

## Typhoid Fever in the Eastern Mediterranean Region: A Systematic Review, 1990–2021

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**Abstract.** The occurrence and antimicrobial resistance (AMR) of typhoid fever in the WHO Eastern Mediterranean Region (EMR) are poorly characterized. Robust surveillance data are needed to inform strategies for typhoid control and prevention in the region. We conducted a systematic review of typhoid fever occurrence, complications, and AMR patterns in EMR countries. We identified 70 studies published from 1990 to 2021, including a total of 44,541 cases with blood culture confirmed typhoid fever in 12 EMR countries, with 48 (69%) studies and 42,008 cases from Pakistan. Among 56 studies with AMR data, fluoroquinolone (68% of 13,013 tested isolates), and multidrug resistance (40% of 15,765 tested isolates) were common. Forty (57%) of the 56 studies were from Pakistan, and all reports of extensively drug resistant *Salmonella* Typhi (48% of 9,578 tested isolates) were from studies in Pakistan. Our findings support the need for continued efforts to strengthen surveillance and laboratory capacity for blood-culture detection of typhoid fever in the region, including data from an ongoing collaboration among CDC, the American University of Beirut, and the WHO EMR office.

### INTRODUCTION

*Salmonella enterica* serotype Typhi (Typhi), the etiologic agent of typhoid fever, causes an estimated 11 to 21 million cases and 65,000 to 188,000 deaths worldwide each year.<sup>1,2</sup> Disease burden is highest in low- and middle-income countries (LMIC) with limited access to safe water and poor sanitation infrastructure. Since 2016, the global urgency of typhoid prevention and control has been heightened by emergence and dissemination of an extensively drug resistant (XDR) strain of Typhi in Pakistan, defined as multidrug resistance (MDR) to the traditional first-line agents (ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole) and resistance to third-generation cephalosporins and fluoroquinolones.<sup>3,4</sup>

The WHO Eastern Mediterranean Region (EMR), with a population of more than 700 million people, has multiple risk factors for importation and local spread of XDR and highly drug resistant Typhi strains within and among the 22 diverse countries and territories across the region. The 22 countries and territories of the WHO EMR include seven geographically located in the Middle East (Iran, Iraq, Jordan, Lebanon, Palestinian territory, Syria, Yemen), seven located in North Africa (Djibouti, Egypt, Libya, Morocco, Somalia, Sudan, Tunisia), the six Arab states of the Persian Gulf (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates), and two countries located in South Asia (Afghanistan, Pakistan). Risk factors for drug-resistant Typhi importation include regional proximity and ties to South Asia, weak or nonexistent national and regional surveillance systems, limited laboratory diagnostic capacity, and restricted data sharing essential for rapid detection, reporting, and monitoring antimicrobial resistance (AMR) and disease transmission.<sup>5</sup> Several countries in the region (e.g., Afghanistan, Iraq, Libya, Sudan, Syria, and Yemen) continue to face humanitarian crises from armed conflicts that have forcefully displaced millions of people and

destroyed public health infrastructure.<sup>6,7</sup> Environmental conditions in the region, including vulnerability to climate change, low coverage with safe drinking water and sanitation systems, and water scarcity, also favor Typhi spread and persistence.<sup>8,9</sup>

The incidence and burden of typhoid fever in the WHO EMR's LMICs is largely unknown, with limited data on the occurrence and severity of typhoid fever cases, outbreaks, and associated antimicrobial susceptibility patterns. Several systematic multi-country, multi-year studies of typhoid fever burden and AMR have been conducted in South Asia and sub-Saharan Africa.<sup>10,11</sup> However, these studies have included few countries in the WHO EMR region. On the basis of relatively sparse data, the Global Burden of Disease study estimated that 246,600 typhoid fever cases occurred in 2017 in the Middle East and North Africa region, covering many of the same countries as the EMR.<sup>12</sup> High-resolution incidence data are needed to inform global policy decisions, including appropriately targeted typhoid conjugate vaccine introduction for typhoid prevention and for outbreak control in the region's six Gavi eligible countries (Afghanistan, Djibouti, Somalia, Sudan, Syria, and Yemen), and other high-risk countries (e.g., Iraq, Libya). AMR data on circulating Typhi strains is crucial for informing empiric treatment of patients and carriers.

To begin to address these data gaps, in collaboration with partners in the WHO Eastern Mediterranean Regional Office (EMRO), American University of Beirut (AUB), CDC and with financial support from Gavi, we conducted a systematic review for published articles on typhoid fever occurrence, complications, and AMR in the WHO EMR of 22 member States and the Palestinian Territories.

