



Burden of *Clostridium (Clostridioides) difficile* Infection among Patients in Western Asia: A Systematic Review and Meta-Analysis

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Abstract

Background: *Clostridium difficile* is the most common causes of hospital-acquired diarrhea affecting particularly hospitalized patients globally. This organism has re-emerged in recent years with significant morbidity and mortality. The present study aimed to estimate the burden of *C. difficile* infection (CDI) and to acquire information on the overall rates of community- and hospital-acquired CDI in western Asia.

Methods: A systematic literature search was performed to identify articles published from the eight Persian Gulf countries in western Asia including Iran, Iraq, Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates in the electronic databases within Jan of 2000 to Dec of 2017. Then, 20 publications which met our inclusion criteria were selected for data extraction and analysis by Comprehensive Meta-Analysis Software.

Results: Twenty studies reported the prevalence of toxigenic strains of *C. difficile* among patients from Persian Gulf countries, of these the pooled prevalence of CDI was 9% (95% CI: 6.5%-12.5%). Totally, 8 studies showed the prevalence of hospital-acquired CDI, from those studies the prevalence of CDI was estimated 8.4% (95% CI: 4.9%-14.1%). Moreover, 7 studies reported the prevalence of community-acquired CDI, from those studies the prevalence of CDI was estimated 1.8% (95% CI: 1.2%-2.9%).

Conclusion: The prevalence of CDI in western Asia is lower than southern and eastern region. Moreover, the lower prevalence of community-acquired CDI compared to hospital-acquired CDI, indicate that the source of infection in western Asia is more likely in the hospitals.

Keywords: *Clostridium difficile* infection (CDI); Western Asia; Infection control; Meta-analysis

Introduction

Hospital-acquired infections (HAIs) are a serious public health concern resulting in prolonged hospitalization and risk of death (1). The occur-

rence of HAIs according to the WHO estimates is around 7.1 million cases every year (2). Among the wide range of bacteria has been reported as a

cause of HAIs, vancomycin-resistant enterococci (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridium difficile*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacteriaceae* are the most prevalent pathogens (3, 4).

Clostridium difficile is the most common cause of hospital-acquired diarrhea affecting particularly hospitalized patients globally (5). This organism has re-emerged in recent years with apparent greater morbidity and mortality and also associated with increased health care costs (6). Factors contributing to the development of this phenomenon include usage of broad-spectrum antibiotics such as fluoroquinolones, clindamycin and third generation cephalosporins as well as prolonged hospitalization, antineoplastic chemotherapy, and severe underlying diseases (7, 8). Treatment of *C. difficile* infection (CDI) is challenging and demand new approaches because most of antibiotics used for the treatment of every kind of infections can potentially encourage CDI (9, 10). The currently available antibiotics that remain the first-line therapy for CDI are metronidazole and vancomycin (11, 12).

Antibiotic-associated diarrhea is mostly linked to strains of *C. difficile* that produce a range of virulence factors including toxins and adherence factors (13). Toxin A (TcdA) and toxin B (TcdB) are two homologous exotoxin and main virulence factors of toxigenic *C. difficile* that encoded by the *tcdA* and *tcdB* genes, respectively. Expression of these toxins causing proinflammatory and cytotoxic effects including disruption of the actin cytoskeleton and impairment of tight junctions in human intestinal epithelial cells that are responsible for the clinical symptoms of CDI (13).

The incidence of CDIs is an important quality indicator to reflect the effectiveness of the basic hospital policies include infection control and antimicrobial stewardship. The objectives of the present study were to estimate the burden of CDI and to acquire information on the overall rates of community- and hospital-acquired CDI in western Asia. Results from this survey indicate progress across Persian Gulf countries towards comprehensive monitoring and reporting of CDI.

Methods

Search strategies

A systematic literature search was performed to identify papers published from the eight Persian Gulf countries in western Asia including Iran, Iraq, Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates in the Web of Science, PubMed, Scopus, and Google Scholar electronic databases within Jan of 2000 to Dec of 2017. The keywords and terms were searched using Medical Subject Headings (MeSH) such as “*Clostridium difficile*” or “*Clostridioides difficile*” or “*C. difficile*” or “*Clostridium difficile* infection (CDI)” or “Pseudomembranous colitis” in combination with “Names of countries” in the title, abstract and keywords fields.

