


The Prevalence of Nosocomial Infections in the Eastern Mediterranean: Systematic Review and Meta-analysis

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Abstract

Background: Evidence-based information on the prevalence of nosocomial infections (NIs) and the determination of influencing factors can play a key role in developing effective infection control activities in healthcare settings, particularly in the East Mediterranean Region (EMR). This study aimed to determine the prevalence of NIs in the EMR.

Methods: A comprehensive search of electronic databases—including EMBASE, Google Scholar, Scopus, PubMed, and Web of Science—was done between 2000 and 2021. To estimate the pooled prevalence of NIs in the EMR, a random-effects model was used to measure the effect size with a 95% confidence interval (CI). All analyses were done using a comprehensive meta-analysis.

Results: The prevalence of NI in hospital settings was reported to be 13% (95% CI, 0.1-0.16). The highest rate of nosocomial infection was related to wound infection at 39% (95% CI, 0.23-0.58), followed by bloodstream infection at 32% (95% CI, 0.27-0.38). Among the common organisms that infected patients, *E. coli* was the cause of 16% (95% CI; 0.13-0.2) of NIs followed by Coagulase-negative staphylococci with the prevalence of 15% (95% CI, 0.11-0.19), *Acinetobacter* at 15% (95% CI, 0.13-0.18) and *Staphylococcus* at 13%. Study results also revealed a significant relationship between the prevalence of NI, age, and hospital length of stay ($P < 0.05$).

Conclusion: Study results mentioned NI as a widespread challenge in the EMR, which mainly affects elderly patients with complicated clinical symptoms that need long-term hospital stay. To resolve the issue, early detection of infected individuals could improve the quality of response toward the infection.

Keywords: Healthcare-Associated Infections, Nosocomial Infection, Eastern Mediterranean, Systematic Review

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↑What is “already known” in this topic:

Nosocomial infections are among the most common occupational infections among healthcare workers. In the Eastern Mediterranean Region, during a series of Ebola outbreaks in Sudan, 81 workers were reported to be infected while serving care to the patients.

→What this article adds:

This study aimed to systematically review the existing literature to estimate the prevalence of healthcare-related infections to consequently guide clinicians in conducting effective prevention strategies. The highest prevalence of nosocomial infections (NI) was reported for Afghanistan at 47%. The results of the analysis showed a higher prevalence of NI in women compared to men.

Introduction

Nosocomial infections (NIs), also known as healthcare-related infections (HAIs), are a subgroup of infectious diseases that patients acquire during the process of receiving healthcare services in hospital settings or other healthcare facilities. These infections are absent at the time of admission and might develop at least 48 hours after admission time. In addition, they are among the most common occupational infections among healthcare workers (1, 2). Health care-related infection has become a significant challenge globally, particularly in developing countries leading to major mortality, morbidity, and financial burden. Evidence has shown that in these countries, the risk of hospital-acquired infection is considerably higher and the rate of infected patients surpasses 25% (3).

Long-term disability, extended periods of hospital stay, antimicrobial resistance, preventable deaths, rising costs for patients, and economic burden for health systems are among the important adverse effects of the increasing rate of nosocomial infections (4). A survey conducted on the prevalence of HAI in hospital settings of 4 World Health Organization (WHO) regions in the 1980s revealed that the highest prevalence was related to the hospitals in the Eastern Mediterranean Region (EMR) (5). For example, in Jordan, Morocco, and Tunisia the prevalence of HAIs was reported to be between 12% and 18% (6).

The literature affirmed that more than 80% of all nosocomial infections belonged to 1 of the 4 types of infections including urinary tract infection (UTI), surgical-site infection, bloodstream infection, and pneumonia. UTI constitutes 40% of all nosocomial infections and is regarded as the most common type of healthcare-related infection worldwide. Urinary catheters are an important risk factor for this infection. Furthermore, gram-negative bacilli such as *E. coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* are the most common pathogens of this infection (7). Nosocomial pneumonia is another common infection having a direct association with the use of a mechanical ventilator. The principal etiological agents for this type of infection are gram-negative bacilli such as *P. aeruginosa*, *K. pneumoniae*, *A. Baumannii*, and *Staphylococcus*. In addition, 14% to 16% of nosocomial infections are associated with surgical site infections (8). In developing countries, the rate of surgical-site infection was much higher and was reported at a range of 12% to 39% (9). Likewise, the reported incidence rate of infections that are mainly associated with the devices used in medical procedures such as urinary tract infections, bloodstream infections, and pneumonia was nearly 20 times higher in developing compared to developed countries (10).

