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Research Article

Nasopharyngeal Carriage of *Staphylococcus aureus* and its Antimicrobial Resistance Pattern among Healthy People: Systematic Review and Meta-Analysis

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ABSTRACT

Background: *Staphylococcus aureus* nasopharyngeal colonization is common in all age group and genetic evidences have supported the causal pathway between *S. aureus* carriage and invasive disease. Nasopharyngeal colonization with *S. aureus* is dependent on a number of factors being responsible for the gain and loss of carriage. Thus, this study aimed to review global nasopharyngeal carriage of *S. aureus* and its antimicrobial resistance pattern among healthy people.

Methods: Electronic data bases searches of literature was conducted on PubMed, Google Scholar, Cochrane library, Embase, Hinari, Scopus, and the Directory of Open Access Journals (DOAJ). Additionally the reference lists of all identified articles were scrutinized for potentially eligible studies. Only studies published in English from January 2000 to July 2020 were considered.

Results: Globally, the estimated pooled prevalence of nasopharyngeal carriage of *S. aureus* using the random effects model was 22%. The highest rate of nasopharyngeal carriage of *S. aureus* observed in Europe 25%, followed by studies in Asia and Africa which was 22% and 21%, respectively. On the other hand, the highest nasopharyngeal carriage of *S. aureus* was observed in the children with age range of 6-15 years that accounted 25%. The estimated pooled global nasopharyngeal carriage of methicillin resistant *S. aureus* (MERSA) was 13%, while the nasopharyngeal carriage of methicillin sensitive *S. aureus* (MSSA) was 81%.

Conclusion: The present study showed that there is a high rate of nasopharyngeal carriage of *S. aureus* and MERSA among healthy people.

Keywords: Carriage; Colonization; MERSA; Multidrug resistance

ABBREVIATIONS

MRSA: Methicillin Resistant *Staphylococcus Aureus*; MSSA: Methicillin Sensitive *Staphylococcus Aureus*; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

BACKGROUND

Staphylococcus aureus nasopharyngeal colonization is common in all age group despite a difference in different age groups and genetic evidences have supported the causal pathway between *S. aureus* carriage and invasive disease [1]. Nasopharyngeal colonization with *S. aureus* is dependent on a number of factors being responsible for the gain and loss of carriage [2]. It is one of an identified risk factor for *S. aureus* invasive disease [3].

The prevalence of nasopharyngeal carriage of *S. aureus* multidrug resistant strains is growing worldwide, including methicillin resistant *S. aureus* (MRSA) [4,5]. Its invasive disease pose threat to public health [6]. Multidrug-resistant *S. aureus* strains, especially MRSA are responsible for a greater number of nosocomial infections which are tough to combat in humans [7]. Previously, MRSA was recognized as a nosocomial pathogen [8]. However, several studies have recently reported MRSA nasopharyngeal colonization in asymptomatic people, placing them as potential vectors of MRSA dissemination in the community [9].

Risk of consequent infection in a person colonized with *S. aureus* as well as MRSA upsurges with time and remains insistently increased [10]. *S. aureus* is a human pathogen that causes problems ranging from mild skin and soft tissue infections to severe systemic infections like sepsis and necrotizing pneumonia.

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Various range of nasopharyngeal carriage of *S. aureus* among healthy people reported in different countries. Due to a wide variability between results from different countries and different studies regarding rate of nasopharyngeal carriage of *S. aureus*, particularly MRSA, a comprehensive understanding of prevalence of nasopharyngeal carriage of *S. aureus* and its antimicrobial resistance pattern is highly required. This will help to predict people with high risk of developing *S. aureus* invasive disease. Thus, this study aimed to review global nasopharyngeal carriage of *S. aureus* and its antimicrobial resistance pattern among healthy people.

MATERIALS AND METHODS

Study design

This study was a systematic review and meta-analysis of global nasopharyngeal colonization of *S. aureus* and its antimicrobial resistance. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were employed for conducting this meta-analysis [11].

