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Türk Hijyen ve Deneysel Biyoloji Dergisi

The investigation of nasal carriage rate of methicillin-resistant *Staphylococcus aureus* among Turkish healthcare workers, 1990-2019: meta-analysis

Türk sağlık çalışanlarında metisiline dirençli *Staphylococcus aureus*'un burun taşıyıcılığı oranının incelennesi, 1990-2019: meta-analiz

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ABSTRACT

Objective: Methicillin-resistant *Staphylococcus aureus* (MRSA) is among the most prevalent pathogens causing healthcare-associated infections. Healthcare workers may act as reservoirs for the spread of MRSA to patients and other healthcare workers. The purpose of this study was to determine the prevalence of nasal carriage rate of *S. aureus* in hospital staff in Turkey.

Methods: Meta-analysis by PRISMA guidelines was performed. We performed a systematic search of published studies in national and international databases from 1990 to 2019. Of the remaining 440 Articles, only 26 studies were included in this meta-analysis. The Cochrane Q statistic was calculated to assess the heterogeneity of results in studies. Heterogeneity among studies was evaluated using the I2 statistics. The effect size was estimated by reported with its 95% confidence interval.

Results: Based on the 26 selected articles, the pooled prevalence of *S. aureus* and MRSA was 24.0% [95% confidence interval (CI): 0,19-0,29] and 16.0% (95% CI: 0,12-0.21), respectively. Heterogeneity between studies (I^2 = 95,62, p=0.000 for *S. aureus* and I^2 = 81,10 p =0.000 for MRSA) was found, so a random-

ÖZET

Amaç: Metisiline dirençli *S. aureus (MRSA)*, sağlık hizmeti ile ilişkili enfeksiyonlara neden olan en yaygın patojenler arasındadır. Sağlık çalışanları, MRSA'nın hastalara ve diğer sağlık çalışanlarına yayılması için rezervuar görevi görebilir. Bu çalışmanın amacı, Türkiye'deki sağlık çalışanlarında *Staphylococcus aureus*'un nazal taşıyıcılık prevalansının belirlenmesidir.

Yöntem: Yapmış olduğumuz meta analiz PRISMA (Meta-analysis by Preferred Reporting Items for Systematic Reviews and Meta-Analyses) kurallarına uygun olarak gerçekleştirildi. 1990'dan 2019'a kadar ulusal ve uluslararası veritabanlarında yayımlanan çalışmaların sistematik araştırması yapılarak kayıt altına alındı. Yapılan araştırma sonucunda 440 makaleden sadece 26 araştırma kriterlerimize uyduğu için meta analiz çalışmamıza dahil edildi. Cochrane Q istatistiği, çalışmalarda sonuçların heterojenliğini değerlendirmek için hesaplandı. Çalışmalar arasında heterojenlik I2 istatistikleri kullanılarak değerlendirildi. Etki büyüklüğü %95 güven aralığı ile tahmin edildi.

Bulgular: Araştırmada seçilen 26 çalışmaya göre toplanan *S. aureus* ve MRSA prevalansı sırasıyla %24.0 [%95 güven aralığı (CI): 0.19-0.29] ve %16.0 (%95 CI: 0.12-0.21)

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effects model was used for the meta-analysis. This study is registered in the PROSPERO database (ID= CRD42018117306).

Conclusion: Hospital infections are a significant problem for our country as it is all over the World. Healthcare workers may act as reservoirs for the spread of MRSA to patients and other healthcare workers. The most critical step in preventing hospital infection from hospital staff is training in hospital infection and hygiene. Cost-effective health policies should be developed in Turkey for the control and Prevention of hospital infections and resistant microorganisms.

Key Words: Health-care workers, healthcare-associated infections, nosocomial infection methicillin-resistant, *Staphylococcus aureus*, nasal colonization

olarak tespit edilmiştir. Çalışmalar arasında heterojenite (*S. aureus* için I2 = 95.62, MRSA için p = 0.000 ve I2 = 81.10; p =0.000) bulunmasından dolayı araştırmada meta-analiz için rastgele etki modeli kullanılmıştır. Bu araştırma PROSPERO (The International Prospective Register of Systematic Reviews) veri tabanına (ID= CRD42018117306) protocol numarası ile kayıtlıdır.