### MATERIALS AND METHODS

We searched six databases (EMBASE, MEDLINE, Global Health, Ebsco CINAHL, Scopus, and Cochrane Library) for articles on typhoid fever occurring in a WHO EMRO country and published between January 1, 1990 and December 31, 2019. On March 28, 2022, we conducted an updated search in the same databases for potentially relevant studies published from January 1, 2020, through December 31, 2021.

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The Medical Subject Headings search terms used are listed in Supplemental Table 1. No language restrictions were applied.

All identified references were imported into a reference manager, Endnote X9 (Clarivate Analytics, Boston, MA), and duplicates were removed; the list of citations was then screened by title and abstract by two coauthors (P. L. and M. B.). As outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA) 2020 checklist, we first screened titles and abstracts for relevance, followed by full-text screening of articles reviewed for inclusion using eligibility criteria. Studies that reported on typhoid occurrence, complications, and/or AMR were included. We excluded case reports, letters to the editor and editorials, and studies limited to special populations (travelers, HIV-infected, military, surgical patients). Noneligible reports were excluded and rationale for exclusion recorded. We excluded any studies that did not include blood culture confirmation.

We then created an Excel database and data code book to synthesize and assess available data on typhoid fever in each country. Data extraction terms used are listed in Supplemental Table 2 and can be categorized as terms involving case information, symptoms, AMR, or hospitalization. Multidrug resistance was defined as resistance to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole. XDR strains were defined as having resistance to third generation cephalosporins and fluoroquinolones in addition to MDR. Bias assessment was performed on studies based on proxy variables for selection bias (e.g., eligibility, recruitment, and screening), detection bias (e.g., diagnostic methods), and reporting bias for either disease

or antimicrobial resistance; the studies were then classified as high, moderate, and low quality. Authors P. L., M. B., and C. P. piloted standardized data abstraction; G. D. A. checked data accuracy and served as a tie-breaker. After pilot testing by checking for congruency between data extracted from different researchers, data from all selected studies was extracted. For studies in French, E. D. M. provided translation for data extraction. Descriptive statistics for study characteristics were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC) and R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

**Study selection.** A systematic literature search identified an initial 3,574 records published between January 1, 1990 and December 31, 2019 (Figure 1). This was narrowed down to 64 reports after duplicate removal, and screening by title, abstract, and full text-review for data on typhoid fever epidemiology in an EMR country. Of these, an additional 23 reports were excluded based on diagnostic method exclusive of blood culture confirmation (i.e., stool culture,<sup>13–15</sup> serologic test,<sup>16–23</sup> wastewater testing,<sup>24</sup> or clinical diagnosis alone,<sup>25</sup> method unspecified<sup>26,27</sup>), or non-full text articles.<sup>28–35</sup> The remaining 41 unique studies met selection criteria and were included in analyses.

The updated literature search identified an additional 556 records published between January 1, 2020, and December 31, 2021. After removal of duplicates and screening of title,

