

Etiology of fever in returning travelers and migrants: a systematic review and meta-analysis

Imogen Buss MD, MPH¹, Blaise Genton MD, PhD^{1,2}, Valérie D'Acremont MD, PhD^{1,2}

¹Centre for Primary Care and Public Health (Unisanté), University of Lausanne, Switzerland

²Swiss Tropical and Public Health Institute, University of Basel, Switzerland

Corresponding email : blaise.genton@unisante.ch

Running title: Etiology of fever in returning travelers a systematics review and meta-analysis

Key-words: predictor – likelihood ratio – COVID-19 – diagnosis – febrile – tropical disease – guidelines

Word count:

Abstract 300, article body 4809

© International Society of Travel Medicine 2020. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com

Abstract

Background: Numerous publications focus on fever in returning travelers, but there is no known systematic review considering all diseases, or all tropical diseases causing fever. Such a review is necessary in order to develop appropriate practice guidelines.

Objectives: Primary objectives of this review were i) to determine the etiology of fever in travelers/migrants returning from (sub) tropical countries as well as the proportion of patients with specific diagnoses, and ii) to assess the predictors for specific tropical diseases.

Method: Embase, MEDLINE and Cochrane Library were searched with terms combining fever AND travel/migrants. All studies focusing on causes of fever in returning travelers and/or clinical and laboratory predictors of tropical diseases were included. Meta-analyses were performed on frequencies of etiological diagnoses.

Results: 10,064 studies were identified; 541 underwent full-text review; 30 met criteria for data extraction. Tropical infections accounted for 33% of fever diagnoses, with malaria causing 22%, dengue 5% and enteric fever 2%. Non-tropical infections accounted for 36% of febrile cases, with acute gastroenteritis causing 14% and respiratory tract infections 13%. Positive likelihood ratios demonstrated that splenomegaly, thrombocytopenia and hyperbilirubinemia were respectively 5-14, 3-11 and 5-7 times more likely in malaria than non-malaria patients. High variability of results between studies reflects heterogeneity in study design, regions visited, participants' characteristics, setting, laboratory investigations performed, and diseases included.

Conclusion: Malaria accounted for one fifth of febrile cases, highlighting the importance of rapid malaria testing in febrile returning travelers, followed by other rapid tests for common tropical diseases. High variability between studies highlights the need to harmonize study designs and to promote multi-center studies investigating predictors of diseases, including of lower incidence, which may help to develop evidence-based guidelines. The use of clinical decision support algorithms by health workers which incorporate clinical predictors, could help standardize studies as well as improve quality of recommendations.

Introduction

International movement of people is increasingly common, whether for travel or migration¹. International tourist arrivals reached 1.4 billion in 2018, an increase of 5% from the previous year, with uninterrupted growth over the past nine consecutive years, with 42.6% of these visiting (sub)tropical countries². Additionally a recent United Nations report highlights that 3.4% of the world's inhabitants are international migrants, an increase by almost 50% since 2000³.

In the context of globalization, “tropical diseases” are becoming less restricted to the tropics, partly due to migration and global warming⁴⁻⁶. Clinicians in temperate regions may lack expertise in managing febrile patients traveling from tropical regions^{7,8} as the differential diagnoses and possible diagnostic tests are numerous. Additionally, clinicians may be concerned about the possibility of rapid deterioration with certain tropical diseases or the propensity for high human-to-human transmission^{9,10}. Therefore, clinicians in all settings should be equipped to initially investigate and manage the most common tropical diseases and recognize when to refer to a specialist or admit to hospital urgently. Guidelines can aid clinicians in this decision-making process and help maintain consistency in practice. Additionally, by increasing healthcare workers knowledge of travel medicine and migrant health, they can lead to earlier diagnosis and treatment, thereby contributing to improved health outcomes¹¹.

A structured review in 2001 formed the basis of developing evidence-based guidelines regarding clinical signs, investigations and management of fever in returned travelers, including an online website (www.fevertravel.ch)^{12,13}. These guidelines have been demonstrated to be the most rigorous existing practice guideline in the field¹⁴. Additionally, a validation study assessed compliance of clinicians to the guidelines and their safety (health outcome)¹⁵. Maintaining up-to-date guidelines based on current literature is vital as the epidemiology of diseases shifts, travel patterns change, and advances in diagnostics, prophylaxis and management progress. A revision of the guidelines was performed in 2010 following an updated structured literature review (unpublished).

Numerous reviews and individual case series investigate the etiology of fever and/or illness among returning travelers and/or migrants. However, the majority are either conducted in single centers with small numbers of participants, or they combine data from global GeoSentinel centers without segregating etiologies by presenting symptoms, such as fever. There has been no known systematic review investigating the prevalence of diagnoses among febrile returned travelers and migrants or predictors of tropical diseases. Heterogeneity among studies has hindered the performance of a systematic review, including differences in study design with wide variability in documentation of diagnoses (from laboratory-confirmed to presumed cases) and fever definition (from documented temperature >38°C to febrile sensation). This systematic review is important to enable clinicians to better estimate an individual's probability of different diseases after travel, and therefore target both pre-travel recommendations and post-travel management.

The objectives of this systematic review were i) to determine the etiology of fever in travelers/migrants returning from (sub) tropical countries as well as the proportion of patients with specific diagnoses, and ii) to assess the demographic, clinical and laboratory predictors for common tropical diseases.

Methods

Study design

A systematic review following the PRISMA statement¹⁶, was conducted to identify studies focusing on different diagnoses and predictors of diagnoses among travelers or migrants returning from the (sub)tropics with a fever. The protocol followed the PRISMA-P recommendations¹⁷, and is registered on PROSPERO (ID: CRD42019117514). Three databases (Embase, MEDLINE and Cochrane Library) were searched on the 22nd November 2018.

Search strategy (see supplementary file)

Search strategies were created in collaboration with an expert medical librarian. Two main components were combined: fever and travel/migrants. Articles were restricted to those published after 1st January 2001, to follow on from a previous review¹² and because epidemiology alters over time.

Population

Travelers and migrants of all ages, presenting to medical settings with a fever or symptoms suggestive of fever, with international travel in a (sub)tropical country within one year prior to onset of symptoms, were included. Since the term of ‘migrant’ is ill-defined^{18,19}, and because the separate frequencies of diagnoses were not provided, except in one study¹⁸, no distinction was made in the review and analysis between the group of travelers and that of migrants.

Study selection: inclusion and exclusion criteria

Observational studies, reviews and guidelines were included. Only case series with >100 cases or cross-sectional studies were included for the prevalence of diagnoses. Case-control studies were permitted for the assessment of diagnostic predictive factors. Reviews and guidelines were not included in the final review but were kept for full-text analysis for hand-searching the reference lists to ensure completeness. No language limitations were applied.

Febrile returning travelers or migrants were the focus because ‘fever’ is an easily recognized and common symptom raising suspicion of acute infections, as well as a common reason for presentation to healthcare settings. A Canadian study based on GeoSentinel data in travelers¹⁹ showed that 92% of malaria diagnoses, 78% of dengue, 30% of active tuberculosis, 82% of enteric fever, and 88% of rickettsioses presented with the primary complaint of fever, thus highlighting the presence of fever in most post-travel cases of tropical diseases.

Studies were excluded if they focused on the following: non-travelers, autochthonous cases or non-febrile travelers; pre-travel advice or vaccinations; prevention or public health measures; or non-human subjects. Studies including travelers/migrants both with and without fever, where segregation between these two groups could not be performed, were excluded.