Selection criteria

Two reviewers independently screened the search results at the databases with the related keywords and analysis the titles, abstracts, and full texts to applied eligibility for inclusion according to inclusion criteria, and the disagreement between reviewers was resolved by consensus. English and Persian or Arabian language articles with English abstract indexed in PubMed, Scopus or Web of Science with the following criteria were considered in our study: 1) Clearly mentioned to method used for *C. difficile* and toxins detection; 2) cross-sectional or retrospective studies investigating the prevalence of toxigenic *C. difficile* collected from diarrhea samples. Meanwhile, exclusion criteria were: 1) studies that did not report a standardized method for detection of *C. difficile* and toxins; 2) studies with sample size was less than 10 isolates; 3) studies that origin of samples was unclear or isolates obtained from formed stool or environment sources, and 4) studies which focused on non-toxigenic *C. difficile* or the prevalence of toxigenic strains was unclear. Furthermore, reviews and systematic review articles, case reports, and articles which were only available in abstract form were ignored.

Definition

According to the European Center for Disease Prevention and Control (ECDC), an episode of CDI was defined as a patient with diarrhea whose stool takes the shape of the container, and it is positive for *C. difficile* toxin A and/ or B without other etiology (14).

Quality assessment

The quality of eligible studies was judged independently by two authors using the STROBE checklist (Strengthening the Reporting of Observational Studies in Epidemiology). Items related title and abstract, introduction, methods, results, discussion, and other information were determined and a score was assigned to each item. One score was assigned to each question and studies achieved at least eight quality scores were considered eligible and included in the study (15).

Data extraction

For all selected studies, the following details were extracted: the first author's name, the study performing time, publication date, research location, sample type, patients age range, nature of patients (hospitalized or outpatient), toxins detection methods, primary sample size, the frequency of toxigenic *C. difficile*, source of infection, origin of infection, and proportion of toxigenic strains in each gender.

Statistical analysis

Analysis of data was performed using Comprehensive Meta-Analysis Software Ver. 2.2 (BioStat Company). Meta-analysis was performed using random-effects model to estimate the pooled prevalence and corresponding 95% confidence interval (CI). Statistical heterogeneity between and within groups was determined using Cochran's Q statistic and the I^2 index. The funnel plot, Begg's rank correlation test, and Egger's weighted regression tests were used to evaluate possible publication bias ($P < 0.05$ is indicative of publication bias).

The present study designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Results

Initially, 5440 citations were yielded from the database search. Among them, 5404 were excluded on the initial screening of the index, title and abstract and 36 were reviewed in full text. Of 36 full text reviewed articles, five studies did not report the prevalence of toxigenic strains of *C. difficile*, four studies did not report primary samples size, three studies had unclear results, three studies performed on random stools, and results of one study duplicated in their recent study. Finally, 20 studies were eligible for inclusion and were subjected to meta-analysis. A flowchart of the literature search, the selection procedures and reasons for exclusion are presented in Fig. 1. The characteristics of the included studies in the meta-analysis are available in Table 1.

Of the total number of included studies, 10 of which were from Iran (16-25), four from Saudi Arabia (26-29), four from Kuwait (30-33), and one for each of Iraq (34), and Qatar countries (35). Totally, 13 studies conducted only among hospitalized patients, five studies contained both hospitalized and outpatients and two studies enrolled only outpatients.

Twenty studies reported the prevalence of toxigenic strains of *C. difficile* among patients from Persian Gulf countries, of these the pooled prevalence of CDI was 9% (95% CI: 6.5%-12.5%) ranging from 0.6% to 22.2% (Fig. 2). There was a significant heterogeneity among the included studies ($\chi^2 = 410.893$; $P < 0.001$; $I^2 = 95.4\%$). Moreover, a symmetric funnel plot of the included studies showed no evidence of publication bias (Fig. 3). Additionally, Begg's and Egger's tests were performed to quantitatively evaluate the probable publication bias among studies. According to the results of Begg's test ($z = 0.097$, $P = 0.92$) and Egger's test ($t = 0.34$, $P = 0.74$), no evidence of publication bias was observed.