Sonuç: Tüm dünyada olduğu gibi hastane enfeksiyonları ülkemiz için de önemli bir sorun arz etmektedir. Sağlık çalışanları, MRSA'nın hastalara ve diğer sağlık çalışanlarına yayılması için rezervuar görevi görebilir. Hastane personeli kaynaklı olan enfeksiyonların önlenmesinde en önemli adım, hastane enfeksiyonu ve hijyen konusunda verilecek eğitimlerdir. Hastane enfeksiyonlarının ve dirençli mikroorganizmaların kontrolü ve önlenmesi için Türkiye'de maliyeti de göz önüne alarak etkin sağlık politikaları geliştirilmelidir.

Anahtar Kelimeler: Sağlık çalışanları, sağlık çalaşanları ile ilişki enfeksiyon, metisiline dirençli nozokomiyal enfeksiyon, *Staphylococcus aureus*, nazal kolonizasyon

INTRODUCTION

S. aureus is an epidemiologically important pathogen. Despite antibiotic therapy, staphylococcal infections are common in hospitalized patients and have serious consequences (1). While staphylococci are present as normal flora in the skin and mucous membranes, it can cause serious infections such as skin, soft tissue, bone, and joint infections associated with catheter, infective endocarditis, bacteremia, and sepsis. After birth, *S. aureus* colonizes the belly, perineum, and the skin. In the following years, mainly, the nose is settled. In the newborn, the nasal carriage rate of up to 90% decreases with age, which varies between 10 and 50% in adults (1,2). Approximately 20% of healthy persons have persistent carriage, 60% have intermittent carriage, and 20% have no carriage. The prevalence of *S. aureus* nasal carriage varies according to the population studied and affected by many factors such as age, race, antibiotic use, hospitalization. *S. aureus* is a leading cause of both hospital-acquired and community-onset infections, and a steady increase in methicillin resistance was reported in many regions of the world. Methicillin-resistant *S. aureus* (MRSA) is one of the most important pathogens causing healthcare-associated infections (3). The nose is the primary ecological reservoir of *S. aureus* in humans. Nasal carriage of *S. aureus* is a significant risk factor for infections in various clinical settings. The biology of nasal colonization with *S. aureus* remains subtle. Host factors seem to play an essential role (4). Nosocomial

outbreaks caused by MRSA have become a severe health problem worldwide due to limited treatment options and the financial burden of infection control measures (5-7). The most important reservoir for the spread of MRSA are asymptomatic carriers (1,8). MRSA usually spreads through direct contact with the contaminated hands of healthcare workers, but nasal carriage among hospital staff has accounted for some nosocomial MRSA outbreaks (9,10). The purpose of this study was to determine the prevalence of nasal carriage rate of *S. aureus* in hospital staff in Turkey.

MATERIAL and METHOD

Search strategy and screening

Meta-analysis by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was performed (11). The literature search was carried out in October 2019. We performed a computerized search of published studies in national and international databases from 1990 to 2019. ULAKBİM (Ulakbim Turkish Medical Literature) and Turkish Medline (TürkMedline National Biomedical Periodicals) were used as national databases. As an international database, the literature was searched in PubMed, Embase, Scopus and Web of Science databases. We used the following terms during the search: *S. aureus* or *S. aureus* and methicillin-resistant *S. aureus* or MRSA and nasal carriage and Healthcare workers in combination with Turkey. Studies reporting the prevalence of MRSA in nasal passages of healthcare workers were evaluated. Three independent researchers made this evaluation. This analysis was restricted to studies published in English and Turkish language and only taken into consideration the work done in Turkey. The isolates identified as *S. aureus* were resistant to methicillin resistance, and susceptibility to antibiotics were determined according to the criteria of the Clinical and Laboratory Standards Institute (CLSI) by Kirby-Bauer disc diffusion method and polymerase chain reaction (PCR).

