESPIRATORY

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.

The outputs of these searches were combined and de-duplicated in R.[1] The complete list of all subject headings associated with these articles was extracted and each heading was classified by two independent reviewers to identify headings for named disease causing agents or named diseases. Headings that referred to non-specific pathogen groups e.g., 'arboviruses' and those that referred to non-specific clinical symptoms, signs, syndromes, 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 be pathogenic to humans[2]. Non-zoonotic pathogens or diseases based on the classification by Taylor et al.[2] were excluded. The frequency of appearance of each zoonosis-related heading in the initial search output dataset was tabulated. Pathogen/disease subject headings that appeared in >10 references identified through the initial 'Fever and Zoonoses' searches were retained.

For the 'zoonoses' concept, the list of zoonotic pathogens identified above was combined with lists of zoonotic diseases from the World Health Organization (WHO)[3] and World Organisation of Animal Health (OIE)[4].

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 was made following the definitions used in Wolfe et al.[5] Three reviewers (JAC, SC, and MPR) independently classified listed pathogens or diseases using the stages in the transformation of an animal pathogen into a specialized pathogen of humans described in Wolfe et al.:[5]

- Stage 1. A microbe that is present in animals but that has not been detected in humans under natural conditions (that is, excluding modern technologies that can inadvertently transfer microbes, such as blood transfusion, organ transplants, or hypodermic needles).
- Stage 2. A pathogen of animals that, under natural conditions, has been transmitted from animals to humans ('primary infection') but has not been transmitted between humans ('secondary infection').
- 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.
- Stage 4. A disease that exists in animals, and that has a natural (sylvatic) cycle of infecting humans by primary transmission from the animal host, but that also undergoes long sequences of secondary transmission between humans without the involvement of animal hosts.
- Stage 5. A pathogen exclusive to humans.[5]

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

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

- Identified through the WHO list, OIE list or preliminary zoonoses search approach AND
- Classified as a zoonoses[2] AND
- Classified as a stage 1, 2 or 3 zoonosis.[5]

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., 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 include all zoonotic and non-zoonotic species and articles relating to non-zoonotic species were excluded at a later stage. Finally, the list of pathogen- or disease-specific searches were combined using OR syntax to generate the full 'zoonoses' search concept (Medline Search Syntax and Embase Search Syntax sections below).

Medline Search Syntax

(exp Anaplasmosis/ OR anaplasmosis.mp. OR exp Anaplasma/ OR anaplasma.mp.) [set database shortcode to 'pmez']
(exp Babesiosis/ OR babesiosis.mp. OR exp Babesia/ OR babesia.mp.)
(exp Anthrax/ OR anthrax.mp. OR exp Bacillus anthracis/ OR bacillus anthracis.mp.)
(exp Bartonella Infections/ OR bartonellosis.mp. OR exp Bartonella/ OR bartonella.mp.)
(exp Borrelia Infections/ OR borrelia Infection$1.mp. OR exp Borrelia/ OR borrelia.mp.)
(exp brucellosis/ OR brucellosis.mp. OR exp Brucella/ OR brucella.mp.)
(exp Burkholderia Infections/ OR glanders.mp. OR exp Burkholderia/ OR burkholderia.mp.)
(exp Campylobacter Infections/ OR exp Campylobacter/ OR campylobacter$.mp.)
(exp Psittacosis/ OR psittacosis.mp. OR exp Chlamydophila psittaci/ OR chlamydophila psittaci.mp.)
(exp Cowpox/ OR exp Cowpox virus/ OR cowpox.mp.)
(exp Q Fever/ OR q fever.mp. OR exp Coxiella/ OR coxiella.mp.)
(exp Hemorrhagic Fever, Crimean/ OR crimean-congo h?emorrhagic fever.mp. OR exp Hemorrhagic Fever 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.)
(exp Ehrlichiosis/ OR ehrlichiosis.mp. OR exp Ehrlichia/ OR ehrlichia.mp.)
(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 encephalomyelitis.mp.)
(exp Escherichia coli Infections/ 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.)
(exp Tularemia/ OR tular?emia.mp. OR exp Francisella tularensis/ OR francisella tularensis.mp.)
(exp Hantavirus Infections/ OR hantavirus infection$1.mp. OR exp Hantavirus/ OR hantavirus.mp.)
(exp Henipavirus Infections/ OR exp Henipavirus/ OR hendra.mp. OR nipah.mp. OR henipavirus.mp.)
(exp Encephalitis, Japanese/ OR exp Encephalitis Virus, Japanese/ OR japanese encephalitis.mp.)
(exp Lassa Fever/ OR exp Lassa virus/ OR lassa.mp.)
(exp Leishmaniasis/ OR leishmaniasis.mp. OR exp Leishmania/ OR leishmania.mp.)
(exp Leptospirosis/ OR leptospirosis.mp. OR exp Leptospira/ OR leptospira.mp.)
(exp Listeriosis/ OR listeriosis.mp. OR exp Listeria/ OR listeria.mp.)
(exp Marburg Virus Disease/ OR marburg h?emorrhagic fever.mp. OR exp Marburgvirus/ OR marburg$.mp.)
(exp Monkeypox/ OR exp Monkeypox virus/ OR monkeypox.mp.)
(exp Tuberculosis, Bovine/ OR bovine tuberculosis.mp. OR exp Mycobacterium bovis/ OR mycobacterium bovis.mp.)
(exp Paratuberculosis/ OR paratuberculosis.mp. OR exp "Mycobacterium avium subsp. paratuberculosis"/ OR mycobacterium paratuberculosis.mp.)
(exp Newcastle Disease/ OR exp Newcastle disease virus/ OR newcastle disease.mp.)
(exp Pasteurella Infections/ OR pasteurellosis.mp. OR exp Pasteurella/ OR pasteurella.mp.)
(exp Prion Diseases/ OR exp Prions/ OR prion.mp.)
(exp Rabies/ OR rabies.mp. OR exp Rabies virus/ OR rabies virus.mp.)
(exp Rat-Bite Fever/ OR rat-bite.mp. OR rat bite.mp. OR exp Streptobacillus/ OR exp Spirillum/ OR streptobacillus.mp. OR spirillum.mp.)
(exp Rickettsiaceae Infections/ OR rickettsiaceae infection$1.mp. OR rickettsiosis.mp. OR exp Rickettsieae/ OR rickettsia.mp.)
(exp Rift Valley Fever/ OR rift valley fever.mp. OR exp Rift Valley fever virus/ OR rift valley fever virus.mp.)
(exp Salmonella Infections/ OR salmonellosis.mp. OR exp Salmonella/ OR salmonella.mp.)
(exp Schistosomiasis/ OR schistosomiasis.mp. OR exp Schistosoma/ OR schistosoma.mp.)
(exp Streptococcal Infections/ OR streptococcal.mp. OR exp Streptococcus/ OR streptococcus.mp.)
(exp Pseudorabies/ OR pseudorabies.mp. OR exp Herpesvirus 1, Suid/ OR suid herpesvirus.mp. OR aujeszky$.mp.)
(exp Swine Vesicular Disease/ OR swine vesicular.mp. OR exp Enterovirus/ OR enterovirus.mp.)
(exp Cysticercosis/ OR cysticercosis.mp. OR exp Taenia/ OR taenia.mp.)
(exp Encephalitis, Tick-Borne/ OR tick borne encephalitis.mp. OR exp Encephalitis Viruses, Tick-Borne/ OR tick borne encephalitis virus.mp.)
(exp Toxocariasis/ OR toxocariasis.mp. OR exp Toxocara/ OR toxocara.mp.)
(exp Toxoplasmosis/ OR toxoplasmosis.mp. OR exp Toxoplasma/ OR toxoplasma.mp.)

(exp Trichinellosis/ OR trichinellosis.mp. OR exp Trichinella/ OR trichinella.mp.)
(exp Trypanosomiasis/ OR trypanosomiasis.mp. OR exp Trypanosoma/ OR trypanosoma.mp.)
(exp Vaccinia/ OR exp Vaccinia virus/ OR vaccinia.mp.)
(exp Vesicular Stomatitis/ OR exp Vesiculovirus/ OR vesicular stomatitis.mp.)
(exp West Nile Fever/ OR west nile fever.mp. OR exp West Nile virus/ OR west nile virus.mp.)
(exp Yersinia Infections/ OR yersinia infection$1.mp. OR exp Yersinia/ OR yersinia.mp. OR plague.mp.)
(exp "Georgia (Republic)"/ OR "Georgia (Republic)".mp.)
(exp Afghanistan/ OR Afghanistan.mp.)
(exp Algeria/ OR Algeria.mp.)
(exp Angola/ OR Angola.mp.)
(exp Argentina/ OR Argentina.mp.)
(exp Armenia/ OR Armenia.mp.)
(exp Azerbaijan/ OR Azerbaijan.mp.)
(exp Bahamas/ OR Bahamas.mp.)
(exp Bangladesh/ OR Bangladesh.mp.)
(exp Belize/ OR Belize.mp.)
(exp Benin/ OR Benin.mp.)
(exp Bhutan/ OR Bhutan.mp.)
(exp Bolivia/ OR Bolivia.mp.)
(exp Botswana/ OR Botswana.mp.)
(exp Brazil/ OR Brazil.mp.)
(exp Burkina Faso/ OR Burkina Faso.mp.)
(exp Burundi/ OR Burundi.mp.)
(exp Cambodia/ OR Cambodia.mp.)
(exp Cameroon/ OR Cameroon.mp.)
(exp Cape Verde/ OR Cape Verde.mp.)
(exp Central African Republic/ OR Central African Republic.mp.)
(exp Chad/ OR Chad.mp.)
(exp China/ OR China.mp.)
(exp Colombia/ OR Colombia.mp.)
(exp Comoros/ OR Comoros.mp.)
(exp Congo/ OR Congo.mp.)
(exp Costa Rica/ OR Costa Rica.mp.)
(exp Cote d'Ivoire/ OR Cote d'Ivoire.mp.)
(exp Democratic People's Republic of Korea/ OR Democratic People's Republic of Korea.mp.)
(exp Democratic Republic of the Congo/ OR Democratic Republic of the Congo.mp.)
(exp Djibouti/ OR Djibouti.mp.)
(exp Dominican Republic/ OR Dominican Republic.mp.)
(exp East Timor/ OR East Timor.mp.)
(exp Ecuador/ OR Ecuador.mp.)
(exp Egypt/ OR Egypt.mp.)
(exp El Salvador/ OR El Salvador.mp.)
(exp Equatorial Guinea/ OR Equatorial Guinea.mp.)
(exp Eritrea/ OR Eritrea.mp.)
(exp Ethiopia/ OR Ethiopia.mp.)
(exp French Guiana/ OR French Guiana.mp.)
(exp Gabon/ OR Gabon.mp.)
(exp Gambia/ OR Gambia.mp.)
(exp Ghana/ OR Ghana.mp.)
(exp Guatemala/ OR Guatemala.mp.)
(exp Guinea/ OR Guinea.mp.)
(exp Guinea-Bissau/ OR Guinea-Bissau.mp.)
(exp Guyana/ OR Guyana.mp.)
(exp Haiti/ OR Haiti.mp.)
(exp Honduras/ OR Honduras.mp.)
(exp India/ OR India.mp.)
(exp Indonesia/ OR Indonesia.mp.)
(exp Iran/ OR Iran.mp.)
(exp Iraq/ OR Iraq.mp.)
(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

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

Embase Search Syntax

(exp anaplasmosis/ OR exp human granulocytic anaplasmosis/ OR anaplasmosis.mp. OR exp Anaplasma/ OR anaplasma.mp.) [set database shortcode to 'emczd']
(exp babesiosis/ OR babesiosis.mp. OR exp Babesia/ OR babesia.mp.)
(exp anthrax/ OR anthrax.mp. OR exp Bacillus anthracis/ OR bacillus anthracis.mp.)
(exp bartonellosis/ OR bartonellosis.mp. OR exp Bartonella/ OR bartonella.mp.)
(exp Borrelia infection/ OR borrelia Infection$1.mp. OR exp Borrelia/ OR borrelia.mp.)
(exp brucellosis/ OR brucellosis.mp. OR exp Brucella/ OR brucella.mp.)
(exp Burkholderia infection/ OR glanders.mp. OR exp Burkholderia/ OR burkholderia.mp.)
(exp campylobacteriosis/ OR exp Campylobacter/ OR campylobacter$.mp.)
(exp ornithosis/ OR psittacosis.mp. OR exp Chlamydophila psittaci/ OR chlamydophila psittaci.mp.)
(exp cowpox/ OR exp Cowpox virus/ OR cowpox.mp.)
(exp Q fever/ OR q fever.mp. OR exp Coxiella/ OR coxiella.mp.)
(exp Crimean Congo hemorrhagic fever/ OR crimean-congo h?emorrhagic fever.mp. OR exp Nairo virus/ OR crimean-congo h?emorrhagic fever virus.mp.)
(exp Ebola hemorrhagic fever/ OR ebolavirus infection$1.mp. OR exp Ebola virus/ OR ebola$.mp.)
(exp echinococcosis/ OR echinococcosis.mp. OR exp Echinococcus/ OR echinococcus.mp.)
(exp ehrlichiosis/ OR ehrlichiosis.mp. OR exp Ehrlichia/ OR ehrlichia.mp.)
(exp Eastern equine encephalitis/ OR exp Venezuelan equine encephalitis/ OR exp Western equine encephalitis/ OR exp Eastern equine encephalomyelitis virus/ OR exp Venezuelan equine encephalomyelitis alphavirus/ OR exp Western equine encephalomyelitis alphavirus/ OR equine encephalitis.mp. OR equine encephalomyelitis.mp.)
(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.)
(exp tularemia/ OR tular?emia.mp. OR exp Francisella tularensis/ OR francisella tularensis.mp.)
(exp Hantavirus infection/ OR hantavirus infection$1.mp. OR exp Hantavirus/ OR hantavirus.mp.)
(exp Nipah virus infection/ OR exp Hendra virus infection/ OR exp Nipah virus/ OR exp Hendra virus/ OR hendra.mp. OR nipah.mp. OR henipavirus.mp.)
(exp Japanese encephalitis/ OR exp Japanese encephalitis virus/ OR japanese encephalitis.mp.)
(exp Lassa fever/ OR exp Lassa virus/ OR lassa.mp)
(exp leishmaniasis/ OR leishmaniasis.mp. OR exp Leishmania/ OR leishmania.mp.)
(exp leptospirosis/ OR leptospirosis.mp. OR exp Leptospira/ OR leptospira.mp.)
(exp listeriosis/ OR listeriosis.mp. OR exp Listeria/ OR listeria.mp.)
(exp Marburg hemorrhagic fever/ OR marburg h?emorrhagic fever.mp. OR exp Marburg virus/ OR marburg$.mp.)
(exp monkeypox/ OR exp Monkeypox virus/ OR monkeypox.mp.)
(exp bovine tuberculosis/ OR bovine tuberculosis.mp. OR exp Mycobacterium bovis/ OR mycobacterium bovis.mp.)
(exp paratuberculosis/ OR paratuberculosis.mp. OR exp Mycobacterium paratuberculosis/ OR mycobacterium paratuberculosis.mp.)
(exp Newcastle disease/ OR exp Newcastle disease paramyxovirus/ OR newcastle disease.mp.)
(exp pasteurellosis/ OR pasteurellosis.mp. OR exp Pasteurella/ OR pasteurella.mp.)
(exp prion disease/ OR exp prion/ OR prion.mp.)
(exp rabies/ OR rabies.mp. OR exp Rabies virus/ OR rabies virus.mp.)
(exp rat bite fever/ OR rat-bite.mp. OR rat bite.mp. OR exp Streptobacillus/ OR exp Spirillum/ OR streptobacillus.mp. OR spirillum.mp.)
(exp Rickettsiaceae infection/ OR rickettsiaceae infection$1.mp.OR rickettsiosis.mp. OR exp Rickettsiaceae/ OR rickettsia.mp.)
(exp Rift Valley fever/ OR rift valley fever.mp. OR exp Rift Valley fever bunyavirus/ OR rift valley fever virus.mp.)
(exp salmonellosis/ OR exp animal salmonellosis/ OR salmonellosis.mp. OR exp Salmonella/ OR salmonella.mp.)
(exp schistosomiasis/ OR schistosomiasis.mp. OR exp Schistosoma/ OR schistosoma.mp.)
(exp Streptococcus infection/ OR streptococcal.mp. OR exp Streptococcus/ OR streptococcus.mp.)
(exp pseudorabies/ OR pseudorabies.mp. OR exp Pseudorabies herpetovirus/ OR suid herpesvirus.mp. OR aujeszky$.mp.)
(exp swine vesicular disease/ OR swine vesicular.mp. OR exp Enterovirus/ OR enterovirus.mp.)

