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MAJOR ARTICLE

Geographic Variation of Infectious Disease Diagnoses Among Patients With Fever of Unknown Origin: A Systematic Review and Meta-analysis

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Background. Fever of unknown origin (FUO) investigations yield a substantial number of patients with infectious diseases. This systematic review and meta-analysis aimed to quantify more common FUO infectious diseases etiologies and to underscore geographic variation.

Methods. Four databases (PubMed, Embase, Scopus, and Web of Science) were searched for prospective studies reporting FUO rates among adult patients from 1 January 1997 to 31 March 2021. The pooled proportion for infectious diseases etiology was estimated using the random-effects meta-analysis model.

Results. Nineteen prospective studies were included with 2667 total cases. No studies were available for Africa or the Americas. Overall, 37.0% (95.0% confidence interval [CI], 30.0%–44.0%) of FUO patients had an infectious disease etiology. Infections were more likely from Southeastern Asia (pooled proportion, 0.49 [95% CI, .43–.55]) than from Europe (pooled proportion, 0.31 [95% CI, .22–.41]). Among specifically reported infectious diseases (n = 832), *Mycobacterium tuberculosis* complex predominated across all geographic regions (n = 285 [34.3%]), followed by brucellosis (n = 81 [9.7%]), endocarditis (n = 62 [7.5%]), abscesses (n = 61 [7.3%]), herpesvirus (eg, cytomegalovirus and Epstein-Barr virus) infections (n = 60 [7.2%]), pneumonia (n = 54 [6.5%]), urinary tract infections (n = 54 [6.5%]), and enteric fever (n = 40 [4.8%]).

Conclusions. FUO patients from Southeastern Asia were more likely to have an infectious diseases etiology when compared to other regions. The predominant factor for this finding appears to be differences in disease prevalence among various geographical locations or other factors such as access to timely care and diagnosis. Noting epidemiological disease factors in FUO investigations could improve diagnostic yields and clinical outcomes.

Keywords. clinical thermometry; fever; fever of unknown origin; pyrexia; pyrexia of unknown origin.

Infections comprise the largest category in many fever of unknown origin (FUO) series, accounting for an estimated 16%–55% of cases [1]. Exceptions, where noninfectious inflammatory disorders (NIIDs) predominate, include reports from Japan (30%–34%) [1, 2] and the Netherlands (31.4%) [3]. Most reports organize etiologies into 5 categories: infection, cancer, NIIDs, miscellaneous disorders, and unexplained illness [4–9]. Although there are ample individual series demonstrating infectious disease diagnoses, few aggregate data are available about diagnostic outcomes across groups or geographic regions [1].

In his 1896 address at the 47th annual American Medical Association meeting, William Osler, MD (1849–1919), recognized difficulties in determining the nature of varied forms of obscure infection-related fevers long before the phrase first appeared in the published medical literature [4, 10]. Petersdorf and Beeson [5] were the first to prospectively establish criteria for this syndrome—a temperature exceeding 38.3°C (100.9°F) on several occasions of 3 weeks' duration or more, and no established diagnosis despite 1 week of inpatient investigation. Subsequent investigators have modified these original criteria to reflect changes in the practice of medicine [6–9], including a recent standardized set of proposed criteria [11].

Recommended approaches investigating specific infections among patients who meet criteria are currently based on expert opinion [1, 5–7, 11, 12], whereas some also advocate for a structured approach. Some, such as Petersdorf [5, 13], have argued the contrary, emphasizing the uniqueness of patients, arguing against a "routine battery of laboratory tests." Despite

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improved serologic, laboratory, and imaging technologies and structured protocols [7–9], prolonged fevers often continue to elude a diagnosis, suggesting that fevers may have "too many origins" [14].

Since infectious disease and internal medicine specialists are asked to see these patients, this systematic review with meta-analysis aims to synthesize available data from recent prospective studies to estimate the overall proportion of infectious diseases among adult FUO patients and geographical variations. Results of the analysis may inform subsequent research and clinical practice.

METHODS

Literature Search

The International Prospective Register of Systematic Reviews (PROSPERO)–registered protocol of this systematic review and meta-analysis follows the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA checklist, Supplementary Table 1) [15]. An electronic search of prospective clinical studies was executed using PubMed, Embase, Scopus, and Web of Science databases with librarian-assisted query strings "(FUO), (fever of unknown origin [MeSH]), (PUO), (pyrexia of unknown origin [MeSH]), (clinical trial), (clinical trial [Publication Type]), and (prospective studies [MeSH])" from 1 January 1997 to 31 March 2021. The search period was chosen based on the last modification to the adult FUO criteria published by de Kleijn et al in 1997 [7, 8, 11]. English-language and non-English-language articles were included. Non-English abstracts or full-text articles were translated with online document translation systems (translate.google.com). Articles resulting from these searches and relevant cited references were reviewed. Patients meeting adult FUO definitions [5–9] were included to minimize unintended selection bias. Articles were excluded if patients did not precisely fit a standard adult FUO definition [5–9] or if studies were not classified as prospective. Data extraction from reports included publication year, study time period, country, setting (eg, university vs community hospital), FUO criteria, structured or unstructured diagnostic protocol evaluation, male and female composition, and contribution of potential diagnostic clues (PDCs), biochemical and immunological serology, microbiology cultures, and serology, histology, and imaging studies. Requests for further details of listed diagnoses, additional information on missing data, or confirmation of published data were executed by directly contacting study investigators individually.

Patient Consent

The patients' written consent and requirement of informed patient consent was not required due to this study being secondary research of publicly available published data sets. The design of the work has also been exempt from approval by the local ethical committee and institutional review boards due to secondary research of publicly available published datasets.

Statistical Analysis

Meta-analysis of the proportion of infectious diseases contributing to FUO was performed using study-specific 95% confidence intervals (CIs) calculated using the exact method [16]. Freeman-Tukey double arcsine transformation was used to compute the pooled estimate and perform back-transformation on the pooled estimate. The pooled proportions were estimated using the DerSimonian and Laird random-effects model. Study heterogeneity was assessed using I^2 with test-based CIs and determined as low if I^2 was <25.0%, moderate if between 25.0% and 50.0%, and high if >50.0%. This model was also used for subgroup analysis by region.

Analyses were performed using metaprop and heterogi commands in Stata version 16 (StataCorp, College Station, Texas). Statistical significance was set at .05.

RESULTS

Literature Review

Our search produced 20 publications representing 19 prospective studies [2, 7–9, 17–32] meeting inclusion criteria (Figure 1) with 2667 participants. Seventeen were university hospital studies, 1 was a mixed university and community hospital setting [9], and 1 was a community hospital study [32]. Seven studies utilized a structured diagnostic protocol [7–9, 17, 19, 23, 24, 31]. Nine studies [7–9, 17–21, 30, 31] (47.4%, total n = 1268) used Peterdorf's criteria [5, 11] for FUO, 7 studies [2, 23, 24, 26, 28, 29, 32] (36.8%, total n = 1135) used Durack's criteria [6, 11], and 3 studies [22, 25, 27] (15.8%, total n = 264) used either criterion. There were 1049 (39.3%) infections, 568 (21.3%) NIIDs, and 404 (15.1%) cancers with 1236 (46.3%) total female participants. Several reports, including de Kleijn et al [7, 8], enrolled patients <18 years of age [17, 18, 21, 23–25, 27] as long as patients met the adult FUO criteria. Therefore, the ages of participants ranged from 10 to 94 years. Undiagnosed cases were reported in all but 2 studies [29, 30] (n = 616) and occurred in 449 of 2051 (21.9%) cases. The contribution of PDCs, biochemical and immunological serology, and microbiology cultures, as well as histological and imaging studies, was insufficiently reported in several studies for analysis. Table 1 lists study characteristics. The diagnostic yield for each infectious disease category is shown in Table 2. Geographical distribution was based upon the 6 World Health Organization (WHO) regions (https://www.who.int/about/who-we-are/regional-offices).