Data extraction and definitions

Within the scope of the PRISMA report, the exclusion criteria were determined at the first stage, and the literature review was carried out. In the next steps, the literature was re-examined with the exclusion criteria in mind; study data were collected and statistical analysis was performed. Studies had the following characteristics were excluded: non-human studies, studies published in languages other than English or Turkısh, duplicate and overlapping, using nonstandard methods, studies that did not report MRSA prevalence, congress abstracts, meta-analyses, systematic reviews and articles available only in abstract form. The following variables were extracted from included studies: author-name, study period; year of publication; where the study took place; study population; number of *S. aureus* and MRSA isolates; proportion or frequency of MRSA; source of isolates; and diagnostic methods. Working group data were obtained only from published and accepted articles in national and international well-known journals. Two investigators extracted data from all of the included studies independently. Three reviewers individually assessed the quality of the included studies. Inconsistencies between reviewers were discussed to obtain consensus.

Statistical analysis

In this study, the meta-analysis was done with the help of ProMeta 3 software. The Cochrane Q statistic was calculated to assess whether the results of the studies are heterogeneous. The heterogeneity between studies was assessed using I2 statistics. The effect size (ES) was reported to be 95% confidence interval (CI). The statistical heterogeneity between the studies was assessed by the I2 statistic (high heterogeneity if $I2 > 60\%$; $p > 0.10$) (10). In this study, $p < 0.05$ was considered statistically significant. To test the bias in the study, the random effect model was applied according to the heterogeneity (Egger's and Begg's test) found to calculate the pooled effect. Finally, the funnel plot was visually assessed to assess

possible bias.

Ethical approval and systematic review registration

The study was conducted in accordance with the approved (16.01.2019/ 28-1) by the Ethics Committee of the University of Suleyman Demirel. The design, purpose, sub-objectives of this research, which is carried out using the Meta-analysis method, and the stages involving the collection and analysis of the data are explained.

The protocol of the research is recorded in the "PROSPERO" database with record ID=CRD42018117306(https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=117306),which allows the recording of systematic compilation and meta-analyses around the world.

RESULTS

Study Characteristics

Overall, 2,276 studies were detected. 1,576 articles remained after the duplicates were removed. After the headings and abstracts were scanned, 460 articles were excluded because they were not relevant. The remaining 435 articles were analyzed in detail and only 26 articles were found suitable for this meta-analysis. The summary or full text of 5 articles that were compatible with our study could not be reached. The literature review of the study and the selection process of the article are summarized in Figure 1. The main characteristics of the selected studies are described in Table 1 (12-37).