Infants, elderly patients, those with underlying conditions, patients with exposure to forceful surgical interventions using invasive devices such as organ transplantations, and patients under treatment with immune suppressor drugs are among the most vulnerable individuals (11). In some countries of the EMRO region, per 1000 live hospital-born babies the estimated prevalence of blood infec-

tion in infants younger than 90 days old was between 6.5 and 38 (12). Healthcare workers (HCWs) are also at a considerable risk of exposure to several microbiological agents while delivering healthcare services to patients. In the EMR, during a series of Ebola outbreaks in Sudan, 81 workers were reported to be infected while serving care to the patients (13).

As most of the countries in the EMR face NIs issues and their adverse impacts, prevention of hospital-acquired infections is an important strategy to both improve the quality of healthcare services delivered to patients and maintain the health and safety of HCWs in the workplace. Evidence-based information on the prevalence of these infections and the determination of influencing factors can play a key role in developing effective infection control activities in healthcare settings, particularly in the EMR. Thus, this study aimed to systematically review the existing literature to estimate the prevalence of HAI to consequently guide clinicians in conducting effective prevention strategies.

Methods

Databases and Search Terms

A comprehensive search of electronic databases—including EMBASE, Google Scholar, Scopus, PubMed, and Web of Science—was done between 2000 and 2021. Search Mesh terms included ("infection cross"[Title] OR "cross infections"[Title] OR "healthcare associated infections"[Title] OR "healthcare associated infection"[Title] OR "health care associated infection"[Title] OR "health care associated infections"[Title] OR "hospital infection"[Title] OR "infections hospital"[Title] OR "nosocomial infection"[Title] OR "nosocomial infections"[Title] OR "hospital infections"[Title]) AND ("Afghanistan"[Title/Abstract] OR "Bahrain Djibouti"[Title/Abstract] OR "Islamic Republic of Iran"[Title/Abstract] OR "Iraq"[Title/Abstract] OR "Jordan"[Title/Abstract] OR "Kuwait"[Title/Abstract] OR "Lebanon"[Title/Abstract] OR "Libya"[Title/Abstract] OR "Morocco"[Title/Abstract] OR "Palestine"[Title/Abstract] OR "Oman"[Title/Abstract] OR "Pakistan"[Title/Abstract] OR "Qatar"[Title/Abstract] OR "Saudi Arabia"[Title/Abstract] OR "Somalia"[Title/Abstract] OR "Sudan"[Title/Abstract] OR "Syrian Arab Republic"[Title/Abstract] OR "Tunisia"[Title/Abstract] OR "United Arab Emirates"[Title/Abstract] OR "Yemen"[Title/Abstract] OR "EMRO"[Title/Abstract] OR "Eastern Mediterranean"[Title/Abstract] OR "Middle East West of Asia"[Title/Abstract] OR "Arab Nations"). In the first step of searching databases, 806 records were identified, which was reduced to 558 articles after removing the duplicates. To provide an up-to-date estimation of the prevalence of hospital-acquired infection in the EMR we included studies containing quantitative data on related measures for further consideration. The reference lists of included articles and conference abstracts were also screened to ensure any relevant data were added to the

review process.

Inclusion and Exclusion Criteria

Studies were included if they reported quantitative data on NI prevalence and its determining factors among the general population in the EMR to find a set of articles based on the research keywords. Different types of observational studies—including cross-sectional, prospective, case-study, and cohort—were included. Furthermore, articles with available full texts published in English between 2000 and 2021 were considered for further consideration in this review. The reason for including articles from the year 2000 was to estimate the trend of the current century. On the other hand, interventional studies, reviews, reports, letters to the editor, books, case-control studies, and commentaries were excluded. Furthermore, studies using invalid methods or containing insufficient data that mainly focused on diagnostic approaches, treatment methods, and

medication were kept out of the review.

Study Selection

Searching electronic databases resulted in 806 articles. After removing the duplicates, the remaining 558 records were reviewed by 2 independent investigators based on their titles and abstracts. In the next step, the full texts of 227 remaining studies were systematically evaluated to determine whether they met the eligibility criteria. Finally, 103 records with 10,662,335 participants were selected to be evaluated in this meta-analysis (Figure 1).