Systematic Review

Our systematic literature search produced no prospective reports for the regions of Africa and the Americas. Table 3 groups

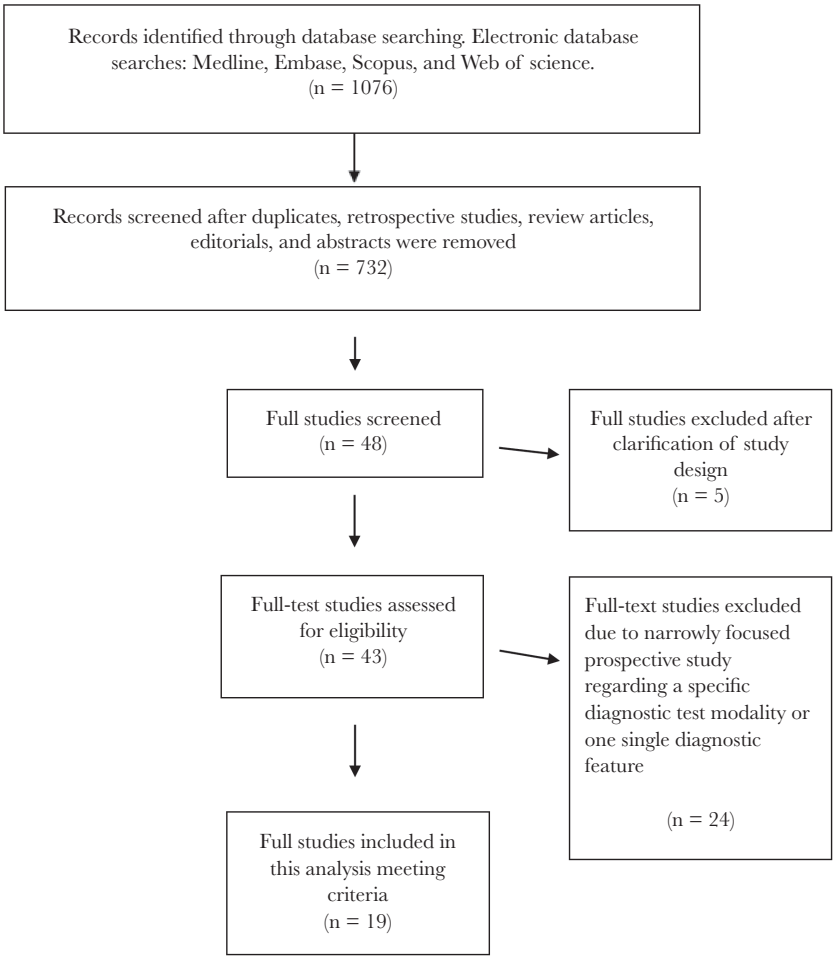

Figure 1. Literature review flow diagram.

individual studies by WHO region and highlights the most commonly reported infections.

Eastern Mediterranean Region

Two prospective studies [24, 25] represent this region (Table 3) for a combined total of 57 infections. Adil Khalil et al [24] from Iraq reported infections from 18 of 55 (32.7%) FUO patients. Ali-Eldin et al [25] in Egypt reported 39 (41.9%) infections among 93 FUO cases. Overall, the most common infections included brucellosis (19.3% [n = 11]), *Mycobacterium tuberculosis* (*Mtb*) (14.0% [n = 8]), infective endocarditis (IE) (14.0% [n = 8]), urinary tract infection (UTI) (10.5% [n = 6]), cytomegalovirus (CMV) (8.8% [n = 5]), abscesses (8.8% [n = 5]), Epstein-Barr virus (EBV) (7.0% [n = 4]), enteric fever (EF) (7.0% [n = 4]), and human immunodeficiency virus (HIV) (5.3% [n = 3]).

Adil Khalil et al [24] reported that *Brucella* agglutination confirmed 2 cases, Widal titers assisted with 1 case of EF diagnosis, 2 *Staphylococcus aureus* IE cases were confirmed with blood cultures and echocardiography, 2 cases of pyelonephritis were based on pyuria and ultrasonographic (US) features of infection, and repeat serial thick and thin smears (n = 3) confirmed the case of malaria. Ali-Eldin et al [25] did not report the contribution of diagnostic testing modalities.

European Region

Ten articles [7–9, 17, 19–23, 28, 32] represent this region with 381 of 1255 (30.4%) of FUO cases due to infections (Table 3). Overall, cases included *Mtb* (n = 106), IE (n = 34), renal and prostate infections (n = 31), abscesses (n = 25), herpesvirus (n = 25), brucellosis (n = 22), pulmonary and pleural infections (n = 22), EF (n = 13), parasites (n = 12), and bone and joint infections (n = 9). Toxoplasmosis accounted for 8 of 12 (66.7%) parasite cases and CMV accounted for 20 of 25 (80.0%) herpesvirus infections.

Northern European Countries

Among the 5 studies [7–9, 20, 28, 32] in this region, there were 139 infections (Table 3). The most commonly reported infections included IE (13.7% [n = 19]), *Mtb* (11.5% [n = 16]), CMV (10.8% [n = 15]), UTI (8.6% [n = 12]), abscesses (8.6% [n = 12]), pneumonia (7.9% [n = 11]), yersiniosis (5.8% [n = 8]), and bone and joint infections (3.7% [n = 5]).

Table 1. General Characteristics of Studies by the 6 World Health Organization Regional Groupings[a]

