Prevalence of nosocomial infections in Iran: A systematic review and meta-analysis

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Abstract

Background: Nosocomial infections represent a serious public health concern worldwide, and, especially, in developing countries where, due to financial constraints, it is difficult to control infections. This study aimed to review and assess the prevalence of nosocomial infections in Iran.

Methods: Different databases were searched between January 2000 and December 2017. To determine the pooled prevalence, the stochastic DerSimonian-Laird model was used, computing the effect size with its 95% confidence interval. To examine the heterogeneity among studies, the I2 test were conducted. The reporting of observational studies in epidemiology (STROBE) checklist was used to assess the methodological quality of observational studies. To further investigate the source of heterogeneity, meta-regression analyses stratified by publication year, sample size and duration of hospitalization in the hospital were carried out.

Results: 52 studies were included. Based on the random-effects model, the overall prevalence of nosocomial infection in Iran was 4.5% [95% CI: 3.5 to 5.7] with a high, statistically significant heterogeneity (I2=99.82%). A sensitivity analysis was performed to ensure the stability results. After removing each study, results did not change. A cumulative meta-analysis of the included studies was performed based on year of publication and the results did not change. In the present study, a high rate of infections caused by *Klebsiella pneumoniae* (urinary tract, respiratory tract, and bloodstream infections) was found.

Conclusion: Preventing and reducing hospital infections can significantly impact on reducing mortality and health-related costs. Implementing ad hoc programs, such as training healthcare staff on admission to the hospital, may play an important role in reducing infections spreading.

Keywords: Nosocomial infections, Prevalence, Iran, Systematic review, Meta-analysis, Hospital

Introduction

Nosocomial infections (NIs) represent a serious public health concern worldwide (1), and, especially, in developing countries where, due to financial constraints, it is difficult to control (2,3). Increased prevalence of NIs in some cases leads to patient's arbitrary use of drugs, causing serious health hazards as well as other problems such as drug resistance and death in patients (4). Worldwide, about 8.7% of hospitalized patients are at risk of exposure to NIs which considered as hospital-acquired infections and can complicate certain conditions such as cancer, organ transplant, and surgery, and also increasing mortality rate. As such, NIs generate a high societal burden, taking

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↑*What is "already known" in this topic:*
Nosocomial infections (NIs) represent a serious public health concern worldwide. Increased prevalence of NIs in some cases leads to patient's arbitrary use of drugs, causing serious health hazards as well as significant problems such as drug resistance and death in patients.

→*What this article adds:*
This study aimed to inform and assess the prevalence of NIs in Iran using a meta-analytic approach. Based on the random-effects model, the overall prevalence of NIs in Iran was 4.5%. Proper training of healthcare staff in hospital, can play an important role in reducing NIs spreading in Iran.

into account the costs for treatment, the increased length of hospital stay and the related mental and emotional stress (5).

Due to the wide variation of health-care systems in different countries, numerous reports have reported varying nosocomial infection rates (6,7). The World Health Organization (WHO) carried out an epidemiological study conducted in 14 countries worldwide and found that the overall prevalence of NIs was 8.7% (ranging from 5.0% in North America and in Europe to 40.0% in Asia, Latin America, and Sub-Saharan Africa) (7). The knowledge of the epidemiology of NIs is crucial in establishing programs for controlling this acquired infection in hospitals, implementing effective and reliable plans (8).

Iran represents one of the developing countries, which faces with the issue of NIs imposing a high economic onus, in terms of high costs annually for the Ministry of Health (MoH) and private hospital managers. Several studies have been performed in different parts of the country related to the epidemiology of nosocomial infections. These studies can be valuable for healthcare workers and managers in developing an effective control program. This study aimed to review and assess the prevalence of NIs in Iran using a meta-analytic approach.

Methods
Literature search
The results and their analysis in this study were reported according to the PRISMA guidelines (Appendix 1) (9). Embase, PubMed/MEDLINE via Ovid, Web of Science, Scopus and Google Scholar as well as national Iranian databases, including SID, Magiran, and Irandoc, with medical subject headings (MeSH) terms and a proper use of keywords. The search strategy was as follows: (Nosocomial Infections OR Hospital Infections OR Healthcare Associated Infections OR Cross Infections) AND Iran. Articles written in Farsi and English were searched and a time filter (between January 2000 and December 2017) applied. Reference lists of articles as well as national and international conferences related to the topic were also searched.

Inclusion and exclusion criteria
Inclusion criteria were: 1) population-based observational studies reporting the prevalence of NIs, 2) cross-sectional, retrospective and case-control studies, and 3) pertinent studies with clear and detailed data. Case reports, case series, letters to editor, editorials, commentaries, reviews and clinical trials as well as studies not calculating the prevalence of NIs , as well as studies not calculating the prevalence of NIs were excluded.