(exp cysticercosis/ OR cysticercosis.mp. OR exp Taenia/ OR taenia.mp.)
(exp tick borne encephalitis/ OR tick borne encephalitis.mp. OR exp Tick borne encephalitis flavivirus/ OR tick borne encephalitis virus.mp.)
(exp toxocariasis/ OR toxocariasis.mp. OR exp Toxocara/ OR toxocara.mp.)
(exp toxoplasmosis/ OR exp congenital toxoplasmosis/ OR toxoplasmosis.mp. OR exp Toxoplasma/ OR toxoplasma.mp.)
(exp trichinosis/ OR trichinellosis.mp. OR exp Trichinella/ OR trichinella.mp.)
(exp trypanosomiasis/ OR trypanosomiasis.mp. OR exp Trypanosoma/ OR trypanosoma.mp.)
(exp vaccinia/ OR exp Vaccinia virus/ OR vaccinia.mp.)
(exp vesicular stomatitis/ OR exp Vesicular stomatitis virus/ OR vesicular stomatitis.mp.)
(exp West Nile fever/ OR west nile fever.mp. OR exp West Nile flavivirus/ OR west nile virus.mp.)
(exp Yersinia infection/ OR yersinia infection$1.mp. OR exp Yersinia/ OR yersinia.mp. OR plague.mp.)
(exp "Georgia (republic)"/ OR "Georgia (republic)".mp.)
(exp "Turkey (republic)"/ OR "Turkey (republic)".mp.)
(exp Afghanistan/ OR Afghanistan.mp.)
(exp Algeria/ OR Algeria.mp.)
(exp Angola/ OR Angola.mp.)
(exp Argentina/ OR Argentina.mp.)
(exp Armenia/ OR Armenia.mp.)
(exp Azerbaijan/ OR Azerbaijan.mp.)
(exp Bahamas/ OR Bahamas.mp.)
(exp Bangladesh/ OR Bangladesh.mp.)
(exp Belize/ OR Belize.mp.)
(exp Benin/ OR Benin.mp.)
(exp Bhutan/ OR Bhutan.mp.)
(exp Bolivia/ OR Bolivia.mp.)
(exp Botswana/ OR Botswana.mp.)
(exp Brazil/ OR Brazil.mp.)
(exp Burkina Faso/ OR Burkina Faso.mp.)
(exp Burundi/ OR Burundi.mp.)
(exp Cambodia/ OR Cambodia.mp.)
(exp Cameroon/ OR Cameroon.mp.)
(exp Cape Verde/ OR Cape Verde.mp.)
(exp Central African Republic/ OR Central African Republic.mp.)
(exp Chad/ OR Chad.mp.)
(exp China/ OR China.mp.)
(exp Colombia/ OR Colombia.mp.)
(exp Comoros/ OR Comoros.mp.)
(exp Congo/ OR Congo.mp.)
(exp Costa Rica/ OR Costa Rica.mp.)
(exp Cote d'Ivoire/ OR Cote d'Ivoire.mp.)
(exp Democratic Republic Congo/ OR Democratic Republic Congo.mp.)
(exp Djibouti/ OR Djibouti.mp.)
(exp Dominican Republic/ OR Dominican Republic.mp.)
(exp Ecuador/ OR Ecuador.mp.)
(exp Egypt/ OR Egypt.mp.)
(exp El Salvador/ OR El Salvador.mp.)
(exp Equatorial Guinea/ OR Equatorial Guinea.mp.)
(exp Eritrea/ OR Eritrea.mp.)
(exp Ethiopia/ OR Ethiopia.mp.)
(exp French Guiana/ OR French Guiana.mp.)
(exp Gabon/ OR Gabon.mp.)
(exp Gambia/ OR Gambia.mp.)
(exp Ghana/ OR Ghana.mp.)
(exp Guatemala/ OR Guatemala.mp.)
(exp Guinea/ OR Guinea.mp.)
(exp Guinea-Bissau/ OR Guinea-Bissau.mp.)
(exp Guyana/ OR Guyana.mp.)
(exp Haiti/ OR Haiti.mp.)
(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.)

(exp Zimbabwe/ OR Zimbabwe.mp.)
(exp Africa/ OR africa.mp)
(exp fever/ OR fever$1.mp. OR febrile.mp.)
or/1-52
or/53-162
164 AND 165
163 AND 166
..l/167 yr=2004-2019

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 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.

Table S1. Criteria applied for abstract screening.

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

Full Text Review

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

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	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 >1 of the following criteria and are used to test >1 febrile people? 1 – culture of the pathogen from sample(s) collected from a febrile person 2 – direct detection of the pathogen (e.g., by PCR based techniques) from sample(s) collected from a febrile person 3 – serological diagnosis of acute infection based on testing of both acute and convalescent phase serum samples and demonstration of seroconversion 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) 5 – IgM detection in CSF for selected pathogens for which widely accepted case definitions include IgM detection in CSF (table 2 in main paper)	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 classified on the basis of a common (e.g., 100% frequency) aetiological diagnosis, some proportion of which may also have fever?	If Yes, exclude. If No, retain and carry forward for data extraction.

Data extraction

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

Article level data collection on individual pathogens included the names of each of the zoonotic pathogens that the article described diagnostic methods for and the names of the zoonotic pathogens that were diagnosed in the study. These classifications record the named zoonoses that each study reported looking for and diagnosing, irrespective of the diagnostic approach used or level of detail given.

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

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

Table S3. Data extracted for each article included in the review.

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 aetiologies 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 patients	Was any proportion of the reported febrile population diagnosed with a zoonotic 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.

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 valid methods	Record the number of febrile patients tested using the valid diagnostics described in this row of the dataset specifically.
Number of individuals diagnosed as positive for that pathogen by valid methods	Record the number of febrile patients classified as positive using the valid diagnostics described in this row of the dataset specifically.
Indicator for multiple diagnostic methods for given pathogen in this reference	Record Yes (1) if there is more than one row of data for this pathogen and 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.

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

Criteria	Risk of bias classification	Description
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 ≤385.
	High	Number of individuals tested ≤ 139.

Results

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

Study population abbreviations: UN = undifferentiated; D = differentiated; COMORBID = febrile co-morbid group GI = febrile gastrointestinal; HEM = febrile haemorrhagic; NEU = febrile neurological; RESP; febrile respiratory; SP = specific febrile aetiology suspected.

Diagnostics abbreviations: ELISA = enzyme linked immunosorbent assay; HI = haemagglutination inhibition test; IFA = immunofluorescence assay; IgM = IgM detection; MAT = microscopic agglutination test; PCR = polymerase chain reaction-based test; PRNT = plaque reduction neutralisation test. When multiple diagnostics used different tests are separated by ",".

An excel format version of this table, including additional data fields is accessible at: http://dx.doi.org/10.5525/gla.researchdata.890

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 phagocytophilum	Lee et al. (2018)[6]	Republic of Korea	2015-2017	UN	PCR	380	14	Medium	Medium
Anaplasma phagocytophilum	Yi et al. (2017)[7]	Republic of Korea	2003-2012	UN	PCR	70	5	Low	High
Anaplasma phagocytophilum	Zhang et al. (2011)[8]	China	2004-2006	D SP	PCR, IFA	26	8	High	High
Anaplasma phagocytophilum	Zhang et al. (2013)[9]	China	2009-2010	UN	Culture, IFA, PCR	421	46	Low	Low
Babesia microti	Zhou et al. (2013)[10]	China	2012-2013	UN	PCR	449	10	Low	Low
Bartonella spp.	Chaudhry et al. (2018)[11]	India	2012-2016	UN	PCR	28	2	Medium	High
Bartonella spp.	Faruque et al. (2017)[12]	Thailand	2008-2009	UN	Culture	720	1	Medium	Low
Bartonella spp.	Hercik et al. (2017)[13]	United Republic of Tanzania	2014-2015	UN	PCR	842	4	Low	Low
Bartonella spp.	Kosoy et al. (2010)[14]	Thailand	2002-2003	UN	Culture, PCR	261	14	Low	Medium
Bartonella spp.	Simpson et al. (2018)[15]	South Africa	2012-2013	UN	PCR	74	7	Medium	High
Bartonella spp.	Sokhna et al. (2013)[16]	Senegal	2011-2012	UN	PCR	440	23	Low	Low
Borrelia spp.	Aarsland et al. (2012)[17]	Ethiopia	2009-2010	UN	PCR	102	2	Low	High
Borrelia spp.	Elhelw et al. (2014)[18]	Egypt	2008-2009	UN	PCR	15	4	Medium	High
Borrelia spp.	Fotso Fotso et al. (2015)[19]	Algeria	2012-2012	UN	PCR	257	4	Low	Medium
Borrelia spp.	Mediannikov et al. (2014)[20]	Senegal	2010-2011	UN	PCR	1566	115	Low	Low
Borrelia spp.	Nordstrand et al. (2007)[21]	Togo	2002-2004	UN	PCR	237	21	Low	Medium
Borrelia spp.	Parola et al. (2011)[22]	Senegal	2008-2009	UN	PCR	206	27	Medium	Medium

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
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)[24]	Morocco	2005-2006	UN	PCR	127	23	Medium	High
Borrelia spp.	Sokhna et al. (2013)[16]	Senegal	2011-2012	UN	PCR	440	35	Low	Low
Borrelia spp.	Toure et al. (2017)[25]	Mali	2012-2012	UN	PCR	8	3	Medium	High
Brucella spp.	Afifi et al. (2005)[26]	Egypt	1999-2003	D SP	Culture	9883	275	High	Low
Brucella spp.	Barua et al. (2016)[27]	India	2010-2012	D SP	Culture	102	18	High	High
Brucella spp.	Boone et al. (2017)[28]	Madagascar	2011-2013	UN	PCR	1020	15	Low	Low
Brucella spp.	Bouley et al. (2012)[29]	United Republic of Tanzania	2007-2008	UN	MAT	455	16	Low	Low
Brucella spp.	Carugati et al. (2018)[30]	United Republic of Tanzania	2007-2014	UN	MAT	1680	45	Low	Low
Brucella spp.	Cash-Goldwasser et al. (2018)[31]	United Republic of Tanzania	2012-2014	UN	Microagglutination test	562	39	Low	Low
Brucella spp.	Ciftdogan et al. (2011)[32]	Turkey	2003-2008	UN	Culture	92	3	Low	High
Brucella spp.	Crump et al. (2013)[33]	United Republic of Tanzania	2007-2008	UN	MAT	453	16	Low	Low
Brucella spp.	Fadeel et al. (2006)[34]	Egypt	1999-2003	UN	Culture	1177	202	Low	Low
Brucella spp.	Jennings et al. (2007)[35]	Egypt	2002-2003	UN	Culture	4490	115	Medium	Low
Brucella spp.	Kamal et al. (2013)[36]	Saudi Arabia	2009-2011	UN	PCR	101	50	Low	High
Brucella spp.	Kuila et al. (2017)[37]	India	2013-2015	UN	PCR	2088	88	Low	Low
Brucella spp.	Manock et al. (2009)[38]	Ecuador	2001-2004	UN	ELISA	275	4	Medium	Medium
Brucella spp.	Mattar et al. (2017)[39]	Colombia	2012-2013	UN	Rose Bengal plate test	100	1	Medium	High
Brucella spp.	Migisha et al. (2018)[40]	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)[42]	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 reference	Country	Study Period	Study Population Classification	Diagnostics Used	Number Tested	Number Positive	Representativeness Bias Coding	Precision Bias Coding
Campylobacter spp.	Ali et al. (2016)[44]	Pakistan	2011-2014	D RESP	Culture	356	2	High	Medium
Campylobacter spp.	Bottieau et al. (2011)[45]	No Specific Country	2000-2006	D GI	Stool examination, Culture	512	47	High	Low
Campylobacter spp.	Hogan et al. (2018)[46]	Ghana	2013-2015	UN	PCR	240	21	Low	Medium
Campylobacter spp.	Naheed et al. (2008)[47]	Bangladesh	2003-2004	UN	Culture	867	1	Low	Low
Coxiella burnetii	Angelakis et al. (2014)[48]	No Specific Country	2008-2012	UN	PCR	1888	7	Low	Low
Coxiella burnetii	Crump et al. (2013)[33]	United Republic of Tanzania	2007-2008	UN	IFA	482	24	Low	Low
Coxiella burnetii	Esmaeili et al. (2017)[49]	Iran (Islamic Republic of)	2013-2013	UN	ELISA	116	16	Medium	High
Coxiella burnetii	Greiner et al. (2018)[50]	Thailand	2002-2005	UN	IFA	1784	5	Medium	Low
Coxiella burnetii	Hamilton et al. (2011)[51]	Iraq	2008-2008	UN	PCR, IFA	18	8	Low	High
Coxiella burnetii	Hercik et al. (2017)[13]	United Republic of Tanzania	2014-2015	UN	PCR	842	2	Low	Low
Coxiella burnetii	Khalili et al. (2016)[52]	Iran (Islamic Republic of)	2014-2015	UN	PCR	92	7	Low	High
Coxiella burnetii	Manock et al. (2009)[38]	Ecuador	2001-2004	UN	ELISA	33	15	Medium	High
Coxiella burnetii	Mazyad et al. (2007)[53]	Egypt	2006-2006	UN	PCR	150	5	Low	Medium
Coxiella burnetii	Metanat et al. (2014)[54]	Iran (Islamic Republic of)	2011-2011	UN	IFA	105	23	Low	High
Coxiella burnetii	Njeru et al. (2016)[55]	Kenya	2014-2015	UN	PCR	448	10	Low	Low
Coxiella burnetii	Pradeep et al. (2017)[56]	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)[58]	Nicaragua	2008-2009	UN	IFA	748	10	Low	Low
Coxiella burnetii	Sokhna et al. (2013)[16]	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)[59]	Pakistan	2008-2008	D HEM	PCR, IgM	44	16	High	High