Author, Study Period, Location [Ref]	Study Size, No. (% Female)	Age, y, Range (Median)	FUO Criteria	INF, No. (%)	NIID, No. (%)	ONC, No. (%)	MIS, No. (%)	UD, No. (%)
African Region								
Total	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
Region of the Americas								
Total	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
South-East Asian Region								
Kejariwal, 1998–2001, India [18]	100 (41.0)	12–65 (32)	Petersdorf	53 (53.0)	11 (11.0)	17 (17.0)	5 (5.0)	14 (14.0)
Bandyopadhyay, 2008–2009, India [26]	164 (50.0)	27–57 (42)	Durack	90 (55.0)	18 (11.0)	36 (22.0)	0 (0.0)	20 (12.0)
Mir, 2010–2012, India [27]	91 (21.0)	16–49 (NL)	Petersdorf/ Durack	40 (44.0)	11 (12.1)	11 (12.1)	4 (4.4)	25 (27.5)
Pannu, 2018–2019, India [31]	152 (38.2)	NL	Petersdorf	66 (43.4)	30 (19.7)	32 (21.1)	5 (3.3)	19 (12.5)
Total	507			249 (49.1)	70 (13.8)	96 (18.9)	14 (2.8)	78 (15.4)
European Region								
Vanderschueren, 1990–1999, Belgium [20]	290 (43.0)	33–65 (54)	Petersdorf	57 (19.7)	68 (23.4)	29 (10.0)	38 (13.1)	98 (33.8)
de Kleijn, 1992–1994, Netherlands [7, 8]	167 (52.0)	16–87 (53)	Petersdorf	43 (25.7)	40 (24.0)	21 (13.0)	13 (7.8)	50 (29.9)
Ergönül, 1993–1999, Turkey [22]	80 (51.0)	29–59 (44)	Petersdorf/ Durack	42 (52.5)	10 (12.5)	14 (17.5)	5 (6.25)	9 (11.25)
Altiparmak, 1994–1998, Turkey [17]	50 (64.0)	15–75 (38)	Petersdorf	22 (44.0)	3 (6.0)	13 (26.0)	8 (16.0)	4 (8.0)
Saltoglu, 1994–2002, Turkey [21]	87 (29.9)	14–80 (38)	Petersdorf	51 (58.6)	16 (18.3)	12 (13.7)	2 (2.2)	6 (6.8)
Baicus, 1997–1998, Romania [19]	164 (51.8)	18–78 (46)	Petersdorf	74 (45.1)	30 (18.3)	41 (25.0)	7 (4.3)	12 (7.3)
Robine, 2002–2012, France [28]	103 (48.0)	19–84 (53)	Durack	12 (11.6)	31 (30.1)	3 (2.9)	5 (4.9)	52 (50.5)
Bleeker-Rovers, 2003–2005, Netherlands [9]	73 (54.8)	26–87 (54)	Petersdorf	12 (16.0)	16 (22.0)	5 (7.0)	3 (4.0)	37 (51.0)
Kucukardali, 2003–2004, Turkey [23]	154 (46.1)	17–75 (42)	Durack	53 (34.4)	47 (30.5)	22 (14.3)	8 (5.2)	24 (15.6)
Cachot, 2009–2017, Spain [32]	87 (47.2)	37–75 (56)	Durack	15 (17.2)	19 (21.8)	13 (15.0)	14 (16.1)	26 (29.9)
Total	1255	14–87		381 (30.4)	280 (22.3)	173 (13.8)	103 (8.2)	318 (25.3)
Eastern Mediterranean Region								
Adil Khalil, 2002–2009, Iraq [24]	55 (50.9)	10–76 (43)	Durack	18 (32.7)	14 (25.4)	9 (16.4)	3 (5.4)	11 (20.0)
Ali-Eldin, 2009–2010, Egypt [25]	93 (51.6)	15–65 (34)	Petersdorf/ Durack	39 (41.9)	14 (15.1)	28 (30.1)	0 (0.0)	12 (12.9)
Total	148	10–76		57 (38.5)	28 (18.9)	37 (25.0)	3 (2.0)	23 (15.5)
Western Pacific Region								
Wu, 2014–2017, China [29]	431 (44.8)	NL	Durack	241 (55.9)	93 (21.6)	62 (14.4)	35 (8.1)	NL

Table 1. Continued

Author, Study Period, Location [Ref]	Study Size, No. (% Female)	Age, y, Range (Median)	FUO Criteria	INF, No. (%)	NIID, No. (%)	ONC, No. (%)	MIS, No. (%)	UD, No. (%)
Naito, 2016–2017, Japan [2]	141 (55.3)	22–94 (62)	Durack	24 (17.0)	48 (34.0)	22 (15.6)	17 (12.1)	30 (21.3)
Xu, 2017–2019, China [30]	185 (43.8)	32–67 (53)	Petersdorf	97 (52.4)	49 (26.5)	14 (7.6)	NL	NL
Total	757			362 (47.8)	190 (25.2)	98 (12.9)		

Abbreviations: FUO, fever of unknown origin; INF, infectious diseases; MIS, miscellaneous causes; NAD, no available data; NIID, noninfectious inflammatory conditions; NL, not listed; ONC, oncology/neoplastic conditions; UD, undiagnosed.
[a]Source: World Health Organization (https://www.who.int/about/who-we-are/regional-offices). Accessed 28 September 2021.

De Kleijn et al [7, 8] from the Netherlands reported 43 (25.7%) infections among 167 total FUO cases. Extrapulmonary tuberculosis (EPTB) (n = 3) cases were diagnosed with biopsy cultures. Tuberculin skin testing (TST) contributed to the diagnosis in 2 of those cases. US with biopsy contributed to detecting 4 bacterial abscesses (2 hepatic and 2 pelvic). Two pleural empyema cases, 1 with *Peptostreptococcus* spp, were discovered by computed tomography (CT) imaging and pleural culture. One case of *Actinomyces* spp was discovered by pleural biopsy culture. Plain-film chest imaging (CXR) assisted in all 6 pneumonia cases, with bronchoscopy cultures helpful in 4 cases. Blood culture sets contributed to fewer diagnoses (8 of 167 cases [4.8%]) than false positives (19 [11.4%]). Urine culture results (n = 134) revealed only 5 (3.7%) renal infections. Serologic testing (n = 961) was helpful for only 17 (1.8%) cases: parainfluenza virus, *Salmonella enterica* subsp *enterica* serovar Typhi (*S* Typhi) by Widal test, and *Yersinia enterocolitica* (n = 3).

Bleeker-Rovers et al [9] from the Netherlands reported that only 4 of 509 (0.79%) microbiological serology tests and 3 of 11 lymph node biopsy cultures (27.3%) assisted in diagnosing chronic *Y enterocolitica*. In this same report, only 1 other bacterial culture (a hepatic abscess sample) helped in diagnosis among 1193 (<0.1%) culture samples (eg, blood, urine, and other) used in the series. A false-negative 2-deoxy-2-[^{18}F] fluoro-D-glucose positron emission tomography combined with CT (^{18}FDG-PET/CT) with subsequent CT revealed diverticulitis in 1 patient. Among 12 (11.7%) patients in the series from France by Robine [28], ^{18}FDG-PET/CT and molecular diagnostic testing methods did not yield any infection. Still, they were considered contributory (ie, led to true-positive diagnoses) in 6 NIID cases (4 giant cell arteritis and 2 sarcoidosis) and 4 cancer cases (1 lymphoma, 1 solid tumor, 1 Rosai-Dorfman disease, and 1 Kikuchi-Fujimoto disease).

A Belgian study by Vanderschueren et al [20] reported that microbiologic cultures and serology had an overall diagnostic yield of 13.6% (n = 28). Except for *Mtb* and HIV, 37 of 57 (64.9%) infections were diagnosed within 7 days after beginning a formal FUO evaluation. Authors reported 4 of 16 (25%) infection-related deaths: disseminated *Mtb* (n = 2), *Salmonella* spp aortic root prosthetic infection, and *Campylobacter* spp prosthetic heart valve infection during the index admission. There were 11 of 18 (61.1%) febrile illness-related deaths during the follow-up period (median, 810 days [range, 180–2085 days]), of which only 1 was infection related due to HIV complications.