Totally, eight studies showed the prevalence of hospital-acquired CDI, from those studies the prevalence of CDI was estimated 8.4% (95% CI: 4.9%-14.1%) ranging from 2.8% to 21.7% (Fig. 4).

Table 1: Characteristics of studies included in the meta-analysis

| First author | Publication year | Performed time | Country | Sample type | Age range | Hospitalized (H) or outpatient (OP) | Detection method | Sample size | Toxigenic <i>C. difficile</i> No. | HA/CA No. | M/F No. | Ref |
|-------------------------|------------------|----------------|--------------|---------------------|-------------|-------------------------------------|------------------------------|-------------|-----------------------------------|-----------|---------|------|
| Sadeghifard | 2010 | 2002-2006 | Iran | Diarrheal stool | No limit | H | Cytotoxicity assay | 942 | 57 | - | 30/27 | (16) |
| Nazemalhosseini-Mojarad | 2011 | UN | Iran | Diarrheal stool | No limit | H and OP | ELISA | 356 | 19 | - | 13/6 | (17) |
| Nasri | 2012 | 2009-2010 | Iran | Diarrheal stool | No limit | H | ELISA | 162 | 36 | - | 24/12 | (18) |
| Jalali | 2012 | 2010-2011 | Iran | Diarrheal stool | No limit | H | Molecular | 86 | 17 | 13/4 | 9/8 | (19) |
| Goudarzi | 2013 | 2010-2011 | Iran | Diarrheal stool | No limit | H | Molecular | 350 | 75 | - | 39/36 | (20) |
| Farshad | 2013 | 2012 | Iran | Nosocomial diarrhea | No limit | H | Cytotoxicity assay and ELISA | 122 | 9 | 9/- | 5/4 | (21) |
| Azizi | 2013 | 2010 | Iran | Nosocomial diarrhea | No limit | H | Molecular | 98 | 15 | - | - | (22) |
| Alinejad | 2015 | 2013-2014 | Iran | Nosocomial diarrhea | 6-60 months | H | ELISA | 38 | 8 | 8/- | 6/2 | (23) |
| Rezazadeh Zarandi | 2017 | 2014-2015 | Iran | Diarrheal stool | No limit | H | Molecular and ELISA | 233 | 11 | - | - | (24) |
| Azimirad | 2017 | 2011-2012 | Iran | Diarrheal stool | No limit | H | Molecular | 105 | 18 | - | 9/10 | (25) |
| Sandokji | 2009 | 2007-2008 | Saudi Arabia | Diarrheal stool | >2 yr | H | ELISA | 258 | 56 | 56/- | - | (26) |
| Al-Tawfiq | 2010 | 2007-2008 | Saudi Arabia | Diarrheal stool | No limit | H and OP | ELISA | 913 | 42 | 26/16 | 23/19 | (27) |
| Al-Eidan | 2013 | 2011 | Saudi Arabia | Diarrheal stool | Adult | H | ELISA | 2927 | 171 | 98/73 | - | (28) |
| Senok | 2017 | 2014-2015 | Saudi Arabia | Diarrheal stool | No limit | H and OP | Molecular | 210 | 31 | - | - | (29) |
| Jamal | 2010 | 2003-2005 | Kuwait | Diarrheal stool | No limit | H and OP | ELISA | 697 | 73 | 56/17 | - | (30) |
| Jamal | 2014 | 2012 | Kuwait | Diarrheal stool | >2 yr | OP | Molecular | 409 | 13 | -/13 | - | (31) |
| Jamal | 2015 | 2011-2013 | Kuwait | Diarrheal stool | >2 yr | OP | ELISA | 2548 | 16 | -/16 | - | (32) |
| Albert | 2016 | 2014-2015 | Kuwait | Diarrheal stool | No limit | H | Molecular | 109 | 3 | - | - | (33) |
| Alrifai | 2009 | 2004-2005 | Iraq | Nosocomial diarrhea | 1-60 months | H | ELISA | 81 | 17 | - | - | (34) |
| Al-Thani | 2014 | 2011-2012 | Qatar | Diarrheal stool | >1 yr | H and OP | EIA and Molecular | 1,532 | 122 | 98/14 | 72/50 | (35) |

Abbreviations: ELISA: enzyme-linked immunosorbent assay; EIA: Enzyme Immunoassay; HA: hospital-acquired; CA: community-acquired; M: male; F: female.