Data sources and search strategy

The literature search was conducted from July 1-11/2020. We systematically searched PubMed, Google Scholar, Cochrane library, Embase, Hinari, Scopus, and the Directory of Open Access Journals (DOAJ) databases for articles published from 1 January 2000 to 11 July 2020 2017. Additionally we also simultaneously searched the reference lists of all identified articles for potentially eligible studies. During literature search, terms relevant to nasopharyngeal carriage *S. aureus*, antimicrobial susceptibility, and MRSA were used (i.e., "nasopharyngeal colonization, nasopharyngeal carriage, nasal colonization, nasal carriage, antimicrobial resistance, Methicillin Resistant *Staphylococcus aureus* (MRSA), *Staphylococcus aureus*, *S. aureus*, America, Africa, Asia, Europe and Australia". All identified keywords and mesh terms were combined using the "OR" operator and "AND" operator for searching literatures. Only studies published in English from January 2000 to July 2020 were included in the study.

Eligibility criteria

Inclusion criteria: In this meta-analysis, we included all studies that were conducted on nasopharyngeal carriage of *S. aureus* worldwide. Only articles published in English were included. Regarding *S. aureus* identification, studies that at least conducted cultural isolation and identification and other highly standardized techniques (ELISA, PCR, and other molecular techniques) were included. Observational studies except case study and case series, conducted on human originated nasopharyngeal samples were included in the study. Studies that conducted nasopharyngeal carriage among apparently healthy people were included in this study.

Exclusion criteria: Studies that used samples other than human origin and samples other than nasopharyngeal swab were excluded. In addition, studies that didn't describe the standard microbial isolation and identification techniques and studies with no full information to calculate the prevalence *S. aureus* were excluded. Studies that conducted nasopharyngeal carriage among unhealthy people were excluded.

Outcome of interest

The major outcomes of interest were the prevalence of *S. aureus* in the nasopharynex of healthy people and its antimicrobial resistance pattern.

Quality assessment and critical appraisal

Studies selected for inclusion were assessed for methodological quality by two team independent reviewers. In this meta-analysis, the qualities of each included studies were assessed by using a critical appraisal tool in systematic reviews for prevalence study; condition, context, and population (CoCoPop) [12,13]. The employed methods for isolation and identification of *S. aureus* were assessed based on eligibility criteria approved for inclusion of potentially eligible studies. Disagreements were resolved by consensus.

Data extraction

Data were extracted by two teams of the investigator using a standardized data extraction form. Data from appropriate studies were pull out independently by teams of investigators and potted into an excel spreadsheet. Then the extracted data were merged for systematic analysis. The main outcomes extracted from each study were: the name of the author, publication year, study area, study population, total sample size, number of *S. aureus* isolates, drug resistance pattern, study design, and methods of identification of *S. aureus*. Additional findings extracted were participant's demographic characteristics. Disagreements were discussed with other reviewers and subsequently resolved via consensus.

Data analysis and synthesis

The extracted data were analyzed using R software version 3.6.1 with user-contributed commands for meta-analyses: metaprop, metan, metainf, metabias, and metareg [11]. A random effect model was used to estimate the overall pooled prevalence of *S. aureus* and antimicrobial resistance pattern and this model was emphasized to due to heterogeneity between studies expected [14,15].

Risk of bias and sensitivity analysis

Evidence for statistical heterogeneity of the results was assessed using the Cochrane Qx2 test and I2 statistic. A significance level of $p<0.10$ and $I2>50\%$ was interpreted as evidence of heterogeneity [16]. A potential source of heterogeneity was investigated by subgroup analysis and meta-regression analysis [17]. Where statistical pooling was not possible, the findings were presented in a narrative form including tables and figures to aid in data presentation where appropriate.

Sensitivity analyses were conducted to weigh up the relative influence of each individual study on the pooled effect size using a user-written function, metainf. The presence of publication bias was assessed informally by visual inspection of funnel plots [18].

Additional analysis

Additional analysis conducted on associated demographic characteristics for nasopharyngeal colonization of *S. aureus* was conducted.