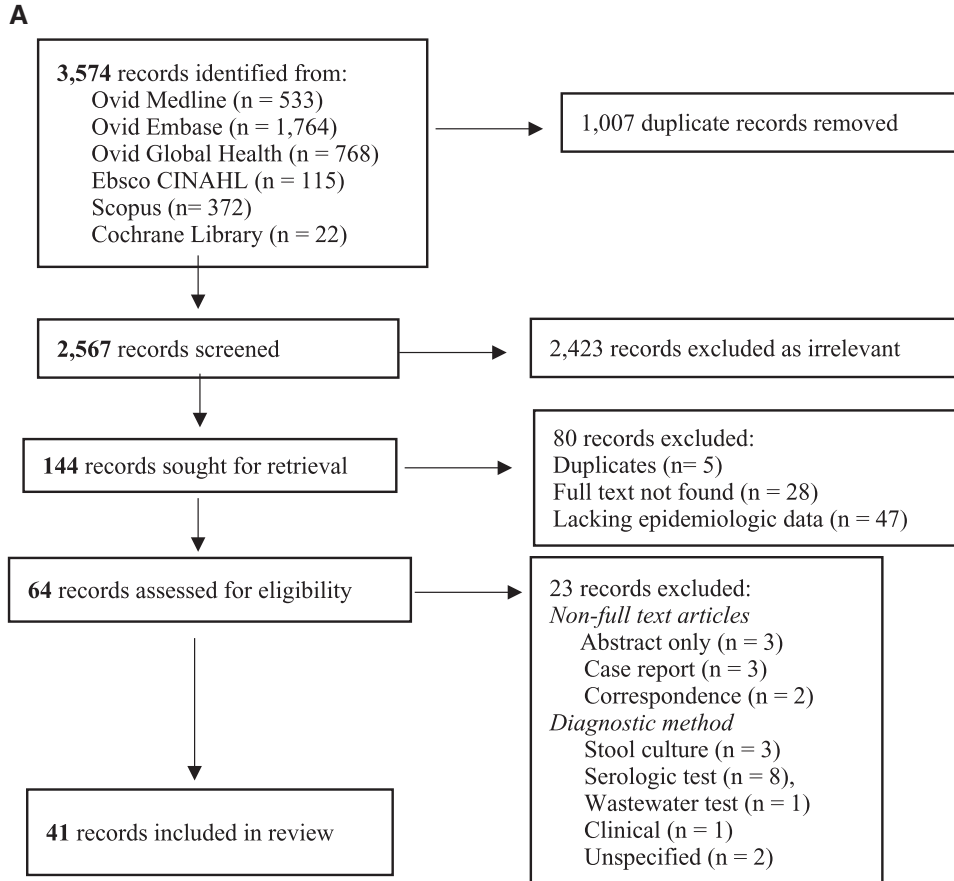


FIGURE 1. (A) PRISMA diagram of study selection process, publications from 2009 to 2019, and (B) flow diagram from 2019 to 2021.

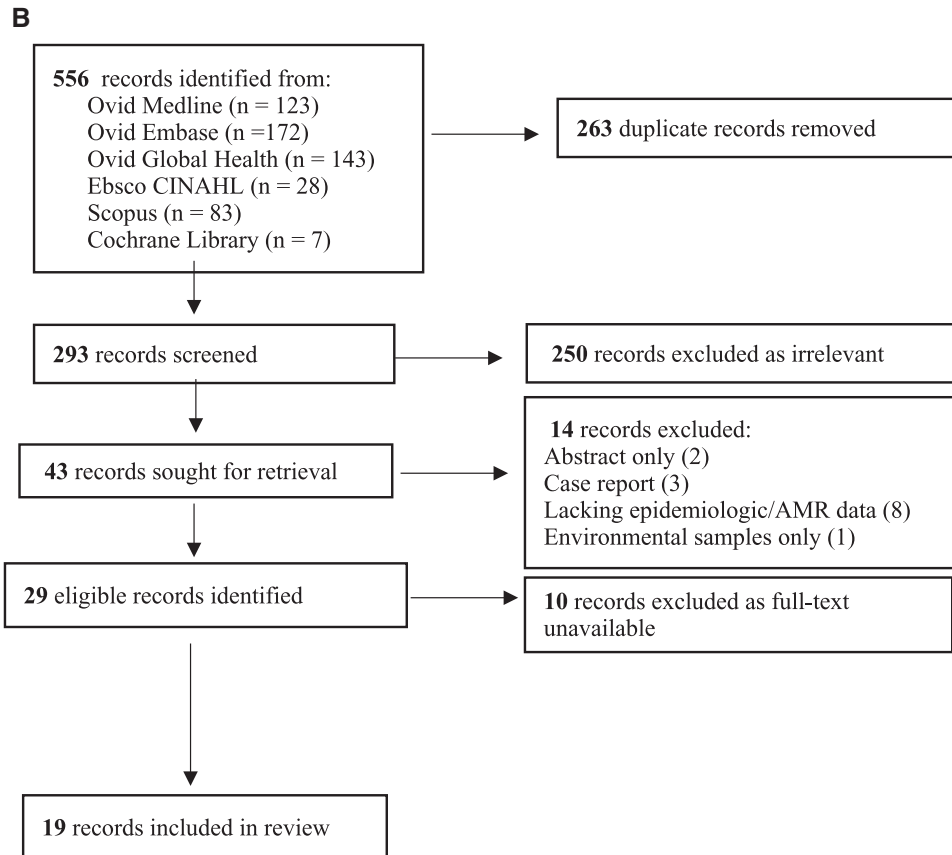


FIGURE 1. (Continued).

abstract, and full text, a total of 29 records were included in the review.