Quality Assessment

We evaluated the methodological quality of the articles using the Newcastle-Ottawa Scale (NOS) based on the procedures suggested in the Cochrane Handbook of Systematic Reviews. The NOS consists of a star system in which a study is evaluated in 3 areas—including 4 items

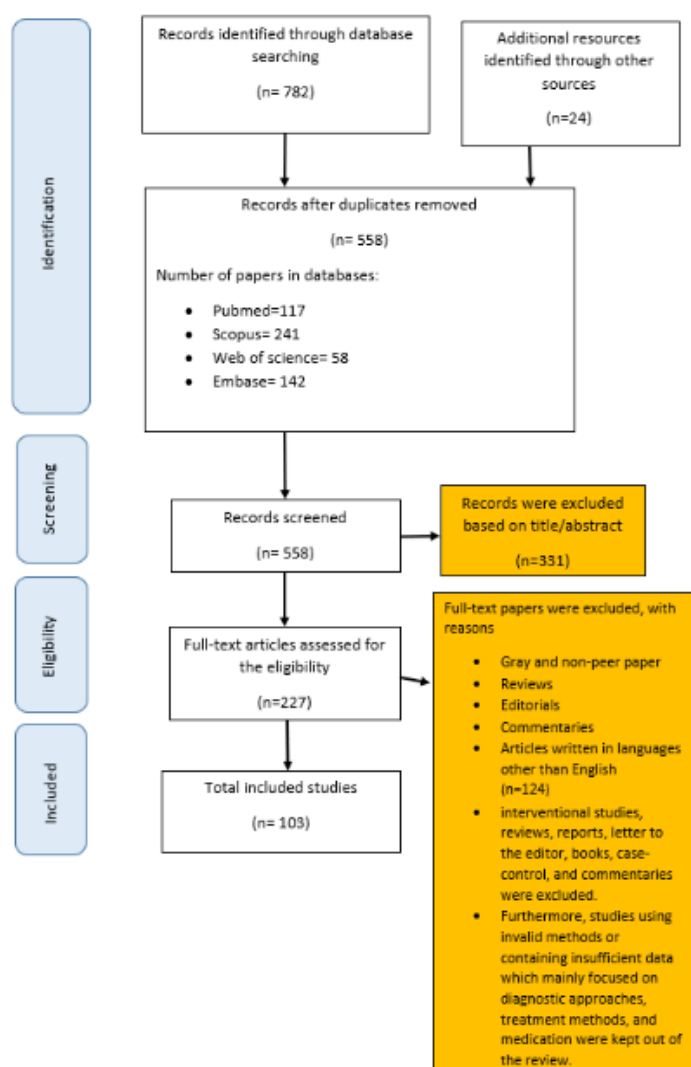


Figure 1. Flow diagram of our review process (PRISMA)

on the selection of study groups, 2 items on the comparability of groups, and 3 items in terms of exposure or outcome ascertainment. If any of the items in the NOS were not reported in the article, a zero score was assigned; while for each of the areas addressed in the study, a score of 1 was given. We categorized studies based on their methodological quality in different groups from poor (score between 0 and 3), to high quality (score between 7 and 9) (14). Two independent reviewers engaged in the quality assessment process; in case of any disagreement, the issue was resolved by a third investigator.

Data Excretion

A data extraction form was used to enter data from included studies by 1 reviewer, which included the author's name, the title of the study, publication year, study setting, sample size, characteristics of the study population (eg, age, and sex), the total prevalence of hospital-acquired infection, and the prevalence of hospital-acquired infection based on the infection type and related organisms.

Statistical Analysis

To estimate the pooled prevalence of healthcare-associated infection in the EMR, a random-effects model was used to measure the effect size with a 95% confidence interval (CI) and illustrated the graphical results with Forest plots. The statistical heterogeneity was quantified by the I^2 test, and the Egger test was applied to assess publication bias. Furthermore, due to the variability of estimates based on different study settings, subgroup analyses were used to determine the type of infection and socio-demographic characteristics of study populations. All analyses were done using the Comprehensive Meta-Analysis and R software. All figures with $P < 0.05$ were considered statistically significant.

Results

Overview of the Prevalence of HAI

After analyzing 103 studies, out of 10662335 participants, 156605 individuals acquired various types of nosocomial infection; consequently, the prevalence of nosocomial infection in hospital settings was reported to be 13% (95% CI, 0.1-0.16) (Table 1).