RESULTS

Selection and identification of studies

A total of 1428 studies were identified through an electronic database search. Of these studies, 469 were excluded after reviewing their title and abstracts. About 332 duplicates articles were excluded. The other 276 articles were disregarded because they did not directly relate to the topic of interest i.e., not nasopharyngeal colonization of *S. aureus*. After methodological quality assessment, 562 articles were excluded with reason. Finally, 60 articles were eligible for systematic review and meta-analysis (Figure 1).

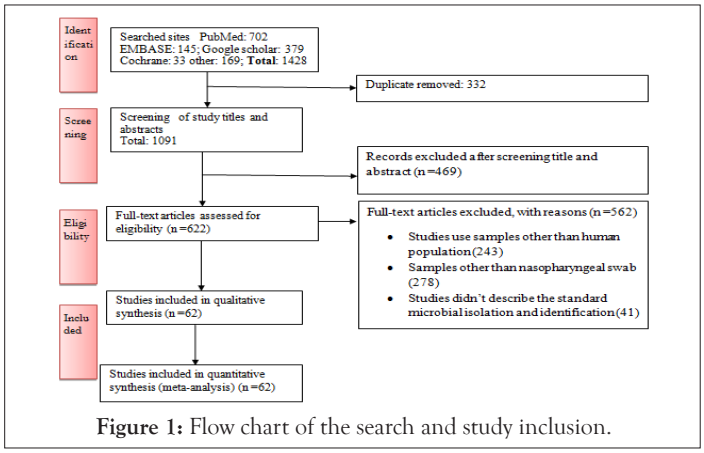

Figure 1: Flow chart of the search and study inclusion.

Characteristics of included studies

The studies were conducted from 2000 to 2020 in different countries in the world. Among 60 studies, 9 were conducted in America, 27 were in Europe, 10 were in Asia, 4 were in Australia and the other 10 studies were in Africa [19-73]. All of them were articles published in English. In addition, all studies enrolled in this meta-analysis conducted on apparently healthy individuals. In the included studies a total of 52, 544 participants were assessed for nasopharyngeal carriage of *S. aureus* and the total events of nasopharyngeal carriage of *S. aureus* were 10, 789. The highest rate of nasopharyngeal carriage of *S. aureus* reported by study conducted in Saud Arabia (89%) followed by study conducted in Belgium (86%) [41,51]. On the other hand the highest MERSA was reported by study conducted in German (54%) [50].

Nasal colonization of *S. aureus*

Globally, the estimated pooled prevalence of nasopharyngeal carriage of *S. aureus* using the random effects model was 22% [95% CI 18%-26%] with significant heterogeneity between studies (I2=99%, p=0) (Figure 2).