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
Crimean-Congo haemorrhagic fever virus	Ali et al. (2007)[60]	Pakistan	2001-2001	D HEM	PCR	10	3	High	High
Crimean-Congo haemorrhagic fever virus	Bukbuk et al. (2016)[61]	Nigeria	2010-2014	D SP	PCR	380	1	High	Medium
Crimean-Congo haemorrhagic fever virus	Kuchuloria et al. (2016)[62]	Georgia	2008-2011	UN	IgM	537	3	Medium	Low
Eastern equine encephalitis virus	Aguilar et al. (2007)[63]	Peru	NA-NA	D NEU	ELISA	153	2	High	Medium
Ehrlichia spp.	Chikeka et al. (2016)[64]	Nicaragua	NA-NA	UN	IFA	748	1	Low	Low
Ehrlichia spp.	Ndip et al. (2009)[65]	Cameroon	2003-2003	UN	PCR	118	12	Medium	High
Hantavirus	Armien et al. (2013)[66]	Panama	2006-2010	D SP	PCR	150	117	High	Medium
Hantavirus	Castillo Ore et al. (2012)[67]	Peru	2007-2010	UN	IgM	5174	9	Low	Low
Hantavirus	Chandy et al. (2005)[68]	India	2002-2003	D HEM	ELISA	152	23	High	Medium
Hantavirus	Chandy et al. (2009)[69]	India	2005-2007	UN	ELISA, IFA, PCR	347	86	Low	Medium
Hantavirus	Chau et al. (2017)[70]	Mozambique	2012-2014	UN	ELISA	200	4	Low	Medium
Hantavirus	Chen et al. (2014)[71]	China	2011-2012	D HEM	PCR, IFA	85	33	High	High
Hantavirus	Chrispal et al. (2010)[72]	India	2007-2008	UN	ELISA	398	1	Low	Low
Hantavirus	Cruz et al. (2012)[73]	Bolivia (Plurinational State of)	2008-2009	UN	PCR, IgM	372	9	Low	Medium
Hantavirus	Klempa et al. (2010)[74]	Guinea	2001-2005	D HEM	ELISA, Neutralization test	717	8	High	Low
Hantavirus	Kuchuloria et al. (2014)[75]	Georgia	2008-2011	UN	IgM	537	2	Low	Low
Hantavirus	Liu et al. (2007)[76]	China	2002-2004	UN	IFA, PCR	130	49	Low	High
Hantavirus	Mattar et al. (2017)[39]	Colombia	2012-2013	UN	ELISA	100	4	Medium	High
Hantavirus	Suharti et al. (2009)[77]	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)[79]	China	2011-2011	D SP	IgM, PCR	141	2	High	Medium

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
Japanese encephalitis virus	Anga et al. (2010)[80]	Papua New Guinea	2007-2008	D NEU	IgM	129	2	High	High
Japanese encephalitis virus	Chatterjee et al. (2004)[81]	India	1996-1999	D NEU	HI	72	24	High	High
Japanese encephalitis virus	Chheng et al. (2013)[82]	Cambodia	2009-2010	UN	ELISA	107	6	Low	High
Japanese encephalitis virus	Dias et al. (2018)[83]	India	2014-2014	UN	RNA sequencing	4	1	Low	High
Japanese encephalitis virus	Ellis et al. (2006)[84]	Thailand	1999-2002	UN	ELISA	530	1	Low	Low
Japanese encephalitis virus	Joshi et al. (2013)[85]	India	2007-2007	D NEU	ELISA	152	4	High	Medium
Japanese encephalitis virus	Kakoti et al. (2013)[86]	India	2012-2012	D HEM	IgM	223	49	High	Medium
Japanese encephalitis virus	Kumar et al. (2015)[87]	India	NA-NA	D NEU	IgM	108	54	High	High
Japanese encephalitis virus	Maude et al. (2016)[88]	Bangladesh	2012-2012	UN	IgM	300	1	Medium	Medium
Japanese encephalitis virus	Medhi et al. (2017)[89]	India	2012-2014	D NEU	ELISA	1707	601	High	Low
Japanese encephalitis virus	Rasul et al. (2012)[90]	Bangladesh	2007-2009	D NEU	ELISA	130	2	High	High
Japanese encephalitis virus	Rauf et al. (2018)[91]	India	2014-2014	D NEU	IgM, PCR	54	8	High	High
Japanese encephalitis virus	Rayamajhi et al. (2006)[92]	Nepal	2000-2001	D NEU	IgM	117	54	High	High
Japanese encephalitis virus	Rayamajhi et al. (2007)[93]	Nepal	2000-2001	D NEU	IgM	94	54	High	High
Japanese encephalitis virus	Rayamajhi et al. (2011)[94]	Nepal	2006-2008	D NEU	IgM	86	9	High	High
Japanese encephalitis virus	Sarkar et al. (2012)[95]	India	2010-2010	D NEU	IgM	43	23	High	High
Japanese encephalitis virus	Singh et al. (2009)[96]	Nepal	2003-2004	D NEU	IgM	107	19	High	High
Japanese encephalitis virus	Singh et al. (2014)[97]	India	2008-2011	D NEU	PCR	1410	10	High	Low
Japanese encephalitis virus	Swami et al. (2008)[98]	India	2003-2005	D NEU	IgM, PCR	40	9	High	High
Japanese encephalitis virus	Taraphdar et al. (2012)[99]	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)[101]	Sierra Leone	2012-2012	D SP	PCR, Antigen detection	53	29	High	High

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
Lassa virus	Ehichioya et al. (2012)[102]	Nigeria	2005-2008	D SP	PCR	451	2	High	Low
Lassa virus	Schoepp et al. (2014)[103]	Sierra Leone	2006-2008	D SP	ELISA	253	7	High	Medium
Lassa virus	Shehu et al. (2018)[104]	Nigeria	2016-2016	D SP	PCR	34	11	High	High
Lassa virus	Stremlau et al. (2015)[105]	Nigeria	NA-NA	D HEM	Sequencing	195	104	High	Medium
Leishmania donovani	Hailu et al. (2006)[106]	Ethiopia	NA-NA	D SP	Microscopy, Culture	103	49	High	High
Leishmania donovani	Joshi et al. (2006)[107]	Nepal	1998-2002	D SP	Bone marrow examination	996	284	High	Low
Leishmania donovani	Mukhtar et al. (2015)[108]	Sudan	2012-2014	D SP	Culture	285	191	High	Medium
Leishmania donovani	Rijal et al. (2004)[109]	Nepal	2000-2002	D SP	Microscopy	261	155	High	Medium
Leptospira spp.	Albuquerque Filho et al. (2011)[110]	Brazil	2009-2009	UN	Culture	97	56	Low	High
Leptospira spp.	Alia et al. (2019)[111]	Malaysia	2016-2017	D SP	PCR	50	13	High	High
Leptospira spp.	Barragan et al. (2016)[112]	Ecuador	2013-2015	UN	PCR	668	100	Low	Low
Leptospira spp.	Biggs et al. (2011)[113]	United Republic of Tanzania	2007-2008	UN	MAT	831	70	Low	Low
Leptospira spp.	Blacksell et al. (2006)[114]	Lao People's Democratic Republic	2001-2003	UN	MAT	186	5	Medium	Medium
Leptospira spp.	Boonsilp et al. (2011)[115]	Thailand	2001-2002	UN	Culture, PCR	418	120	Medium	Low
Leptospira spp.	Chansamouth et al. (2016)[116]	Lao People's Democratic Republic	2006-2010	UN	MAT	158	1	Medium	Medium
Leptospira spp.	Chheng et al. (2013)[82]	Cambodia	2009-2010	UN	Culture, PCR	1179	17	Low	Low
Leptospira spp.	Chiriboga et al. (2015)[117]	Ecuador	2011-2012	UN	PCR	210	132	Low	Medium
Leptospira spp.	Cohen et al. (2007)[118]	Thailand	2002-2003	UN	MAT	704	67	Low	Low
Leptospira spp.	Crump et al. (2013)[33]	United Republic of Tanzania	2007-2008	UN	MAT	453	40	Low	Low
Leptospira spp.	Dassanayake et al. (2009)[119]	Sri Lanka	2007-2008	UN	MAT	123	62	Low	High
Leptospira spp.	Dittrich et al. (2018)[120]	Lao People's Democratic Republic	2014-2015	D SP	MAT	248	12	High	Medium

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
Leptospira spp.	Ellis et al. (2006)[84]	Thailand	1999-2002	UN	IgM, MAT	613	107	Low	Low
Leptospira spp.	Faruque et al. (2017)[12]	Thailand	2008-2009	UN	Culture	720	1	Medium	Low
Leptospira spp.	Gasem et al. (2009)[121]	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)[123]	Cambodia	2007-2009	UN	MAT	2044	17	Low	Low
Leptospira spp.	Hercik et al. (2017)[13]	United Republic of Tanzania	2014-2015	UN	PCR	842	22	Low	Low
Leptospira spp.	Hercik et al. (2018)[124]	United Republic of Tanzania	2014-2014	UN	PCR	191	3	Low	Medium
Leptospira spp.	Ismail et al. (2006)[125]	Egypt	1999-2003	UN	MAT	886	141	Low	Low
Leptospira spp.	Kendall et al. (2010)[126]	Bangladesh	2001-2001	UN	MAT	78	7	Low	High
Leptospira spp.	Koizumi et al. (2009)[127]	Sri Lanka	2008-2008	D SP	PCR	107	3	High	High
Leptospira spp.	LaRocque et al. (2005)[128]	Bangladesh	2001-2001	D SP	PCR	359	63	High	Medium
Leptospira spp.	Libraty et al. (2007)[129]	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)[130]	Peru	2003-2006	UN	Culture	881	45	Medium	Low
Leptospira spp.	Mayxay et al. (2013)[131]	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)[135]	Nepal	2001-2001	UN	PCR	26	11	Low	High
Leptospira spp.	Murray et al. (2011)[136]	Egypt	2005-2007	UN	Culture	2441	47	Low	Low
Leptospira spp.	Natarajaseenivasan et al. (2004)[137]	India	2000-2000	D SP	MAT, Culture	29	7	High	High