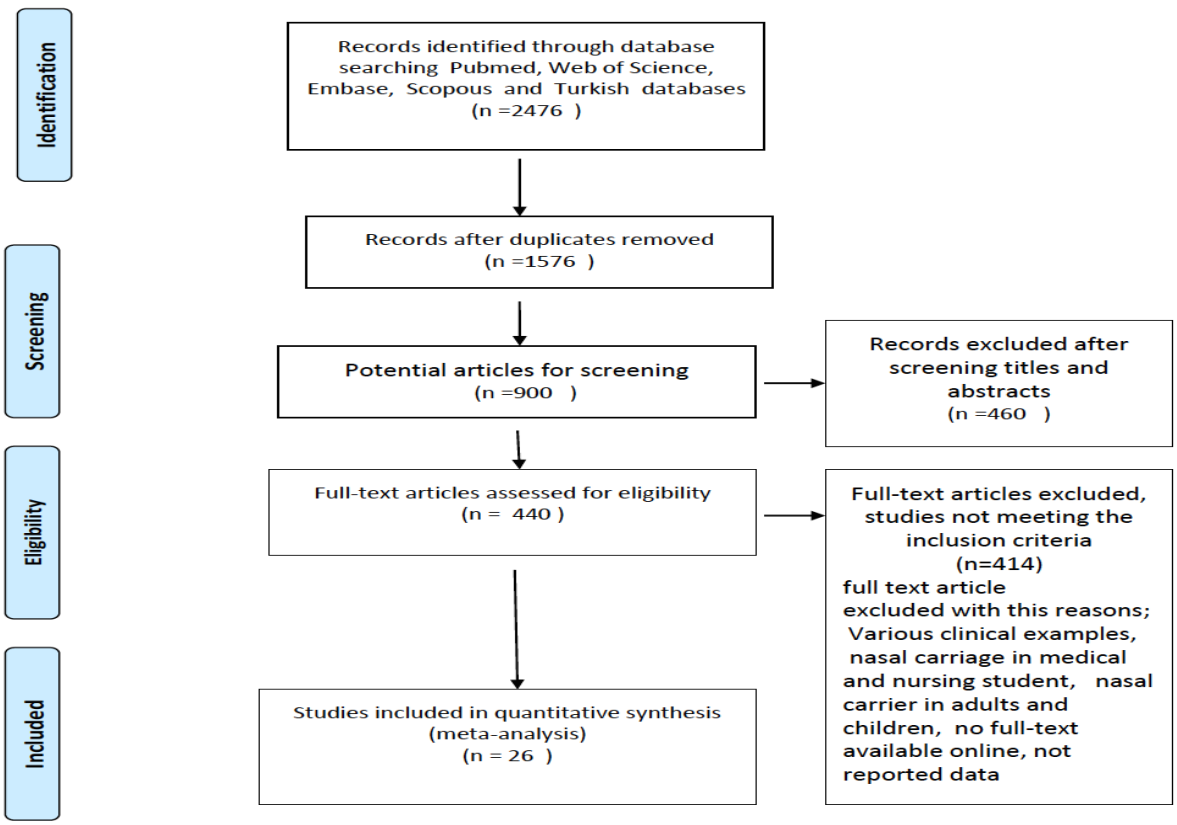

Figure 1. Summary of the literature search and study selection process of *Staphylococcus aureus* and MRSA in Turkish health workers

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

No	First author of the study	Year of publication	Time of study	Province	Nasal swab	*S. aureus*	MRSA	Detection method
1	Arabacı et al.[12]	2008	2007	Çanakkale	106	84	35	Disc diffusion
2	Oğuzkaya A.et al.[13]	2008	2008	Kayseri	136	18	1	Disc diffusion
3	Bozkurt et al.[14]	2007	2007	Van	326	68	4	Disc diffusion
4	Çelik et al.[15]	2005	2004	Elazığ	118	37	13	Disc diffusion
5	Çetinkol et al.[16]	2013	2012	Ordu	104	78	22	Disc diffusion
6	Demirdal et al.[17]	2006	2006	Afyon	189	59	9	Disc diffusion
7	Durmaz et al.[18]	1999	1999	Malatya	133	42	15	Disc diffusion
8	Dundar et al.[19]	1994	1994	Edirne	268	110	2	Disc diffusion
9	Erdenizmenli et al.[20]	2004	2004	İzmir	102	9	1	PCR[X]
10	Gül et al.[21]	2004	2002	Kahramanmaraş	217	23	5	Disc diffusion
11	Gündüz et al.[22]	2004	2004	Manisa	162	35	5	Disc diffusion
12	Hızel et al.[23]	2005	2005	Kırıkkale	219	34	5	Disc diffusion
13	Kökoglu et al.[24]	2003	2003	Diyarbakır	408	132	52	Disc diffusion
14	Kurtoğlu et al.[25]	2009	2009	Konya	310	27	3	Disc diffusion
15	Kurutepe et al.[26]	2005	2005	Manisa	483	176	28	Disc diffusion
16	Mert et al.[27]	1996	1996	İstanbul	300	100	9	Disc diffusion
17	Mutlu et al.[28]	2001	2001	Kocaeli	468	74	6	Disc diffusion
18	Naz et al.[29]	2006	2006	Eskişehir	500	60	9	Disc diffusion
19	Öncül et al.[30]	2002	2000	İstanbul	495	66	12	Disc diffusion
20	Özdemir et al.[31]	2009	2005	Kars	191	29	1	Disc diffusion
21	Uluğ et al.[32]	2012	2012	Eskişehir	81	21	9	Disc diffusion
22	Usluer et al.[33]	1997	1997	Eskişehir	321	41	10	Disc diffusion
23	Yağmur et al.[34]	2014	2009	Kayseri	203	41	2	Disc diffusion
24	Yazgı et al[35].	2003	2003	Erzurum	262	72	7	Disc diffusion
25	Yetkin et al.[36]	2006	2005	Malatya	139	47	2	Disc diffusion
26	Kocazeybek et al.[37]	2003	2003	İstanbul	400	45	6	Disc diffusion

X= polymerase chain reaction

The prevalence of *Staphylococcus aureus* and MRSA

Heterogeneity between studies (I^2 = 95,62, p=0.000 for *S. aureus* and I^2 = 81,10 p=0.000 for MRSA) were found, so a random-effects model was used for the meta-analysis. Based on the 26 selected articles, the pooled prevalence of *S. aureus* and MRSA was 24.0% (95% confidence interval (CI): 0,19-0,29) and 16.0% (95% CI: 0,12-0.22), respectively, as shown in Figure 2.