Definitions

Specific definitions follow. “Travelers” are people temporarily staying in (sub)tropical countries, different to their country of birth or where they usually inhabit (tourists, visiting friends and relatives (VFRs), workers, volunteers, expatriates). “Migrants” are people moving from or through (sub)tropical countries to another country (migrants, asylum seekers,

refugees). “(Sub)tropical countries” are those where the epidemiology of communicable diseases is different from temperate climates. “Fever” comprises a history of raised temperature / feeling hot and cold / chills, sweating or headache / axillary temperature $>37.5^{\circ}\text{C}$. A broad definition of fever was employed to encompass all possible cases and diagnoses. “Endemic” is when a disease is present at a fairly constant level in a geographical area without external inputs. “Tropical diseases” are those found more commonly (not necessarily exclusively) in tropical regions, whereas “non-tropical diseases” are commonly diagnosed among non-travelers in temperate regions as causes of fever. This categorization distinguishes between diseases found more commonly in tropical regions and those found in similar prevalence globally. Although this distinction could be viewed as arbitrary, it is a useful manner to simplify classification of diseases, and is common practice in published literature¹².

Outcomes

Primary outcomes were the different causes of fever and predictors that increased the likelihood of the most prevalent tropical diagnoses. Tropical diseases categorized by region visited and category of traveler are presented where available. Statistically significant demographic, clinical and laboratory predictive factors of diagnoses for the most common tropical diseases are presented.

Data extraction

Search results were uploaded to Covidence software. Duplicate articles were removed, including where the same population’s data were analyzed. Two reviewers (IB & BG) assessed eligibility independently. Discrepant results were resolved by a collaborative second assessment involving both reviewers. Full-text articles were then screened to assess eligibility. Additional information was directly sought from corresponding authors if eligibility was unclear. Disagreements between reviewers were resolved by discussion and reaching a consensus. Reasons for exclusion of articles were documented. Reference lists of relevant full-text articles and reviews were searched.

Data were extracted using standardized pre-specified forms by one reviewer and confirmed by a second reviewer. The extracted data comprised of the following:

- Study characteristics: Authors, year of publication, dates of data collection, study design, healthcare setting, healthcare city/country, number of centers.
- Study population: number of participants, sex, median age, age range, inclusion and exclusion criteria, region visited, type of traveler, duration of travel.
- Clinical information: number of cases of different diseases, hospitalization (including tropical disease cases hospitalized), intensive care admissions, fatalities.
- Prevalence of tropical diseases categorized by region visited and type of traveler (where available).
- Odds ratios, p-values, sensitivity, specificity, and likelihood ratios of diagnostic predictive variables for tropical diseases (where available/calculable).

Quality assessment

Quality assessments for individual studies were undertaken during data extraction. As the majority of studies included were case series, the quality appraisal tool for case series studies was used²⁰, as recommended in a systematic review of quality assessment tools²¹.

Analysis

A meta-analysis was performed solely on the frequencies of etiologies of fever in returning travelers and migrants. The total number of cases having a specific disease were divided by the total number of all febrile cases from all studies. Studies not specifying any cases having the particular disease were presumed to not have any cases of that disease present for the analysis. Ranges describe the distribution of the prevalence of different diagnoses and show the level of variability between studies. These were computed using simple formulas and graphic representations are presented. A narrative synthesis is made comparing etiologies of fever in returning travelers and migrants.

Demographic, clinical and laboratory predictors of common tropical diseases are presented. Where statistical calculations were not performed, but relevant data were provided, computed calculations of sensitivity, specificity, positive and negative likelihood ratios (LR+, LR-) were performed to allow direct comparison between studies²². One study²³ presented adjusted LRs, preventing direct comparisons, so unadjusted LRs were recalculated. Likelihood ratios determine how much more likely a predictor is among people with a condition of interest (e.g. malaria) than those without^{22,24}. For example, for a diagnosis of malaria, a LR+ of 5 for splenomegaly demonstrates that splenomegaly is five times more likely to be present in people with malaria than those without²². Building on an accurate pre-test probability of disease, likelihood ratios can refine clinical judgement²⁴.

Results

The search strategy identified 14,047 studies. After duplicate exclusion, 10,064 studies underwent title and abstract screening; 541 were included for full-text review. Reasons for exclusion of full-text articles are documented in supplementary figure 1. In total, 30 articles underwent data extraction: 26 case series with more than 100 cases, and four case-control studies included only for the clinical predictors.

Etiology of fever

Supplementary Table 1 presents the individual studies included and the detailed causes of fever in each study. Large heterogeneity between studies (including types of patients included, regions visited, setting, study design or lack of clarification in these fields) has been observed.

Demographic, travel-related and hospitalization data

Table 1 presents the meta-analysis of demographic and travel-related data. Females accounted for 41% of cases (some studies were missing information). Most travelers/migrants returned from Africa (51%), although this was highly variable (range 5-88%). Asia accounted for the next most visited regions (29%, 7-95%), and Latin America following (11%, 0-48%).

Regarding the type of traveler, tourists accounted for the greatest proportion of febrile cases (58%, 21-88%), followed by VFRs (15%, 7-21%), business/research/volunteers (14%, 11-23%) and migrants (6%, 2-60%). The mean duration between return from travel and presentation to healthcare was 13 days (median 7), based on seven contributing studies. Most cases travelled for less than 30 days (62%, 60-74%), took inadequate malaria

chemoprophylaxis (73%, 41-83%), and received pre-travel medical advice (52%, 9-73%), although only two studies contributed to this information.

Amongst the nine studies including data on hospitalization rates, 32% (range 9-70%) of febrile cases presenting to healthcare facilities were hospitalized. Malaria accounted for 11% (7-67%) of hospitalizations among the seven studies including this data, followed by dengue (7%) and enteric fever (0.8%, 5-10%), although only one and two studies respectively contributed to this information. Among febrile travelers and migrants, only 2% (1-2%, 4 studies) were admitted to intensive care units, and the mortality rate was 0.22% (0-1.5%, 8 studies).

Combined etiological data

Table 2 presents the meta-analysis and ranges for each cause of fever. Tropical diseases were responsible for 33% of febrile cases among returning travelers and migrants (figure 1). Malaria accounted for the greatest proportion of all febrile cases (22.2%) and of tropical disease (70.9%), followed by dengue (5.2% and 15.9% respectively), enteric fever (2.3% and 7.1%), and rickettsioses (1.7% and 4.8%). Other tropical diagnoses including schistosomiasis, helminth infections, amebiasis accounted for <2% of all fever cases. Fever of unknown origin accounted for 17.8% of all febrile cases, acute febrile diarrhea for 13.6%, and respiratory tract infections for 13.4%.

The box-plot graph (figure 2) shows variability between studies of the most common tropical and non-tropical diagnoses. There was large variability between studies for the prevalence of malaria (2.6-75.2%). Less variability was seen for other tropical diseases, although they each accounted for much fewer febrile cases. Among non-tropical diagnoses, acute febrile diarrhea, respiratory diseases and fever of unknown origin all had a relatively similar prevalence, but the range of prevalence was much broader for the latter (1-45%).

Diagnoses segregated by travel-related data

Only one study²³ provided sufficient data on the prevalence of tropical diagnoses according to category of traveler. Bottieau et al. showed that malaria accounted for approximately twice the proportion of febrile cases among expatriates (45%), VFRs (37%) and migrants (33%) than tourists (19%). In comparison, the proportion of febrile cases accounted for by other tropical diseases were all much higher among tourists (rickettsioses 5.4%, dengue 4.4%, schistosomiasis 2.7%), although enteric fever accounted for an equivalent proportion of febrile cases between traveler types (<1%).

Differences in distribution of common tropical infectious diseases according to region visited (figure 3) are presented. Only four studies provided sufficient data for inclusion^{23,25-27}. Among travelers returning from Africa, 28-47% of febrile cases were due to malaria, compared to 4-11% of travelers to Asia. Other fairly common tropical diagnoses amongst returnees from Africa included schistosomiasis (3-6%) and rickettsioses (1-5%). Travelers and migrants from Asia were more likely to be diagnosed with dengue (13-18%) or enteric fever (3-17%). In Latin America the most common tropical illness diagnosed was dengue, representing 8-13% of febrile cases. Leptospirosis was also fairly common (10% according to one study)²⁵.