Cachot et al [32] reported 15 (17.2%) infections among 87 total FUO cases from Spain. EPTB accounted for 2 cases. *Neisseria gonorrhoeae* and *Gemella morbillorum* were the causes of subacute IE. The authors reported 9 (60%) patients with PDCs but 6 with misleading PDCs. CT scans (26.7% [n = 4]) and ^{18}FDG-PET/CT (13.3% [n = 2]) were helpful in establishing diagnoses. Nitrofurantoin caused 1 of 3 drug fever

Table 2. Frequency of Specifically Reported Infections by the 6 World Health Organization Regional Groupings

	No. (%)					
Infection	AMR	AFR	EMR	EUR	SEAR	WPR
Abscess[a]	ND	ND	5 (8.8)	25 (7.2)	21 (8.4)	10 (5.6)
Brucellosis	ND	ND	11 (19.3)	22 (6.3)	10 (4.0)	38 (21.3)
Encephalitis, viral	ND	ND	NL	3 (<1.0)	1 (<1.0)	NL
Endocarditis	ND	ND	8 (14.0)	34 (9.8)	12 (4.8)	8 (4.5)
Enteric fever	ND	ND	4 (7.0)	13 (3.7)	20 (8.0)	3 (1.6)
Fungal	ND	ND	NL	5 (1.4)	NL	NL
Head and neck tissue	ND	ND	NL	3 (<1.0)	NL	NL
Histoplasmosis/endemic molds	ND	ND	NL	NL	2 (<1.0)	NL
HIV	ND	ND	3 (5.3)	5 (1.4)	12 (4.8)	NL
Intra-abdominal (not abscess)	ND	ND	NL	7 (2.0)	3 (1.2)	NL
Leptospirosis	ND	ND	NL	1 (<0.5)	1 (<0.5)	NL
Malaria	ND	ND	1 (1.8)	6 (1.7)	11 (4.4)	NL
Meningitis	ND	ND	NL	5 (1.4)	6 (2.4)	4 (2.2)
Mycoplasma	ND	ND	NL	2 (<1.0)	NL	4 (2.2)
NTM	ND	ND	NL	1 (<0.5)	NL	NL
Odontogenic	ND	ND	NL	5 (1.4)	NL	NL
Parasite (not malaria)	ND	ND	NL	12 (3.4)	NL	6 (3.4)
Pneumonia/pleural	ND	ND	1 (1.8)	22 (6.3)	4 (1.6)	27 (15.2)
Salmonellosis (not enteric fever)	ND	ND	NL	2 (<1.0)	NL	NL
STI	ND	ND	1 (1.8)	3 (<1.0)	NL	NL
TB, total	ND	ND	8 (14.0)	106 (30.5)	120 (48.2)	51 (28.7)
TB, pulmonary	ND	ND	1 (12.5)	21 (19.8)	9 (7.5)	NL
TB, extrapulmonary	ND	ND	7 (87.5)	52 (49.1)	94 (78.3)	NL
TB, pulmonary and extrapulmonary	ND	ND	NL	NL	4 (3.3)	NL
UTI[b]	ND	ND	6 (10.5)	31 (8.9)	11 (4.4)	6 (3.4)
Viral infections[c]	ND	ND	9 (15.8)	25 (7.2)	5 (2.0)	21 (11.8)
Visceral larva migrans	ND	ND	NL	NL	4 (1.6)	NL
Visceral leishmaniasis	ND	ND	NL	3 (<1.0)	6 (2.4)	NL
Yersiniosis	ND	ND	NL	7 (2.0)	NL	NL
Total[d]			57	348	249	178

Abbreviations: AMR, Region of the Americas; AFR, African Region; EMR, Eastern Mediterranean Region; EUR, European Region; HIV, human immunodeficiency virus; ND, no data; NL, not listed; NTM, nontuberculous mycobacteria; SEAR, South-East Asian Region; STI, sexually transmitted infection; TB, tuberculosis; UTI, urinary tract infection; WPR, Western Pacific Region.

[a]Any site including intra-abdominal.

[b]Includes both lower and upper tract infections.

[c]Includes herpesviruses (eg, Epstein-Barr virus, cytomegalovirus) and other chronic viral infections (eg, hepatitis C virus).

[d]The total number of geographically listed infections in this table is different from those listed in Table 1 given the varying differences in individual reporting of specific infectious disease conditions among individual studies.

cases. No infection-related deaths were reported from the index admission or during the follow-up period.

Southern European Countries

Among the 5 studies [17, 19, 21, 22, 32] in this region there were 242 total infections (Table 3). The most common conditions reported included *Mtb* (37.2% [n = 90]), UTI (9.5% [n = 23]), brucellosis (7.9% [n = 19]), IE (7.0% [n = 17]), abscesses (4.9% [n = 12]), CMV (4.1% [n = 10]), EF (3.3% [n = 8]), salmonellosis (3.3% [n = 8]), and parasite infections (2.5% [n = 6]).

Ergönül et al [22] from Turkey reported pulmonary *Mtb* in 8 of 12 (66.7%) cases diagnosed by serial CXR and pulmonary biopsy cultures. Three EPTB cases were meningeal, diagnosed by cerebrospinal fluid examination, and 1 case of lymphadenitis was secured through lymph node biopsy. Brucellosis occurred in 9 (21.4%) cases diagnosed with a combination of blood culture and serology with Coombs test when Wright agglutination testing was negative. Malaria, EF, and intra-abdominal abscesses occurred among 4 (9.5%) cases each. Serial blood smears (n = 4) revealed malaria cases. Repeat serology and clinical follow-up established the diagnosis of EF. Intra-abdominal abscesses required a combination of US and CT scan in each case. Less common causes included IE (n = 2) diagnosed with serial blood cultures and echocardiogram, aseptic meningitis (n = 2), immunoglobulin M (IgM) antibody–positive psittacosis (n = 1), and toxoplasmosis (n = 1) diagnosed with the Sabin-Feldman dye test.

From Turkey, Altiparmak et al [17] reported that 79% (n = 15) of *Mtb* cases required invasive procedures to establish a diagnosis. Abdominal US and CT were valuable tools to

Table 3. Most Common Infectious Diseases Diagnoses by World Health Organization Region and Individual Study