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
Leptospira spp.	Natarajaseenivasan et al. (2012)[138]	India	2009-2009	D SP	PCR	75	71	High	High
Leptospira spp.	Phimda et al. (2007)[139]	Thailand	2003-2005	D SP	Culture, MAT	296	55	High	Medium
Leptospira spp.	Rafizah et al. (2013)[140]	Malaysia	NA-NA	UN	MAT	999	53	Medium	Low
Leptospira spp.	Rao et al. (2005)[141]	India	NA-NA	D SP	ELISA	70	2	High	High
Leptospira spp.	Ravindar et al. (2018)[142]	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)[144]	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)[146]	Central African Republic	2012-2015	UN	MAT	32	2	Medium	High
Leptospira spp.	Sengupta et al. (2017)[147]	India	2012-2014	UN	PCR	150	5	Medium	Medium
Leptospira spp.	Suttinont et al. (2006)[148]	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)[152]	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)[154]	India	2001-2001	D NEU	PCR	6	5	High	High
Orientia tsutsugamushi	Blacksell et al. (2007)[155]	Nepal	2002-2004	UN	IFA	103	5	Low	High
Orientia tsutsugamushi	Blacksell et al. (2010)[156]	Lao People's Democratic Republic	2003-2007	D SP	IFA	1030	101	High	Low
Orientia tsutsugamushi	Blacksell et al. (2016)[157]	Thailand	2006-2007	UN	IFA, PCR, Culture	152	37	Medium	Medium
Orientia tsutsugamushi	Blacksell et al. (2016)[158]	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 reference	Country	Study Period	Study Population Classification	Diagnostics Used	Number Tested	Number Positive	Representativeness Bias Coding	Precision Bias Coding
Orientia tsutsugamushi	Chen et al. (2014)[71]	China	2011-2012	D HEM	PCR	85	1	High	High
Orientia tsutsugamushi	Chheng et al. (2013)[82]	Cambodia	2009-2010	UN	PCR, IFA	1179	17	Low	Low
Orientia tsutsugamushi	Jung et al. (2015)[159]	Democratic People's Republic of Korea	2009-2013	UN	IFA	382	3	Low	Medium
Orientia tsutsugamushi	Kingston et al. (2018)[160]	Bangladesh	2014-2015	UN	PCR	416	45	Low	Low
Orientia tsutsugamushi	Kocher et al. (2017)[161]	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)[76]	China	2002-2004	UN	IFA, PCR	130	46	Low	High
Orientia tsutsugamushi	Maude et al. (2015)[163]	Bangladesh	2012-2012	UN	PCR	300	1	Low	Medium
Orientia tsutsugamushi	Mayxay et al. (2013)[131]	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)[134]	Cambodia	2008-2010	UN	PCR	1193	47	Low	Low
Orientia tsutsugamushi	Paris et al. (2011)[164]	Thailand	2007-2008	UN	IFA, Culture, PCR	138	26	Medium	High
Orientia tsutsugamushi	Phimda et al. (2007)[139]	Thailand	2003-2005	D SP	IFA	230	34	High	Medium
Orientia tsutsugamushi	Reller et al. (2012)[165]	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)[170]	Bhutan	2014-2015	UN	PCR	1044	7	Medium	Low
Pasteurella spp.	Bengre et al. (2012)[171]	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 reference	Country	Study Period	Study Population Classification	Diagnostics Used	Number Tested	Number Positive	Representativeness Bias Coding	Precision Bias Coding
Rickettsia (SFGR)	Aarsland et al. (2012)[17]	Ethiopia	2009-2010	UN	PCR	102	4	Low	High
Rickettsia (SFGR)	Bouchaib et al. (2018)[172]	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)[33]	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)[175]	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)[176]	China	2015-2016	UN	PCR	261	6	Medium	Medium
Rickettsia (SFGR)	Hidalgo et al. (2013)[177]	Colombia	2010-2011	D SP	IFA	26	7	High	High
Rickettsia (SFGR)	Kingston et al. (2018)[160]	Bangladesh	2014-2015	UN	PCR	416	2	Low	Low
Rickettsia (SFGR)	Kuloglu et al. (2012)[178]	Turkey	2003-2009	D SP	PCR, IFA	126	97	High	High
Rickettsia (SFGR)	Liu et al. (2016)[179]	China	2014-2014	D SP	PCR	733	56	High	Low
Rickettsia (SFGR)	Maina et al. (2012)[180]	Kenya	2008-2010	UN	PCR	699	50	Low	Low
Rickettsia (SFGR)	Manock et al. (2009)[38]	Ecuador	2001-2004	UN	ELISA	214	6	Medium	Medium
Rickettsia (SFGR)	Mattar et al. (2017)[39]	Colombia	2012-2013	UN	IFI	100	2	Medium	High
Rickettsia (SFGR)	Mayxay et al. (2013)[131]	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)[183]	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 reference	Country	Study Period	Study Population Classification	Diagnostics Used	Number Tested	Number Positive	Representativeness Bias Coding	Precision Bias Coding
Rickettsia (SFGR)	Ndip et al. (2004)[186]	Cameroon	2003-2003	UN	PCR	118	7	Medium	High
Rickettsia (SFGR)	Prakash et al. (2012)[187]	India	2006-2008	D SP	PCR	58	34	High	High
Rickettsia (SFGR)	Reller et al. (2012)[165]	Sri Lanka	2007-2007	UN	IFA	883	108	Low	Low
Rickettsia (SFGR)	Reller et al. (2016)[58]	Nicaragua	2008-2009	UN	IFA	748	6	Low	Low
Rickettsia (SFGR)	Richards et al. (2010)[188]	Kenya	2006-2008	UN	PCR	163	6	Medium	Medium
Rickettsia (SFGR)	Sokhna et al. (2013)[16]	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)[155]	Nepal	2002-2004	UN	IFA	103	9	Low	High
Rickettsia (TGR)	Blacksell et al. (2010)[156]	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)[71]	China	2011-2012	D HEM	IFA	85	1	High	High
Rickettsia (TGR)	Chheng et al. (2013)[82]	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)[33]	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)[121]	Indonesia	2005-2006	UN	IFA	137	4	Low	High
Rickettsia (TGR)	Hidalgo et al. (2008)[190]	Colombia	2005-2005	UN	IFA	120	14	Low	High
Rickettsia (TGR)	Hidalgo et al. (2013)[177]	Colombia	2010-2011	D SP	IFA	26	2	High	High
Rickettsia (TGR)	Kingston et al. (2018)[160]	Bangladesh	2014-2015	UN	PCR	416	24	Low	Low
Rickettsia (TGR)	Manock et al. (2009)[38]	Ecuador	2001-2004	UN	ELISA	255	8	Medium	Medium
Rickettsia (TGR)	Maude et al. (2015)[163]	Bangladesh	2012-2012	UN	PCR	300	2	Low	Medium

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
Rickettsia (TGR)	Mayxay et al. (2013)[131]	Lao People's Democratic Republic	2008-2010	UN	PCR	1849	12	Low	Low
Rickettsia (TGR)	McGready et al. (2010)[133]	Thailand	2004-2006	UN	Culture, PCR, IFA	203	14	Medium	Medium
Rickettsia (TGR)	Mongkol et al. (2018)[183]	Thailand	2012-2014	D SP	PCR	168	3	High	Medium
Rickettsia (TGR)	Pradhan et al. (2012)[191]	Nepal	2006-2007	UN	PCR	1039	22	Low	Low
Rickettsia (TGR)	Reller et al. (2012)[165]	Sri Lanka	2007-2007	UN	IFA	883	61	Low	Low
Rickettsia (TGR)	Reller et al. (2016)[58]	Nicaragua	2008-2009	UN	IFA	748	1	Low	Low
Rickettsia (TGR)	Thompson et al. (2015)[78]	Nepal	2008-2011	UN	IFA	125	21	Low	High
Rickettsia (TGR)	Zimmerman et al. (2008)[192]	Nepal	2001-2001	UN	PCR	756	50	Low	Low
Rickettsia spp.	Hercik et al. (2017)[13]	United Republic of Tanzania	2014-2015	UN	PCR	842	2	Low	Low
Rickettsia spp.	Kingston et al. (2018)[160]	Bangladesh	2014-2015	UN	PCR	416	3	Low	Low
Rickettsia spp.	Mongkol et al. (2018)[183]	Thailand	2012-2014	D SP	PCR	168	15	High	Medium
Rickettsia spp.	Mueller et al. (2014)[134]	Cambodia	2008-2010	UN	PCR	1193	2	Low	Low
Rickettsia spp.	Ricapa-Antay et al. (2018)[145]	Peru	2016-2016	UN	PCR	139	9	Medium	Medium
Rift Valley fever virus	Baudin et al. (2016)[193]	Sudan	2011-2012	UN	IgM	130	17	Medium	High
Rift Valley fever virus	Guillebaud et al. (2018)[122]	Madagascar	2014-2015	UN	PCR	682	1	Low	Low
Rift Valley fever virus	Schoepp et al. (2014)[103]	Sierra Leone	2006-2008	D SP	ELISA	253	5	High	Medium
Rift Valley fever virus	Sow et al. (2016)[194]	Senegal	2009-2013	UN	PCR	13845	1	Low	Low
Salmonella (non-Typhi)	Akinyemi et al. (2007)[195]	Nigeria	2004-2005	D GI	Culture	235	16	High	Medium
Salmonella (non-Typhi)	Akinyemi et al. (2015)[196]	Nigeria	2010-2011	UN	Culture	135	2	Low	High
Salmonella (non-Typhi)	Al-Emran et al. (2016)[197]	No Specific Country	2011-2013	UN	Culture	8161	28	Low	Low
Salmonella (non-Typhi)	Al-Emran et al. (2016)[198]	No Specific Country	NA-NA	UN	Culture	10636	77	Low	Low

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
Salmonella (non-Typhi)	Andualem et al. (2014)[199]	Ethiopia	2010-2011	D SP	Culture	270	7	High	Medium
Salmonella (non-Typhi)	Bello et al. (2018)[200]	Nigeria	NA-NA	D COMORBID	Culture	225	10	High	Medium
Salmonella (non-Typhi)	Biggs et al. (2014)[201]	United Republic of Tanzania	2006-2008	UN	Culture	4106	163	Low	Low
Salmonella (non-Typhi)	Bilman et al. (2017)[202]	Turkey	2014-2014	D GI	Culture	48	10	High	High
Salmonella (non-Typhi)	Brooks et al. (2005)[203]	Bangladesh	2000-2001	UN	Culture	888	2	Low	Low
Salmonella (non-Typhi)	Brown et al. (2017)[204]	Nigeria	2013-2014	D COMORBID	Culture	116	1	High	High
Salmonella (non-Typhi)	Chheng et al. (2013)[82]	Cambodia	2009-2010	UN	Culture	1180	1	Low	Low
Salmonella (non-Typhi)	Crump et al. (2011)[205]	United Republic of Tanzania	2007-2008	UN	Culture	224	2	Low	Medium
Salmonella (non-Typhi)	Crump et al. (2011)[206]	United Republic of Tanzania	2007-2008	UN	Culture	139	1	Low	Medium
Salmonella (non-Typhi)	D'Acremont et al. (2014)[207]	United Republic of Tanzania	2008-2008	UN	Culture	424	1	Low	Low
Salmonella (non-Typhi)	Davies et al. (2016)[208]	Nigeria	NA-NA	UN	Culture	129	15	Low	High
Salmonella (non-Typhi)	Dong et al. (2014)[209]	China	2009-2011	UN	Culture	2529	3	Low	Low
Salmonella (non-Typhi)	Eibach et al. (2016)[210]	Ghana	2007-2012	UN	Culture	7172	215	Low	Low
Salmonella (non-Typhi)	Gordon et al. (2010)[211]	Malawi	NA-NA	UN	Culture	355	70	Low	Medium
Salmonella (non-Typhi)	Hercik et al. (2017)[13]	United Republic of Tanzania	2014-2015	UN	PCR	842	4	Low	Low
Salmonella (non-Typhi)	Hogan et al. (2018)[46]	Ghana	2013-2015	UN	Culture	1238	28	Low	Low
Salmonella (non-Typhi)	Saha et al. (2017)[212]	Bangladesh	2012-2016	UN	Culture	5185	1	Medium	Low
Salmonella (non-Typhi)	Jeon et al. (2018)[213]	No Specific Country	2010-2014	UN	Culture	13431	94	Low	Low
Salmonella (non-Typhi)	Kibuuka et al. (2015)[214]	Uganda	2012-2012	UN	Culture	250	11	Medium	Medium
Salmonella (non-Typhi)	Kiemde et al. (2018)[215]	Burkina Faso	2015-2015	UN	Culture	684	31	Low	Low
Salmonella (non-Typhi)	Ley et al. (2009)[216]	United Republic of Tanzania	2008-2009	UN	Culture	1680	49	Low	Low
Salmonella (non-Typhi)	Mahende et al. (2014)[217]	United Republic of Tanzania	2013-2013	UN	Culture	808	2	Low	Low

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
Salmonella (non-Typhi)	Marks et al. (2017)[218]	No Specific Country	2010-2014	UN	Culture	13431	94	Low	Low
Salmonella (non-Typhi)	Meremo et al. (2012)[219]	United Republic of Tanzania	NA-NA	UN	Culture	346	12	Low	Medium
Salmonella (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-Typhi)	Mtove et al. (2010)[222]	United Republic of Tanzania	2008-2009	UN	Culture	1502	45	Low	Low
Salmonella (non-Typhi)	Mtove et al. (2011)[223]	United Republic of Tanzania	2006-2010	UN	Culture	6836	232	Low	Low
Salmonella (non-Typhi)	Mtove et al. (2011)[224]	United Republic of Tanzania	2009-2010	UN	Culture	965	1	Medium	Low
Salmonella (non-Typhi)	Nadjm et al. (2010)[225]	United Republic of Tanzania	NA-NA	UN	Culture	3639	160	Low	Low
Salmonella (non-Typhi)	Nadjm et al. (2012)[226]	United Republic of Tanzania	2007-2007	UN	Culture	198	5	Low	Medium
Salmonella (non-Typhi)	Ochaya et al. (2018)[227]	Uganda	2013-2013	D COMORBID	Culture	256	3	High	Medium
Salmonella (non-Typhi)	Onchiri et al. (2016)[228]	Kenya	2012-2014	UN	Culture	1496	19	Low	Low
Salmonella (non-Typhi)	Onyango et al. (2008)[229]	Kenya	2004-2005	D GI	Culture	20	18	High	High
Salmonella (non-Typhi)	Onyango et al. (2009)[230]	Kenya	2004-2005	D GI	Culture	40	20	High	High
Salmonella (non-Typhi)	Park et al. (2016)[231]	No Specific Country	2010-2014	UN	Culture	13431	73	Low	Low
Salmonella (non-Typhi)	Peters et al. (2004)[232]	Malawi	2000-2000	UN	Culture	352	44	Low	Medium
Salmonella (non-Typhi)	Pradhan et al. (2012)[191]	Nepal	2006-2007	UN	Culture	1039	2	Low	Low
Salmonella (non-Typhi)	Preziosi et al. (2015)[233]	Mozambique	2011-2014	UN	Culture	841	10	Low	Low
Salmonella (non-Typhi)	Sothmann et al. (2015)[234]	Ghana	2012-2012	UN	Culture	2306	24	Low	Low
Salmonella (non-Typhi)	Tezcan et al. (2006)[235]	Turkey	1996-2004	D COMORBID	Culture	621	1	High	Low
Salmonella (non-Typhi)	Wiersinga et al. (2015)[236]	Gabon	2012-2013	UN	Culture	941	5	Low	Low
Schistosoma mansoni	Degarege et al. (2012)[237]	Ethiopia	2010-2011	UN	Microscopy	702	82	Low	Low
Streptococcus spp.	Hinjoy et al. (2017)[238]	Thailand	2015-2015	UN	Culture	70	1	Medium	High

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)[239]	India	NA-NA	D COMORBID	PCR	162	21	High	Medium
Venezuelan Equine Encephalitis virus	Forshey et al. (2010)[240]	No Specific Country	2000-2007	UN	Culture, PCR, ELISA	13259	250	Low	Low
Venezuelan Equine Encephalitis virus	Kocher et al. (2016)[241]	Peru	2013-2014	UN	PCR	2054	22	Low	Low
Venezuelan Equine Encephalitis virus	Manock et al. (2009)[38]	Ecuador	2001-2004	UN	Culture, IgM, IFA, PCR	229	2	Medium	Medium
Venezuelan Equine Encephalitis virus	Morrison et al. (2008)[242]	Peru	2005-2006	UN	IFA, PCR	1136	34	High	Low
West Nile virus	Boisen et al. (2015)[101]	Sierra Leone	2012-2012	D SP	PCR	23	4	High	High
West Nile virus	Chinikar et al. (2012)[243]	Iran (Islamic Republic of)	2008-2009	D NEU	PCR	249	3	High	Medium
West Nile virus	Elyan et al. (2014)[244]	Afghanistan	2008-2010	UN	PRNT	277	24	Medium	Medium
West Nile virus	Hercik et al. (2017)[13]	United Republic of Tanzania	2014-2015	UN	PCR	842	1	Low	Low
West Nile virus	Kumar et al. (2014)[245]	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)[247]	Kenya	2009-2012	UN	PRNT	379	47	Low	Medium
West Nile virus	Williams et al. (2018)[248]	United Republic of Tanzania	2013-2014	UN	Sequencing	12	2	Medium	High
Yersinia pestis	Sinyange et al. (2016)[249]	Zambia	2015-2015	D SP	PCR	12	6	High	High

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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[1])
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%)

[1]Table includes data from 235 of 244 articles included in the review, excluding 9 articles reporting data from 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.