The Prevalence of HAI Based on Countries

According to the analysis, the highest prevalence of NI was reported for Afghanistan at 47% (95% CI; 0.46-0.49) while the lowest rate was in Bahrain at 1% (95% CI, 0-0.02) and United Arab Emirates at 1% (95% CI, 0.01-0.02) (Table 2).

Prevalence of HAIs Based on the Infection Type and Organism

According to Table 3, the highest rate of nosocomial infection was related to wound infection at 39% (95% CI, 0.23-0.58). Bloodstream infection got second place with a prevalence of 32% (95% CI, 0.27-0.38), and the lowest rate of NI was associated with gastrointestinal infections at 8% (95% CI, 0.04-0.17).

Furthermore, results of conducted analyzes depicted that *E. coli* was the cause of 16% (95% CI, 0.13-0.2) of nosocomial infections which accounted for the highest percentage followed by Coagulase-negative staphylococci with a prevalence of 15% (95% CI, 0.11-0.19), *Acinetobacter* spp at 15% (95% CI; 0.13-0.18) and *Staphylococcus aureus* at 13% (95% CI, 0.11-0.15) (Table 3).

Prevalence of HAIs Based on the Hospital Ward

According to the results, the highest prevalence of nosocomial infection was in the trauma ward with a rate of 99% (95% CI; 0.87-1), followed by the transplant ward and intensive care unit (ICU) with respectively a rate of 83% (95% CI, 0.01-1) and 69% (95% CI, 0.58-0.78). Also, the lowest prevalence of NI was reported for Cardiac

Table 1. Total Prevalence of Nosocomial Infections based on random effects model

Effect size and 95% interval				Test of null (2-Tail)		Heterogeneity
Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	I^2
103	0.13	0.10	0.16	-13.94	<0.001	85%

Table 2. Prevalence of NI based on countries

Country	Point estimate	Lower limit	Upper limit	Z-value	P-value	Heterogeneity I^2
Afghanistan	0.47	0.46	0.49	-3.46	<0.001	91%
Bahrain	0.01	0.00	0.02	-9.42	<0.001	96%
Egypt	0.15	0.04	0.42	-2.41	0.020	89%
Iran	0.10	0.07	0.15	-11.14	<0.001	91%
Iraq	0.27	0.21	0.33	-6.91	<0.001	93%
Jordan	0.26	0.13	0.46	-2.34	0.023	95%
Kuwait	0.09	0.06	0.13	-10.38	<0.001	88%
Lebanon	0.04	0.01	0.12	-5.32	<0.001	91%
Libya	0.14	0.12	0.16	-21.43	<0.001	94%
Morocco	0.28	0.15	0.45	-2.48	0.010	97%
Oman	0.03	0.02	0.03	-51.57	<0.001	92%
Pakistan	0.16	0.08	0.31	-3.88	<0.001	89%
Saudi Arabia	0.10	0.03	0.27	-3.58	<0.001	95%
Sudan	0.33	0.18	0.51	-1.82	0.070	92%
Tunisia	0.29	0.12	0.56	-1.52	0.130	91%
United Arab Emirates	0.01	0.01	0.02	-14.10	<0.001	97%
Multiple Countries	0.08	0.03	0.23	-4.04	<0.001	98%