Clinical predictors of frequent tropical diagnoses

Various demographic, clinical and laboratory predictors of the most common tropical diagnoses amongst febrile travelers are presented in supplementary table 2. Eleven studies were included in this analysis, four were case-control studies and therefore not included in the meta-analysis of etiological diagnoses^{23,28-30}. Six studies focused on malaria^{28,29,31-34}, four on multiple diagnoses^{23,35-37}, and one on enteric fever³⁰. The highest likelihood ratios (LR) for a positive diagnosis were: for malaria - splenomegaly (LR+ 5.1 – 13.6), thrombocytopenia (2.9 – 11), and hyperbilirubinemia (5.3 – 7.3); for dengue - returning from Asia (1.6 – 7.9), having a skin rash (2.8)* and leucopenia (3.3)*; for enteric fever - returning from South-East Asia (4.0 – 4.1) and splenomegaly (5.9 – 10); for rickettsioses - a skin rash (3.8)*, or specifically a skin ulcer (11.1)*; and for schistosomiasis - eosinophilia (32)*. Values indicated with ‘*’ were obtained from only one study²³, and hence should be interpreted with caution.

Supplementary figure 2 shows the LR+ for predictors of malaria. Only significant predictors with more than one study contributing were included. Splenomegaly had the highest LR+ (range 5.3 – 13.6). In other words, splenomegaly was 5 to 14 times more likely in patients with malaria than those without, indicating that its presence strongly increases the probability of a diagnosis of malaria. However, its utility is affected by splenomegaly only being present in approximately 8% of febrile cases. Both thrombocytopenia and hyperbilirubinemia had a LR+ of 3 to 11 and 5 to 7 respectively, indicating that their individual presence also significantly increases the probability of malaria. Other variables (inadequate chemoprophylaxis, return from Africa, expatriate, males, myalgia, chills, fever, headache, anemia and raised LDH), all individually slightly increase the probability of malaria if present.

Supplementary figure 3 shows the LR- for predictors of malaria. The closer the value is to zero, the more the predictor decreases the probability of having malaria if it is absent³⁸. Hence, the absence of thrombocytopenia (LR- 0.2) strongly reduced the probability of malaria. The absence of documented fever and returning from elsewhere than Africa (LR- 0.3) decreased the probability of malaria, although variability was broad.

LR+ and LR- for other tropical diseases are shown in supplementary figures 3 and 4. Only three variables had more than one study contributing, and only significant variables are included. For dengue, returning from Asia had a LR+ from 2 to 8, while leucopenia and thrombocytopenia had LR+ of 6 and 5 respectively. The absence of a headache, absence of myalgia, and returning from elsewhere than Asia reduced the probability of dengue. For enteric fever, splenomegaly had a LR+ of 6 to 10 (hence must be distinguished from malaria), whereas returning from elsewhere than South Asia, having pre-travel advice, no abdominal symptoms, no relative bradycardia and no eosinopenia moderately reduced the probability of this disease. Having a skin rash or ulcer, respectively moderately (LR+ 5) and strongly (LR+ 20) increased the probability of rickettsioses, whereas the lack of a skin ulcer and not being a Western traveler reduced the probability. Finally, the presence of eosinophilia very strongly (LR+ 22) increased the probability of schistosomiasis, although it was only found in 6% of febrile travelers and migrants. No eosinophilia and not being a Western traveler strongly reduced the probability of this disease (LR- 0.1 and 0.2 respectively).

Discussion

This is the first systematic review investigating etiology of fever in returning travelers and migrants. The nature of the systematic review methodology process encapsulated all relevant studies fulfilling the inclusion criteria and presents a meta-analysis on the frequency of etiological diagnoses. It provides an updated viewpoint on the prevalence and predictors of tropical diseases in this population. However, challenges in conducting a systematic review with such a diverse and heterogenous dataset must be recognized and are further developed.

Malaria was the most common diagnosis amongst febrile travelers and migrants, and is important to rule out, as it can rapidly progress and become fatal³⁹. Parola et al.³⁶ was an outlier in this review, with a high proportion of malaria cases (90%), likely linked to a large proportion of cases coming from Comoros (55%) due to migration (60%). This aligns with a GeoSentinel study conducted in Marseille, where 59% of systemic febrile illnesses were due to malaria⁴⁰, the majority of which were VFRs returning from sub-Saharan Africa, who are less likely to seek pre-travel advice, highlighting a need to understand and target these barriers⁴¹. Differing demographics can strongly impact disease prevalence, highlighting the need to conduct multi-center large-scale studies, involving different continents and levels of health care.

Worldwide, dengue cases are increasing, partly associated with better availability of diagnostic tests and improved surveillance^{42,43}. In this review, only one dengue case was severe, out of the 49 cases in four studies including this information^{35,36,44,45}. Similar proportions were observed in a large GeoSentinel study with 18 (0.9%) severe cases among 1910 dengue cases³⁹. Evidently, most dengue cases in febrile travelers or migrants presenting to healthcare settings are mild, as they are probably a first episode, and therefore less likely to be severe. Additionally, many cases never present, due to either being asymptomatic or the short incubation period meaning that they are unwell during rather than after travel. A 3-7% seroconversion rate for dengue has been observed among travelers to dengue-endemic regions, with only 18% of these being symptomatic⁴⁶.

The large proportion of cases of “fever of unknown origin” with a wide variability (0.7 – 45%), can be partially explained by differing study designs. Some studies excluded patients whose diagnoses were unknown^{19,47,48}, while retrospective studies may prevent final diagnoses if incomplete testing was performed. It is likely that if potentially severe causes of fever were ruled out and the patient was clinically improving, no further diagnostic investigations were requested. This is a pragmatic approach used in most clinical settings, as most unspecific fevers are self-limiting viruses. Camps et al. detected self-limiting respiratory viruses among 37% of travelers with undifferentiated febrile illnesses⁴⁹. However, additional investigations in soldiers with acute undifferentiated febrile illness found cases of Q fever and rickettsioses, requiring antibiotic treatment⁵⁰.

Similarly, in a global GeoSentinel study based in tertiary specialized centers, febrile travelers were most frequently diagnosed with malaria (29%), followed by dengue (15%), but as expected, at higher proportions than in our study. Interestingly, even in the specialized centers, no specific cause for febrile illness was found in 40%⁵¹, further supporting the pragmatic approach discussed above.

Region visited impacted the distribution of diagnoses, as evidenced by the fact that visiting a certain continent or region was a strong predictor for several diseases. However, vast inter-regional differences in tropical diagnoses have been observed throughout Sub-Saharan Africa: malaria predominates in Central and Western Africa, schistosomiasis, strongyloidiasis and dengue in Eastern and Western Africa⁵². Stratifying etiologies of tropical diseases by country visited is thus recommended.

Contextualizing this paper, the incidence of fever among travelers returning from South-East Asia was 5%, whereas diarrhea was much more common (21%), especially during the first two weeks of travel⁵³. Only 5% of travelers visited an outpatient department, with a mere 0.5% being hospitalized, a figure much below our results. Although there is known bias with self-reporting of illness, this study puts our results into context, and further highlights regional differences.

The clinical predictors found in the present review do not present novel information, but provide quantitative likelihood ratios for clinical predictors, which could enhance developing more accurate diagnostic algorithms.

We acknowledge shifting epidemiology and this impact on diagnoses, highlighting the importance of regularly updating recommendations, as well as recognizing the limited usefulness of such guidelines or predictors during epidemics. Recalling all disease epidemiology is vital in pandemics as the focus shifts to the most current concern, and cases of other tropical diseases can go misdiagnosed and therefore mismanaged^{54,55}. In particular, COVID-19 will have to be incorporated into future diagnostic algorithms of febrile travelers and migrants, as this pandemic arose after the conduction of this systematic review.