Author, Country (No. of Infections) [Ref]	Diagnosis, No. (%)									
Eastern Mediterranean Region										
Adil Khalil, Iraq (n = 18) [24]	*Mtb*, 4 (22.2)	EF, 3 (16.7)	Br, 3 (16.7)	IE, 2 (11.1)	UTI, 2 (11.1)	PNA, 1 (5.5)	EBV, 1 (5.5)	MAL, 1 (5.5)	Absc, 1 (5.5)	NAD
Ali-Eldin, Egypt (n = 39) [25]	Br, 8 (20.5)	IE, 6 (15.4)	CMV, 5 (12.8)	*Mtb*, 4 (10.3)	UTI, 4 (10.3)	Absc, 4 (10.3)	EBV, 3 (7.7)	HIV, 3 (7.7)	EF, 1 (2.6)	PID 1 (2.6)
European Region										
Northern European countries										
Vanderschueren, Belgium (n = 57) [20][a]	IE, 11 (19.3)	*Mtb*, 8 (14.0)	UTI, 6 (10.5)	CMV, 6 (10.5)	Absc, 5 (8.8)	BJI, 4 (7.0)	EBV, 3 (5.3)	MAL, 2 (3.5)	PAR, 2 (3.5)	HIV, 1 (1.7)
Robine, France (n = 12) [28][b]	CMV, 4 (33.3)	IE, 2 (16.7)	Absc, 1 (8.3)	BJI, 1 (8.3)	NTM, 1 (8.3)	*Mtb*, 1 (8.3)	NAD	NAD	NAD	NAD
de Kleijn, Netherlands (n = 43) [7, 8][c]	PNA, 6 (13.9)	UTI, 5 (11.6)	CMV, 5 (11.6)	Absc, 4 (9.3)	IE, 4 (9.3)	*Mtb*, 3 (6.9)	YER, 3 (6.9)	EMP, 2 (4.6)	HN, 2 (4.6)	GI, 2 (4.6)
Bleeker-Rovers, Netherlands (n = 12) [9][d]	YER, 4 (33.3)	PNA, 2 (16.7)	Osteo, 2 (16.7)	UTI, 1 (8.3)	Absc, 1 (8.3)	GI, 1 (8.3)	HN, 1 (8.3)	NAD	NAD	NAD
Cachot, Spain (n = 15) [32][e]	*Mtb*, 4 (26.7)	PNA, 3 (20.0)	IE, 2 (13.3)	HN, 2 (13.3)	Br, 1 (6.7)	YER, 1 (6.7)	V, 1 (6.7)	BIL, 1 (6.7)	NAD	NAD
Southern European Countries										
Ergönül, Turkey (n = 42) [22][f]	*Mtb*, 12 (28.6)	Br, 9 (21.4)	EF, 4 (9.5)	MAL, 4 (9.5)	IE, 2 (4.8)	UTI, 2 (4.8)	MEN, 2 (4.8)	SAL, 2 (4.8)	PNA, 1 (2.4)	HN, 1 (2.4)
Altiparmak, Turkey (n = 22) [17]	*Mtb*, 15 (68.2)	CMV, 2 (9.1)	Absc, 1 (4.5)	BIL, 1 (4.5)	NAD	NAD	NAD	NAD	NAD	NAD
Saltoglu, Turkey (n = 51) [21][g]	*Mtb*, 15 (29.4)	IE, 6 (11.8)	Absc, 6 (11.8)	Br, 5 (9.8)	UTI, 5 (9.8)	Zyg, 4 (7.8)	SAL, 3 (5.9)	VL, 3 (5.9)	PNA, 1 (1.9)	CMV, 1 (1.9)
Kucukardali, Turkey (n = 53) [23]	*Mtb*, 21 (39.6)	Absc, 5 (9.4)	CMV, 5 (9.4)	Br, 5 (9.4)	UTI, 4 (7.5)	PAR, 4 (7.5)	SAL, 3 (5.7)	PID, 2 (3.8)	IE, 1 (1.9)	MEN, 1 (1.9)
Baicus, Romania (n = 74) [19]	*Mtb*, 27 (36.5)	UTI, 12 (16.2)	IE, 8 (10.8)	EF, 4 (5.4)	HIV, 4 (5.4)	HN, 3 (4.1)	BIL, 2 (2.7)	CMV, 2 (2.7)	PNA, 2 (2.7)	PAR, 2 (2.7)
South-East Asian Region										
Pannu, northern India (n = 66) [31][h]	*Mtb*, 43 (65.2)	EF, 5 (7.6)	Absc, 3 (4.5)	Br, 3 (4.5)	IE, 3 (4.5)	HIS, 3 (4.5)	PNA, 1 (1.5)	VL, 1 (1.5)	UTI, 1 (1.5)	LEP, 1 (1.5)
Mir, northern India (n = 40) [27]	Br, 10 (25.0)	SAL, 10 (25.0)	*Mtb*, 7 (17.5)	IE, 4 (10.0)	EBV, 4 (10.0)	MAL, 4 (10.0)	CMV, 1 (2.5)	NAD	NAD	NAD
Kejariwal, eastern India (n = 53) [18]	*Mtb*, 24 (45.2)	Absc, 7 (13.2)	IE, 5 (9.4)	VL, 5 (9.4)	EF, 5 (9.4)	UTI, 4 (7.5)	MAL, 3 (7.5)	NAD	NAD	NAD

Table 3. Continued

Author, Country (No. of Infections) [Ref]	Diagnosis, No. (%)									
Bandyopadhyay, Western India (n = 90) [26][i]	*Mtb*, 46 (51.1)	HIV, 12 (13.3)	Absc, 8 (8.9)	UTI, 6 (6.7)	MEN, 6 (6.7)	MAL, 4 (4.4)	VL, 4 (4.4)	PNA, 2 (2.2)	Sepsis, 2 (2.2)	NAD
Western Pacific Region										
Wu, China (n = 241) [29]	*Mtb*, 49 (20.3)	Br, 38 (15.8)	PNA, 27 (11.2)	EBV, 14 (5.8)	Absc, 10 (4.1)	UTI, 6 (2.5)	PAR, 6 (2.5)	IE, 4 (1.7)	MEN, 4 (1.7)	Myco, 4 (1.7)

Abbreviations: Absc, Abscess; BIL, biliary tract infection; BJI, bone and joint infection; Br, brucellosis; CMV, cytomegalovirus; EBV, Epstein-Barr virus; EF, enteric fever; EMP, empyema; GI, gastrointestinal infection; HIS, histoplasmosis; HIV, human immunodeficiency virus; HN, head and neck infection; IE, infective endocarditis; LEP, leptospirosis; MAL, malaria; MEN, meningitis; *Mtb, Mycobacterium tuberculosis*; Myco, mycoplasma; NAD, no additional data; NTM, nontuberculous mycobacteria; Osteo, osteomyelitis; PAR, parasites; PID, pelvic inflammatory disease; PNA, pneumonia; SAL, salmonellosis; UTI, urinary tract infection; V, viral infection; VL, visceral leishmaniasis; YER, *Yersinia enterocolitica*; Zyg, zygomycosis.

[a]In this series, parasite infections included giardiasis and trypanosomiasis.

[b]In this series, there were 2 additional infections reported only as bacteremia and infectious polyserositis.

[c]In this series, there were 2 gastrointestinal infections with diverticulitis, 2 head and neck infections with sinusitis and dental infection, and additional infections with 1 each of secondary syphilis, enteric fever, cholangitis, adenitis, ventriculoperitoneal shunt infection with *Escherichia coli*, and central venous catheter infection due to coagulase-negative *Staphylococcus* species.

[d]In this series there was 1 gastrointestinal infection with diverticulitis and 1 head and neck infection with tonsillitis.

[e]In this series, there was 1 biliary tract infection with cholangitis, 1 viral infection with parvovirus, and 2 cases of head and neck infections with lower jaw osteitis and *Cutibacterium acnes* lymphadenitis.

[f]In this series, there were 2 cases of salmonellosis due to paratyphoid B, 1 UTI case involving a perinephric abscess, 1 pneumonia case secondary to psittacosis, 1 head and neck infection with a dental abscess, and 1 parasite case due to toxoplasmosis.

[g]In this series, there were 4 cases of zygomycosis with rhinocerebral mucormycosis, 1 parasite case of cerebral toxoplasmosis, and 1 case of encephalitis.

[h]In this series, there was 1 case of viral encephalitis.

[i]In this series, there were 2 cases of sepsis due to gram-negative pathogens.

establish the need for further invasive procedures [17]. In this same series, 1 (n = 6) bone marrow biopsy and 13 (n = 21) tissue and bone-joint biopsies assisted with diagnoses [17].