Table 3. Prevalence of NI based on Organism, Hospital wards and Infection

Groups	Effect size and 95% interval			Test of null (2-Tail)		Heterogeneity I ²	
	Point estimate	Lower limit	Upper limit	Z-value	P-value		
Organisms	Staphylococcus aureus	0.13	0.11	0.15	-21.31	<0.001	93%
	CoNS	0.15	0.11	0.19	-10.42	<0.001	91%
	Escherichia coli	0.16	0.13	0.20	-12.08	<0.001	88%
	Klebsiella pneumoniae	0.12	0.10	0.15	-18.61	<0.001	85%
	Acinetobacter spp	0.15	0.13	0.18	-17.56	<0.001	97%
	Pseudomonas aeruginosa	0.10	0.08	0.12	-19.30	<0.001	93%
	Enterobacter spp	0.09	0.07	0.11	-17.46	<0.001	92%
	Enterococcus spp	0.07	0.05	0.09	-15.81	<0.001	94%
	Candida spp	0.07	0.05	0.09	-14.43	<0.001	87%
Other¶	0.12	0.09	0.16	-12.73	<0.001	85%	
Hospital Wards	NICU	0.29	0.21	0.39	-4.03	<0.001	82%
	medical wards	0.33	0.22	0.46	-2.50	0.010	81%
	emergency	0.36	0.11	0.71	-0.76	0.440	99%
	CCU	0.02	0.01	0.04	-12.66	<0.001	93%
	Oncology	0.63	0.07	0.98	0.33	0.740	98%
	neonatal	0.36	0.10	0.73	-0.72	0.471	95%
	trauma	0.99	0.87	1.00	3.33	<0.001	92%
	Obstetrics and gynaecology	0.07	0.03	0.19	-4.72	<0.001	88%
	Internal medicine	0.10	0.02	0.39	-2.45	0.010	89%
	general	0.33	0.12	0.63	-1.14	0.250	87%
	PICU	0.11	0.07	0.19	-6.80	<0.001	93%
	Infectious diseases	0.03	0.01	0.11	-5.37	<0.001	95%
	hematology	0.06	0.02	0.15	-5.15	<0.001	93%
	Rehabilitation	0.03	0.00	0.25	-2.90	<0.001	91%
	Pneumology	0.03	0.02	0.04	-19.94	<0.001	94%
	Orthopedic	0.14	0.12	0.16	-19.85	<0.001	96%
	Transplant	0.83	0.01	1.00	0.51	0.610	97%
	ICU	0.69	0.58	0.78	3.40	<0.001	92%
	Burns	0.22	0.13	0.35	-3.87	<0.001	94%
	Labor & postpartum	0.34	0.09	0.72	-0.80	0.420	95%
	nursery	0.03	0.02	0.05	-15.32	<0.001	91%
	Pediatric	0.22	0.11	0.38	-3.13	<0.001	94%
	surgery	0.36	0.24	0.49	-2.06	<0.001	96%
	Nephrology	0.05	0.03	0.09	-10.25	<0.001	93%
	Other wards¶¶	0.22	0.15	0.31	-5.33	<0.001	92%
Infections	Urinary tract infection	0.25	0.22	0.27	-16.58	<0.001	95%
	Respiratory tract infection	0.22	0.14	0.32	-4.81	<0.001	96%
	Surgical site infection	0.24	0.20	0.29	-9.43	<0.001	93%
	Wound infection	0.39	0.23	0.58	-1.13	0.260	92%
	Bloodstream infection	0.32	0.27	0.38	-5.66	<0.001	88%
	Pneumonia	0.26	0.21	0.30	-8.92	<0.001	89%
	Bacteraemia	0.12	0.05	0.24	-4.49	<0.001	93%
	Gastrointestinal infection	0.08	0.04	0.17	-5.93	<0.001	95%
	Other¶¶¶	0.10	0.08	0.14	-13.51	<0.001	93%

NOTE. CoNS, Coagulase-negative Staphylococci

¶There was one missing case

¶¶ENT, Psychiatric

¶¶¶meningitis, encephalitis

Care Unit with 2% (95% CI, 0.01-0.04) (Table 3).

Meta-analysis Based on Sex

Results of the analysis showed the higher prevalence of NI in women 25.2% (95% CI, 0.17-0.34) compared to men 24% (95% CI, 0.18-0.30) (Figure 2).

Meta-analysis Based on Age and Length of Stay

Results of the meta-analysis revealed that age was inversely correlated with the prevalence of nosocomial infection; so a unit of increase in the age of individuals increased the prevalence of infection by 0.03 ($P < 0.05$) (Figure 3).

On the other hand, the findings confirmed a significant direct relationship between the length of hospital stay and the rate of NI; a unit increase in the length of stay led to an increase in the prevalence of infection by 0.01 ($P <$

0.05) (Figure 3).

Meta-regression Based on Publication Year

As Figure 4 depicts the publication year of studies was inversely associated with the prevalence of NI. A unit of increase in the year of study publication resulted in a decreased rate of infection by 0.003 (Figure 4).

Publication Bias

According to Figure 5 and Egger's regression test results (greater than 0.1), no publication bias was found in this review (2-tailed $P = 0.391$).