Heterogeneity of data

The main challenges in analyzing and combining data stemmed from the large heterogeneity between studies. Factors that contributed to this heterogeneity represent limitations inherent in conducting a systematic review combining diverse studies rather than weaknesses of the present review methodology.

Differences in study design were noted. Prospective or retrospective data collection may have influenced the prevalence of “fever of unknown origin” cases. Prospective studies enable more thorough investigations. The number of centers included was variable; results from multi-center studies are generally more generalizable. Inclusion of inpatients versus outpatients could have impacted the prevalence of tropical diseases. In addition, the healthcare setting itself impacts the prevalence of diseases; it is likely that more severe and rarer cases present to tertiary settings, where most data originated from. In some studies, patients presenting with illness prior to travel or where the time period between travel and illness exceeded the known incubation period, were excluded. Other studies did not explicitly document this information.

The country of data collection impacted both the proportion of travelers to different regions as well as the type of traveler, in turn impacting diseases prevalence. Studies conducted in Japan for example constituted mostly of travelers to Asia^{44,56}, whereas European studies involved mostly travelers to and migrants from Africa^{18,31}.

Inclusion and exclusion criteria varied significantly. Including studies focusing on different age groups reflects real-life situations but influences disease prevalence. Due to a lack of segregation of data by age, it was not possible to perform analyses on different age groups. Eight included studies only met the inclusion criteria in their sub-analyses of *febrile travelers*^{19,34,44,47,48,56-58}, preventing analysis of their demographic and travel-related data. Each study also included slightly different diagnoses or case definitions, including variability in the definition of “fever”. Indeed, some diagnoses were never microbiologically confirmed, and remained “presumed diagnoses”. This lack of consistency between studies prevented us from conducting complete meta-analyses involving all studies for each diagnosis and predictor.

Broad inclusion criteria for traveler types enables a more comprehensive dataset but prevents distinction between traveler groups. This systematic review aimed to be a pragmatic, all-encompassing compilation of diagnoses of fever, for use with anyone presenting to a healthcare setting after travel. During initial patient management, physicians do not habitually delve into their migration status, and therefore inclusion of both population groups (travelers and migrants) is pragmatic and in corroboration with D’Acremont et al. (2003), where both patient groups were included based on their exposure to similar agents and therefore similar diseases¹².

Quality of studies included

Most included studies were case series, generally recognized as providing weak to moderate evidence with variable validity. Certainty of evidence depends on various factors including study design, imprecision and inconsistency⁵⁹. However, they were the most appropriate studies to answer the research questions in this systematic review of causes of fever, and inferences from the results can aid decision-making⁶⁰. The assessment of the quality of individual studies showed variable results, but all included studies were of at least moderate to good quality.

Assumptions had to be made for some of the data for the meta-analyses, as certain diagnoses were not expressly included in each study. If a diagnosis was not mentioned, it was assumed that there were no cases in that study. This could have been incorrect, relating back to the heterogeneity of study design, as some had very extensive investigations performed while others did not.

Lastly, outcome data were limited, with only nine studies including hospitalization rates and eight including the mortality rate.

Implications for practice

This systematic review supports the practice of performing a rapid malaria test among all febrile travelers and migrants returning from malaria-endemic countries, as this common tropical disease can rapidly progress. The relatively high frequency of dengue fever probably justifies the use of the dengue rapid test if the malaria test is negative. Rapid diagnostic tests (RDTs) for dengue are widely available and commonly used in clinical practice. The combined NS1 antigen and IgG RDT has a very high positive likelihood ratio⁶¹ and could thus optimize management by reducing numerous testing and prescription of unnecessary

empirical antibiotics. RDTs for other tropical diseases, such as chikungunya, are under evaluation⁶² and will certainly be increasingly used in clinical practice.

The use of this data to support targeted pre-travel advice on the prevention of vector-borne diseases could help reduce infection rates, as travelers cite a low presumed risk as reasons preventing seeking or adhering to pre-travel advice⁶³. Indeed, the data regarding regional risks could assist in providing more targeted travel advice to individuals, which they may in turn be more likely to retain.

Clinical, laboratory and demographic predictors can help clinicians predict the likelihood of diseases but should not be employed in isolation. Their use could be enhanced by combining them within decision-making algorithms to provide post-test probabilities of different diagnoses. However, with only few studies currently contributing to this essential information, algorithms have to be based on uncertain data, which limits their performance. Indeed, as highlighted by McDonald et al.⁶⁴, establishing the diagnosis in a febrile patient is important to guide management, but perhaps even more useful is predicting the patients who have more severe disease, and therefore require more attentive monitoring and in-hospital management.

Implications for research

Future research should focus on standardized data collection in primary care settings to complement current data originating mainly from large tertiary centers. Further assessment of clinical and laboratory predictors for tropical diseases (especially other than malaria) would enable developing better diagnostic algorithms. Additionally, stratifying etiologies of fever in travelers and migrants by traveler type and region visited would be useful. Presenting data on febrile travelers in syndromic classification (such as skin lesions, urinary symptoms) may enable more focused disease analysis, as disease pattern and clinical management are strongly impacted by associated symptoms.

Reducing heterogeneity between studies would enable better comparison and more complete meta-analyses. Standardizing data collection would enable this. GeoSentinel centers already collate data on travelers presenting to their clinics using pre-defined diagnoses, and a significant proportion of our knowledge regarding diagnoses among travelers comes from their database. However, most of the GeoSentinel case series were excluded during the full-text review process in this systematic review. Reasons for this were: (i) unclear if inclusion criteria of (sub)tropical travel was met; (ii) not distinguishing between traveler's presenting symptoms, fever or no fever for example, or main complaints only presented⁶⁵; (iii) overlap of data as the same database was used repeatedly for different research questions; (iv) only included probable or confirmed diagnoses, hence do not provide an estimation of "fever of unknown origin" cases. These large existing travelers' networks could expand the manner of data collection and presentation of data, including the syndromic presentation of individuals and their related potential diagnoses. Data could be categorised by traveler type or region visited, enabling calculating frequencies of different diagnoses dependant on these variables.

Movement towards better homogeneity among studies could be achieved by having a high number of healthcare settings, including specifically primary care, using a decision support algorithm to manage febrile travelers and migrants. The tool could assist in the decision-

making process regarding diagnoses and management, as well as educating clinicians. In the use of such a tool, it could simultaneously collect detailed clinical data and final diagnoses. Thereby, a broader and more complete data collection could be obtained, filling the gap on causes of fever among those presenting to primary care. This more standardized data collection would enable direct comparisons and meta-analyses of data, thereby producing a stronger evidence base from which guidelines and recommendations could be further improved.

UNCORRECTED MANUSCRIPT

Conclusion

Tropical diseases accounted for one third of all diagnoses of fever, with malaria accounting for 70% of these, highlighting the importance of testing for malaria in febrile returning travelers. Further research on clinical predictors of other tropical diseases would be an asset. The review emphasized the large heterogeneity between studies. This could be reduced by including several healthcare settings, from primary to tertiary care, using a common decision-making tool to document diagnoses and manage patients, simultaneously improving practice and data collection.

Authors' contribution:

IB performed the paper screening, data extraction, meta-analysis, paper writing.

BG performed paper screening and contributed to the meta-analysis and paper writing.

VDA contributed to the meta-analysis, paper writing and overall coordination

Source of funding: None

Acknowledgements

We would like to acknowledge Beat Stoll for his review of the manuscript, as well as Jolanda Elmers for her expertise and assistance in formulating, revising and conducting the systematic review search strategy, as well as the exportation of references and removal of duplicate publications. Dr Rainer Tan provided assistance and advice regarding practical tools to conduct systematic reviews.

Conflict of interest/Disclosure

The authors have declared no conflicts of interest.