**Study characteristics and bias assessment.** Of the 70 included studies published from 1990 to 2021, 34 (49%) were hospital-based case series/surveillance studies, 31 (44%) were cross-sectional studies, three (4%) were case-control studies, and two (3%) were cohort studies (Supplemental Table 3). The studies were conducted in 12 EMR countries from 1985 to 2021 (Table 1) and included a total of 44,541 reported typhoid fever cases (Figures 2 and 3). Pakistan alone accounted for 48 (69%) of 70 included studies

and 42,008 (94%) of the total cases; the median number of cases per country was 136 (range 48–354) (Table 1). Egypt and Tunisia were the only North African countries represented, accounting for three (4%) studies<sup>36–38</sup> and 377 (1%) cases. Together, the remaining nine Middle Eastern countries that had one (Jordan, Oman, Qatar, United Arab Emirates), two (Iran, Lebanon), three (Egypt, Kuwait, Saudi Arabia), or four (Iraq) studies accounted for 2,156 (5%) cases (Table 1). All the included studies used blood culture, and the proportion of cases that were confirmed by blood culture ranged from 30% to 100%, with an average of 53%.

TABLE 1  
Characteristics of included studies (N = 70), by WHO EMR country, 1990–2021

Country	No. studies	Study years	Total no. cases	Median no. cases	Proportion blood culture-confirmed cases (%)
Egypt	3	1990–2002	301	75	30
Iran	2	1995–2011	556	278	50
Iraq	4	2011–2020	328	72.5	59
Jordan	1	2004–2006	48	48	42
Kuwait	3	1985–2005	354	101	100
Lebanon	2	1995–2007	172	86	83
Oman	1	1991–1991	58	58	NA*
Pakistan	48	1986–2021	42,008	189	52
Qatar	1	2005–2012	354	354	100
Saudi Arabia	3	1989–2003	168	57	35
Tunisia	1	2004–2005	76	38	66
United Arab Emirates	1	2007–2009	118	118	100
Total	70	1985–2021	44,541	136	53

EMR = Eastern Mediterranean Region.

\* Not available; study used mixed diagnostic methods and did not distinguish number of blood culture-confirmed from stool culture-confirmed cases.

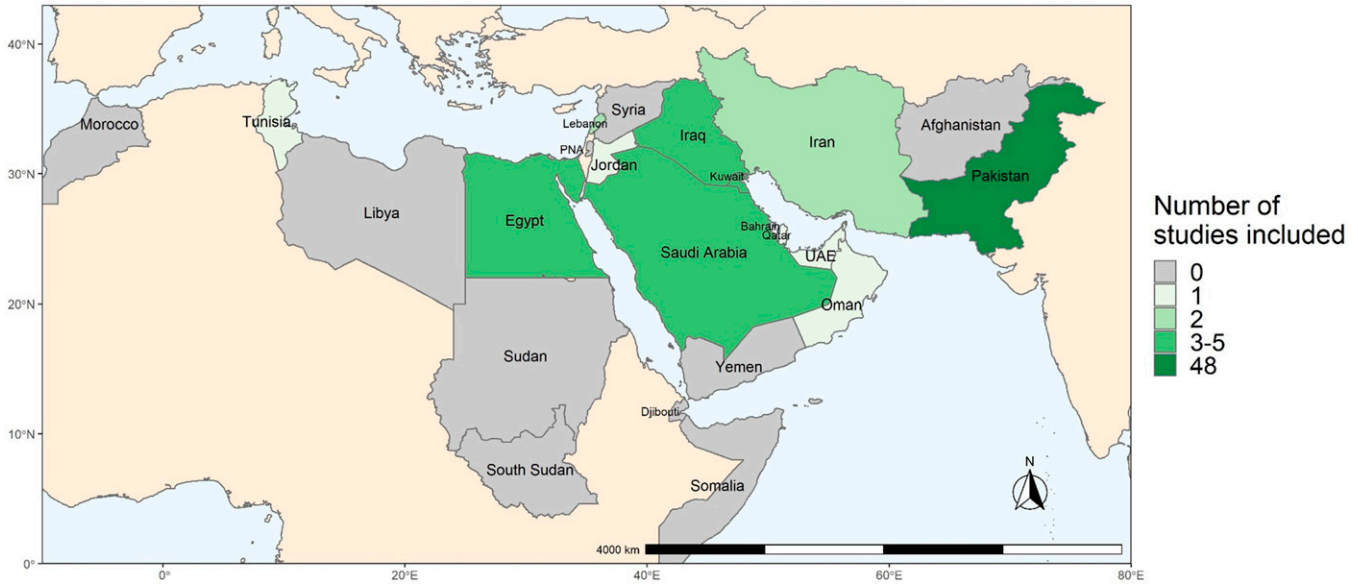


FIGURE 2. Number of included studies ( $N = 70$ ) by WHO Eastern Mediterranean Region country, 1990–2021.