Data extraction
From included papers, two authors independently extracted following data: first author, year of publication, sample size, number of positive cases detected, age, region, the geography of the study, study design, and prevalence rate. Disagreement between them was solved through discussion or including a third person as a judge.

Quality of studies
To check the methodological quality of included studies, the strengthening the reporting of observational studies in epidemiology (STROBE) checklist was used (10), categorizing the studies into three groups of high, medium and low quality.

Statistical analysis
To determine the pooled prevalence, the stochastic Der-Simonian-Laird model was used, computing the effect size with its 95% confidence interval (CI) and pictorially representing it with a Forest plot. To examine the heterogeneity among studies, the I^2 test were conducted (11). To further investigate the source of heterogeneity, meta-regression analyses stratified by publication year, sample size and duration of hospitalization in the hospital were carried out. The sensitivity analysis was performed to ensure the stability and robustness of results. Subgroup analyses were performed based on study quality, geographic areas, sample size, year of publication, type of infection, and hospital wards. The cumulative meta-analysis was performed based on year of publication. Egger's test for publication bias was carried out (12). All analyses were performed using the commercial software Comprehensive Meta-Analysis Ver.2 (Biostat, NJ, USA). All figures with p<0.05 were considered statistically significant.

Results
Selected studies
Finally, after an initial search, removing duplicates and checking the title and abstract of studies, 52 studies were selected based on inclusion and exclusion criteria (13-64). Fig. 1 shows the process of finding and selecting studies.

The total sample size consisted of 8,989,980 subjects. Table 1 shows the main characteristics of the included studies.

The overall prevalence of nosocomial infections in Iran
Based on the random-effects model, the overall prevalence of NIs in Iran was 4.5% [95% CI: 3.5 to 5.7] with a high, statistically significant heterogeneity (I^2=99.82). Fig. 2 shows the overall prevalence.

Sensitivity analysis
A sensitivity analysis was performed to ensure the stability results. After removing each study, results did not change. Appendix 2 shows the sensitivity analysis.

Cumulative meta-analysis
A cumulative meta-analysis of the included studies was performed based on year of publication and the results did not change. Appendix 3 shows the cumulative meta-analysis.

Sub-group analysis
Table 2 shows the results of the different sub-group analyses according to the quality of studies, geographic regions, sample size, year of publication, type of infection, and hospital wards.
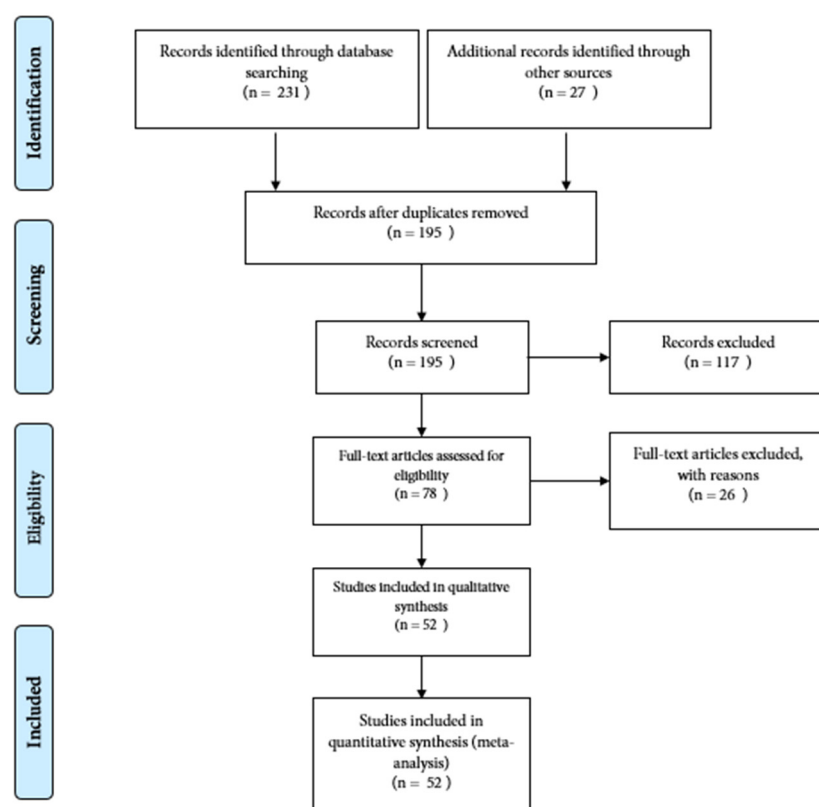
Fig. 1. Flowchart of the present systematic review and meta-analysis

Meta-regression

Table 3 shows the results of the meta-regression analysis.