References

1. Renzaho AM. Globalisation, migration and health: challenges and opportunities. World Scientific; 2016.
2. World Tourism Organization (UNWTO), editor. International Tourism Highlights, 2019 Edition [Internet]. World Tourism Organization (UNWTO); 2019 [cited 2020 May 20]. Available from: <https://www.e-unwto.org/doi/book/10.18111/9789284421152>
3. The International Migration Report 2017 (Highlights) | Multimedia Library - United Nations Department of Economic and Social Affairs [Internet]. [cited 2018 Sep 14]. Available from: <https://www.un.org/development/desa/publications/international-migration-report-2017.html>
4. Rezza G, Nicoletti L, Angelini R, Romi R, Finarelli AC, Panning M, et al. Infection with chikungunya virus in Italy: an outbreak in a temperate region. *Lancet Lond Engl*. 2007 Dec 1;370(9602):1840–6.
5. Medlock JM, Leach SA. Effect of climate change on vector-borne disease risk in the UK. *Lancet Infect Dis*. 2015 Jun;15(6):721–30.
6. Ryan SJ, Carlson CJ, Mordecai EA, Johnson LR. Global expansion and redistribution of Aedes-borne virus transmission risk with climate change. *PLoS Negl Trop Dis*. 2019;13(3):e0007213.
7. Bartalesi F, Bartoloni A, Bisoffi Z, Spinicci M, Giménez Sánchez F, Muñoz J, et al. The emerging problem of biological treatment in migrant and travelling populations: it is time to extend guidelines for the screening of infectious diseases. *Ann Rheum Dis*. 2014 May;73(5):794–6.
8. Wolinsky H. Tropical travel medicine. A growing interest in tropical medicine reflects the increasing incidence of tropical disease in the Western world. *EMBO Rep*. 2008 Aug;9(8):714–6.
9. Leblebicioglu H, Ozaras R, Fletcher TE, Beeching NJ, ESCMID Study Group for Infections in Travellers and Migrants (ESGITM). Crimean-Congo haemorrhagic fever in travellers: A systematic review. *Travel Med Infect Dis*. 2016 Apr;14(2):73–80.
10. Grobusch MP, Schaumburg F, Weitzel T, Rothe C, Hanscheid T, Goorhuis A. Ebola 2018 – Implications for travel health advice and relevance for travel medicine. *Travel Med Infect Dis*. 2018 Jul 1;24:1–3.
11. Crawshaw AF, Kirkbride H. Public Health England’s Migrant Health Guide: an online resource for primary care practitioners. *Public Health*. 2018 May;158:198–202.
12. D’Acremont V, Ambresin A-E, Burnand B, Genton B, Travel clinic, Medical Outpatient Clinic, University of Lausanne, Rue Bugnon 44, 1011 Lausanne, Switzerland. Practice guidelines for evaluation of Fever in returning travelers and migrants. *J Travel Med*. 2003 May;10 Suppl 2:S25-52.
13. Ambresin AE, D’Acremont V, Mueller Y, Martin O, Burnand B, Genton B. www.fevertravel.ch: an online study prototype to evaluate the safety and feasibility of

- computerized guidelines for fever in returning travellers and migrants. *Comput Methods Programs Biomed.* 2007 Jan;85(1):19–31.
14. Collier A, Perry JJ, Nath A. LO072: Fever in the returning traveller: a systematic review and critical appraisal of existing clinical practice guidelines and approaches to returning travellers presenting with fever. *Can J Emerg Med.* 2016 May;18(S1):S54–5.
 15. Mueller Y, D'Acremont V, Ambresin A-E, Rossi I, Martin O, Burnand B, et al. Feasibility and clinical outcomes when using practice guidelines for evaluation of fever in returning travelers and migrants: a validation study. *J Travel Med.* 2014 Jun;21(3):169–82.
 16. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ.* 2009 Jul 21;339:b2535.
 17. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ.* 2015 02;350:g7647.
 18. Bottieau E, Clerinx J, Schrooten W, Van den Enden E, Wouters R, Van Esbroeck M, et al. Etiology and outcome of fever after a stay in the tropics. *Arch Intern Med.* 2006 Aug 14;166(15):1642–8.
 19. Boggild AK, Geduld J, Libman M, Ward BJ, McCarthy A, Hajek J, et al. Travel-acquired infections in Canada: CanTravNet 2011-2012. *Can Commun Dis Rep Relev Mal Transm Au Can.* 2014 Sep 18;40(16):313–25.
 20. Moga C, Guo B, Schopflocher D, Harstall C. Development of a quality appraisal tool for case series studies using a modified Delphi technique. *Edmont AB Inst Health Econ.* 2012;
 21. Zeng X, Zhang Y, Kwong JSW, Zhang C, Li S, Sun F, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. *J Evid-Based Med.* 2015 Feb;8(1):2–10.
 22. Kent P, Hancock MJ. Interpretation of dichotomous outcomes: sensitivity, specificity, likelihood ratios, and pre-test and post-test probability. *J Physiother.* 2016 Oct;62(4):231–3.
 23. Bottieau E, Clerinx J, Van den Enden E, Van Esbroeck M, Colebunders R, Van Gompel A, et al. Fever after a stay in the tropics: diagnostic predictors of the leading tropical conditions. *Medicine (Baltimore).* 2007 Jan;86(1):18–25.
 24. Grimes DA, Schulz KF. Refining clinical diagnosis with likelihood ratios. *Lancet Lond Engl.* 2005 Apr 23;365(9469):1500–5.
 25. Avni C, Stienlauf S, Meltzer E, Sidi Y, Schwartz E, Leshem E. Region-Specific, Life-Threatening Diseases among International Travelers from Israel, 2004-2015. *Emerg Infect Dis.* 2018;24(4):790–3.

26. Naudin J, Blondé R, Alberti C, Angoulvant F, De Lauzanne A, Armoogum P, et al. Aetiology and epidemiology of fever in children presenting to the emergency department of a French paediatric tertiary care centre after international travel. *Arch Dis Child*. 2012 Feb;97(2):107–11.
27. Wilson ME, Weld LH, Boggild A, Keystone JS, Kain KC, von Sonnenburg F, et al. Fever in returned travelers: results from the GeoSentinel Surveillance Network. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2007 Jun 15;44(12):1560–8.
28. Ansart S, Perez L, Thellier M, Danis M, Bricaire F, Caumes E. Predictive factors of imported malaria in 272 febrile returning travelers seen as outpatients. *J Travel Med*. 2010 Apr;17(2):124–9.
29. Badiaga S, Barrau K, Parola P, Brouqui P, Delmont J. Contribution of nonspecific laboratory test to the diagnosis of malaria in febrile travelers returning from endemic areas: value of hypocholesterolemia. *J Travel Med*. 2002 Jun;9(3):117–21.
30. Matono T, Kutsuna S, Kato Y, Katanami Y, Yamamoto K, Takeshita N, et al. Role of classic signs as diagnostic predictors for enteric fever among returned travellers: Relative bradycardia and eosinopenia. *PloS One*. 2017;12(6):e0179814.
31. Casalino E, Le Bras J, Chaussin F, Fichelle A, Bouvet E. Predictive factors of malaria in travelers to areas where malaria is endemic. *Arch Intern Med*. 2002 Jul 22;162(14):1625–30.
32. D'Acremont V, Landry P, Mueller I, Pécoud A, Genton B. Clinical and laboratory predictors of imported malaria in an outpatient setting: an aid to medical decision making in returning travelers with fever. *Am J Trop Med Hyg*. 2002 May;66(5):481–6.
33. Siikamäki HM, Kivelä PS, Sipilä PN, Kettunen A, Kainulainen MK, Ollgren JP, et al. Fever in travelers returning from malaria-endemic areas: don't look for malaria only. *J Travel Med*. 2011 Aug;18(4):239–44.
34. Stienlauf S, Segal G, Sidi Y, Schwartz E. Epidemiology of travel-related hospitalization. *J Travel Med*. 2005 Jun;12(3):136–41.
35. O'Brien D, Tobin S, Brown GV, Torresi J. Fever in returned travelers: review of hospital admissions for a 3-year period. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2001 Sep 1;33(5):603–9.
36. Parola P, Soula G, Gazin P, Foucault C, Delmont J, Brouqui P. Fever in travelers returning from tropical areas: prospective observational study of 613 cases hospitalised in Marseilles, France, 1999-2003. *Travel Med Infect Dis*. 2006 Mar;4(2):61–70.
37. West NS, Riordan F a. I. Fever in returned travellers: a prospective review of hospital admissions for a 2(1/2) year period. *Arch Dis Child*. 2003 May;88(5):432–4.
38. McGee S. Simplifying likelihood ratios. *J Gen Intern Med*. 2002 Aug;17(8):646–9.
39. Jensenius M, Han PV, Schlagenhauf P, Schwartz E, Parola P, Castelli F, et al. Acute and potentially life-threatening tropical diseases in western travelers--a GeoSentinel multicenter study, 1996-2011. *Am J Trop Med Hyg*. 2013 Feb;88(2):397–404.