Statistical analysis

The funnel plot graph was used to evaluate the publication bias in this meta-analysis. When the Funnel Plot graph is evaluated, it is observed that the majority of the work included in the meta-analysis is distributed symmetrically, with the upper part and close to the combined effect size. The forest plots for the prevalence rate of MRSA does not show a potential publication bias. These data were confirmed by Egger's test (intercept -3.57, t= -4.37; p=0.00); and Begg's test (Z value for Kendall's tau: -2.27; p= 0.023) (Figure 2). However, the asymmetric shape of the funnel plot shows some evidence of publication bias among the evaluated studies (Figure 3).

DISCUSSION

Staphylococci continue to be major infectious agents since 1881 and cause many different clinical manifestations (3,4). *S. aureus* can cause acquired infections both in the community and in the hospital. The increase in methicillin resistance in recent years is a serious problem in hospital-acquired infections.

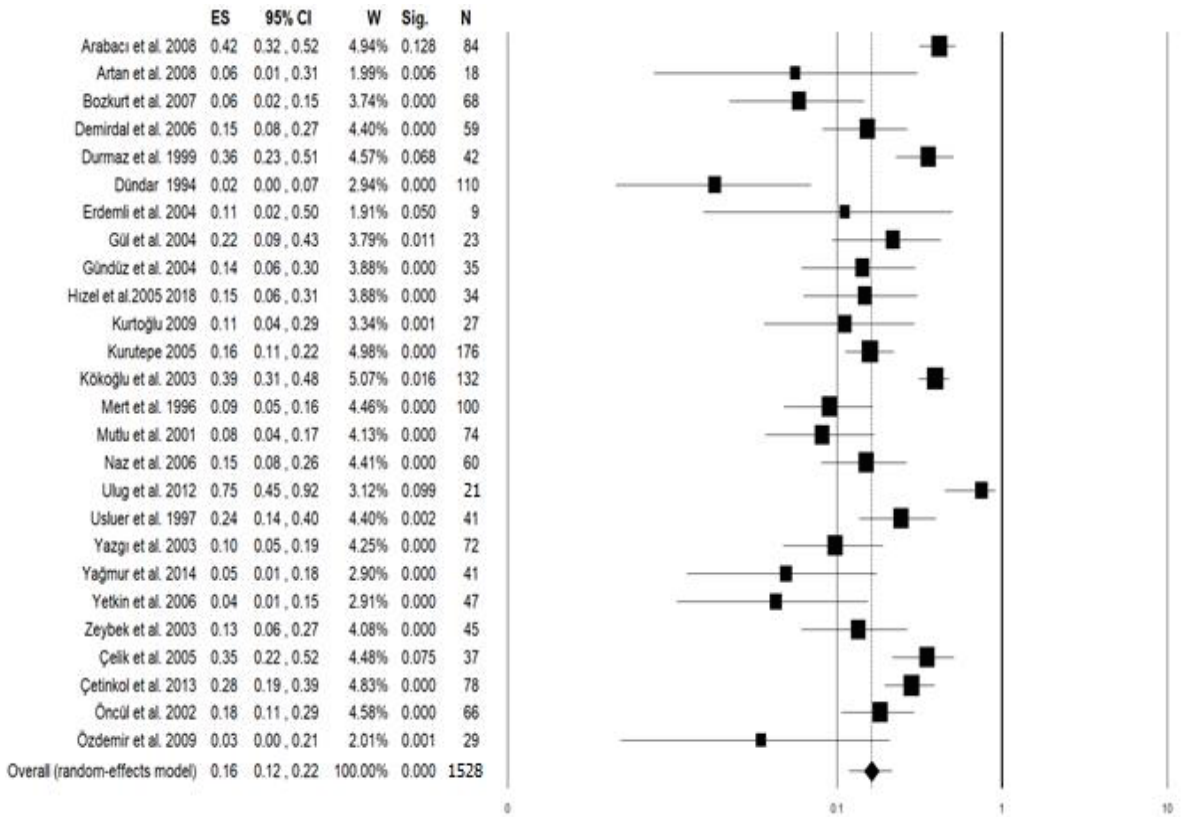

Figure 2. Meta-analysis diagram showing the impact of research

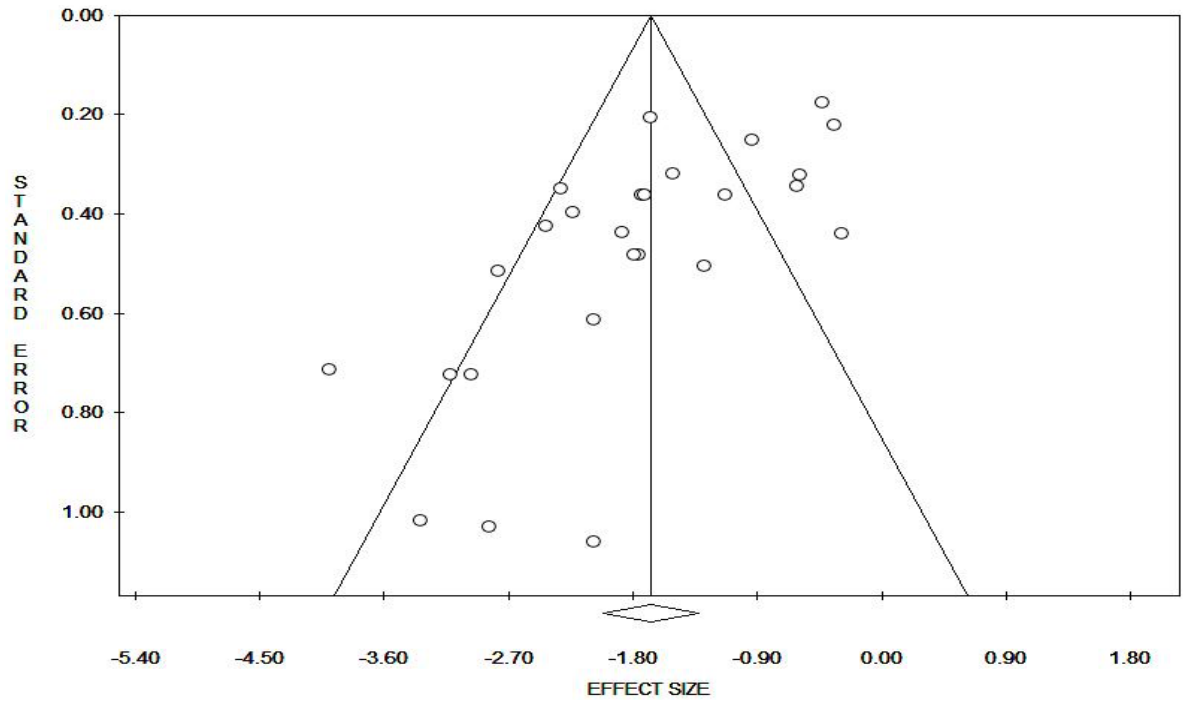

Figure 3. Funnel plot graph

S. aureus is an important cause of community- and hospital-acquired infections. Infections caused by MRSA are increasingly reported from many countries worldwide and Turkey (5,6). In our country, approximately 30-38% of nosocomial infections are associated with MRSA (6).