Discussion

This was a systematic review and meta-analysis study conducted to comprehensively review the prevalence of NI in the EMR and identify the related risk factors with

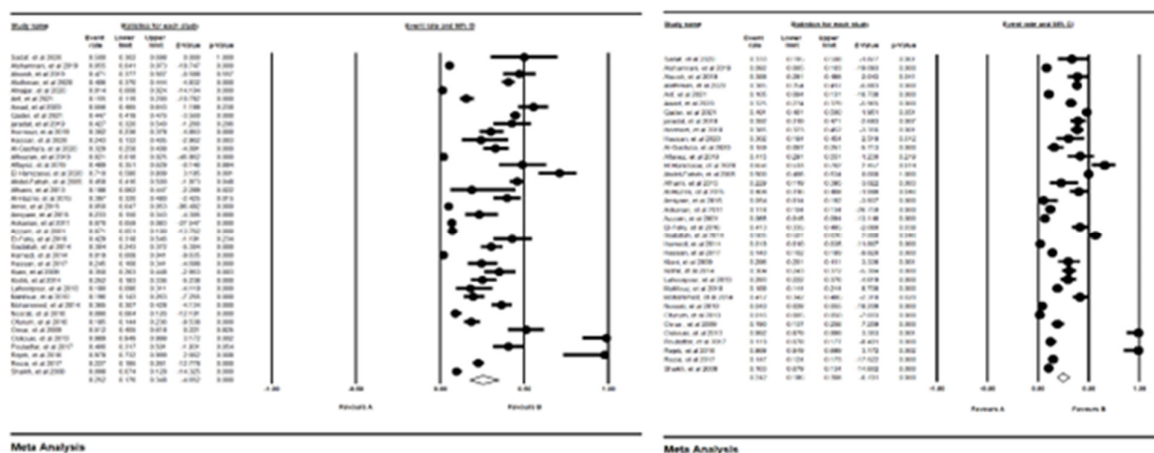


Figure 2. Prevalence of NI based on Gender

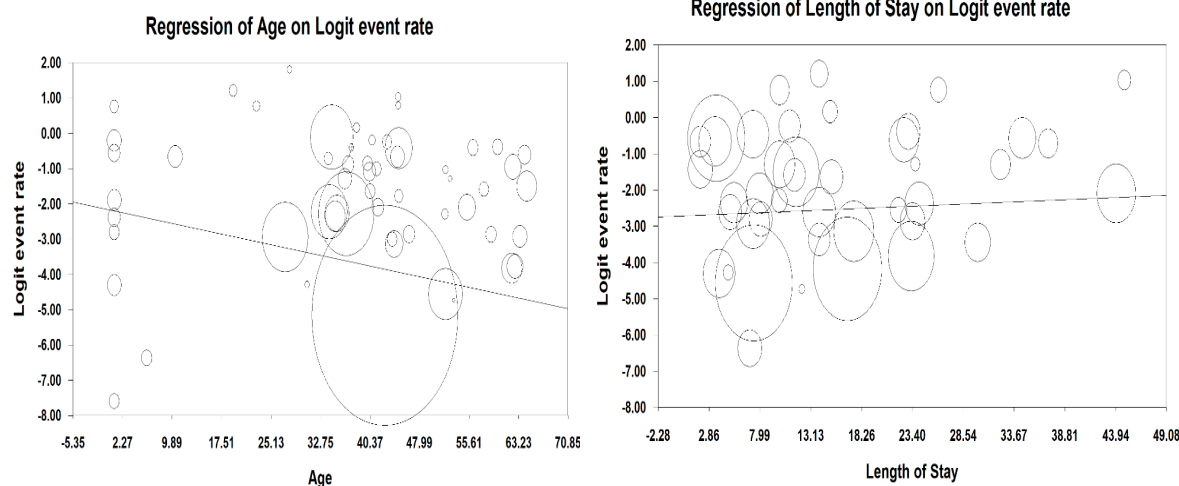


Figure 3. Meta-regression based on Age and Length of stay

emphasis on the demographic characteristics of the study population and hospital length of stay. The pooled prevalence of NI in the EMR was estimated at 13% (95% CI, 0.1-0.16) while significant differences were found between countries of the region. For example, Afghanistan with the highest rate of NI contrary to Bahrain and the United Arab Emirates with the lowest rate of infection reflected these significant differences between countries. It is no wonder that these countries have considerable divergences in terms of socioeconomic conditions, healthcare infrastructure, allocated budget to the health system, health services quality, and the level of compliance with infection control protocols (15). Evidence has shown that >1.4 million people worldwide have acquired healthcare-related infections, with the highest frequencies reported from hospital settings in the Eastern Mediterranean and South-East Asia regions at 11.8% and 10%, respectively (16). Therefore, identifying countries where the burden of NI is high can be more effective in the establishment of infection prevention and control programs in healthcare settings carrying a greater risk for HAI. Due to

the limited resources, targeted infection control interventions have been confirmed to be cost-effective, so that they efficiently direct resources to the areas of greater need and urgency (17). An inclusive program for preventing HAIs within eastern Mediterranean hospitals would reduce hospital length of stay, and subsequently, it would result in several benefits to patients in terms of reduced mortality, morbidity, and cost of care (18).