40. Griffiths KM, Savini H, Brouqui P, Simon F, Parola P, Gautret P. Surveillance of travel-associated diseases at two referral centres in Marseille, France: a 12-year survey. *J Travel Med* [Internet]. 2018 Apr 9 [cited 2020 Sep 15];25(1). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7107586/>
41. Boggild AK, Geduld J, Libman M, Yansouni CP, McCarthy AE, Hajek J, et al. Malaria in travellers returning or migrating to Canada: surveillance report from CanTravNet surveillance data, 2004-2014. *CMAJ Open*. 2016 Jul 6;4(3):E352–8.
42. World Health Organization. Dengue and severe dengue [Internet]. [cited 2019 Jun 18]. Available from: <https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue>
43. The World Health Organization. Dengue Situation Update: Number 574 [Internet]. 2019 [cited 2019 Sep 5]. Available from: https://www.who.int/docs/default-source/wpro---documents/emergency/surveillance/dengue/dengue-20190801.pdf?sfvrsn=fc80101d_20
44. Mizuno Y, Kudo K. Travel-related health problems in Japanese travelers. *Travel Med Infect Dis*. 2009 Sep;7(5):296–300.
45. Moya Notario N, Hernández-Cabrera M, Carranza-Rodríguez C, Pisos-Álamo E, Jaén-Sánchez N, Pérez-Arellano JL. [Febrile syndromes in the traveler returning from tropical regions admitted in a monographic unit]. *Rev Espanola Quimioter Publicacion Of Soc Espanola Quimioter*. 2017 Dec;30(6):436–42.
46. Olivero RM, Hamer DH, MacLeod WB, Benoit CM, Sanchez-Vegas C, Jentes ES, et al. Dengue Virus Seroconversion in Travelers to Dengue-Endemic Areas. *Am J Trop Med Hyg*. 2016 Nov 2;95(5):1130–6.
47. Boggild AK, Geduld J, Libman M, Ward BJ, McCarthy AE, Doyle PW, et al. Travel-acquired infections and illnesses in Canadians: surveillance report from CanTravNet surveillance data, 2009-2011. *Open Med Peer-Rev Indep Open-Access J*. 2014;8(1):e20-32.
48. Boggild AK, Esposito DH, Kozarsky PE, Ansdell V, Beeching NJ, Campion D, et al. Differential diagnosis of illness in travelers arriving from Sierra Leone, Liberia, or Guinea: a cross-sectional study from the GeoSentinel Surveillance Network. *Ann Intern Med*. 2015 Jun 2;162(11):757–64.
49. Camps M, Vilella A, Marcos MA, Letang E, Muñoz J, Salvadó E, et al. Incidence of respiratory viruses among travelers with a febrile syndrome returning from tropical and subtropical areas. *J Med Virol*. 2008 Apr;80(4):711–5.
50. Bailey MS, Trinick TR, Dunbar JA, Hatch R, Osborne JC, Brooks TJ, et al. Undifferentiated febrile illnesses amongst British troops in Helmand, Afghanistan. *J R Army Med Corps*. 2011 Jun;157(2):150–5.
51. Leder K, Torresi J, Libman MD, Cramer JP, Castelli F, Schlagenhauf P, et al. GeoSentinel Surveillance of Illness in Returned Travelers, 2007–2011. *Ann Intern Med*. 2013 Mar 19;158(6):456–68.

52. Mendelson M, Han PV, Vincent P, von Sonnenburg F, Cramer JP, Loutan L, et al. Regional variation in travel-related illness acquired in Africa, March 1997-May 2011. *Emerg Infect Dis*. 2014 Apr;20(4):532–41.
53. Pisutsan P, Soonthornworasiri N, Matsee W, Phumratanaprapin W, Punrin S, Leowattana W, et al. Incidence of health problems in travelers to Southeast Asia: a prospective cohort study. *J Travel Med* [Internet]. 2019 Oct 14 [cited 2020 Sep 16];26(7). Available from: <https://academic.oup.com/jtm/article/26/7/taz045/5520737>
54. Lev D, Biber A, Lachish T, Leshem E, Schwartz E. Malaria in travelers at the time of corona. *J Travel Med*. 2020 Sep 26;27(6):taaa067.
55. Epelboin L, Blondé R, Nacher M, Combe P, Collet L. COVID-19 and dengue co-infection in a returning traveller. *J Travel Med*. 2020 Jul 13:taaa114.
56. Hadano Y, Shirano M, Goto T. Travel-related illness at a tertiary care hospital in Osaka, Japan. *Int J Gen Med*. 2016;9:355–9.
57. Cooper EC, Ratnam I, Mohebbi M, Leder K. Laboratory features of common causes of fever in returned travelers. *J Travel Med*. 2014 Aug;21(4):235–9.
58. O'Brien DP, Leder K, Matchett E, Brown GV, Torresi J. Illness in returned travelers and immigrants/refugees: the 6-year experience of two Australian infectious diseases units. *J Travel Med*. 2006 Jun;13(3):145–52.
59. Murad MH. *Clinical Practice Guidelines: A Primer on Development and Dissemination*. *Mayo Clin Proc*. 2017 Mar 1;92(3):423–33.
60. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. *BMJ Evid-Based Med*. 2018 Apr 1;23(2):60–3.
61. Huits R, Soentjens P, Maniewski-Kelner U, Theunissen C, Van Den Broucke S, Florence E, et al. Clinical Utility of the Nonstructural 1 Antigen Rapid Diagnostic Test in the Management of Dengue in Returning Travelers With Fever. *Open Forum Infect Dis* [Internet]. 2017 Jan 1 [cited 2020 Jun 10];4(1). Available from: <https://academic.oup.com/ofid/article/4/1/ofw273/2871222>
62. Huits R, Okabayashi T, Cnops L, Barbé B, Berg RVD, Bartholomeeusen K, et al. Diagnostic accuracy of a rapid E1-antigen test for chikungunya virus infection in a reference setting. *Clin Microbiol Infect*. 2018 Jan 1;24(1):78–81.
63. Kain D, Findlater A, Lightfoot D, Maxim T, Kraemer MUG, Brady OJ, et al. Factors Affecting Pre-Travel Health Seeking Behaviour and Adherence to Pre-Travel Health Advice: A Systematic Review. *J Travel Med*. 2019 Sep 2;26(6).
64. McDonald CR, Weckman A, Richard-Greenblatt M, Leligdowicz A, Kain KC. Integrated fever management: disease severity markers to triage children with malaria and non-malarial febrile illness. *Malar J*. 2018 Oct 10;17(1):353.
65. Freedman DO, Weld LH, Kozarsky PE, Fisk T, Robins R, von Sonnenburg F, et al. Spectrum of disease and relation to place of exposure among ill returned travelers. *N Engl J Med*. 2006 Jan 12;354(2):119–30.