On the basis of our risk of bias assessment, we determined that 13 (19%) studies were high quality,<sup>4,29,39–52</sup> 27 (38%) were moderate quality, and the remaining 30 (43%) were low quality. High-quality studies were distinguished by well-described study eligibility criteria, case confirmation by blood culture alone, and provision of disease indicators (i.e., frequency and severity measures) and AMR results reported for most cases ( $\geq 75\%$ ). Conversely, low-quality studies were poorly described, cases were confirmed using mixed diagnostic methods, and disease indicators and AMR results were reported for few cases ( $\leq 25\%$ ).

**Signs, symptoms, and complications.** Thirty-five studies reported signs and symptoms for a total of 11,128 typhoid fever cases; fever ( $n = 9,114$ ; 82%), abdominal pain

( $n = 4,118$ ; 37%), vomiting ( $n = 3,400$ ; 31%), and diarrhea ( $n = 3,284$ ; 30%) were most commonly reported (Supplemental Figure 1). Conversely, fatigue ( $n = 137$ ; 1%), hypotension ( $n = 155$ ; 1%), and arthralgia ( $n = 174$ ; 2%) were least commonly reported. Twelve studies reported typhoid fever complications among 4,724 cases (Supplemental Figure 2). The most frequently reported types of complications were typhoid intestinal perforation ( $n = 445$ ; 9%), gastrointestinal ( $n = 430$ , 9%), and sepsis ( $n = 260$ ; 6%). Renal complications were uncommon, reported in 5 (0.1%) cases.

**Antimicrobial resistance.** Fifty-six studies included AMR data from 10 countries. Overall, across all studies, 68% of tested isolates were resistant to fluoroquinolones, 48% were XDR, and 40% were MDR (Table 2). Pakistan accounted for



FIGURE 3. Number of typhoid fever cases ( $N = 44,451$ ) by WHO Eastern Mediterranean Region country, 1990–2021.

TABLE 2  
Antimicrobial resistance profiles of tested isolates in Pakistan compares to other WHO EMR countries, 1990–2021

	Pakistan		Non-Pakistan EMR Office		P value	Total	
	Isolates tested	Resistant isolates (%)	Isolates tested	Resistant isolates (%)		Isolates tested	Resistant isolates (%)
Ampicillin	11,520	67	1,289	33	< 0.001	12,809	64
Chloramphenicol	11,048	63	892	28	< 0.001	11,940	60
TMP-SMX	11,678	67	1,443	25	< 0.001	13,121	63
Nalidixic acid	1,062	76	380	24	< 0.001	1,442	62
Fluroquinolones	11,842	72	1,171	32	< 0.001	13,013	68
Cephalosporins	11,905	23	1,284	20	0.01	13,189	23
Azithromycin	4,541	7	95	63	< 0.001	4,636	4
MDR	14,975	40	790	29	< 0.001	15,765	40
XDR	9,578	48	0	0	–	9,578	48

EMR = Eastern Mediterranean Region; MDR = multidrug resistance; TMP-SMX = trimethaprim-sulfamethoxazole; XDR = extensively drug resistant.

40 (57%) of studies with AMR data and was the only country with reports of XDR isolates (48%) (Supplemental Table 4). Compared with studies in other EMR countries (*n* = 16), AMR rates were higher in Pakistan for all tested agents except azithromycin (7% versus 63%, *P* ≤ 0.001). The high rate of azithromycin resistance (63%) reported from the other EMR countries was based on one study from Iraq<sup>53</sup> in which 60 of 95 tested isolates in were azithromycin resistant. The rate of MDR and fluroquinolone resistant isolates in Pakistan was nearly double that of other EMR countries (40% versus 29%, *P* ≤ 0.001 and 72% versus 32%, *P* ≤ 0.001, respectively). When compared by study period over time, although a great deal of more recent AMR data (1986–2021) were available from Pakistan than from other EMR countries

(1985–2009, 2018–2020), data from Pakistan showed higher proportions of resistance in the most recent years (Figure 4).