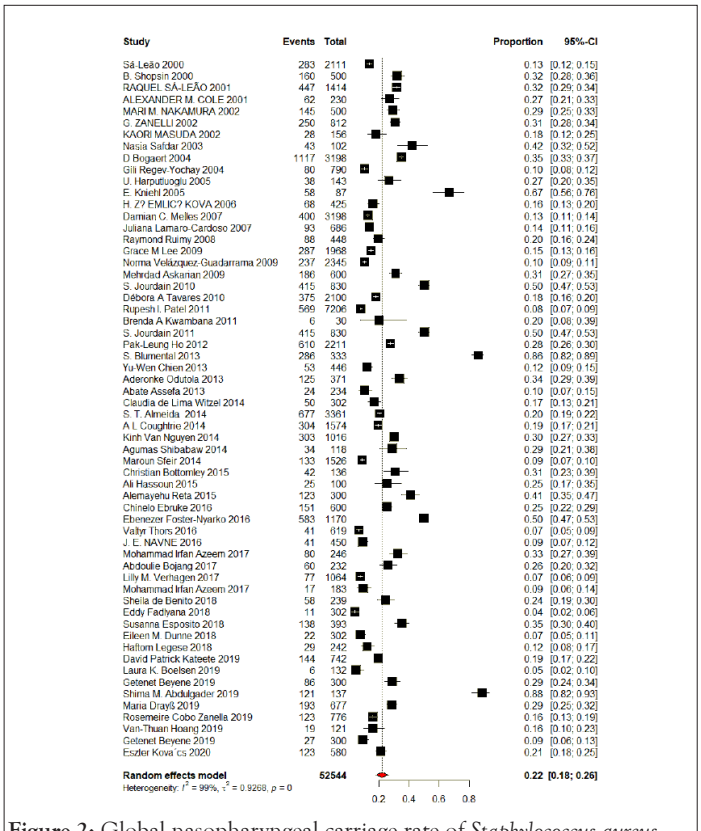

Figure 2: Global nasopharyngeal carriage rate of *Staphylococcus aureus*..

To assess the potential heterogeneity between studies, subgroup analysis by continent of the countries was conducted. Of the 62 studies, the highest rate of nasopharyngeal carriage of *S. aureus* observed in Europe 25% [95% CI 19%-32%], I2=99%, p=0], followed by studies in Asia and Africa which was 22%, and 21%, respectively (Table 1). The least nasopharyngeal carriage of *S. aureus* observed in America that accounted 19%.

Table 1: Nasopharyngeal carriage of *S. aureus* across the world.

Categories		Rate of nasopharyngeal carriage of *S. aureus*	95% CI
Age	0-12 months	16%	7%-23%
	1-5 years	22%	11%-40%
	6-15 years	25%	17%-36%
	>15 years	20%	16%-24%
Continents	Africa	21%	16%-28%
	America	20%	16%-25%
	Asia	22%	10%-40%
	Australia	14%	6%-28%
	Europe	25%	18%-32%

In this review we conducted subgroup analysis by year of publication categorizing in to five consecutives range of publication year. The highest rate of nasopharyngeal carriage of *S. aureus* seen in studies published from 2000-2005 which was 28% (95 CI: 21%-37%, I2=98%, p<0.01). The least rate of nasopharyngeal carriage of *S. aureus* demonstrated in the year range of 2016-2020 which accounted 18% (95 CI: 12%-26%, I2=99%, p<0.01) (Figure 3).

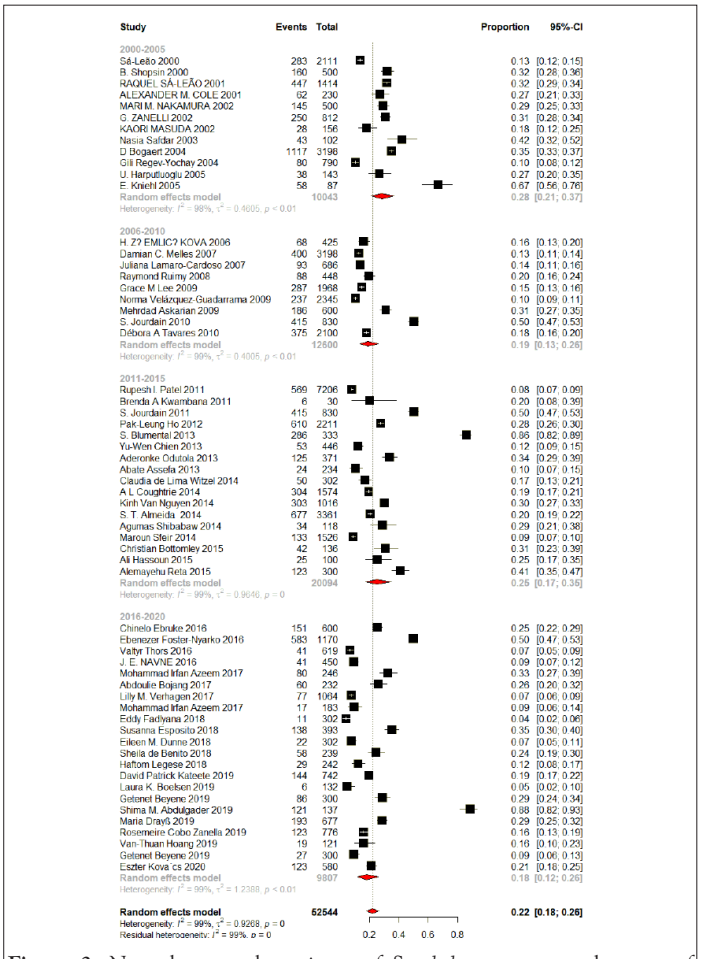

Figure 3: Nasopharyngeal carriages of *Staphylococcus aureus* by year of publication.