Table and figure legends

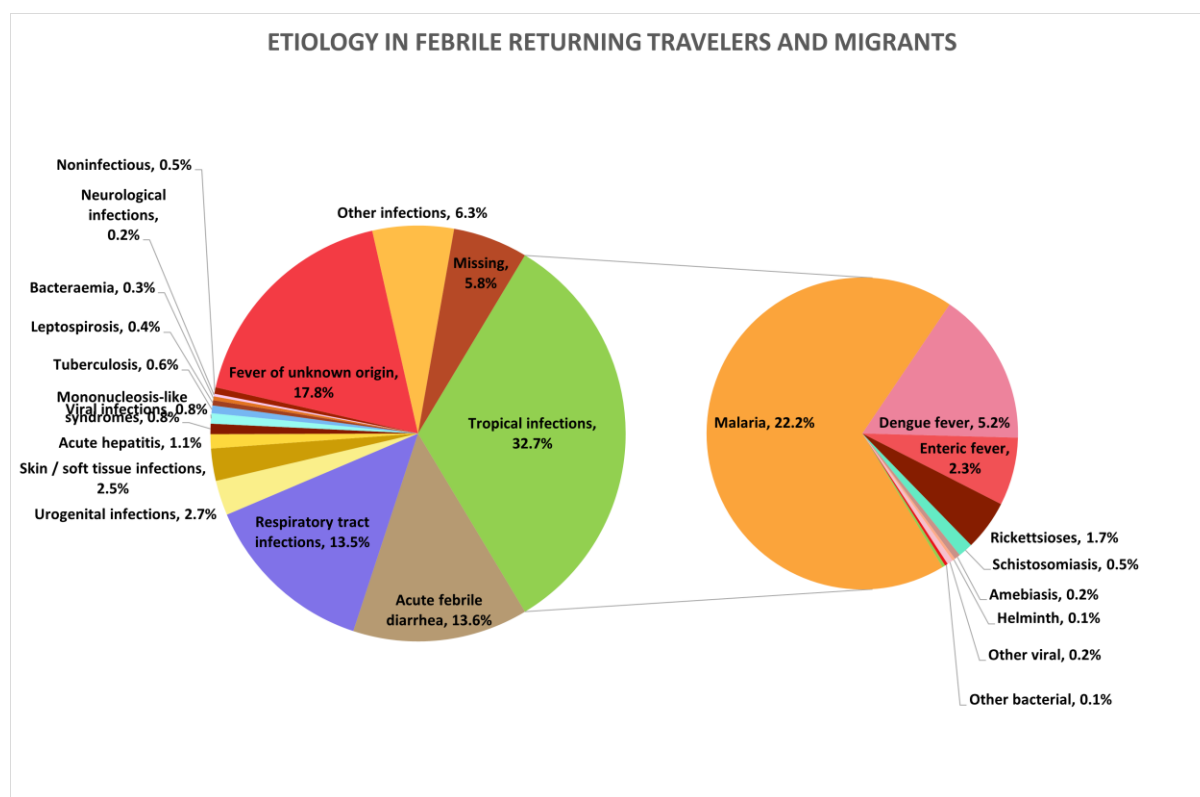


Figure 1. Proportion of febrile returning travelers and migrants with different etiological diagnoses, with tropical diagnoses separately presented

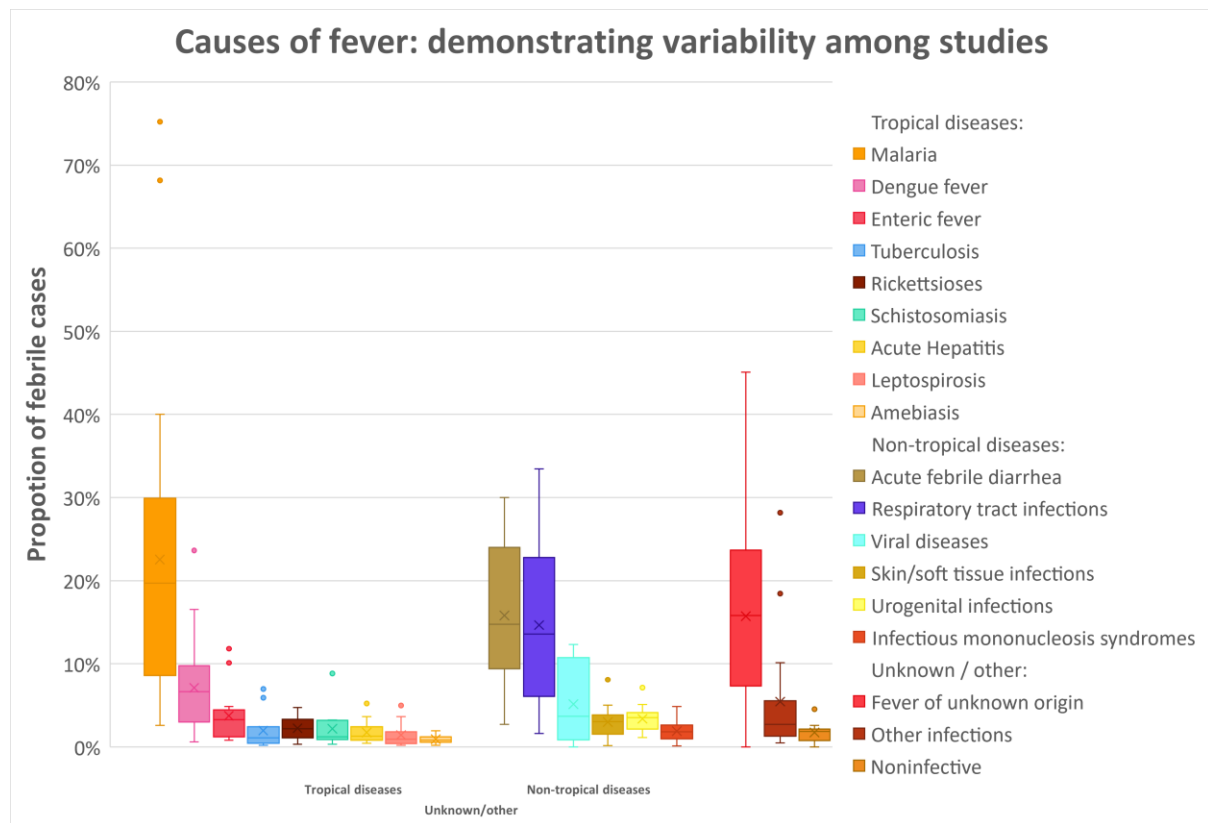


Figure 2. Variations in the proportions of etiological diagnoses among febrile returning travelers and migrants in the different studies