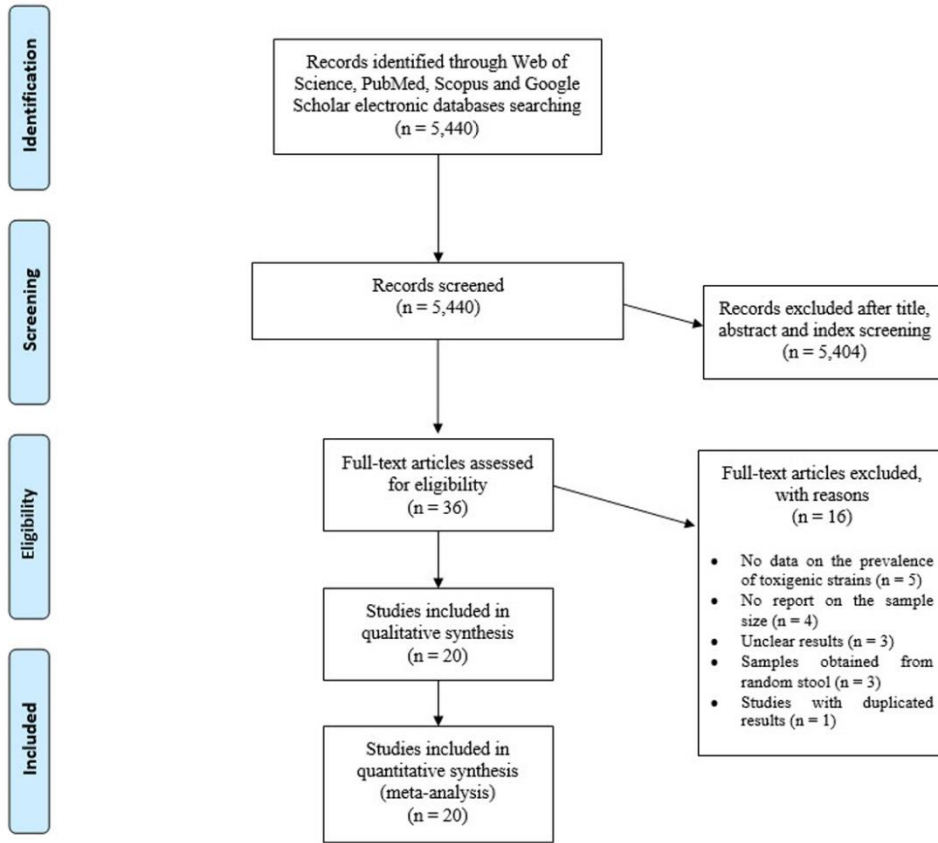


Fig. 1: Flow chart of the literature search strategy and study selection

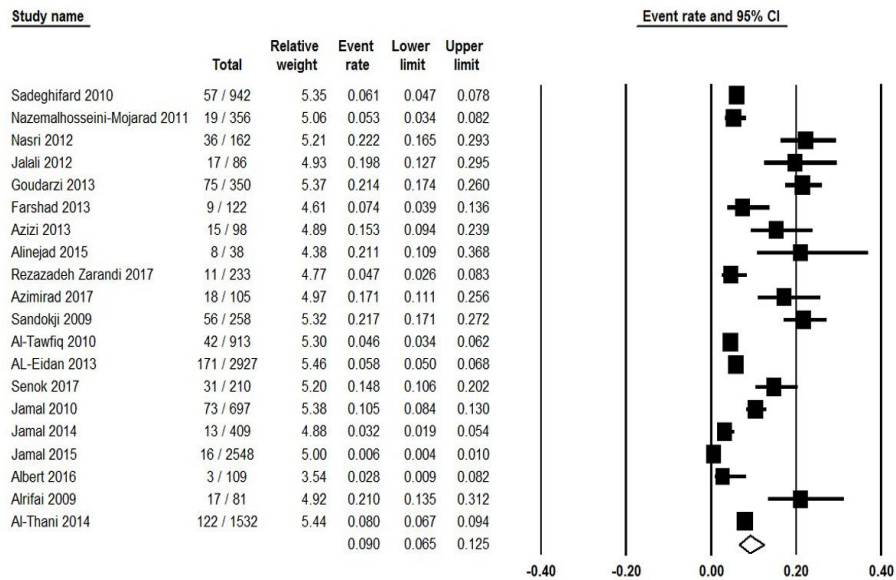


Fig. 2: Forest plot of the pooled prevalence of CDI in western Asia

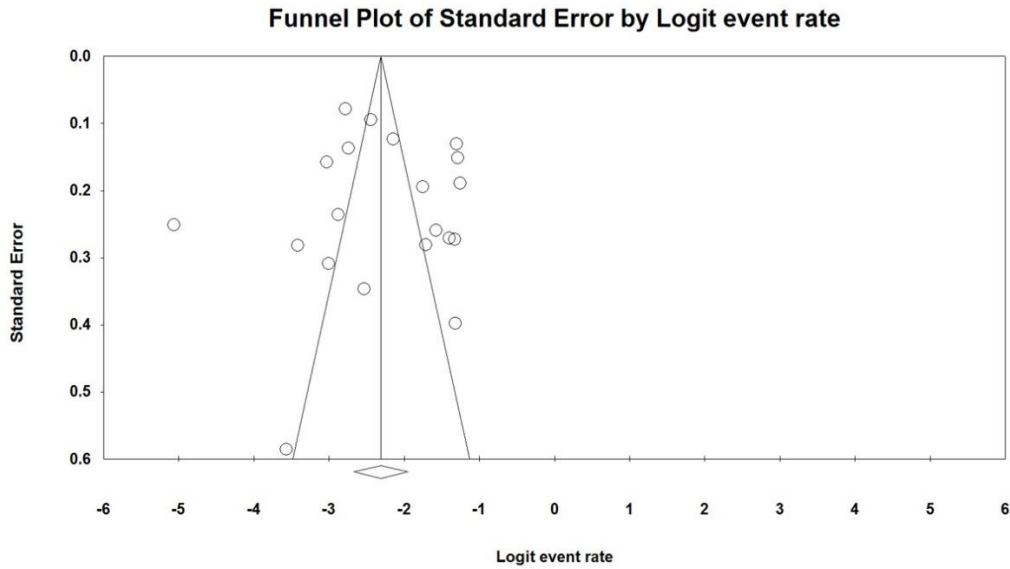


Fig. 3: Funnel plot of meta-analysis on CDI in western Asia

Moreover, seven studies reported the prevalence of community-acquired CDI, from those studies the prevalence of CDI was estimated 1.8% (95% CI: 1.2%-2.9%) ranging from 0.6% to 4.7% (Fig. 4). Ten studies showed the incidence of CDI regarding gender, from those studies the occur-

rence of CDI among male and female patients was estimated 6% (95% CI: 4%-9%) and 4.6% (95% CI: 3.0%-7.1%), respectively (Fig. 5). Finally, subgroups analysis between countries were done and results were presented in Fig. 6.