According to the report of 18 studies, nasopharyngeal carriage of *S. aureus* in pediatrics children with the age group of 01-12 months was 16% (95 CI:7%-33%). The highest nasopharyngeal carriage of *S. aureus* was observed in the children with age range of 6-15 years that accounted 25% (95 CI: 17%-36%, p<0.01).

Antimicrobial resistance patterns of *S. aureus*

According to the report of 24 included studies, from a total of 4545 *S. aureus* isolates 532 isolates were MERSA. This made the estimated rate of nasopharyngeal carriage of methicillin resistant *S. aureus* (MERSA) was 13% [95 CI:6-27%, I2=99%, p<0.01) while the nasopharyngeal carriage of methicillin sensitive *S. aureus* (MSSA) was 81% (95% CI: 62%-92%, I2=99%, p<0.01). Methicillin resistant *S. aureus* (MERSA) found to be increasing in the last 15 years. The highest nasopharyngeal carriage of MERSA observed in the last five years i.e., 2016-2020, which accounted 24% (95 CI:13%-41%, I2=98, p<0.01) (Figure 4).

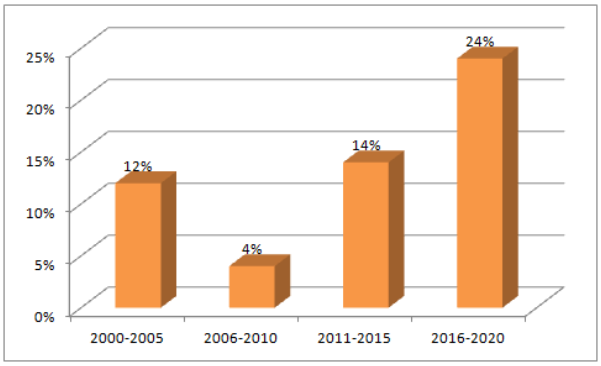

Figure 4: Nasopharyngeal carriage of MERSA in every consecutive five years ranges.

The subgroup analysis by the continent of the included studies, the highest rate of MRSA observed in Africa 31% (95 CI:19478%, I2=84%, p<0.01), followed by Asia 13% (95 CI:5%-30%, I2=96%, p<0.01). The prevalence of nasopharyngeal carriage of MERSA in America and Europe was 8% each. Antimicrobial resistance pattern of *S. aureus* isolated from nasopharynex of healthy people were listed (Table 2). The highest drug resistance was observed against penicillin (88%; 95 CI:83%-92%) followed by erythromycin (25%; 95 CI:14%-41%). Nasopharyngeal carriage of vancomycin resistant *S. aureus* was about 0.4% (95 CI:0.1%-2%, I2=94%, p<0.01). Globally, the antimicrobial resistance rate of *S. aureus* isolated from nasopharynex of healthy people against ciprofloxacin, kanamycin, tobramycin, and gentamycin was 6%, 2%, 13%, and 7%, respectively.

Table 2: Antimicrobial resistance of *S. aureus* Isolated from the nasopharynex of healthy people.