Publication bias

Egger's test was carried out to assess publication bias (Fig. 3). An evidence of publication bias was found (p=0.00)

Table 1. The main characteristics studies included

First Author	Year	Sample	Average Length of Stay	Common infection	Place	Common Bacteria	Hospital unit	Quality study
Hajibagheri	2003	160	16	Pneumonia	Sanandaj	Klebsiella pneumoniae	NA	High
Askarian	2003	170	19	wound infection	Shiraz	NA	NA	High
Askarian	2003	1483	7	Surgical Site Infection	Shiraz	NA	Surgery department	low
Sadeghzadeh	2005	150	NA	Urinary tract infection	Zanjan	Escherichia coli	ICU	High
Soltani Arabshahi	2005	810	17	Surgical Site Infection	Tehran	NA	Surgery department	Medium
Rahbar	2005	6492	NA	Bloodstream infections	Orumieh	Staphylococcus	Neonatal ward	Medium
Sadeghifard	2006	5572	NA	Urinary tract infection	Elam	Escherichia coli	Surgery department	Medium
Ekrami	2007	182	NA	wound infection	Ahvaz	Pseudomonas	NA	Medium
Ghazvini	2008	971	12	Bloodstream infections	Mashhad	Staphylococcus	NICU	Medium
Lahsaeizadeh	2008	2667	NA	Surgical Site Infection	Shiraz	NA	Surgery department	High
Ghorban Alizadegan	2008	3974	2	Respiratory Infection	Tehran	Staphylococcus	ICU	Medium
Hassanzadeh	2009	89	16	Urinary tract infection	Shiraz	Pseudomonas	ICU	High
Asl	2009	102	17	Pneumonia	Tehran	Staphylococcus	PICU	Medium
Mohammadimehr	2009	165	20	Pneumonia	Tehran	Klebsiella pneumoniae	NA	Medium
Amini	2009	691	27	Respiratory Infection	Tehran	Acinetobacter	ICU	Medium
Sohrabi	2009	23816	NA	Urinary tract infection	Shahrod	Escherichia coli	ICU	Medium
Darvishpour	2010	270	NA	NA	NA	Enterobacter	ICU	High
Aletayyeb	2010	1604	16	Pneumonia	Ahvaz	Klebsiella pneumoniae	Neonatal ward	Medium
Nadi	2011	353	4	Pneumonia	Hamadan	Klebsiella pneumoniae	ICU	Medium
Tabatabaei	2011	428	23	Urinary tract infection	Tehran	Escherichia coli	PICU	High
Amini	2011	691	NA	Pneumonia	Tehran	Acinetobacter	ICU	Medium
Ghorbani	2011	772	NA	Urinary tract infection	Ahvaz	Pseudomonas	ICU	Medium
Askarian	2011	4013	NA	Urinary tract infection	Shiraz	NA	NA	Medium
Larypoor	2011	21054	NA	Urinary tract infection	Qom	Escherichia coli	ICU	low
Masoumi Asl	2011	6616520	NA	Urinary tract infection	NA	Pseudomonas	NA	Medium
Mobaien	2012	353	NA	Urinary tract infection	Hamadan	Staphylococcus	ICU	High
Soltani	2012	464	NA	Bloodstream infections	Tehran	Staphylococcus	ICU	Medium
Alaghehbandan	2012	677	21	NA	Tehran	Pseudomonas	NA	High
Pourakbari	2012	1497	8	Respiratory Infection	Tehran	Staphylococcus	Children's section	low
Barak	2012	3254	27	Sepsis	Ardabil	Klebsiella pneumoniae	NICU	Medium
Riahin	2012	3400	NA	Surgical Site Infection	Qom	Staphylococcus	Surgery department	Medium