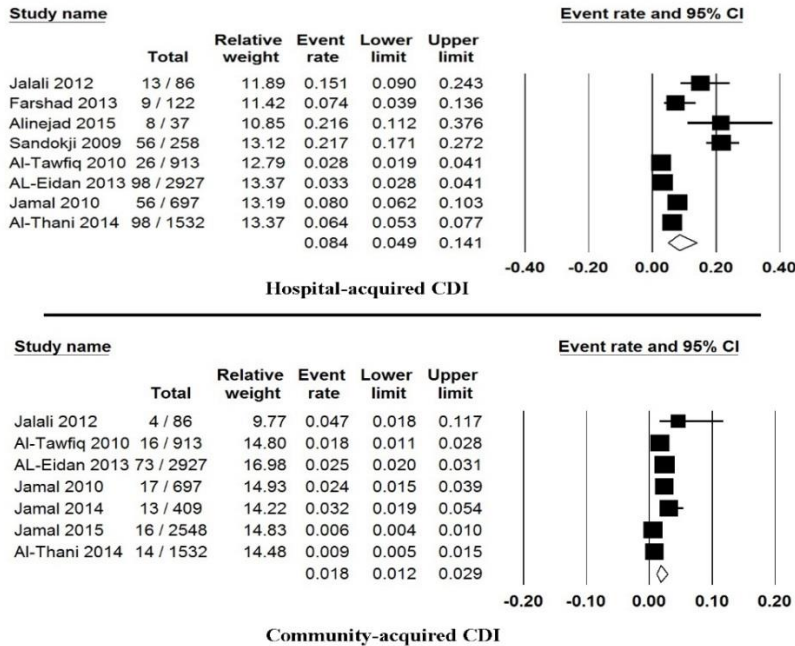


Fig. 4: Forest plot of the pooled prevalence of community- or hospital-acquired

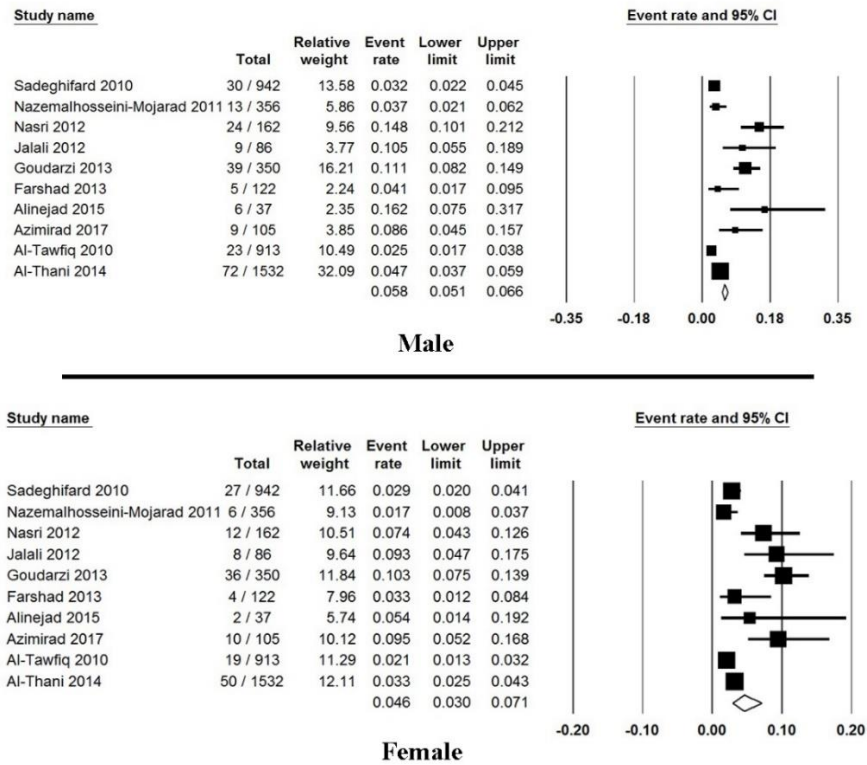


Fig. 5: Forest plot of the pooled prevalence of male and female patients with CDI