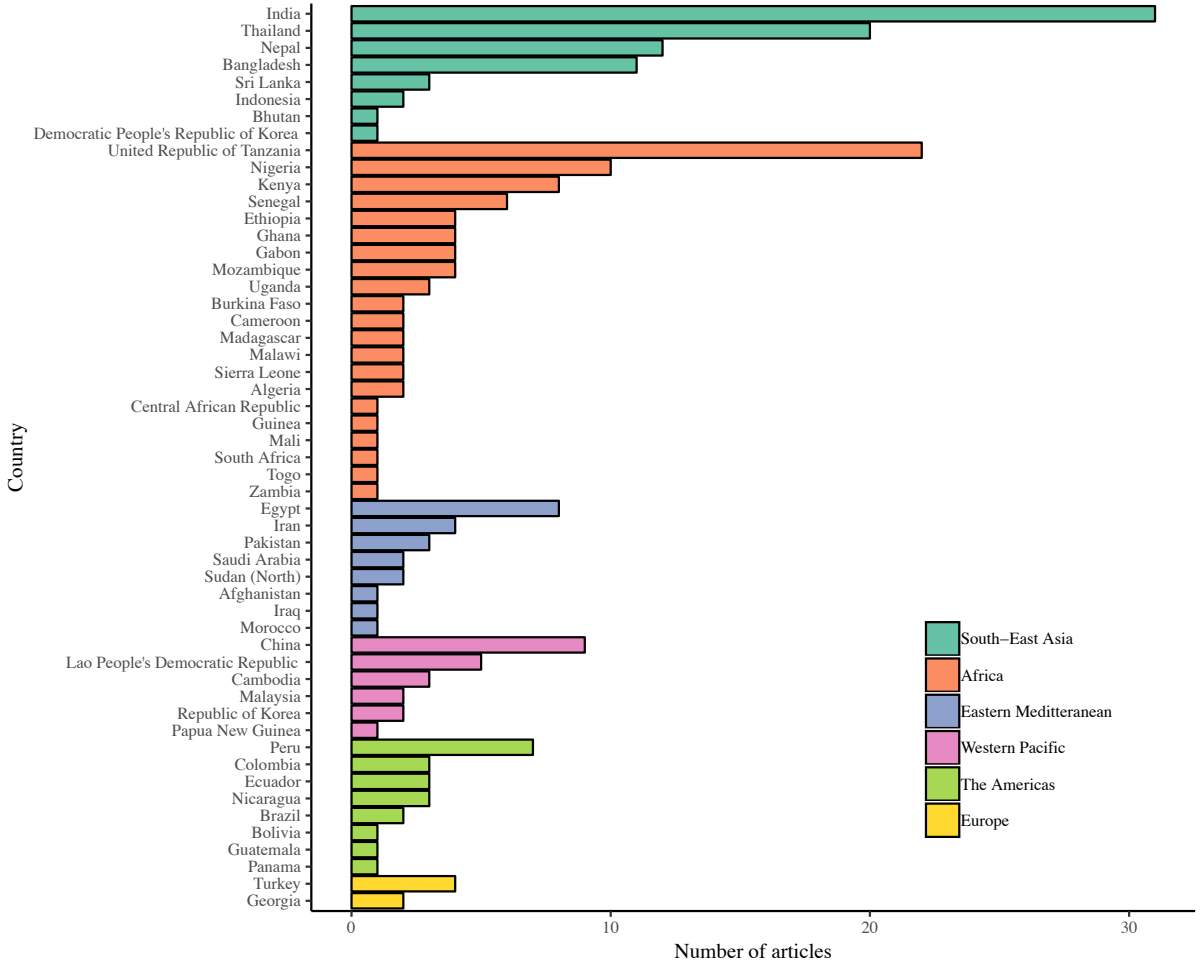
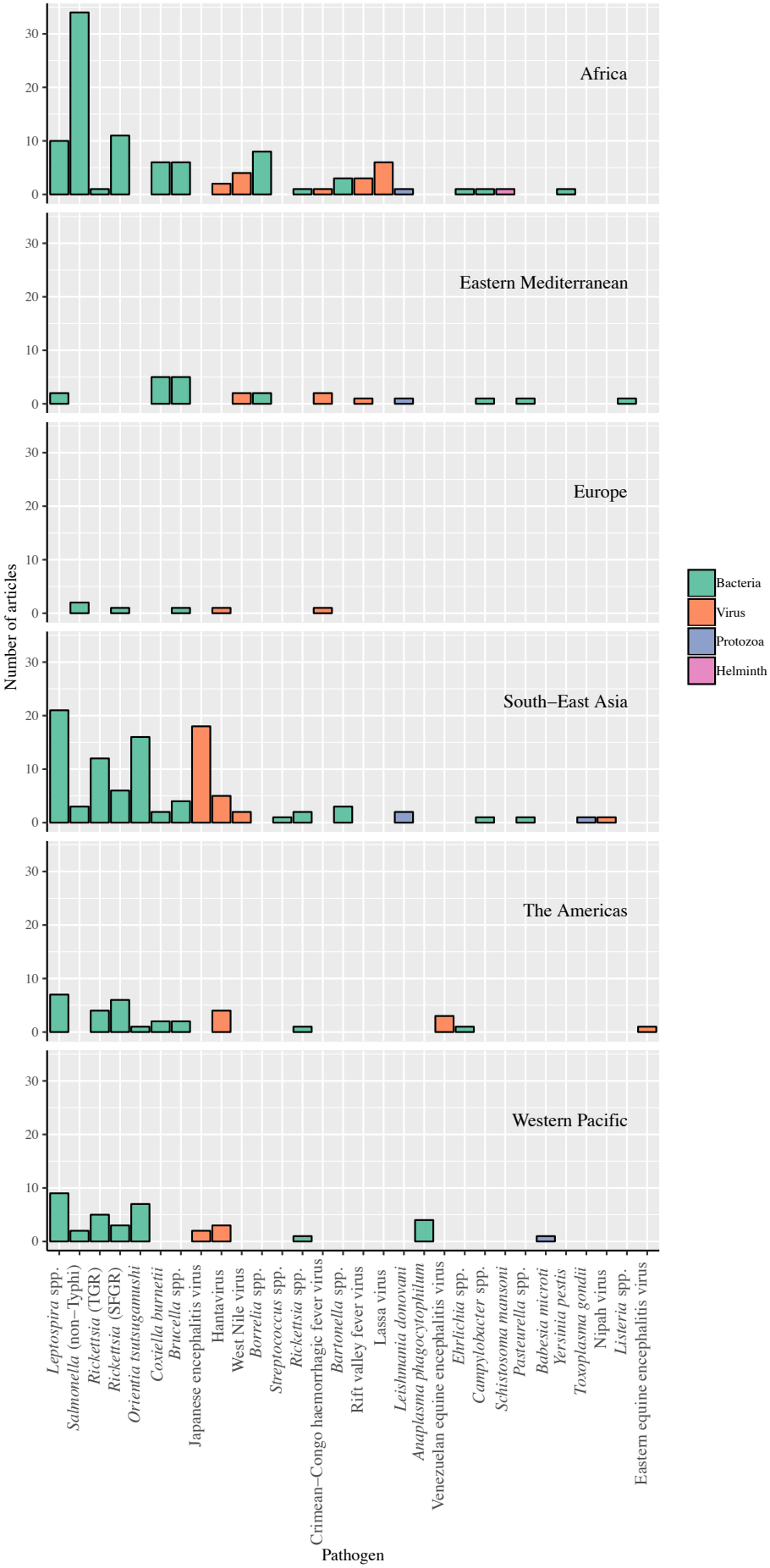


Figure S2: Barcharts showing number of articles from each global region contributing data for each of 30 zoonoses.

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


Africa
Eastern Mediterranean
Europe
South–East Asia
The Americas
Western Pacific
Number of articles
0
10
20
30
Bacteria
Virus
Protozoa
Helminth
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.
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.
Schistosoma mansoni
Pasteurella spp.
Babesia microti
Yersinia pestis
Toxoplasma gondii
Nipah virus
Listeria spp.
Eastern equine encephalitis virus
Pathogen

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512
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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 re-run 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 authorshttps://www.thelancet.com/pb/assets/raw/Lancet/authors/tlid-info-for-authors.pdf)
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(https://www.thelancet.com/pb/assets/raw/Lancet/authors/icmje-coi-form.zip)
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 malaria-endemic 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 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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Zoonotic causes of febrile illness in malaria endemic countries: a systematic review

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Abstract

Fever is one of the most common reasons for healthcare seeking globally and the majority of human pathogens are ~~zoonoses~~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 ~~46 (41·8~~53 (48·2%) of ~~the~~ 110 malaria endemic countries ~~included in searches.~~. The ~~181~~244 articles included described diagnosis of ~~29~~30 zoonoses in febrile people ~~from 46 countries.~~. The majority of zoonoses were bacterial (n=~~16~~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. ~~Improved~~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.

Introduction

Fever is one of the most common ~~syndromes~~symptoms prompting healthcare seeking globally ~~(1-3).~~[1-3] Fever has myriad causes and ~~the~~their non-specific clinical presentation means that clinical history and physical examination are often ~~unable~~insufficient to accurately ~~suggest the~~identify causal ~~pathogen (1).~~pathogens.[1] Limitations in laboratory services and available diagnostic tools further contribute to diagnostic challenges ~~(4).~~[4] In malaria-endemic countries, fever is often assumed to be due to malaria ~~(5).~~[5] The mortality and morbidity attributable to malaria remains considerable, but there is also evidence of widespread over-diagnosis ~~(6,7) and indeed globally~~ within malaria-endemic areas ~~(8).~~[6-8] The recognized over-diagnosis of malaria together with declines in malaria incidence since the peak in global malaria deaths in 2004 ~~(~~[9,10]~~)~~ have prompted attention to non-malaria causes of fever in ~~these~~ malaria-endemic areas ~~.(~~[11,12]~~).~~ Zoonotic pathogens are likely to play a substantial role ~~globally~~ as causes of fever globally. Almost two-thirds of all human pathogens are zoonotic ~~(13),~~[13] and there is growing evidence that many zoonoses cause more cases of human febrile illness than previously appreciated ~~.(~~[12,14-20]~~).~~ Improved understanding of the impacts and burdens of zoonotic causes of fever in malaria-endemic countries would provide the epidemiological evidence base ~~to enable~~for disease control program development and also influence diagnostic and treatment algorithms for fever, with the potential to improve clinical outcomes. The aim of this study was to systematically review the published literature to describe the occurrence and distribution of reported zoonotic causes of human febrile illness in countries where malaria is endemic.

Methods

Search strategy and selection criteria

The target literature for this systematic review was peer-reviewed published articles that described the testing of one or more febrile ~~people~~person from malaria-endemic countries for one or more zoonotic ~~pathogens~~pathogen using robust diagnostic testing criteria to demonstrate acute infection. Literature searches of the Medline and Embase databases were run using the OvidSP gateway. Searches were limited to English language articles published in the period 2004 to ~~2016~~2019 inclusive, to span the period from the described peak of global malaria mortality in 2004 ~~(9).~~to present.[9] The searches were last executed on ~~26 August 2016.~~03 January 2019. Outputs of

database searches were combined and de-duplicated ~~in R (21). Full~~using R.[21] Additional details of searches, screening, review, and data extraction processes are given in the ~~Supplementary Information (SI).~~appendix.

~~We constructed three~~Three search concepts for '~~Fever', 'Zoonoses', and 'Malaria Endemic Countries'.~~fever,' 'zoonoses,' and 'malaria endemic countries' were constructed. To construct the '~~Fever'~~fever' concept the exploded subject heading and keywords were combined using database appropriate syntax (e.g~~.~~., exp Fever/ OR fever$1.mp. OR febrile.mp.). For the '~~Zoonoses'~~zoonoses' concept, a reference list of eligible zoonotic pathogens was compiled using lists of zoonotic diseases from the World Health Organization (WHO~~) (22) and World Organisation of Animal Health (OIE) (23))~~[22] and World Organisation of Animal Health (OIE)[23] as well as literature-based searches to identify 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. ~~Full~~Additional details of ~~these three preliminary searches~~search concept construction are given in the ~~SI~~appendix. All pathogens identified through these approaches were mapped to existing subject headings and keywords at the lowest ~~appropriate~~ taxonomic level possible, typically genus or species. In instances where pathogen species or serovars within the same genus varied in their zoonotic status, search concepts were constructed to include all zoonotic and non-zoonotic species or serovars and articles relating to non-zoonotic species were excluded at the full text stage. The candidate pathogens were classified to differentiate pathogens 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 the majority of human infections are not acquired through zoonotic transmission. We classified pathogens using the stages in the process towards human endemicity defined in Wolfe et al ~~(24). Pathogens classified as stages 1 to 3 were retained and full details are given in the SI.~~.[24] Pathogens classified at stages one to three (normatively acquired through zoonotic transmission) were retained (appendix). 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~~.~~., exp anthrax/ OR anthrax.mp. OR exp Bacillus anthracis/ OR bacillus anthracis.mp.). The list of pathogen~~-~~ or disease~~-~~ specific searches was combined using OR syntax to generate the full 'zoonoses' search concept (~~Table 1 & SI~~appendix). The '~~Malaria Endemic Countries'~~malaria endemic countries' concept was constructed by mapping country names for countries defined as malaria endemic in the WHO global malaria reports for the years 2005 and 2016 to Medline and Embase subject headings ~~(10,25). Each country was searched for using both the exploded subject heading where 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 AND operators and database specific syntax gateway (SI).~~[10,25] Each country was searched for using both the exploded subject heading where possible and keywords in all cases (e.g., exp Kenya/OR Kenya.mp.). The three concepts, fever,' 'zoonoses,' and 'malaria endemic countries' were combined using AND operators and database specific syntax (appendix).