A comparison of different hospital wards in terms of the prevalence of NIs revealed that patients with severe underlying diseases and a greater number of invasive procedures in ICUs more significantly suffered from healthcare-acquired infections, including *Acinetobacter* species (19, 20). A systematic review conducted to determine the prevalence of NIs in the World Health Organization (WHO)-defined regions of Europe, the Eastern Mediterranean, and Africa found that hospital-acquired infections as a result of *Acinetobacter baumannii* pathogen corresponded to a major risk for hospitalized patients in the regions (21). The WHO also mentioned *Acinetobacter baumannii* as a serious pathogen responsible for a great number of

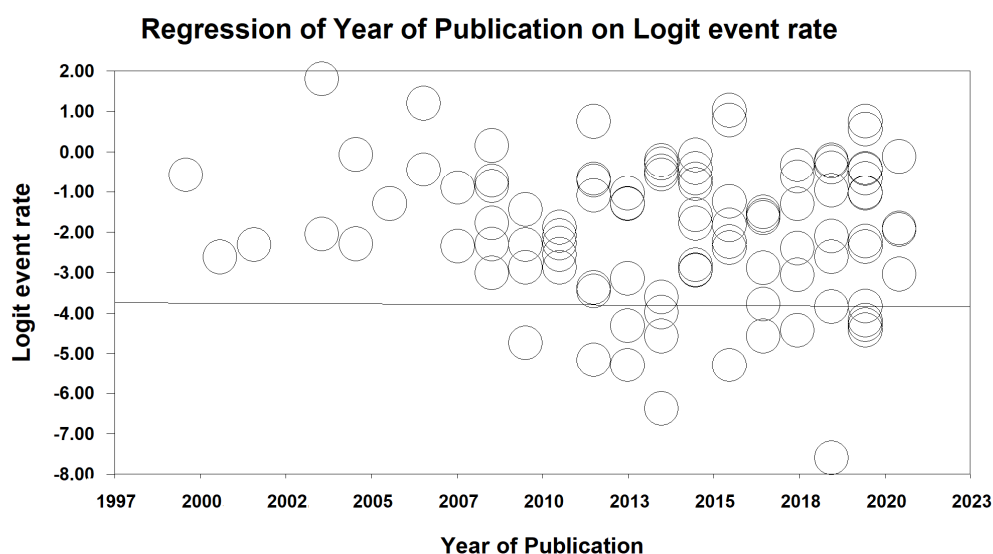


Figure 4. Meta-regression of NI based on Year of publication

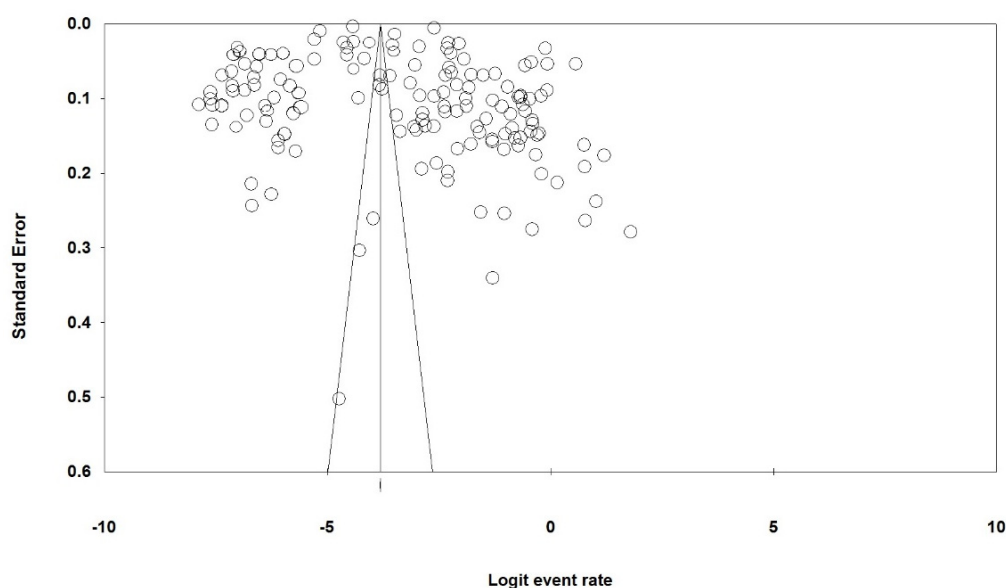


Figure 5. Funnel plot of Standard Error by Logit event rate

clinical infections like wound, bloodstream, pneumonia, and urinary tract infections in humans, particularly patients with severe underlying diseases and those hospitalized in ICUs (22-24). In a study by Mohiuddin et al in hospitals in Dhaka, Bangladesh, *Escherichia coli* was found as the most common nosocomial pathogen followed by *Pseudomonas*, *Staphylococcus aureus*, *Klebsiella* species, and *Acinetobacter* (25). Similarly, several studies confirmed that the most widespread organisms were *Escherichia coli* (51%), *Klebsiella* species (19.6%), and *Proteus mirabilis* (10%) (26). In another study by Sohrabi et al, coagulase-negative staphylococci (11.2%)

was ranked second followed by *Klebsiella* (8.1%) (27). The findings are almost consistent with our study results.

Our review also highlighted that many NIs constituted wound and bloodstream infections. Similarly, a review conducted on patients who underwent cesarean revealed an infection rate of 53% representing an increased number of surgical site infections in Bangladesh (28). Due to the insufficiency of sterilization techniques, the lack of sanitation facilities, overcrowded wards, limited waste disposal, and health infrastructure challenges, an increased rate of HAIs was observed in hospitals, particularly as a result of unsafe invasive surgeries (29). A report released on posi-

tive associations of nosocomial infections with clinical factors in 2011 reported the rate of HAIs to be 46.2% in the surgical, trauma, and burn units (30). Another research conducted in a tertiary referral hospital in northern Tanzania also found that the rate of NI was mainly high in the ICU (40%), followed by surgical wards (36.7%) (31). Nonsurgical healthcare-related infections have also been surveyed in several hospitals in developing countries. The principal nonsurgical infections contained pneumonia, urinary tract, and gastrointestinal infections (30). As mentioned by Mohiuddin et al, some of the common procedures that amplify the probability of HAIs include intubations or mechanical ventilation, urinary bladder catheterization, gastric