In the series from Turkey by Saltoglu et al [21], *Mtb* occurred in 15 of 51 (29.4%) cases. EPTB occurred in 13 (86.7%), requiring liver and bone biopsy cultures (n = 7), renal biopsy cultures (n = 2), and vertebral CT scans (n = 2) for diagnoses. Serial chest CT scans diagnosed pulmonary *Mtb* cases (n = 2). Serology assisted in 8 (15.7%) cases: CMV (n = 1), *Legionella* spp (n = 1), amebic hepatic abscess (n = 1), *Brucella* spp IE (n = 2), EF (n = 1), and *Salmonella* spp osteomyelitis (n = 2). Among imaging modalities, magnetic resonance imaging was helpful in 5 (9.8%) cases, CT scans in 10 (19.6%) cases, and US studies in 7 (13.7%) cases. Seventeen (33.3%) cases required histologic biopsy procedures. Among 17 of 87 (81.6%) patients followed for 1 year, 11 (15.5%) deaths were reported of which 6 (54.5%) were infection related: miliary *Mtb* (n = 2), *Staphylococcus* spp IE (n = 1), cerebral toxoplasmosis, mucormycosis-related infection, and visceral leishmaniasis.

Kucukardali et al [23] from Turkey reported that only 16 of 752 (2.1%) serologic tests were helpful, diagnosing CMV, brucellosis, salmonellosis, and *Mycoplasma pneumoniae* infections. CMV seropositivity was identified in all 5 pulmonary cases. Successive CMV serologic tests repeated at 10-day intervals revealed a course of IgM- and immunoglobulin G (IgG)–type antibodies compatible with acute infection. Four of these patients had mononucleosis-like clinical presentations, with 2 having histopathologic findings concordant with CMV. In this series, bacterial cultures were helpful in only 28 of 514 (5.4%) total samples. The breakdown of the useful cultures obtained was as follows: blood cultures (8/154), urine cultures (7/154), sputum (4/128), stool (1/22), wound (4/15), catheter (2/12), and pleural fluid (2/10). Seven of 22 (31.8%) histologic biopsies (eg, lymph node, peritoneal and pleural) revealed the diagnosis of *Mtb*. Four of 141 (2.8%) US evaluations revealed infection diagnoses: hepatic (n = 2), retroperitoneal abscess, and pyelonephritis. Four of 98 (4.1%) abdominal CT scans revealed abscesses: hepatic (n = 2), retroperitoneal (n = 1), and pelvic (n = 1).

South-East Asian Region

Four studies from India represent this region [18, 26, 27, 31] with a combined total of 249 infections (Table 3). Overall, the most commonly reported infections included *Mtb* (48.2% [n = 120]), abscesses (7.2% [n = 18]), brucellosis (5.2% [n = 13]), HIV (4.8% [n = 12]), IE (4.8% [n = 12]), UTI (4.4% [n = 11]), malaria (4.4% [n = 11]), EF (4.0% [n = 10]), salmonellosis (4.0% [n = 10]), and visceral leishmaniasis (4.0% [n = 10]).

Infections were the cause among 53 (53.0%) patients evaluated by Kejariwal et al [18]. In this series, echocardiogram confirmed 5 cases of blood culture-negative endocarditis, bone marrow or splenic aspirate confirmed 5 cases of visceral leishmaniasis, Widal test confirmed 5 EF cases, and transrectal US confirmed 1 prostate abscess. Empirical antimicrobial therapy delayed diagnoses for 2 IE and 4 UTI cases. Repeat serial thick and thin blood smears revealed 3 cases of malaria.

Bandyopadhyay et al [26] reported 90 infections among 164 (55.0%) total participants. In this report, it was unclear how HIV contributed to FUO (eg, acute HIV, chronic uncontrolled HIV, or other underlying conditions). EPTB occurred in 33 of 46 (71.7%) cases. *Mtb* diagnoses were supported by sputum examinations, chest imaging, adenosine deaminase, and empirical therapeutic trials.

Mir et al [27] reported 40 infections among 91 (44.0%) patients. *Mtb* cases included disseminated disease (n = 5) and meningitis (n = 2). Travel history, serial thick and thin blood films, and antigen testing contributed to malaria diagnoses. The contribution of other diagnostic modalities for infectious diseases cases was not reported.

Pannu et al [31] reported 66 infections among 152 (43.4%) participants. Induced-sputum confirmed 2 nonresolving pneumonia cases, and 1 visceral larva migrans with peripheral eosinophilia and Charcot-Leyden crystals was confirmed on hepatic aspirate cytology. EPTB cases (69.8% [n = 30]) included gastrointestinal (n = 11), lymph nodal (n = 5), and pericardial (n = 3) manifestations. TST was positive in 24 of 127 (18.9%) patients. Splenic abscess–associated EF cases (n = 2) were diagnosed by repeat blood cultures and increasing Widal titers.

Western Pacific Region

Three studies represent this region [2, 29, 30], although only 1 series [29] yielded additional information following attempts to contact authors of these reports [2, 29, 30]. Wu et al [29] from China reported 241 infections (Table 3) among 431 (55.9%) patients in a single-center university hospital observational study, notably to develop a predictive model intended to distinguish infectious vs noninfectious etiologies. The contributions of diagnostic methods were not reported. Infections associated with the diagnosis of sepsis (21.0% [n = 41]) were also not reported. The authors did report that "various antibiotics were administered to a high percentage of patients prior to confirmation of an exact diagnosis," which might have delayed the diagnosis of an acute febrile illness, allowing patients to fulfill FUO criteria. The predictive model found that the combination of feeding and close contact with animals carrying a pathogen had an odds ratio (OR) of 19.71 (95% CI, 4.57–85.05) for an FUO-related infection.

Meta-analysis Results

Table 4 and Figure 2 present the study-specific proportions with 95% exact CIs and the overall pooled estimates from the random-effects model for infectious disease FUO. Compared to other FUO etiologies, infection (INF) had the highest pooled estimate at 37.0% (95% CI, 30%–44%), followed by 20.0% each for undiagnosed (95% CI, 14%–26%) and NIID (95% CI, 17%–23%) (Supplementary Table 2). The pooled estimate for Oncology (ONC) was 15.0% (95% CI, 12%–18%). All analyses showed significant across-study heterogeneity.

Table 4. Results of Random-Effects Meta-analysis Estimating Pooled Proportions

Pooled Proportion Comparison	Statistic (95% CI)
Pooled proportion comparison of infectious diseases	
Pooled proportion	0.37 (.30–.44)
No. of studies included	19
I^2 statistic	93% (90%–95%)
Pooled proportion comparison across regions	
SEAR	0.49 (.43–.55)
EUR	0.31 (.22–.41)
EMR	0.38 (.31–.47)
WPR	0.38 (.18–.58)
P value between groups	.02

Thresholds for interpretation of I^2 statistic heterogeneity were as follows: <40%, low; 30%–60%, moderate; 50%–90%, substantial; and 75%–100%, considerable. Source: Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21:1539–58.

Abbreviations: CI, confidence interval; EMR, Eastern Mediterranean Region; EUR, European Region; SEAR, South-East Asian Region; WPR, Western Pacific Region.

Table 4 also demonstrates the subgroup analyses by WHO region. These results indicate significant heterogeneity in the prevalence of INF-associated FUO across regions, appearing most prevalent in the South-East Asian Region at 49.0% (95% CI, 43%–55%). NIID was most common in the Western Pacific Region with a 27.0% pooled estimate (95% CI, 20%–34%). The highest pooled estimated for ONC was in the Eastern Mediterranean Region at 25% (95% CI, 18%–32%) (Supplementary Table 2).