Table 1. Cntd

Askarian	2012	3450	NA	Bloodstream infections	Shiraz	NA	Surgery department	Medium
Assar	2012	9407	NA	Urinary tract infection	Ahvaz	Enterobacter	ICU	Medium
Zahraei	2012	1879356	NA	Urinary tract infection	NA	NA	ICU	low
Askarian	2013	4013	NA	Urinary tract infection	Shiraz	NA	NA	low
Abdoli Oskouie	2013	7744	4	Urinary tract infection	Tabriz	Staphylococcus	NICU	Medium
Akbari	2013	25776	22	Respiratory Infection	Orumieh	Escherichia coli	ICU	High
Masoumi Asl	2013	47380	NA	Urinary tract infection	NA	Escherichia coli	Burn unit	low
Hamedi	2014	811	NA	Urinary tract infection	Mashhad	Pseudomonas	PICU	low
Hoseini	2014	3129	10	Pneumonia	Tabriz	Staphylococcus	NICU	High
Behzadnia	2014	34556	NA	wound infection	Mazandaran	Pseudomonas	NA	Medium
Davoudi	2014	57122	8	wound infection	Mazandaran	Pseudomonas	Burn unit	low
Shakib	2015	750	2	NA	Sanandaj	Klebsiella pneumoniae	ICU	low
Basiri	2015	1000	13	Bloodstream infections	Hamadan	Escherichia coli	NICU	Medium
Shojaei	2015	12221	NA	Surgical Site Infection	Qom	Pseudomonas	ICU	low
Lavakhamseh	2015	32400	NA	Urinary tract infection	Sanandaj	Escherichia coli	Woman's ward	Medium
Salmanzadeh	2015	15779	NA	Surgical Site Infection	Ahvaz	Staphylococcus	ICU	low
Bijari	2015	36222	NA	Pneumonia	NA	Klebsiella pneumoniae	ICU	low
Tabatabaei	2015	16140	NA	Respiratory Infection	Zahedan	Acinetobacter	ICU	High
Lavakhamseh	2015	32400	NA	Urinary tract infection	Sanandaj	E. coli	Woman's ward	Medium
Darvishpoor	2016	1300	2	Surgical Site Infection	Torbat	NA	NA	low
Kazemian	2016	62601	NA	Urinary tract infection	Ardabil	Escherichia coli	ICU	High
Falahi	2017	35979	NA	Pneumonia	Mashhad	Acinetobacter	ICU	High

Discussion

This study was a comprehensive study on the prevalence of NIs in Iran using a systematic review and meta-analytic approach. The prevalence of NIs in Iran was found as 4.5% (95% CI: 3.5-5.7). Hospital infection rates range between 3.5% and 12% in developed countries and between 5.7% and 19.1% in developing countries (7), calling for the urgent need of better allocating resources and implementing a program for controlling infections (65). Differences in NIs rates among countries may not
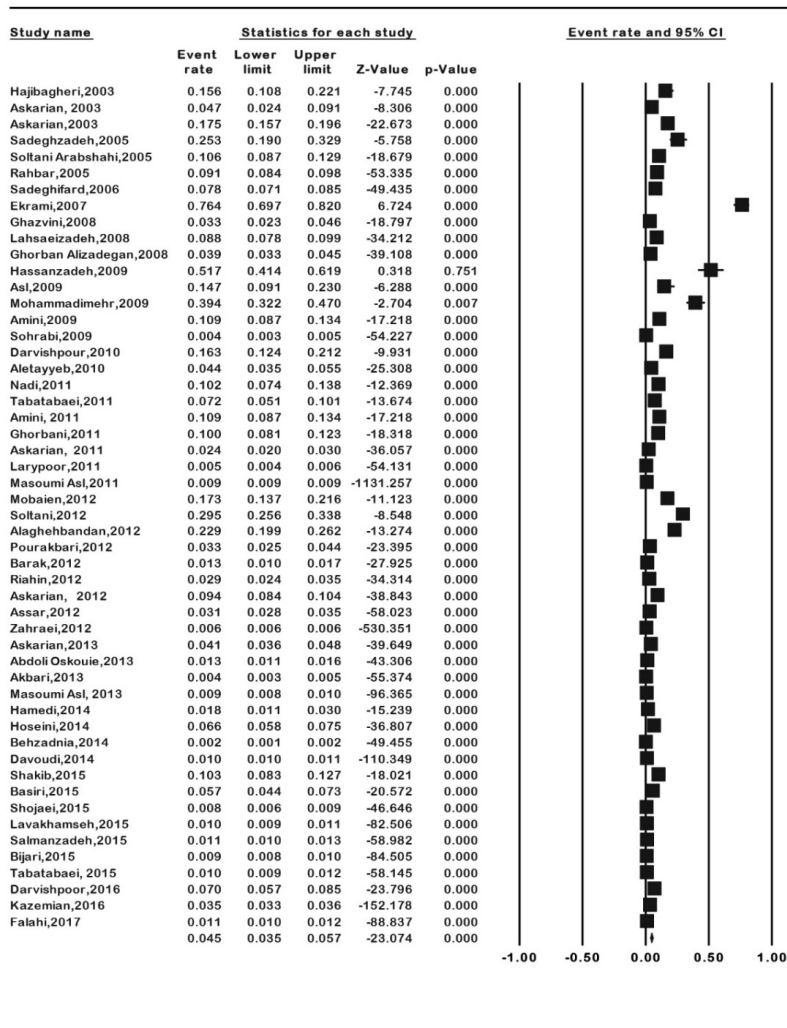