Study selection and validity assessment

Articles that reported the diagnosis of a zoonotic pathogen in a population from a malaria endemic country defined ~~principally~~ on the basis of febrile illness were selected for full-text review. Conference proceedings and records that did not include any abstract text or an abstract in English were excluded. Abstracts and titles were screened by two independent reviewers (two of ~~DVH, GL,~~ MC, ~~and~~ MES, KJA, GAFL, DVH, JAC, SC and MPR) using pre-defined criteria (~~SI Table S2~~appendix table S1). Articles were selected for inclusion if the abstract or title described clinical and/or laboratory evaluation of a group of ≥ 2 people ~~with a~~all of whom had fever and ~~diagnosis~~some of whom were diagnosed of one or more pathogens from the reference list of zoonotic pathogens (~~Table~~table 1). Abstracts referring to the use of blood culture were also retained at this stage even if a zoonosis was not explicitly mentioned in the abstract (~~SI Table S2). Conference proceedings were excluded.~~appendix table S1). When two reviewers disagreed on article classification, a third independent reviewer (~~DVH, GL~~one of JEBH, MC, MES, GAFL, DVH or MPR) resolved the tiebreak. Full text articles were sought for all articles not excluded ~~at the screening step~~during abstract review steps. All articles were searched for using PubMed, Google and the libraries of the University of Glasgow, Duke University, Washington University in St. Louis, and US Centers for Disease Control and Prevention (US CDC). Articles were excluded if a full~~-~~ text for the citation could not be obtained. Two independent reviewers (two of, JEBH, ~~MPR, JB~~MC, MES, JB and ~~MC~~MPR) evaluated full text articles using pre-defined inclusion and exclusion criteria (~~Table~~table 2~~).~~, appendix table S2). Strict diagnostic case definitions ~~were used~~ based on WHO and US CDC guidelines ~~to ensure~~ensured that only studies reporting robust and specific diagnostic methods were retained (~~Table~~table 2). Articles were excluded if they ~~met~~did not meet one or more of the study ~~exclusion~~inclusion criteria or ~~failed to~~if they did meet at least one of the study ~~inclusion criterion (Table~~exclusion criteria (table 2). In cases where reviewers disagreed on article classification, discrepancies were checked and resolved by JEBH in discussion with other reviewers.

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

Pathogen	Species, subspecies, and serovars excluded	Pathogen type[13]
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 spongiform	-	Prion

encephalopathy		
Brucella spp.	-	Bacteria
Burkholderia spp.	*B. cepacia* complex and *B. pseudomallei* excluded	Bacteria
Campylobacter spp.	-	Bacteria
Chlamydia spp.	All species excluded with the exception of *C. psittaci*	Bacteria
Coxiella burnetii	-	Bacteria
Cryptosporidium 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 *E. coli*	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 *F. tularensis*	Bacteria
Hantavirus	-	Virus
Henipaviruses	-	Virus
Lassa virus	-	Virus
Leishmania spp.	*L. donovani* excluded if detected in India	Protozoa
Leptospira spp.	-	Bacteria
Listeria spp.	-	Bacteria
Lyssavirus	All species excluded with the exception of Rabies virus	Virus
Marburg virus	-	Virus
Mycobacterium	All species excluded with the exception of *M. bovis* and *M. avis*	Bacteria
Nairovirus	All species excluded with the exception of Crimean-Congo haemorrhagic fever virus	Virus
Orientia[1]	-	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
Rickettsia spp.[2]	*R. prowazekii* excluded	Bacteria
Salmonella spp.	All species, subspecies, and serovars excluded with the exception of nontyphoidal *Salmonella* serovars	Bacteria
Schistosoma spp.	*S. haematobium*, *S. intercalatum*, and *S.*	Helminth

	mekongi.excluded	
Streptobacillus spp.	-	Bacteria
Streptococcus spp.	All species excluded with the exception of *S. canis*, *S. suis*, *S. equi*, and *S. iniae*	Bacteria
Taenia spp.		Helminth
Toxocara		Helminth
Toxoplasma gondii	-	Protozoa
Trichinella spp.	-	Helminth
Trypanosoma spp.	All species excluded with the exception of *T. brucei* rhodesiense and *T. cruzi*	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 *Y. pestis*, *Y. enterocolitica* and *Y. pseudotuberculosis*	Bacteria

[1] *Orientia* was covered by search syntax for *Rickettsia*.

[2] For data extraction, data on *Rickettsia* were classified as *Rickettsia* (SFGR) or *Rickettsia* (TGR) where the data resolution allowed. When details on the species of *Rickettsia* were not given, these data were classified as *Rickettsia* spp.

Table 2: Inclusion and exclusion criteria for full text review

Outcome	Criterion
Inclusion:	• Febrile population (≥ 2 people with a fever, defined as body temperature ≥ 38·0°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 iii) Serological diagnosis of acute infection based on testing of both acute and convalescent phase serum samples and demonstration of seroconversion 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[1] v) IgM detection in cerebrospinal fluid (CSF) for selected pathogens for which widely accepted case definitions include IgM detection in CSF[2]

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 ≥ 2 people principally classified based on a shared (100% frequency) aetiological diagnosis. • Review

[1]The following met study criteria for valid diagnostics for pathogen detection based on single sera only: *Leptospira* spp. agglutination titer of ≥ 800 by microscopic agglutination test in one serum specimen [26]; detection of Hantavirus-specific IgM in a serum sample [27]; detection of virus-specific IgM antibodies in serum with confirmatory virus-specific neutralizing antibodies for Eastern equine encephalitis virus (EEEV), West Nile virus (WNV), Western equine encephalitis virus (WEEV), and Venezuelan equine encephalitis virus (VEEV) [28]; identification of lyssavirus specific antibody by indirect fluorescent antibody test or complete rabies virus neutralization at 1:5 dilution in the serum of an unvaccinated person [29]; detection of viral antigens in blood by enzyme-linked immunosorbent assay for Ebola [30,31], Marburg [31,32], Lassa [31,33], and Crimean-Congo haemorrhagic fever viruses [31]; detection of Rift Valley fever antigens or IgM in blood by enzyme-linked Immunosorbent assay [34]; and

[2] IgM detection in CSF was considered a valid diagnostic for EEEV, Japanese encephalitis virus (JEV), rabies virus, WEEV, WNV and VEEV [28,29,35].

Data extraction and bias assessment

Data extraction was conducted independently by one of two reviewers (JEBH and MC). Article-level data were extracted on the location (country and WHO regional classification ~~(26)),~~), [36] study period (start and end year of data collection~~)~~), and eligibility criteria used in the study. ~~Data extracted on the study population included whether the population was described inpatient or outpatient and urban or rural.~~ Each population ~~reported~~ was classified according to the clinical presentation as undifferentiated ~~febrile~~ or differentiated ~~febrile~~. Differentiated febrile populations were further classified as: i) febrile neurologic; ii) febrile ~~hemorrhagic~~haemorrhagic; iii) febrile gastrointestinal; iv) febrile respiratory; v) specific febrile aetiology suspected ~~(27-29). Articles were also classified to record if the~~; vi) febrile co-morbid group (i.e., malignancy, immunocompromise).[37-39] Data extracted on each population included any demographic restriction of the study population, the age range of the study participants, whether the population was described as inpatient or outpatient, urban or rural, and whether data were collected during a reported disease outbreak or not. To extract data on ~~the~~ zoonotic pathogens ~~included in each study~~, every ~~included~~ article was ~~first~~ classified to record if the study reported looking for ~~diagnosed~~or diagnosing one or more febrile individuals with ~~each~~any of the zoonotic pathogens included in the study reference list (~~Table~~table 1), irrespective of the diagnostics used. ~~Second, for~~Additional data were extracted when the article reported application of a diagnostic approach that met study validity criteria. For each combination of article and pathogen, details of the valid diagnostic methods used, the type and number of samples tested, and the number of positive samples were recorded~~.~~ (appendix table

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

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).[40-42] 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.

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.

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).~~[21] and plots were made using the package ggplot2.[43]

Role of the funding source

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 to all the data in the study and had final responsibility for the decision to submit for publication.

~~The principal sources of potential bias identified in the course of this study are the lack of standardization of the febrile populations included in different studies, variation in the pathogens tested for, and variation in the diagnostic approaches applied. Data enabling the characterization of study populations (e.g. location, outbreak or not, inpatient or outpatient, rural or urban etc.) were collected to enable assessment of the influence of these factors on reported outcomes. Data on the pathogens looked for in included studies 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. Publication bias is likely to strongly influence the outputs from this review, but it was not possible to systematically evaluate this as publication of negative findings is rare, diagnostic practices are highly variable and no robust methodology exists to estimate the 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 febrile illness in populations that were principally defined by the presence of fever. The application of diagnostic criteria that are strictly comparable across pathogens is not feasible. We applied strict diagnostic criteria, erring towards high specificity but reduced sensitivity to minimize the influence of this source of bias. The implications of these likely biases for the interpretation of study data are discussed.~~

Results

Database searches yielded a total of ~~12,277~~16,332 and ~~8,065~~10,574 records through Embase and Medline, respectively, resulting in a total of ~~12,927~~17,852 unique records following de-duplication (~~Figure~~figure 1). ~~English language abstracts were available for 10,927~~A total of 4,531 (25·4%) records ~~and 687~~were excluded during pre-screening, 13,321 (74·6%) records were screened and 962 (7·2%) of these were retained after title and abstract review. In total, ~~506~~718 (74·6%) articles were excluded during full text review ~~(Figure 1). Finally, 181~~and 244 (25·4%) articles met all study inclusion criteria and were included ~~in this review (Figure 1 and Table 3).~~ (figure 1, appendix table S6).

Articles included in the review yielded data from ~~46 (41·8~~53 (48·2%) of the 110 malaria endemic countries ~~included in searches. Seven~~ (figure 2). The majority of articles with a single country origin (n=235) reported data from ~~multiple countries. The distribution~~Africa (83 of ~~the remaining 174~~235 articles ~~by country and WHO region is shown in Figures 2 and 3, and Table 4. Sixty-seven (37·0%) of the 181 studies included in the review~~, 35·3%) or South-East Asia (81 of 235 articles, 34·5%) (appendix table S7, figure S1). One hundred and six (45·1%) of the 235 articles with a single country origin were conducted in one of ~~four~~six dominant countries: India (n=~~23), Thailand, (n=17~~31), United Republic of Tanzania (n=~~15), and~~ 22), Thailand, (n=20), Nepal (n=12~~).~~), Bangladesh (n=11), and Nigeria (n=10). The data reported in ~~included studies~~the review were gathered ~~from~~between 1994 ~~to 2015~~and 2017 inclusive.

~~The 181~~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 ~~a total of 29~~30 zoonoses~~. The 29 pathogens for which diagnostic data were extracted~~ that included ~~16~~17 bacterial pathogens (~~55·2%), 9~~56·7%), nine viruses (~~31~~30·0%), ~~3~~three protozoa (10·~~30~~%), and ~~1~~one helminth (3·~~4%). Nontyphoidal~~3%). *Leptospira* spp., nontyphoidal *Salmonella* serovars (NTS~~), Leptospira spp.~~) and rickettsioses were the most frequently reported bacteria, while *Japanese encephalitis virus* (JEV), *Hantavirus*, and *West Nile virus* (WNV) dominated among ~~viruses (Figures 4, 5 and 7). Before applying diagnostic test validity criteria, the 181 articles reported looking for and diagnosing 36 and 35 zoonoses respectively in these populations. This list of zoonoses was reduced to 29 after the criteria for diagnostic testing approach were applied (Figure 4). The breakdown of articles contributing data on different pathogens in different WHO regions is shown in Figure 5.~~reported viruses (figures 3, 4).

The number of febrile individuals included in each study population ranged from 4 to 13,845, with a median of 300 (IQR: 120 – 812). In total, 309 records of zoonotic pathogens causing fever were extracted from the 244 articles. The proportion of fevers attributed to each pathogen reported ranged from <1·0% to 95·0% (figure 4). The risk of bias classification in the precision of the proportion of fevers attributed to each zoonosis was 136 (44·0%) of 309 low risk, 79 (25·6%) of 309 medium risk, and 94 (30·4%) of 309 high risk.

Of the ~~181~~244 studies, ~~75 (41·4~~87 (35·7%) described the clinical setting as inpatient, ~~28 (15·5~~36 (14·8%) as outpatient, ~~22 (12·2~~39 (16·0%) as mixed, and ~~for 56 (30·9%),~~82 (33·6%) gave no clear classification of the clinical setting ~~was given. Twenty-five (13·8%)~~ . Thirty (12·3%) studies described the study area as urban, ~~43 (23·8~~59 (24·2%) as rural, ~~24 (13·3~~45 (18·4%) mixed or both, and ~~for 89 (49·2%)~~110 (45·1%) gave no clear classification of the study area ~~was given. Of the 181 febrile study~~. Eighteen (7·4%) studies included adult participants, 43 (17·6%) included children, 153 (62·7%) included both adults and children and 30 (12·3%) gave no clear classification of the ages included. 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. Of the 244 studies, 10 (4·1%) were described as outbreak investigations and 169 (69·3%) populations~~, 41~~ were classified as undifferentiated febrile populations. Among the 75 differentiated populations, 36 (48·0%) had specific febrile aetiologies suspected, 17 (22·7%) were classified as ~~differentiated, 95 (52·5~~febrile neurological, eight (10·7%) as ~~undifferentiated, and 45 (24·9%) were mixed. Among the differentiated~~comorbid populations~~ 4 (9·8%) were~~, eight (10·7%) as febrile haemorrhagic, five (6·7%) as febrile gastrointestinal~~, 5 (12·2%) febrile haemorrhagic, 17 (41·5%) febrile neurological, 12 (29·3%) had specific febrile aetiologies suspected, and the remaining 3 (7·~~ and one (1·3%) ~~were mixed populations (including patients with~~ as febrile respiratory ~~symptoms).~~. The associations between clinical presentation of febrile populations and the ~~29~~subset of 25 pathogens identified in the ~~different groups~~

differentiated populations are shown in ~~Figure 6. All 6 pathogens identified in febrile haemorrhagic populations were also detected in undifferentiated patient groups. *Eastern Equine Encephalitis virus* (EEEV) and *Nipah virus* were only detected~~figure 5. The risk of bias classification in ~~febrile neurological populations and *Campylobacter* spp. was only detected in a~~the representativeness of febrile ~~gastrointestinal population (Figure 6).~~

~~In total, 9 (5·0%) of 181 studies included were described as outbreak investigations. 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, *Leptospira* spp. in Bangladesh and Thailand, *Nipah* virus in India, spotted-fever group rickettsioses (SFGR) in Guatemala, *Venezuelan Equine Encephalitis virus* (VEEV) in Peru, WNV in India (2 studies), and *Yersinia pestis* in Zambia.~~

~~The number of febrile individuals included in each study population ranged from 6 to 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 zoonotic pathogens causing fever were extracted from the 181 articles. Figure 7 plots 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%, median 5.5% and mean 13.5%.~~78 (32·0%,) of 244 high risk.