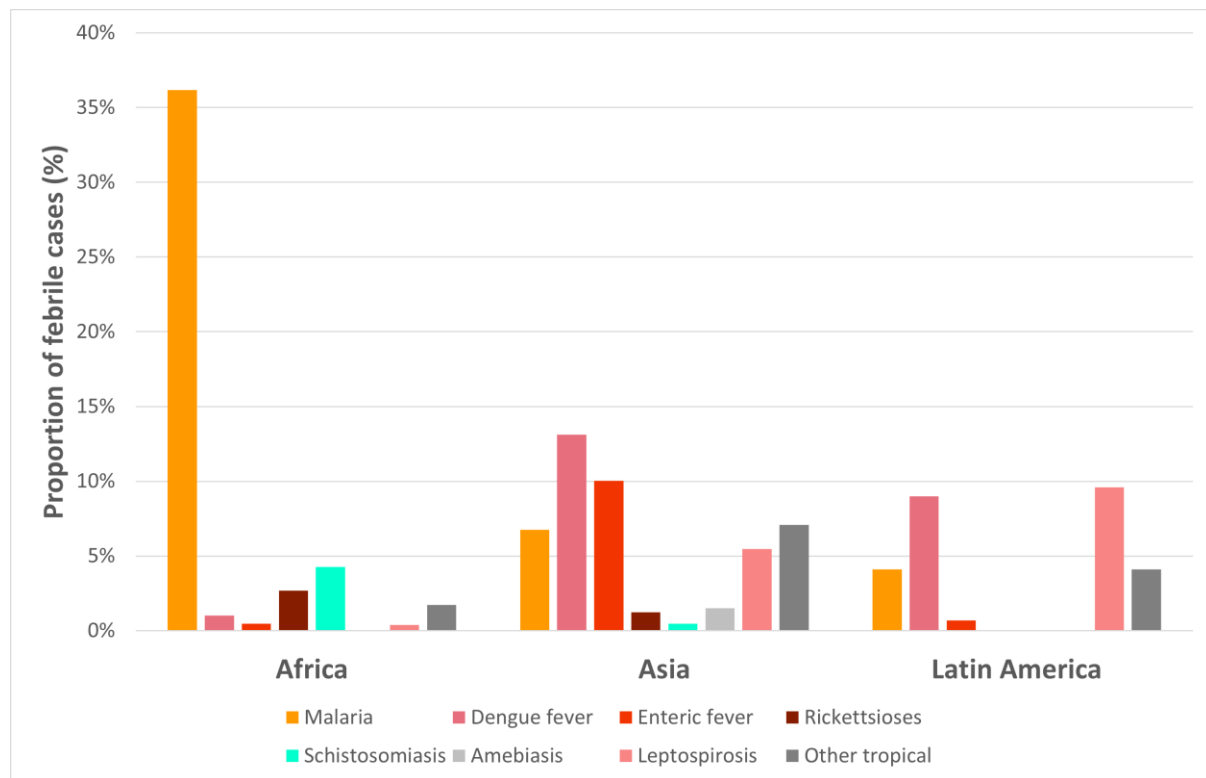


Figure 3. Prevalence of common tropical diseases categorized according to region visited

Table 1. Mean (%) and range of demographic and travel-related data from included studies

		MEAN % OF PATIENTS*	RANGE % OF PATIENTS*	NUMBER OF STUDIES WITH INFORMATION (N)
SEX	Female	41.2	30.8 – 55.8	16
REGION VISITED	Africa	51.1	4.6 – 88.3	14
	Asia	29.3	6.9 – 95.4	14
	(Latin) America	11.3	0 – 48.1	14
	North America / Europe	1.0	0 – 12.5	14
	Oceania	1.4	0 – 20.0	14
	Other / multiple / missing	4.5	0 – 8.3	14
TYPE OF TRAVEL	Tourism	57.6	20.6 – 88.1	11
	VFR	15.4	0 – 21.5	11
	Expatriates	2.9	0 – 14.4	11
	Migration	5.5	0 – 59.4	11
	Business / Research / Voluntary	14.2	0 – 23.1	11
	Visitors	0.4	0 – 6.0	11
	Others / missing	4.0	0 – 10.1	11
DAYS BETWEEN RETURN + PRESENTATION	Median = 7	13	0 – 360	7
DURATION OF TRAVEL	>30 days	36.6	17.3 – 37.3	2
PRE-TRAVEL MEDICAL ADVICE		51.7	9.3 – 73.0	4
INADEQUATE PROPHYLAXIS		72.8	40.6 – 82.5	4
HOSPITALISED	Any disease	32.3	8.5 – 69.3	9
	Malaria	10.9	7.4 – 67.0	7
	Dengue fever	7.3	-	1
	Enteric fever	0.8	0 – 10.1	2
INTENSIVE CARE UNIT ADMISSIONS		1.9	1.1 – 2.1	4
FATALITIES		0.22	0.0 – 1.5	8

* Mean number of patients = 312, range 110-6957

Table 2. Etiologies of fever in returning travelers and migrants, separated into tropical and non-tropical diseases

	MEAN % OF FEBRILE CASES (18755 CASES)	MEAN % OF TROPICAL DISEASES	RANGE % IN THE DIFFERENT STUDIES
TROPICAL INFECTIONS	32.7		
PARASITIC	23.2	70.9	2.7 – 78.0
MALARIA	22.2	67.7	2.6 – 75.2
SCHISTOSOMIASIS	0.5	1.6	0 – 2.0
AMEBIASIS	0.2	0.7	0 – 2.0
ENTERITIS (protozoan & helminths)	0.1	0.3	0 – 2.0
FILARIAL NEMATODES	0.0 ^y	0.1	0 – 4.8
VISCERAL LEISHMANIASIS	0.0 ^y	0.0	0 – 0.9
AFRICAN TRYPANOSOMIASIS	0.0 ^y	0.0	-
LOEFFLER SYNDROME	0.0 ^y	0.1	-
SARCOCYSTOSIS	0.0 ^y	0.0	-
VIRAL	5.4	16.5	0 – 25.5
DENGUE FEVER	5.2	15.9	0 – 23.6
CHIKUNGUNYA	0.2	0.5	0 – 6.5
VIRAL HAEMORRHAGIC FEVERS	0.0 ^y	0.1	0 – 0.7
BACTERIAL	4.1	12.5	0 – 21.8
ENTERIC (TYPHOID) FEVER	2.3	7.1	0 – 11.8
RICKETTSIOSIS	1.7	5.2	0 – 7.0
BRUCELLOSIS	0.1	0.2	0 – 2.8
MELIOIDOSIS	0.0 ^y	0.0	0 – 1.2
BORRELIOSIS	0.0 ^y	0.1	0 – 0.4
FUNGAL	0.0	0.1	0 – 0.3
HISTOPLASMOSIS	0.0 ^y	0.1	0 – 0.3
NON-TROPICAL INFECTIONS	38.6		
ACUTE DIARRHOEAL DISEASE (bacterial/unspecified)	13.6		0 – 30.0
RESPIRATORY TRACT INFECTIONS	13.5		1.6 – 33.5
UPPER RESPIRATORY TRACT INFECTIONS	6.0		0 – 9.1
PNEUMONIA	2.7		0 – 24.6
INFLUENZA / INFLUENZA-LIKE ILLNESS	2.5		0 – 26.4
BRONCHITIS / BRONCHIOLITIS	0.8		0 – 3.3
EOSINOPHILIC PNEUMONITIS	0.1		0 – 1.8
GENITOURINARY TRACT INFECTIONS	2.7		0 – 11.4
SKIN / SOFT TISSUE	2.5		0 – 8.1

INFECTIONS		
ACUTE HEPATITIS (A/B/C/E)	1.1	0 – 8.8
OTHER GASTROINTESTINAL DISEASES	1.0	0 – 4.9
VIRAL DISEASES	0.8	0 – 13.6
MONONUCLEOSIS-LIKE SYNDROMES*	0.8	0 – 2.5
TUBERCULOSIS	0.6	0 – 3.9
LEPTOSPIROSIS	0.4	0 – 5.0
SEPTICEMIA / BACTEREMIA	0.3	0 – 3.0
PRIMARY HIV INFECTION	0.2	0 – 3.1
COXIELLA (Q FEVER)	0.2	0 – 0.9
NEUROLOGICAL INFECTIONS	0.2	0 – 2.7
SEXUALLY TRANSMITTED INFECTIONS	0.1	0 – 2.8
MEASLES / MUMPS / RUBELLA	0.0 ^v	0 – 2.6
UNKNOWN / OTHER	23.6	
FEVER OF UNKNOWN ORIGIN	17.8	0 – 45.1
OTHER INFECTIVE DIAGNOSES	5.2	0 – 28.2
NON-INFECTIOUS DIAGNOSIS	0.5	0 – 4.8
MISSING DATA	5.8	0 – 59.3

*EBV, CMV, parvovirus B19, Toxoplasmosis

^v Filarial nematodes (n=6); Visceral leishmaniasis (n=2); African trypanosomiasis (n=3); Loeffler syndrome (n=4); Sarcocystosis (n=3); Viral hemorrhagic fevers (n=4); Meloidosis (n=3); Borreliosis (n=4); Histoplasmosis (n=6); Measles/mumps/rubella (n=7)