drainage, and invasive intravenous monitoring (25). The high proportion of HAIs in ICUs was also found in the healthcare settings of Southeast Asia, China, and Latin America (32-36). Thus, it is required that all HCWs, particularly those working in ICUs, receive adequate training on the control measures of nosocomial infections. Physicians and nurses must gain the necessary knowledge about hospital guidelines for effectively implementing invasive procedures using intravascular catheters, urinary catheters, endotracheal tubes, or other types of invasive devices (37-39).

The same as our review evidence has shown that older age and a hospital stay of >3 days were among the important risk factors for NIs. For example, a study conducted at a teaching hospital in Sudan found that the majority of patients who suffered from NIs were >55 years old, emphasizing older age as a key risk factor for hospital-acquired infection (40). Similarly, according to Wang et al, sex, age, comorbidity, and invasive procedures were considered important risk factors for NI (41). Considering hospital length of stay as a risk factor for acquiring healthcare-related infection, Hassan et al found that a unit increase in the length of stay enhanced the probability of affecting by infection by 1.37%. Furthermore, hospital-acquired infection was found to increase hospital length of stay by 9.3 days leading to rising costs of healthcare (42).

Limitations

There are some limitations regarding this review. The most important limitation of this study was the small number of articles in some countries such as Afghanistan. We limited the review to English language papers and did not include the grey literature. Other limitations of this study were the lack of free access to some articles, the unavailability of full text in some articles, and the low quality of some articles.

Conclusion

Study results highlighted nosocomial infection as a global challenge in healthcare systems, particularly in Eastern Mediterranean countries. Thus, establishing a safe and disinfected work environment in healthcare settings could efficiently prevent the spread of NIs. To resolve the issue and prevent the spread of infections in hospitals it is recommended to develop and implement an effective infection control program, designate several healthcare staff to employ infection control programs, and provide infection

control education and appropriate personal protective equipment for HCWs. Furthermore, early detection of infected individuals particularly elderly patients, those with severe underlying disease, and patients with complicated clinical symptoms requiring long-term hospital stay could also improve the quality of response toward the infection.

Authors' Contributions

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Ethical Considerations

Not applicable.

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Not applicable.

Conflict of Interests

The authors declare that they have no competing interests.

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