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
Hajibagheri,2003	0.156	0.108	0.221	-7.745	0.000
Askarian, 2003	0.047	0.024	0.091	-8.306	0.000
Askarian,2003	0.175	0.157	0.196	-22.673	0.000
Sadeghzadeh,2005	0.253	0.190	0.329	-5.758	0.000
Soltani Arabshahi,2005	0.106	0.087	0.129	-18.679	0.000
Rahbar,2005	0.091	0.084	0.098	-53.335	0.000
Sadeghifard,2006	0.078	0.071	0.085	-49.435	0.000
Ekrami,2007	0.764	0.697	0.820	6.724	0.000
Ghazvini,2008	0.033	0.023	0.046	-18.797	0.000
Lahsaeizadeh,2008	0.088	0.078	0.099	-34.212	0.000
Ghorban Alizadegan,2008	0.039	0.033	0.045	-39.108	0.000
Hassanzadeh,2009	0.517	0.414	0.619	0.318	0.751
Asl,2009	0.147	0.091	0.230	-6.288	0.000
Mohammadimehr,2009	0.394	0.322	0.470	-2.704	0.007
Amini,2009	0.109	0.087	0.134	-17.218	0.000
Sohrabi,2009	0.004	0.003	0.005	-54.227	0.000
Darvishpour,2010	0.163	0.124	0.212	-9.931	0.000
Aletayyeb,2010	0.044	0.035	0.055	-25.308	0.000
Nadi,2011	0.102	0.074	0.138	-12.369	0.000
Tabatabaei,2011	0.072	0.051	0.101	-13.674	0.000
Amini, 2011	0.109	0.087	0.134	-17.218	0.000
Ghorbani,2011	0.100	0.081	0.123	-18.318	0.000
Askarian, 2011	0.024	0.020	0.030	-36.057	0.000
Larypoor,2011	0.005	0.004	0.006	-54.131	0.000
Masoumi Asl,2011	0.009	0.009	0.009	-1131.257	0.000
Mobaien,2012	0.173	0.137	0.216	-11.123	0.000
Soltani,2012	0.295	0.256	0.338	-8.548	0.000
Alaghehbandan,2012	0.229	0.199	0.262	-13.274	0.000
Pourakbari,2012	0.033	0.025	0.044	-23.395	0.000
Barak,2012	0.013	0.010	0.017	-27.925	0.000
Riahin,2012	0.029	0.024	0.035	-34.314	0.000
Askarian, 2012	0.094	0.084	0.104	-38.843	0.000
Assar,2012	0.031	0.028	0.035	-58.023	0.000
Zahraei,2012	0.006	0.006	0.006	-530.351	0.000
Askarian,2013	0.041	0.036	0.048	-39.649	0.000
Abdoli Oskouie,2013	0.013	0.011	0.016	-43.306	0.000
Akbari,2013	0.004	0.003	0.005	-55.374	0.000
Masoumi Asl, 2013	0.009	0.008	0.010	-96.365	0.000
Hamedi,2014	0.018	0.011	0.030	-15.239	0.000
Hoseini,2014	0.066	0.058	0.075	-36.807	0.000
Behzadnia,2014	0.002	0.001	0.002	-49.455	0.000
Davoudi,2014	0.010	0.010	0.011	-110.349	0.000
Shakib,2015	0.103	0.083	0.127	-18.021	0.000
Basiri,2015	0.057	0.044	0.073	-20.572	0.000
Shojaei,2015	0.008	0.006	0.009	-46.646	0.000
Lavakhamseh,2015	0.010	0.009	0.011	-82.506	0.000
Salmanzadeh,2015	0.011	0.010	0.013	-58.982	0.000
Bijari,2015	0.009	0.008	0.010	-84.505	0.000
Tabatabaei, 2015	0.010	0.009	0.012	-58.145	0.000
Darvishpoor,2016	0.070	0.057	0.085	-23.796	0.000
Kazemian,2016	0.035	0.033	0.036	-152.178	0.000
Falahi,2017	0.011	0.010	0.012	-88.837	0.000
	0.045	0.035	0.057	-23.074	0.000

Fig. 2. The forest plot of the overall prevalence of nosocomial infections in Iran