Discussion

~~The findings of this~~This systematic review ~~reveal a~~reveals diverse ~~group of~~ zoonoses causing febrile illness within multiple malaria-endemic countries, often at high 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, sparse and patchy reporting suggests that the ~~clinical burden~~prevalence of zoonoses is ~~likely to be~~ widely under-estimated. ~~As knowledge~~Knowledge of probable infecting pathogen is ~~paramount~~crucial to inform ~~the~~ clinical management ~~and prevention~~ of febrile illness~~,~~ and 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~~. Our study highlights the clinical importance of several pathogens, including some that occur across a wide range of areas and at high prevalence. The~~ globally. This study should generate greater awareness ~~about~~of the clinical importance of ~~zoonotic pathogens~~zoonoses and provide a pragmatic starting point for actions to better manage these diseases, for example through improved diagnostic and clinical treatment algorithms~~, as well as~~. These findings demonstrate the need for enhanced epidemiological understanding ~~that is needed~~of multiple zoonoses to inform disease prevention.

This review reveals substantial gaps in the evidence base, including a complete absence of eligible studies from more than half of the ~~majority, 64 (58·2%) of~~ 110 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 an English language scientific paper on the occurrence and prevalence of a specific zoonosis that could be included in this review. The underlying distribution and relative clinical importance of individual pathogens ~~will vary~~varies, as ~~well as~~do patient healthcare seeking ~~behavior~~behaviour, clinical, and patient awareness of different pathogens, diagnostic capacities, and probability of publication. It is

therefore not plausible to expect this review to yield data on ~~each zoonosis~~all zoonoses in all countries. However, considering the inclusion of 110 countries and construction of searches for ~~48~~50 pathogens or pathogen groups, the identification of just ~~181~~244 eligible studies underscores the profound overall shortage of robust quantitative data describing the role of any zoonoses as causes of fever in most 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 research and publication effort on the topic of non-malaria febrile illness and cannot be interpreted as an accurate reflection of the underlying distribution of zoonotic pathogens or their clinical importance. The restriction of this review to English language texts will also have reduced the probability that studies from French and Spanish speaking countries were included and may partially account for some specific gaps, such as the 27 countries in Africa and 15 in the Americas for which no eligible studies were identified (Figure 2, Table 4).~~

~~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 significantly greater than expected from the taxonomic distribution of all zoonotic pathogens, which comprise 30.1% bacteria (χ^2 = 26·4, d.f. = 1, p<0·001, data from (31)) and also contrasts with the taxonomic distribution of emerging zoonoses, which are dominated by viruses (13). While this study is unlikely to accurately reflect the true taxonomic distribution of all fever-causing zoonoses, this finding does reinforce the clinical importance of endemic bacterial zoonoses and need for greater awareness of these zoonoses, particularly given the availability of effective treatments that could substantially mitigate these disease burdens.~~

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 ~~rickettioses~~rickettsioses (TGR) reported more frequently in South-East Asia ~~(Figure 5).~~and Western Pacific regions (appendix figure S2). For viruses, Lassa virus was reported only in Africa and JEV ~~only~~predominantly in South-East Asia. ~~These geographic differences in the reporting patterns will only partially reflect the true~~ The distribution of studies cannot be interpreted as an accurate reflection of the underlying distribution ~~and~~of zoonotic pathogens, their prevalence ~~of each pathogen. Diagnostic testing behavior is not uniform and the~~or clinical importance. The pathogens that are looked for ~~also depends~~depend 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 generated in this review cannot be used to formally quantify the under or over representation of different pathogens in different countries but may help indicate potential gaps in what is looked for. Once specific~~Once pathogens are identified in ~~specific locations,~~any location there will likely be ~~improved~~increased clinical ~~and~~, 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 febrile illness in specific locations can arise and contribute to the neglect of other pathogens. ~~The findings of this review can highlight pathogens and locations where these dogmas should be questioned. The relative lack of studies reporting robust diagnoses of illness caused by *Leptospira* spp. in Africa, for example, is likely to~~

~~reflect a lack of research effort and limited diagnostic capacity rather than a relative absence of clinical leptospirosis in the region (14). Similarly, recent studies indicate that the lack of studies investigating *O. tsutsugamushi* in Africa may be a reflection of a presumed absence of scrub typhus in Africa and a consequent failure to test for *Orientia*, rather than an absence of the pathogen itself, potentially allowing a substantial incidence of scrub typhus to go unrecognized (32,33).~~ The findings of this review may help indicate potential gaps in what is looked for and can highlight pathogens and locations where these dogmas should be questioned.

~~Figure 4 shows~~ The majority of the ~~comparison~~30 zoonotic causes of fever contributing data for this review were bacteria (56·7%). This proportion is greater than expected from the taxonomic distribution of all zoonotic pathogens, which comprise 30·1% bacteria[44] and also contrasts with the taxonomic distribution of emerging zoonoses, which are dominated by viruses.[13] This finding reinforces the clinical importance of endemic bacterial zoonoses. The comparisons between the number of articles that looked for, diagnosed, and contributed data for each of ~~36 zoonoses mentioned in the 181 articles analyzed. These three metrics and their comparison provide several insights. First, revealing~~40 zoonoses reveals the range of zoonotic pathogens investigated and ~~providing an indication of~~ indicates the relative investigative effort used for each pathogen~~. The~~ (figure 3). However, the figures for number of articles where a pathogen was looked for but not identified must be interpreted with caution given the high probability of reporting bias and ~~likelihood that studies often omit mention of investigations for pathogens that are not subsequently found. Finally, for~~how rarely negative results are reported. For several pathogens, the number ~~(~~and~~/or~~ proportion~~)~~ of articles that reported a zoonotic diagnosis ~~of a zoonoses~~ but did not contribute further data for ~~this are non-trivial. These articles report diagnosis of zoonoses but data were not extracted as~~analysis (because the diagnostic approaches described ~~do~~did not meet study quality criteria~~. These results demonstrate~~) are substantial (figure 3). This demonstrates that for many, predominantly bacterial pathogens, suboptimal ~~and/or non-standardized~~ diagnostic tests or imprecise case definitions are in widespread use, ~~highlight~~highlighting the challenges of accurately quantifying disease prevalence and comparing studies.

~~Unfortunately, several factors contribute to the ongoing~~Persistent challenges ~~of~~in the diagnosis of febrile patients~~. These~~ include limited laboratory capacity, reliance on demonstration of seroconversion for confirmed diagnosis of many pathogens ~~(with limited utility for management of acute cases), non-sustainable~~, unsustainable costs associated with more advanced ~~diagnostics~~diagnostic technologies, and lack of simple and affordable tests for the accurate and timely diagnosis of several zoonotic pathogens. ~~Linked to this~~In addition, the delays in patient presentation that are typical in many resource limited settings, ~~lead to~~ low magnitude ~~bacteremia~~bacteraemia at presentation ~~or~~and, presentation of patients during the immune phase of illness, ~~factors that further~~all limit the sensitivity of culture or PCR-based diagnostic approaches when available. These challenges necessitate syndromic approaches to patient management and broad-spectrum treatment. One specific issue relates to tetracycline use. ~~*O. tsutsugamushi* and rickettsioses, which this~~This study identified rickettsioses and *O. tsutsugamushi* as common causes of fever~~,~~. These would ~~both~~ benefit from treatment with tetracyclines, which are not currently included in the Integrated Management of Adolescent and Adult Illness (IMAI) algorithms for septic shock and severe respiratory distress without shock ~~(34).~~[45] In light of the extensive

contribution of tetracycline-responsive infections to fever in malaria-endemic countries, revisions to clinical guidelines may be warranted to suggest the empirical use of tetracyclines in addition to beta-lactams in ~~those~~ scenarios where the infection with tetracycline-responsive pathogens ~~could not~~cannot be excluded.

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

~~The most common patient population in this review comprised people with undifferentiated febrile illness. Figure 6 illustrates the associations between different zoonoses and different clinical presentations. While some zoonotic pathogens were associated with specific clinical presentations in addition to fever (e.g. neurological, gastrointestinal, haemorrhagic clinical presentation) in some reports, almost all pathogens were also detected in undifferentiated populations. This suggests that zoonoses commonly linked with specific syndromes (e.g. Crimean-Congo haemorrhagic syndrome and JEV) still need to be considered in the differential diagnosis of undifferentiated fever, even in the absence of other specific clinical features. While documented associations between pathogens and specific clinical presentations may assist clinicians in the differential diagnosis of febrile illnesses, the impact of variation in when specific pathogens are tested for must also be remembered when interpreting these data.~~
The findings of this review show that one or more zoonotic causes of fever are likely to present a threat to health in all of the countries included in this review. Only a small proportion of the febrile populations included in the study were defined as demographically restricted and most were not clinically differentiated. Even zoonoses commonly linked with specific syndromes (e.g., Crimean-Congo haemorrhagic fever virus and JEV) were diagnosed in undifferentiated populations and should thus be considered in the differential diagnosis of undifferentiated febrile illness. 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.[46]

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

~~complexities in~~challenges of systematically quantifying the non-reporting of either diagnostic test performance or the non-detection of specific pathogens. ~~The findings of this study thus include only populations where zoonoses were identified.~~ Biases in testing practices for different pathogens in different locations and with different clinical febrile presentations will influence the pathogens looked for, detected and reported. The application of diagnostic criteria that are strictly comparable across pathogens is not feasible. ~~in this study. The proportions of febrile illnesses attributable to each zoonotic pathogen (Figure 7) thus apply only for populations where the pathogen is known to be present.~~In this study, strict diagnostic criteria were applied, preferentially including diagnostic approaches with a high specificity, to minimize the influence of false positives within the analyses. 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. Figure 5 shows clear variation in risk of representativeness bias across pathogens, potentially linked to variation in clinical presentation. For example, the majority of data points for *Japanese encephalitis virus* and indeed all data points for *Leishmania donovanii* are classified as high risk of representativeness bias. This review focused on studies reporting diagnostic 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 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 consequence, this systematic~~This review therefore had ~~relatively~~an inherently low sensitivity for studies describing ~~outbreaks, with just 9 included studies described as documenting~~ disease outbreaks ~~(but meeting all study criteria and thus retained).~~. This focus explains, for example, the absence of studies describing the 2014-2016 Ebola West Africa outbreak ~~amongst others. Our findings are therefore 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 zoonoses with malaria or of multiple zoonoses ~~that cause outbreaks.~~. 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.[47] Serological diagnosis of acute infection based on testing of both acute and convalescent phase ~~serum samples~~sera is central to the confirmed diagnosis of 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 absence of other valid ~~confirmatory~~ test options) and the ~~proportion~~proportions of fevers attributable to pathogens with high probability of acute fatality will be under-estimated ~~and our findings may not fully capture the contribution of zoonoses in lethal febrile illnesses~~. Furthermore, no validity criteria regarding the timing of sample collection for acute and convalescent samples were imposed, leading potentially to false negative results (e.g., seroconversion not detected because of premature convalescent sampling). For these reasons, our findings are unlikely to capture the full extent of morbidity and mortality attributable to zoonoses.

The data compiled in this review demonstrate the need to consider multiple zoonoses among the potential causes of febrile illnesses in malaria-endemic countries. ~~The diversity of pathogens identified and the geographic variation in their distribution indicates that different~~Different zoonoses are likely to be important in different settings. ~~Nonetheless, our~~Our study provides a starting point for improving awareness of first the zoonoses that are known to contribute to febrile illness in different malaria-endemic regions and second the fever-causing zoonoses with widespread distribution that should ~~also~~ be considered in patient evaluation. The demonstration of major data gaps should ~~also~~ encourage a more open-minded approach when considering zoonoses as a potential cause of febrile illness.

~~Greater research effort is needed to overcome the current paucity of evidence. In addition, untapped~~ 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. Untapped sources of information on the 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 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. ~~Given the diversity~~Control of ~~pathogens, continued efforts~~disease in animal populations and prevention of transmission from animals to humans are ~~also needed~~likely to be the most effective ways to reduce human disease risk with many zoonoses, necessitating active engagement with 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 tested for (and hence detected) are assumed to be present. While there~~sustainable disease control interventions. There are substantial challenges to clinicians and epidemiologists in revealing the true impacts of many zoonoses~~, the~~. The enormous global burden of febrile illness and scope for improvements in the diagnosis and treatment of zoonotic pathogens ~~necessitates~~necessitate efforts to overcome these challenges and translate findings into important public health gains.

~~**Research in Context**~~

~~**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.~~

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

~~**Added value of this study**~~

~~This review reveals the widespread occurrence of zoonotic causes of febrile illness, with a diverse range of pathogens identified. Data were extracted on the zoonotic pathogens detected and the number of individuals tested and positive for each pathogen using diagnostics that met study inclusion criteria. We identified 181 articles, from 46 countries and 7 WHO regions that described diagnosis of 29 zoonoses in febrile people. The majority of zoonoses were bacterial. Our data identify substantial gaps in the current evidence base and highlight areas for future research investment.~~

~~**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.~~

Contributors

The author contributions are as follows. Study design: JEBH, ~~MPR~~KJA, JAC, SC, ~~KJA~~ and ~~JAC~~MPR. 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.