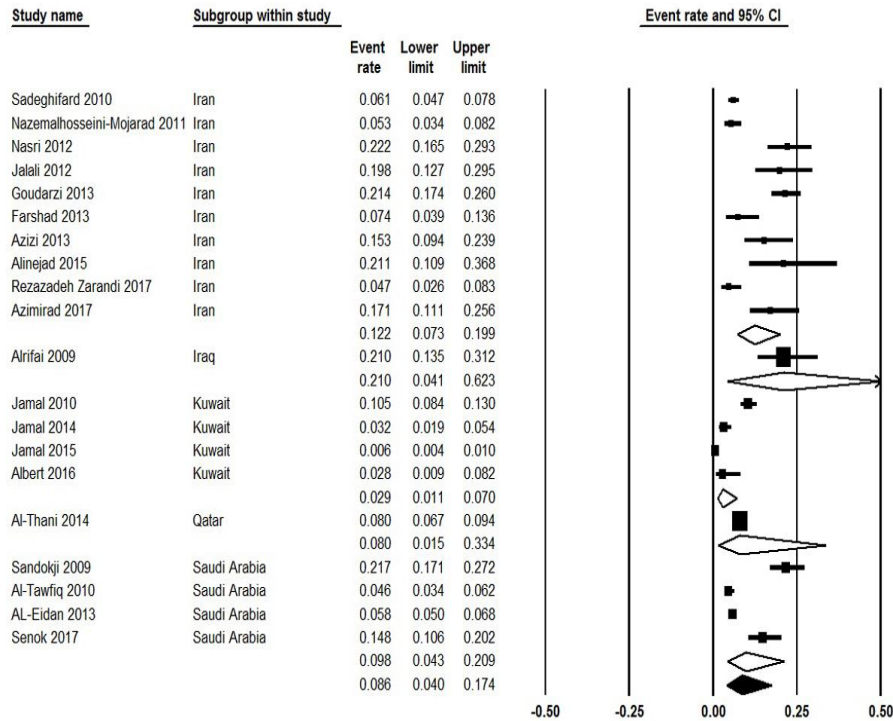


Fig. 6: Forest plot of subgroups analysis of the pooled prevalence of CDI between countries in western Asia

Discussion

The emergence of the hypervirulent *C. difficile* strains increase the prevalence and severity of CDI; however, epidemic strain of NAP1/BI/027 is not common in our region and is a public health problem for other countries, mainly western countries (36). Thus, it is essential to gain a close estimation of the burden of CDI for the development of effective healthcare practice. To the best of our knowledge, the present study is the largest comprehensive survey to date estimated the pooled prevalence of CDI 9% from the Persian Gulf region. Moreover, the prevalence of CDI differed greatly between studied countries and even hospitals in the same country ranging from 0.6% to 22.2%. Despite the discrepancy in literature, our findings are consistent with the median values reported in previous studies. In this regard, the prevalence of CDI in South and East Asia were reported 10.9% in India (37), 14% in China (38), and 14.3% in South-Korea (39). These reports, accompanied by results from a meta-analysis study that indicated the prevalence of CDI in Eastern Asia is higher than other parts (40). In American countries, this rate was reported 8% in Brazil (41), and 13.7% in the USA (42). While a hospital-based survey within 34 European countries showed much more discrepancy in the prevalence of CDI ranging from 0% in Luxembourg to 39% in Poland (43). These variations might be due to differences in predominant epidemic strains, geographical distribution, studied population or the sensitivity of detection methods.

In the present study, from those studies that reported the origin of infection, the prevalence of hospital-acquired CDI was estimated at 8.4%, while the prevalence of community-acquired CDI was 1.8%. International estimation of the burden of community- or hospital-acquired CDI is challenging since in most of the studies the origin of infection was not investigated. Comparison with available reports indicate that the prevalence of community-acquired CDI in our study (1.8%) is closest to reports from Brazil (1%) (41), South-

Korea (1.6%) (39), and Europe (~2%) (43), whereas it is lower than report from China (8%) (44).

The strengths of this systematic review based study were the large number of patients from the major countries of Middle East with a study design adherence to international guidelines for the estimating burden of CDI. Based on the ECDC experiences, continuous or periodical surveillance supplemented with epidemiological and microbiological data is a practical strategy for monitoring CDI (45). Meanwhile, increasing the national coverage of hospital-based CDI surveillance will improve the national estimates of the CDI burden (43, 45).

As the main limitation of the present study, our report was not representative of the actual rate in the Persian Gulf region. Since our estimation was based on published data, so the burden of infection would be expected to be different if a network of data from more hospitals and laboratories in this region were available. Moreover, differences in the severity of illness of patients or antibiotics prescription might be an effect on reporting rates (43).

Conclusion

The results of the present study provide good epidemiological information about the distribution of CDI in the Persian Gulf region in western Asia. The prevalence of CDI in western Asia is lower than southern and eastern region. Moreover, the lower prevalence of community-acquired CDI compared to hospital-acquired CDI, indicate that the source of infection in western Asia is more likely in the hospitals. These findings highlighting the importance of active surveillance, and the demand for improving infection control policy in reducing the risk of CDI in hospitals.

Ethical consideration

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission,

redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interests.

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