Table 2. The results of sub-group analyses

Variables	No. studies	Prevalence% (95% CI)	I2 (%)	p	No. participants
Quality of studies					
High	14	7.2% (4-12.6)	99.54%	0.0001	148589
Medium	25	5.2% (2.9-9)	99.82%	0.0001	6762403
Low	13	2% (1.1-3.6)	99.75%	0.0001	2078988
Regional					
Center	13	7.1% (3.2-15)	99.43%	0.0001	46174
East	8	1.4 (0.9-2.2)	98.49%	0.0001	147639
North	2	0.4% (0.1-2.4)	99.42%	0.0001	91678
South	12	8.8% (4.8-15.7)	99.41%	0.0001	43629
West	13	5.7% (3.6-8.8)	99.34%	0.0001	117334
Several regional	4	1.5% (1.1-2.1)	99.85%	0.0001	8543526
Sample size					
≤1500	24	13.3% (9.6-18.2)	97.79%	0.0001	14339
>1500	28	17% (13-22)	99.84%	0.0001	8975641
Year of publication					
2000-2005	6	12.8% (8.8-18.2)	96.00%	0.0001	9265
2006-2011	19	7.6% (3.7-14.8)	99.78%	0.0001	6683934
2012-2017	27	2.4% (1.6-3.8)	99.82%	0.0001	2296781
Common infections					
Wound	4	4% (3-3.6)	99.76%	0.0001	92030
Bloodstream	5	9% (5.4-14.6)	98.33%	0.0001	12377
NA	3	15.8% (9.2-25.9)	94.99%	0.0001	1697
Pneumonia	9	7.1% (3-15.6)	99.50%	0.0001	78405
Respiratory	5	2.3% (0.8-6.6)	99.38%	0.0001	48078
Sepsis	1	1.3% (1-7)	-	-	3254
Surgical site	7	4.4% (1.7-10.9)	99.55%	0.0001	37660
Urinary tract	18	3.1% (2.3-4.2)	99.85%	0.0001	8716479
Common infection in hospital units					
Burn unit	2	1% (0.8-1.1)	82.49%	0.0001	104502
Children's section	1	3.3% (2.5-4.4)	-	-	1497
ICU	22	3.9% (2.3-6.5)	99.83%	0.0001	2146908
Others	10	7.1% (2.3-20.3)	99.80%	0.0001	6661756
Neonatal	2	6.4% (3.1-12.7)	97.19%	0.0001	8096
NICU	5	2.9% (1.3-6.3)	98.36%	0.0001	16098
PICU	3	5.9% (2-16.6)	94.39%	0.0001	1341
Surgery department	6	8.5% (5.8-12.4)	98.19%	0.0001	17382
Woman's ward	1	1(0.9-1.1)	-	-	32400
Common bacteria					
Klebsiella pneumonia	7	6.6% (2.1-19.6)	99.46%	0.0001	42508
Escherichia coli	10	2.2% (1.1-4.2)	99.67%	0.0001	220177
Staphylococci	11	5.4% (2.9-9.8)	99.29%	0.0001	43905
Pseudomonas	9	4.9% (2-11.3)	99.78%	0.0001	6722950
Acinetobacter	4	3.5% (1-10.8)	99.52%	0.0001	53501
Enterobacter	2	7.3% (1.3-31.4)	99.04%	0.0001	9677
Other infections	9	5.3% (1.5-16.9)	99.90%	0.0001	1897262
Gram bacteria					
Positive	10	5.1% (2.5-10.2)	99.23%	0.0001	37413
Negative	32	4% (2.8-5.7)	99.77%	0.0001	7048813
NA	10	5.6% (1.7-16.7)	99.92	0.0001	1903754

Table 3. Results of the meta-regression

Moderator	No studies	No. participants	Coefficient	Z-value	p
Year of publication	52	8,989,980	-0.06	-24.51	0.00
Sample size of studies	52	8,989,980	-0.00	-67.90	0.00
Average length of stay	23	113,249	0.02	9.23	0.00

only reflect a socio-economical feature of each country but also depend on criteria and diagnostic tests used to detect infections, as well as on the different reporting systems and their quality (66).

We found that bloodstream infections, surgical site infections, and pneumonia were the most common NIs observed (67). Hospital-acquired pneumonia is directly related to air conditioning systems. In many developing countries due to lack of proper facilities, the installed ventilation systems may increase pneumonia rate (68). Studies have shown that surgical infection rates vary between 10% and 20%, and are mainly due to *Staphylococcus au-*

reus (69). In cases of complications, wound healing is delayed, the possibility of further surgery increases, and patients have to be treated with antibiotics. This increases the length of hospital stay and the health-related expenditure (70).