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 reports grants from United States National Institute for Allergy and Infectious 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 to all the data in the study and had final responsibility for the decision to submit for publication.~~

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Tables

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

Pathogen	Species, subspecies, and serovars excluded	Pathogen type (13)
Alphaviruses	All species excluded with the exception of *Eastern equine encephalitis virus* (EEEV) complex, Venezuelan equine encephalitis (VEEV) complex, and Western equine encephalitis virus (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*	Bacteria
Borrelia spp.	*B. recurrentis*	Bacteria
Bovine spongiform encephalopathy	-	Prion
Brucella spp.	-	Bacteria
Burkholderia spp.	*B. cepacia* complex and *B. psuedomallei*	Bacteria
Campylobacter spp.	-	Bacteria
Chlamydia spp.	All species excluded with the exception of *C. psittaci*	Bacteria
Coxiella burnetii	-	Bacteria
Cryptosporidium spp.	*C. hominis*	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 *E. coli*	Bacteria
Flaviviruses	All species excluded with the exception of *Japanese encephalitis virus* (JEV), *West Nile virus* (WNV), and Tick-borne encephalitis viruses.	Virus
Francisella spp.	All species excluded with the exception of *F. tularensis*	Bacteria
Hantavirus	-	Virus

Henipaviruses	-	Virus
Lassa virus	-	Virus
Leishmania spp.	*L. donovani* if detected in India	Protozoa
Leptospira spp.	-	Bacteria
Listeria spp.	-	Bacteria
Lyssavirus	All species excluded with the exception of rabies	Virus
Marburg virus	-	Virus
Mycobacterium	All species excluded with the exception of *M. bovis* and *M. avis*	Bacteria
Nairovirus	All species excluded with the exception of *Crimean-Congo hemorrhagic fever virus*	Virus
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 virus*	Virus
Rickettsia spp.	All species excluded with the exception of *R. prowazekii*	Bacteria
Salmonella spp.	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 spp.	-	Bacteria
Streptococcus spp.	All species excluded with the exception of *S. canis*, *S. suis*, *S. equi*, and *S. iniae*	Bacteria
Taenia spp.	-	Helminth
Toxocara	-	Helminth
Toxoplasma gondii	-	Protozoa
Trichinella spp.	-	Helminth
Trypanosoma spp.	All species excluded with the exception of *T. brucei* rhodesiense and *T. cruzi*	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 *Y. pestis*, *Y. enterocolitica* and *Y. pseudotuberculosis*	Bacteria

Table 2: Inclusion and exclusion criteria for full text review

Outcome	Criterion
Inclusion:	• Febrile population (≥ 2 people with a fever, defined as body temperature ≥ 38.0°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 an febrile person ii) Direct detection of the pathogen (e.g. by PCR based techniques) from sample(s) collected from a febrile person iii) Serological diagnosis of acute infection based on testing of both acute and convalescent phase serum samples and demonstration of seroconversion iv) Diagnosis of acute infection based on detection of pathogen-specific IgM 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[1]) v) IgM detection in CSF (e.g. for JEV and WNV)
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 ≥ 2 people principally classified based on a shared (100% frequency) aetiological diagnosis. • Review

[1]The following were considered valid tests: *Leptospira* spp. agglutination titer of ≥ 800 by microscopic agglutination test in one serum specimen (35); detection of Hantavirus-specific IgM in a serum sample (36); detection of virus-specific IgM antibodies in serum with confirmatory virus-specific neutralizing antibodies for *Eastern equine encephalitis virus* (EEEV), *West Nile virus* (WNV), *Western equine encephalitis virus* (WEEV), and *Venezuelan equine encephalitis virus* (VEEV) (37); identification of lyssavirus specific antibody by indirect fluorescent antibody test or complete rabies virus neutralization at 1:5 dilution in the serum of an unvaccinated person (38); detection of viral antigens in blood by enzyme-linked immunosorbent assay for Ebola (39,40), Marburg (40,41), Lassa (40,42), and Crimean-Congo hemorrhagic fever viruses (40); detection of Rift Valley fever antigens or IgM in blood by enzyme-linked Immunosorbent assay (43); and IgM detection in CSF for EEEV, *Japanese encephalitis virus* (JEV), rabies virus, WEEV, WNV and VEEV (37,38,44).

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

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

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

First author, year of publication and reference	Country	Study Period	Pathogen	Number of Individuals Tested	Number of Individuals Positive
Blacksell et al (2016)(68)	Thailand	2006-2007	*Orientia tsutsugamushi*	152	37
Boisen et al (2015)(69)	Sierra Leone	2012-2012	Lassa virus	53	29
Boisen et al (2015)(69)	Sierra Leone	2012-2012	*West Nile virus*	23	4
Boonsilp et al (2011)(70)	Thailand	2001-2002	*Leptospira* spp.	418	120
Bottieau et al (2011)(71)	No Single Country	2000-2006	*Campylobacter* spp.	512	47
Brooks et al (2005)(72)	Bangladesh	2000-2001	*Salmonella* (non-Typhi) serovars	888	2
Castillo Ore et al (2012)(73)	Peru	2007-2010	Hantavirus	5174	9
Chadha et al (2006)(74)	India	2001-2001	Nipah virus	6	5
Chandy et al (2005)(75)	India	2002-2003	Hantavirus	152	23
Chandy et al (2009)(76)	India	2005-2007	Hantavirus	347	86
Chansamouth et al (2016)(77)	Lao People's Democratic Republic	2006-2010	*Leptospira* spp.	158	1
Chansamouth et al (2016)(77)	Lao People's Democratic Republic	2006-2010	*Orientia tsutsugamushi*	217	16
Chansamouth et al (2016)(77)	Lao People's Democratic Republic	2006-2010	*Rickettsia* (TGR)	217	15
Chatterjee et al (2004)(78)	India	1996-	*Japanese encephalitis*	72	24

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

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

First author, year of publication and reference	Country	Study Period	Pathogen	Number of Individuals Tested	Number of Individuals Positive
		2011	serovars		
dos Santos et al (2012)(93)	Brazil	2009-2010	*Rickettsia* (SFGR)	110	36
Ehichioya et al (2012)(94)	Nigeria	2005-2008	Lassa virus	451	2
Eibach et al (2016)(95)	Ghana	2007-2012	*Salmonella* (non-Typhi) serovars	7172	215
El-Mahallawy et al (2005)(96)	Egypt	1999-1999	*Listeria* spp.	1135	1
El-Mahallawy et al (2005)(96)	Egypt	1999-1999	*Pasteurella* spp.	1135	6
Elhelw et al (2014)(97)	Egypt	2008-2009	*Borrelia* spp.	15	4
Ellis et al (2006)(98)	Thailand	1999-2002	*Japanese encephalitis virus*	530	1
Ellis et al (2006)(98)	Thailand	1999-2002	*Leptospira* spp.	613	107
Elyan et al (2014)(99)	Afghanistan	2008-2010	*West Nile virus*	277	24
Eremeeva et al (2013)(100)	Guatemala	2007-2007	*Rickettsia* (SFGR)	17	1
Fadeel et al (2006)(101)	Egypt	1999-2003	*Brucella* spp.	1177	202
Forshey et al (2010)(102)	No Single Country	2000-2007	Venezuelan equine encephalitis virus	13259	250
Fotso Fotso et al (2015)(103)	Algeria	2012-2012	*Borrelia* spp.	257	4

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

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

First author, year of publication and reference	Country	Study Period	Pathogen	Number of Individuals Tested	Number of Individuals Positive
		2012			
Kumar et al (2014)(128)	India	2009-2010	*West Nile virus*	105	27
Kumar et al (2015)(129)	India	-	*Japanese encephalitis virus*	108	54
LaRocque et al (2005)(130)	Bangladesh	2001-2001	*Leptospira* spp.	359	63
Ley et al (2009)(131)	United Republic of Tanzania	2008-2009	*Salmonella* (non-Typhi) serovars	1680	49
Libraty et al (2007)(132)	Thailand	1994-1999	*Leptospira* spp.	812	14
Liu et al (2007)(133)	China	2002-2004	Hantavirus	130	49
Liu et al (2007)(133)	China	2002-2004	*Orientia tsutsugamushi*	130	46
Liu et al (2016)(134)	China	2014-2014	*Rickettsia* (SFGR)	733	56
Mahende et al (2014)(135)	United Republic of Tanzania	2013-2013	*Salmonella* (non-Typhi) serovars	808	2
Maina et al (2012)(136)	Kenya	2008-2010	*Rickettsia* (SFGR)	699	50
Manock et al (2009)(137)	Ecuador	2001-2004	*Brucella* spp.	275	4
Manock et al (2009)(137)	Ecuador	2001-2004	*Coxiella burnetii*	33	15
Manock et al (2009)(137)	Ecuador	2001-2004	*Rickettsia* (SFGR)	214	6

First author, year of publication and reference	Country	Study Period	Pathogen	Number of Individuals Tested	Number of Individuals Positive
Manock et al (2009)(137)	Ecuador	2001-2004	*Rickettsia* (TGR)	255	8
Manock et al (2009)(137)	Ecuador	2001-2004	Venezuelan equine encephalitis virus	229	2
Matthias et al (2008)(138)	Peru	2003-2006	*Leptospira* spp.	881	45
Maude et al (2015)(139)	Bangladesh	2012-2012	*Orientia tsutsugamushi*	300	1
Maude et al (2015)(139)	Bangladesh	2012-2012	*Rickettsia* (TGR)	300	2
Mayxay et al (2013)(140)	Lao People's Democratic Republic	2008-2010	*Leptospira* spp.	1932	137
Mayxay et al (2013)(140)	Lao People's Democratic Republic	2008-2010	*Orientia tsutsugamushi*	1871	170
Mayxay et al (2013)(140)	Lao People's Democratic Republic	2008-2010	*Rickettsia* (SFGR)	1849	2
Mayxay et al (2013)(140)	Lao People's Democratic Republic	2008-2010	*Rickettsia* (TGR)	1849	12
Mazyad et al (2007)(141)	Egypt	2006-2006	*Coxiella burnetii*	150	5
McGready et al (2010)(142)	Thailand	2004-2006	*Leptospira* spp.	203	5
McGready et al (2010)(142)	Thailand	2004-2006	*Orientia tsutsugamushi*	203	11
McGready et al (2010)(142)	Thailand	2004-2006	*Rickettsia* (TGR)	203	14
Mediannikov et al (2010)(143)	Senegal	2008-	*Rickettsia* (SFGR)	204	8

First author, year of publication and reference	Country	Study Period	Pathogen	Number of Individuals Tested	Number of Individuals Positive
		2009			
Mediannikov et al (2013)(144)	No Single Country	2010-2012	*Rickettsia* (SFGR)	2612	321
Mediannikov et al (2014)(145)	Senegal	2010-2011	*Borrelia* spp.	1566	115
Meremo et al (2012)(146)	United Republic of Tanzania	-	*Salmonella* (non-Typhi) serovars	346	12
Metanat et al (2014)(147)	Iran (Islamic Republic of)	2011-2011	*Coxiella burnetii*	105	23
Moon et al (2013)(148)	Mozambique	2012-2012	*Salmonella* (non-Typhi) serovars	258	28
Morrison et al (2008)(149)	Peru	2005-2006	Venezuelan equine encephalitis virus	1136	34
Mourembou et al (2015)(150)	Gabon	2011-2012	*Rickettsia* (SFGR)	793	8
Mourembou et al (2015)(151)	Gabon	2013-2014	*Rickettsia* (SFGR)	410	42
Mourembou et al (2016)(152)	Gabon	-	*Salmonella* (non-Typhi) serovars	410	3
Mtove et al (2010)(153)	United Republic of Tanzania	2008-2009	*Salmonella* (non-Typhi) serovars	1502	45
Mtove et al (2011)(154)	United Republic of Tanzania	2006-2010	*Salmonella* (non-Typhi) serovars	6836	232
Mtove et al (2011)(155)	United Republic of Tanzania	2009-2010	*Salmonella* (non-Typhi) serovars	965	1
Mueller et al (2014)(156)	Cambodia	2008-2010	*Leptospira* spp.	1193	112

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

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

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

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

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

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

Table 4: 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=174[1])
Africa	17 of 44 (38·6%)	56 (32·2%)
Americas	8 of 23 (34·8%)	16 (9·2%)
Eastern Mediterranean	8 of 14 (57%)	17 (9·8%)
Europe	2 of 9 (22·2%)	5 (2·9%)
South-East Asia	6 of 10 (60·0%)	63 (36·2%)
Western Pacific	6 of 10 (60·0%)	17 (9·8%)

[1]Table includes data from 174 of 181 articles included in the review, excluding 7 articles reporting data from multiple countries excluded for this analysis.

Figures

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).

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).

Figure 3: Barchart showing the number of articles contributing data for each country included in the study, displayed by country and WHO region.

Figure 4Figure 3: Barchart showing the number of articles that looked for, reported diagnosis of and contributed data for each zoonosis. of 40, 31 and 30 zoonoses respectively. These data were tabulated for all pathogenszoonoses (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 partial shadinglighter 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 4: Proportion of fevers attributed to each zoonosis.
The plot includes one data point per study and pathogen combination. The different panels 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 overlapping points.

Figure 5: Barchart showing number of articles from each global region contributing data for each of 29 zoonoses.
Plot panels indicate the WHO defined global region and bar colour indicates type of pathogen

Figure 6
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 patient population. Undifferentiated, shown in green, 22 pathogens; febrile neurological, shown in blue, 5 pathogens; febrile gastrointestinal, shown in pink, 2 pathogens; febrile haemmorhagic, shown in orange, 4 pathogens, *Leishmania donavanii*, *Toxoplasma gondii*, *Rickettsia* spp., and *Yersinia pestis* are not represented as they were only detected in febrile populations classified as mixed.

~~Figure 7: Proportion of fevers attributed to each zoonosis.~~ 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*).

~~The plot includes one data point per study and pathogen combination.~~ ~~Point colour indicates pathogen type and point size is proportional to the number of individuals tested.~~ ~~Points are jittered on the x-axis and shaded to visualize overlapping points.~~