The results from this systematic review and meta-analysis suggest that geographical area is an important consideration in FUO investigations. Pooled odds of infectious diseases were higher when compared to all FUO subcategories (eg, infection, cancer, NIIDs, miscellaneous disorders, and unexplained illness). Infectious etiologies much more in patients from Southeast Asia (pooled effect size, 0.49 [95% CI, .43–.55]) compared to those in Europe (pooled effect size, 0.31 [95% CI, .22–.41]). Despite a total of 1049 infections among the pooled studies, details were reported for 832 specific infectious diseases conditions (Tables 2 and 3). Analysis found *Mtb* complex as the leading infectious FUO condition across all geographic regions (n = 285 [34.3%]) followed by brucellosis (n = 81 [9.7%]), endocarditis (n = 62 [7.5%]), abscesses (n = 61 [7.3%]), herpesvirus (eg, CMV and EBV) infections (n = 60 [7.2%]), pneumonia (n = 54 [6.5%]), UTIs (n = 54 [6.5%]), and EF (n = 40 [4.8%]).

DISCUSSION

The results from this systematic review and meta-analysis are consistent with earlier findings from a systematic review of a mixture of 18 prospective and retrospective studies from 2005 to 2015 by Fusco et al [1]. Those authors reported >4 times

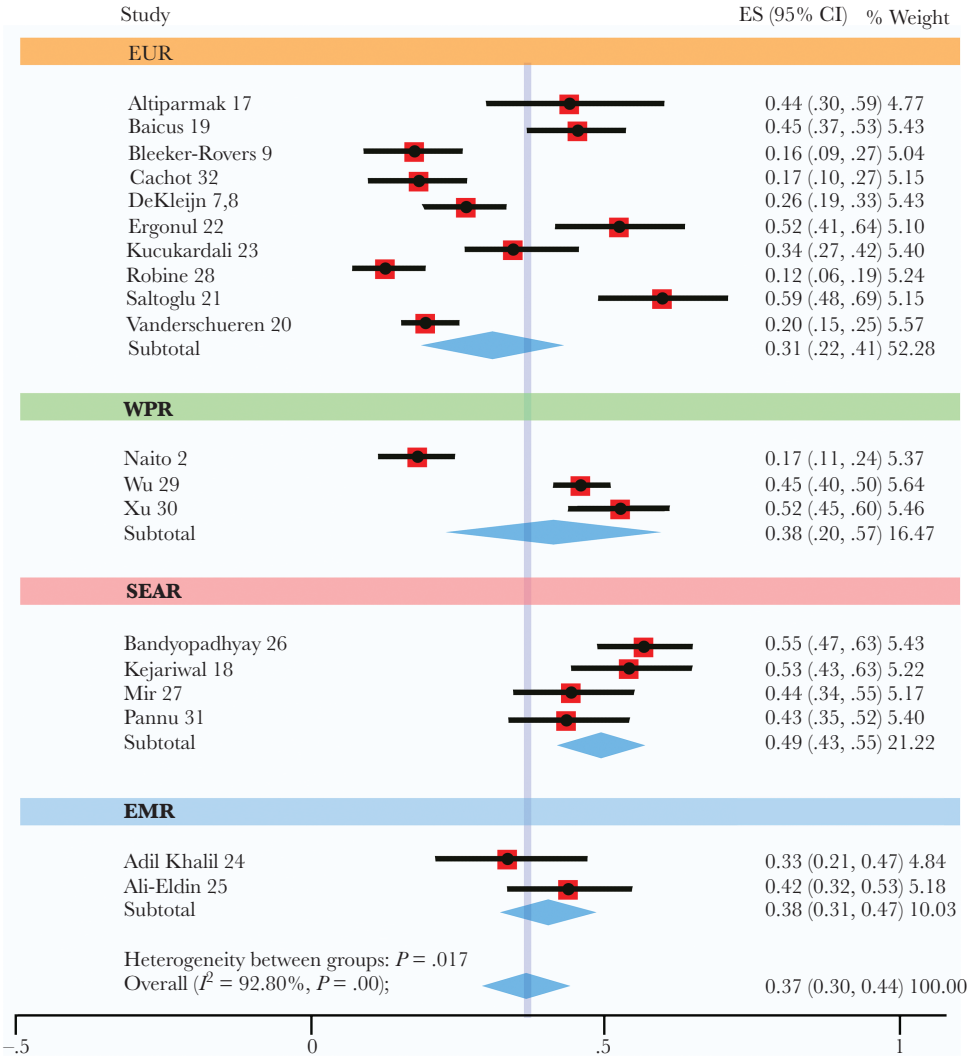

Figure 2. Forest plot of 19 studies estimating the fever of unknown proportion attributed to infection etiology. ●, Effect estimates of study. —, 95% confidence interval (CI). Gray squares, Size of weight assigned to each study. <>, Pooled effect size and range of 95% CI. Abbreviations: CI, confidence interval; EMR, Eastern Mediterranean Region; EUR, European Region; SEAR, South-East Asian Region; WPR, Western Pacific Region.

increased odds of infection in Southern Asia (OR, 4.6 [95% CI, 1.89–11.91]) and 3 times increased odds in Far East Asia (OR, 3.0 [95% CI, 1.67–5.62]) compared to Europe. In the same series, of 1197 infectious diseases conditions, mycobacterial diseases predominated at 36.8% (n = 440) followed by endocarditis (n = 119 [9.9%]), brucellosis (n = 58 [4.8%]), internal abscesses (n = 49 [4.1%]), and salmonellosis (n = 43 [3.6%]). However, the estimates derived from our study were more robust due to the inclusion of only prospective studies over a longer period and the use of different statistical models. The major strength derived from using prospective cohort studies in our protocol is the accuracy of data collection concerning exposures, confounders, and endpoints.

Our present analysis also enabled a more in-depth examination and interpretation of infection-related FUO investigations between prospective studies and geographic locations that have been absent from the medical literature. As mentioned, the probability of *Mtb* remained high across all regions, including among Northern European studies, but remained higher than 20.0% in the South-East Asian and Western Pacific regions, particularly EPTB manifestations. Chin et al [33] also reported a similar rate of *Mtb*-related FUO in their 2-week prospective study from Taiwan. Despite a known higher prevalence in some geographic regions, *Mtb* should remain high on the list of FUO diagnostic possibilities in all areas, due to immigration or earlier high prevalence. In our study, disseminated disease without the characteristic miliary pattern or extrapulmonary disease without clear localizing features on conventional imaging methods, requiring more invasive diagnostic methods, may account for disease patterns not related to geography [18, 21, 23] that are related to aging populations reported in some countries [7, 8, 26] rather than malnutrition or poor living

conditions. Differences in our study may also be explained by not excluding patients with HIV (n = 21) or other immunocompromised patients. *Mtb* therapeutic trials [24], more commonly used in low-resource settings, or selection of FUO cases from infectious disease consultations rather than from the general patient population may be additional explanations for these nongeographical differences. TST was only beneficial in 26 of 170 (15.3%) total patients. The contribution of interferon-γ release assays was not reported. Therefore, based on the findings from this meta-analysis, imaging and more invasive procedures are required for *Mtb*-related FUO diagnoses.