In our study, most infections occurred in the surgical ward. A study carried out in America reported a 2-5% rate (71), while a meta-analysis of surgical infection rate estimated a pooled prevalence of 3.7% (72). Surgical infections are particularly challenging (73). Identifying patients who are prone to such infections could minimize the incidence of nosocomial infections and reduce their burden in
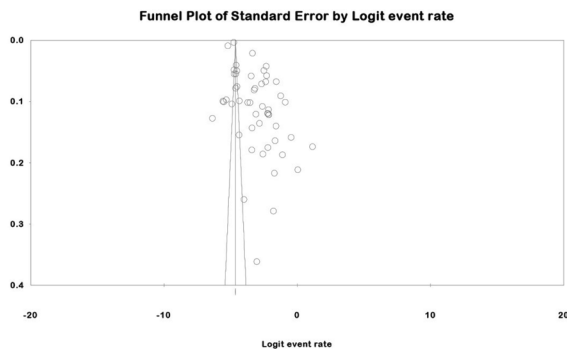
Funnel Plot of Standard Error by Logit event rate

Fig. 3. The Egger test for publication bias

terms of deaths (71).

Further, our study computed a higher effect-size of infections caused by Gram-positive bacteria. A study computed a prevalence of these infections of about 5% (3). Similar results were found by other scholars (74, 75). In the ICU, a significant amount of infections are due to Gram-positive bacteria, and this trend is increasing (76).

In the present study, a high rate of infections caused by Klebsiella pneumoniae (urinary tract , respiratory tract , and bloodstream infections) was found (77). This is particularly alarming in that the organism can become resistant to Carbapenem, which leads to increased use of Colistin, absorbing higher costs (78). Moreover, our study showed a strong correlation between length of stay in the hospital and hospital infections rate, in agreement with other studies (79-81). Based on geographical regions of Iran, the south of the country reported the highest incidence of NIs (8.8%), due to weather conditions, being warm and dry, with high air temperature and humidity. The prevalence of NIs can vary according to the specific month of the year (82).

Meta-regression analysis based on year of publication showed a significant decreasing trend over the years, which may be due to the recent implementation of health promotion programs (83). Despite some strengths (including the systematic approach, and the robustness of findings as proven by the meta-regressions and by the subgroup, cumulative, and sensitivity analyses), some limitations of this study should be properly recognized. First, the heterogeneity was significantly high. This could reflect methodological differences among studies. Moreover, insufficient information was available to stratify the prevalence by gender. Further, in some provinces of Iran, epidemiological studies related to the prevalence of NIs were missing and, therefore, urgently needed.

Conclusion

The prevalence of NIs in Iran was determined as 4.5%. Preventing and reducing hospital infections can significantly impact on reducing mortality and health-related costs tor. Implementing *ad hoc* programs, such as training healthcare staff in hospital, can play an important role in reducing spread of infections. The use of appropriate and advanced features for secure hospital environment is a major contribution to the decrease of NIs. Health policymakers in Iran can help reduce hospital infections by implementing appropriate policies, such as educational programs and improving the quality of surveillance system.

Conflict of Interests

The authors declare that they have no competing interests.

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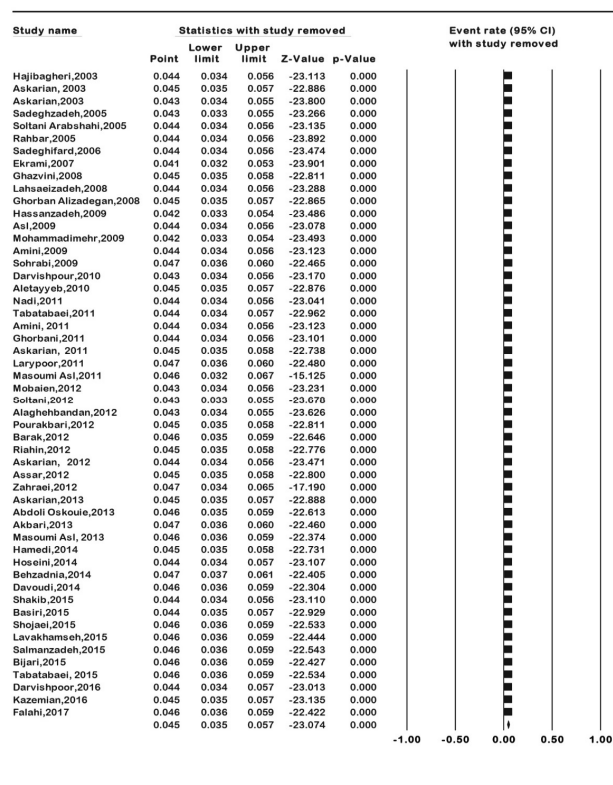
Appendix 1. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE: Prevalence of nosocomial infections in Iran: a systematic review and meta-analysis			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Background
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Background
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Methods
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methods
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Methods
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methods
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Methods
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Methods
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Methods
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Methods