DISCUSSION

We identified 70 studies of blood culture–confirmed typhoid fever cases in 12 countries across the EMR in the 31-year review period. Among 44,541 reported typhoid fever cases, 17,387 (39%) were identified from one retrospective longitudinal study<sup>54</sup> of tertiary care hospitals in Pakistan. Data across countries were heterogenous, with 48 studies from Pakistan and studies from other EMR countries. There were no blood culture–confirmed studies of typhoid fever in any of the six Gavi-eligible countries in the region. Similarly, in a recent global



FIGURE 4. Trends in antimicrobial resistance profiles of tested isolates by resistant type in Pakistan (bottom) vs. other WHO Eastern Mediterranean Region countries (top) over study years, 1990–2021.



systematic review of blood culture–confirmed typhoid fever incidence, only three published studies were identified from North Africa and none from the Middle East.<sup>55</sup>

Although XDR Typhi strains were only reported in Pakistan, the geographic proximity and prevalence of intraregional travel suggests high risk of importation to other EMR countries. An estimated eight million Pakistani migrant workers are used in the Gulf countries of Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and UAE.<sup>56</sup> Arba'een, a large religious pilgrimage in the region, has also contributed to the travel-associated introduction of highly drug-resistant Typhi, including a cluster of ceftriaxone-resistant Typhi infections among travelers to Iraq.<sup>57</sup> Isolates from the cluster were resistant to ceftriaxone but exhibited intermediate susceptibility to ciprofloxacin, and full susceptibility to chloramphenicol and trimethoprim-sulfamethoxazole. Our findings include a cross-sectional study from Iraq in 2018, which similarly showed isolates with ceftriaxone resistance and susceptibility to chloramphenicol and trimethoprim-sulfamethoxazole but also with ciprofloxacin and azithromycin resistance.<sup>53</sup> The potential for local spread after an introduction of XDR Typhi strains into LMIC countries in the region—particularly those with ongoing complex humanitarian emergencies—is of considerable concern. Strengthening local surveillance and laboratory capacity to detect and confirm XDR typhoid fever cases within EMR countries will help trigger a more timely and effective response for its control.

Our findings are subject to several limitations. First, we did not search the Arabic gray literature, which may have included data from countries underrepresented in the databases searched. We excluded publications limited to travel-related cases, which may have led to missed reports of cases associated with intraregional travel (e.g., travelers of any country in the region who had acquired typhoid fever during a trip to Pakistan). We also excluded publications limited to surgical cases, which may have led to missed reports of cases with typhoid intestinal perforation and other surgical complications of typhoid fever. A small percentage of reported cases were not confirmed by blood culture and may have been from patients who were chronic carriers of Typhi or patients with an illness other than typhoid fever. Given the limited sensitivity of blood culture<sup>58</sup> for typhoid detection, even studies that exclusively relied on blood culture confirmation may have underestimated the true burden of typhoid fever. Laboratory data were interpreted as presented, without verification of the reported laboratory results, including the isolate serotype and the antimicrobial susceptibility test (AST) results. Our findings may overestimate or underestimate the typhoid occurrence in the EMR because data were unavailable from all countries and many included studies had low quality of evidence based on the risk of bias assessment. The data presented are predominantly from Pakistan, which limits the generalizability of our findings to other EMR countries. There may also have been selection bias affecting which studies are conducted, and which are published, based on economic, social, and political factors.

Additional Gavi funding support has allowed CDC, WHO EMRO, and AUB to build on this systematic literature review through two additional projects (publications forthcoming). The first project, led by AUB, will ask reference laboratories in the region to provide information including AST results on all Typhi strains isolated from blood culture since 2016 and

to share select isolates for confirmation, and additional testing including whole genome sequencing. The second project, led by EMRO and CDC, includes a survey of WHO country offices and Ministries of Health about national typhoid fever surveillance systems and recommendations for the use of typhoid vaccines. In July 2022, WHO-EMRO hosted a workshop with representatives from WHO country offices and public health agencies to identify support required for improving national laboratory and surveillance capacities and for supporting advocacy for typhoid conjugate vaccine introduction. Together these collaborative efforts will inform understanding of the occurrence of typhoid fever in the region, improve laboratory and surveillance capacity for identification of blood culture–confirmed cases and AMR, and increase preparedness for future introduction of typhoid conjugate vaccines for emergency or routine use.

In conclusion, our systematic review of typhoid fever occurrence in the EMR from 1990 to 2021 identified more than 44,000 cases in 12 countries. We found high reported rates of MDR across the region, and continued transmission of XDR Typhi strains in Pakistan. These findings highlight the need for improved surveillance and increased typhoid prevention and control efforts in the region, including introduction of typhoid conjugate vaccines in areas with drug-resistant Typhi.

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