In this analysis, the high proportion of herpesvirus cases, particularly CMV causing FUO, was surprising in some particular geographic regions. Rates of CMV among Eastern Mediterranean [24, 25] and European [7, 8, 16, 19–21, 28, 32] cohorts ranged from 55.6% (5 of 9 total cases) to 80.0% (20 of 25 total cases), respectively. Among 123 healthy Italian adult patients with an unexplained fever >38.0°C for the previous 3–11 weeks, Manfredi et al [34] reported 18 (14.6%) cases of primary IgM-positive CMV with 13 (72.2%) episodes presenting as a mononucleosis-like syndrome. In that report, 11 cases were further confirmed by a positive CMV-DNA polymerase chain reaction (PCR) blood assay [34]. Among Western Pacific [29] and South-East Asian [27] cohorts in our analysis, EBV accounted for 18 of 21 herpesvirus cases (85.7%). Although there were 2 CMV diagnoses in our study supported by a 4-fold rise in IgG titer [7, 8] or positive PCR [28], the majority of cases were supported by IgM serology and no study reported on clinical findings or treatment of herpesvirus infections. It should be noted that without compatible mononucleosis-like presentations, herpesvirus (eg, EBV and CMV) or HIV [20, 26] diagnoses may be overestimated in these studies given that IgM serology suffers disproportionately from false-positive results, which in turn can lead to misdiagnoses, inappropriate therapy, and premature closure of a diagnostic workup [35].

An important lesson from our study is that empirical antimicrobial therapy delayed the diagnosis of IE in 7 of 62 (11.3%) cases, allowing patients to fulfill FUO criteria [7, 8, 18, 31]. IE cases ranged from 2.1% to 14.0%, with the highest rates among Eastern Mediterranean and European cohorts. Clinicians should avoid empirical antimicrobial therapy and further scrutinize any new murmur from the physical examination to increase diagnostic yields.

Other important observations from our analysis pertinent to conducting FUO infection-related investigations are that brucellosis rates were highest (19.3%–19.5%) among Eastern Mediterranean and Western Pacific cohorts and EF was an important consideration among Eastern Mediterranean and South-East Asian cohorts. Additionally, when Wright agglutination testing was negative, the Coombs gel test for brucellosis improved the diagnostic yield [22]. However, enzyme-linked immunosorbent assays (ELISAs) are now the test of choice for complicated and chronic cases of brucellosis [36]. Rates of suspected malaria cases requiring repeat serial thick and thin smears for diagnosis was 55.6% (10 of 18 cases) [18, 22, 24], allowing patients to fulfill FUO criteria. Finally, abscess rates of 5.1%–8.8% were reported among Eastern Mediterranean, European, South-East Asian, and Western Pacific cohorts. Higher rates among older studies may reflect recent improvements in diagnostic imaging modalities.

FUO traditionally requires 3 weeks of fever and negative blood and urine cultures. Therefore, traditional microbiology cultures have a meager yield and low sensitivity [7, 8]. Among 57 patients meeting Petersdorf's [5] FUO criteria, Jha et al [37] reported that bone marrow cultures were associated with a 10.5% increased yield over blood cultures, particularly for *S* Typhi. Though infectious diseases serologic testing is often used for fastidious or challenging-to-detect organisms, their contribution in FUO is limited in most series [7, 8]. For example, de Kleijn et al [7, 8] reported that infectious disease serology was helpful in only 1 of 19 patients who tested positive for *S* Typhi by the Widal test. While other recent authors [18, 24, 31] also reported the contribution of Widal testing for *S* Typhi, ELISAs are now the test of choice [38]. Bleeker-Rovers et al [9] reported that 509 microbiologic serologic tests yielded only 4 positive *Y enterocolitica* serologies, but none helped establish a diagnosis. Moreover, serology may be less useful in hosts with depressed humoral responses.

More recent pooled data indicate a substantial contribution of ^{18}FDG-PET/CT to the final FUO diagnosis, primarily when obtained before conventional imaging modalities [39]. A recent single-center retrospective study among 303 patients meeting Petersdorf's FUO criteria reported an overall sensitivity of 88.7% for ^{18}FDG-PET/CT, compared to conventional CT (75.2%) [40]. In that same study, the highest specificity for ^{18}FDG-PET was infectious diseases (83.3%) [40]. In our study, there were 166 (6.2% [n = 2667]) total participants from 4 studies [9, 28, 31, 32] who underwent FDG-PET scans, of which only 43 (26%) contributed to a final diagnosis. In the Bleeker-Rovers series [9], 23 (31.5% [n = 73]) ^{18}FDG-PET scans contributed to final diagnosis with 11 (47.8% [n = 23]) scans localizing infections.

Although broad-based molecular methods (eg, next-generation sequencing, multiplex PCR, and broad-range molecular assays) hold promising potential for infectious disease testing, multiple challenges remain [41]. These include automation, standardizing protocols and bioinformatics, improving reference databases and threshold measurements for known pathogens, establishing laboratory proficiency testing and quality control measures, and reducing cost and turnaround time, all of which would be necessary for widespread application to FUO investigations [41]. Other challenges with these molecular diagnostic methods include differentiating colonization from infection.

The question then becomes: What is a rational approach to evaluating FUO-related infections among immunocompetent patients in the absence of PDCs (Supplementary Figure 1)? Online sophisticated natural language processing may assist in these evaluations and understand the local prevalence of diseases, especially if more traditional epidemiology is lacking [11]. For example, the global data source GIDEON (Global Infectious Diseases and Epidemiology Online Network) uses Bayesian analysis to help rank infectious diagnostic considerations based on available country-specific epidemiology [11].

This systematic review of prospective data offers a comprehensive global and regional view of FUO infections but has limitations. First, we did not have access to individual data for many trials despite contacting authors to glean further details of some diagnostic categories. This absence did not allow for a thorough exploration of study variations. We were also unable to perform a complete analysis with between-study variations and geographical representation because of incomplete reporting of data. In addition, Turkey was categorized as a European country with the WHO system but may be more representative in infectious disease prevalences of an Eastern Mediterranean or Asian country. Therefore, outcomes for Europe in our study may be more pronounced as Turkey was included and may have more infections than Northern Europe. Nonetheless, the results reported in this systematic review and meta-analysis are valuable in supplementing previous findings reported by Fusco et al [1], as an additional 12 prospective studies have been included in this analysis.

Second, the heterogeneity of included studies is high. This is likely due to differences in the populations, diagnostic tests and their yield, and reporting across studies. Therefore, the regional findings can help inform clinicians with a common list of infectious considerations but should not be constricting in an individual patient's diagnostic care.

Last, there was likely the presence of publication bias toward studies that reported effect sizes among European regions compared to other WHO regions due to a smaller number of studies from these regions. This suggests the possibility that unpublished or future studies in those regions, especially Africa and America, would influence results. In addition, FUO might be a topic where a prospective analysis does not offer an advantage compared to the totality of including a mixture of prospective and retrospective studies. Notwithstanding these limitations, it would appear that this analysis still enables a rich interpretation of the spectrum of FUO-associated infections across broad geographic areas.

CONCLUSIONS

Osler's lecture demonstrated a keen appreciation for understanding the prevalence of infectious diseases, especially in an era when robust epidemiology was unavailable [10]. This interpretation of results, either considered in isolation or in the context of previous knowledge [1], also suggested with a reasonable probability that geographical factors are relevant to infection-related FUO investigations. Initial diagnostic approaches to FUO patients in Asia or Africa will probably differ from those in Europe and North America. However, clinicians must also recognize the need for individual personalization and consequently acknowledge that careful elucidation of the history, particularly regarding local epidemiologic and individual occupational factors, is essential.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. All authors had access to the data and participated in the development of this manuscript and meet the ICMJE authorship requirements.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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