Appendix 1. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Methods
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Methods
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Results
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Results
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Results
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Results
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Results
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Results
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Conclusion
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Funding

Appendix 2. Result of sensitivity analysis

Appendix 3. Result of cumulative meta-analysis based on year of publication

Study name	Cumulative statistics					Cumulative event rate (95% CI)
	Point	Lower limit	Upper limit	Z-Value	p-Value	
Hajibagheri,2003	0.156	0.108	0.221	-7.745	0.000	
Askarian, 2003	0.090	0.026	0.265	-3.508	0.000	
Askarian,2003	0.121	0.068	0.206	-6.088	0.000	
Sadeghzadeh,2005	0.150	0.098	0.224	-6.922	0.000	
Soltani Arabshahi,2005	0.139	0.095	0.199	-8.344	0.000	
Rahbar,2005	0.128	0.088	0.182	-8.985	0.000	
Sadeghifard,2006	0.119	0.087	0.160	-11.448	0.000	
Ekrami,2007	0.165	0.104	0.253	-5.935	0.000	
Ghazvini,2008	0.140	0.089	0.214	-6.900	0.000	
Lahsaeizadeh,2008	0.134	0.090	0.194	-8.271	0.000	
Ghorban Alizadegan,2008	0.120	0.081	0.175	-8.866	0.000	
Hassanzadeh,2009	0.139	0.093	0.201	-7.963	0.000	
Asl,2009	0.139	0.095	0.199	-8.276	0.000	
Mohammadimehr,2009	0.152	0.104	0.217	-7.729	0.000	
Amini,2009	0.148	0.103	0.208	-8.331	0.000	
Sohrabi,2009	0.121	0.074	0.191	-7.144	0.000	
Darvishpour,2010	0.123	0.077	0.191	-7.347	0.000	
Aletayyeb,2010	0.116	0.074	0.179	-7.904	0.000	
Nadi,2011	0.116	0.075	0.175	-8.233	0.000	
Tabatabaei,2011	0.113	0.074	0.169	-8.626	0.000	
Amini, 2011	0.113	0.075	0.166	-9.017	0.000	
Ghorbani,2011	0.112	0.076	0.163	-9.437	0.000	
Askarian, 2011	0.105	0.071	0.153	-9.853	0.000	
Larypoor,2011	0.093	0.060	0.142	-9.364	0.000	
Masoumi Asl,2011	0.086	0.045	0.157	-6.763	0.000	
Mobaien,2012	0.088	0.047	0.160	-6.766	0.000	
Soltani,2012	0.092	0.049	0.168	-6.569	0.000	
Alaghehbandan,2012	0.096	0.051	0.173	-6.456	0.000	
Pourakbari,2012	0.092	0.050	0.165	-6.727	0.000	
Barak,2012	0.087	0.047	0.154	-7.098	0.000	
Riahin,2012	0.084	0.046	0.147	-7.427	0.000	
Askarian, 2012	0.084	0.047	0.146	-7.564	0.000	
Assar,2012	0.082	0.047	0.138	-8.033	0.000	
Zahraei,2012	0.075	0.055	0.102	-14.682	0.000	
Askarian,2013	0.074	0.054	0.100	-14.970	0.000	
Abdoli Oskouie,2013	0.071	0.052	0.095	-15.537	0.000	
Akbari,2013	0.066	0.049	0.088	-16.280	0.000	
Masoumi Asl, 2013	0.062	0.046	0.083	-17.081	0.000	
Hamedi,2014	0.061	0.045	0.081	-17.496	0.000	
Hoseini,2014	0.061	0.045	0.081	-17.524	0.000	
Behzadnia,2014	0.056	0.042	0.074	-18.288	0.000	
Davoudi,2014	0.054	0.041	0.071	-19.132	0.000	
Shakib,2015	0.055	0.041	0.072	-19.121	0.000	
Basiri,2015	0.055	0.041	0.072	-19.295	0.000	
Shojaei,2015	0.052	0.040	0.068	-19.880	0.000	
Lavakhamseh,2015	0.050	0.039	0.066	-20.559	0.000	
Salmanzadeh,2015	0.049	0.038	0.063	-21.128	0.000	
Bijari,2015	0.047	0.036	0.061	-21.821	0.000	
Tabatabaei, 2015	0.046	0.035	0.059	-22.393	0.000	
Darvishpoor,2016	0.046	0.036	0.059	-22.444	0.000	
Kazemian,2016	0.046	0.036	0.059	-22.422	0.000	
Falahi,2017	0.045	0.035	0.057	-23.074	0.000	
	0.045	0.035	0.057	-23.074	0.000	

-1.00　-0.50　0.00　0.50　1.00