Following MRSA entry into a hospital, eradication is challenging. The main reservoir in hospitals is patients colonized or infected with MRSA (2,4). Nasal colonization, number of invasive procedures, contact frequency with the patient, hospitalization for three weeks or longer, and occupational intensity of the health personnel are the most important risk factors for nosocomial hospital infections (2,4,5). *S. aureus*, infectious by airborne and nasal carriage, is one of the most important causes of nosocomial infections and causes nosocomial epidemics (2,4,7). *S. aureus* carriage in hospital personnel is usually nasal carriage. Staphylococci located in the nose are colonized by patients through their hands and infection can lead to life-threatening infections if there is predisposition factors (2). The nasal carriage of *S. aureus* is problematic because it can lead to outbreaks, multiple resistance, and high cost of treatment (2,7). The most important step in the control of hospital epidemics is the detection of nasal staphylococcal carriage in hospital personnel (2). The current study is the first systematic review and meta-analysis regarding the prevalence of *S. aureus* and MRSA among Turkish hospital staff based on the 26 selected articles (11-36). The pooled prevalence of *S. aureus* and MRSA was 24.0% [95% confidence interval (CI): 0,19-0,29] and 16.0% (95% CI: 0,12-0.21), respectively, as shown in (Table 2). Dulon et al. showed that the prevalence of nasal carriage of *S. aureus* among Healthcare workers ranged from 0.2% to 15% in Europe and the United States (1). When evaluated according to the countries, these rates change as follows; in USA, Johnston et al. (8) and Schwarzkopf et al. (9) showed that nasal carriage

rates of *S. aureus* and MRSA among Healthcare workers was 28.0% -2.0 % and 35.7% -15.0% respectively. Orsi G.et al. (10) reported that the prevalence of nasal carriage of *S. aureus* and MRSA among Italian healthcare workers was 19% and 1.5%, respectively. Boisseau et al. (38) showed that the prevalence of nasal carriage of *S. aureus* and MRSA among French healthcare workers was 34.2% and 2.4%, respectively. The meta-analysis study conducted in Iran showed that the prevalence of *S. aureus* and MRSA was 22.7% and 32.8% respectively (39). A study conducted in Nepal also found that 15.7% of the 204 health workers were nasal carriers of *S. aureus* and 21.9% were MRSA carriers (40). In a study conducted in Egypt, the prevalence of nasal carriage of *S. aureus* in health care workers was 22.9%, and 58.8% of these rates were MRSA (41). In Ethiopian health care workers, this rate was 28.8% and 44.1% respectively (42). When we compare our work with the work done in various countries of the world, MRSA carriage was higher among healthcare workers in Turkey than in Europe and the United States. When we compare our work with the work done in Asian and African countries, the results are lower than the Asian countries and two times lower than the African countries. The common characteristics of the countries that are most successful in MRSA control should not compromise on the existence of active surveillance programs and compliance with the isolation measures associated with the transmission route. Northern European countries such as Denmark, Finland, and the Netherlands are the best examples of this group. The success of MRSA control in these countries has been shown to be possible not only by the use of controlled antibiotics but also by implementing intensive infection control measures (43). Especially in the underdeveloped and developing countries, there are some obstacles related to MRSA control due to the high number of patients per staff and the heavy workload (44).

In our country, there have been significant developments in recent years in different areas in terms of control of community- based and nosocomial infections. The surveillance system established in line with the goals of the "Health Transformation Program" provided the opportunity to compare the data of domestic and foreign hospitals. Following the launch of the Certification Programs and the Publication of National Standards, the National Hand Hygiene Campaign and MRSA Control Studies were conducted in 2009. In this context, the control and prevention of hospital infections, resistant microorganisms are carried out effectively and continuously in line with international standards (45).

As a conclusion we hope to see the impact of these regulations on new MRSA carriage research to be held in Turkey. Hospital infections are an essential problem for our country as it is all over the world. Nasal *S. aureus* carriers are highly responsible for hospital-acquired staphylococcal infections. Nosocomial infections are of great importance because of increased treatment costs, mortality rates and the ability of agents to resist antibiotics. Taking all of these into account, although the determination of carrier states with certain periods is a controversial issue in terms of cost-effectiveness, the treatment of these people is vital in preventing hospital infections. The most critical step in avoiding hospital infection from hospital staff is training in hospital infection and hygiene. Training of healthcare personnel with MRSA carriers, recruitment of appropriate hand washing habits, and assignment to departments requiring fewer patient contacts is a short-term solution to infection. The solution in the long term is to implement active surveillance programs and to observe the isolation measures related to the transmission route adequately.

The rate of community-acquired MRSA is considerably lower than that of hospital-acquired MRSA. Healthcare workers may act as reservoirs for the spread of MRSA to patients and other healthcare workers. The most crucial step in preventing hospital infection from hospital staff is training in hospital infection and hygiene. Cost-effective health policies should be developed in Turkey for the control and prevention of hospital infections and resistant microorganisms.

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