Antimicrobials	Number of studies	Resistance of *S. aureus*	95% CI
MERSA	24	13%	6%-25%
Penicillin	24	88%	83%-92%
Oxacillin	24	2%	1%-9%
Erythromycin	24	25%	14%-41%
Clindamycin	24	12%	5%-23%
Tetracycline	24	17%	6%-43%
Rifampicin	8	2%	1%-25%
Ciprofloxacin	5	6%	2%-17%
Ceftriaxone	5	7%	4%-14%
Trimethoprim-sulphamethoxazole	8	16%	4%-44%
Gentamycin	11	7%	2%-29%
Kanamycin	5	13%	2%-53%
Tobramycin	5	2%	1%-31%
Chloramphenicol	8	19%	5%-49%
Vancomycin	8	0.90%	0.1%-2%

Additional analysis

Antimicrobial resistance of *S. aureus* isolated from nasopharynex of healthy people showed that about 31% (95 CI:16-49%, I2=84%, p<0.01) of healthy people were carrier of multidrug resistant *S. aureus* in their nasopharynex. Multidrug resistance *S. aureus* was found to be increasing in the last 20 years. Subgroup analysis of by every consecutive five years ranges indicated that prevalence of nasopharyngeal carriage of multidrug resistant *S. aureus* was 19% in the year range of 2000-2005, 26% in the year range of 2006-2010, 37% in the year range of 2011-2015 and 43% in the year range of 2016-2020.

DISCUSSION

Summary of evidence

This systematic review is designed to synthesize published studies to provide recent point prevalence of nasopharyngeal carriage of *S. aureus* and its antimicrobial resistance in the last 20 years among healthy people of the world. A comprehensive understanding of nasopharyngeal carriage of *S. aureus* has become an important concept since the nasopharyngeal niche has been recognized as a reservoir for major pathogens and antibiotic resistance. The review found that nasopharyngeal carriage of *S. aureus* was frequent all over the world.

In the present study, we demonstrated that global nasopharyngeal carriage of *S. aureus* was about 22%. The highest carriage was observed in children with age ranges of 6-15 years (25%). On the other hand, the lowest nasopharyngeal carriage of *S. aureus* observed in individual aged greater than 15 years.

High rate of MERSA was observed over the last 15 years. Where the highest carriage of MERSA documented in the year range of 2016-2020 (24%) This is one of cause of concerns for public health. Because the appearance and possible increase in the prevalence of MRSA isolates in the healthy people will be evidence for subsequent development of invasive staphylococcal disease and antimicrobial resistance. MERSA is big concern for developing countries where there is misuse of antimicrobials. The finding of this study also showed high rate of nasopharyngeal carriage of MERSA in Africa (31%) followed by Asia (13%). The emergence of MRSA strains outside hospitals among healthy people of the community indicated that the spread of MRSA from large hospitals to the community and/or due to an increased tendency in home therapy with early discharge of MRSA carriers may amplify this trend and contribute to the spread of MRSA from hospitals to the community at large.

In the present study, vancomycin resistant *S. aureus* has been observed in about 0.4%. This could be due to wide spread use of vancomycin as a treatment of MERSA. This will pose a great challenge in the management of multidrug resistance *S. aureus*. The highest resistance was observed against penicillin (88%). Penicillin resistant *S. aureus* has long been described in the community. The proportion of *S. aureus* resistant to penicillin in combination with

erythromycin was much higher in the children less than 15 years. This is probably due to the increased use of antimicrobial drugs in children.

Nasopharyngeal carriage of multidrug resistance *S. aureus* was found to be increasing over the last 20 years. *S. aureus* resistant to three and more classes of drug was considered as multi drug resistant. In the present study, about 31% was multi drug resistant. The highest rate of multi drug resistance observed in the year range of 2016-2020 (43%).

Limitation

However, this systematic review and meta-analysis came up nasopharyngeal carriage rate of *S. aureus* and its antimicrobial resistance; we acknowledge a few limitations of the present systematic review and meta-analysis, which may affect the results. First of all, we only considered nasopharyngeal sample which probably not preferred niche for *S. aureus*. This might underestimate prevalence of MERSA. The other limitation of the present study was that it was limited to articles published in English. Regardless of these limitations, we consider that this study contains valuable information on the evolution of nasopharyngeal carriage of *S. aureus* and its antibiotic resistance pattern among healthy people.

CONCLUSION

The present study showed that there is a high rate of nasopharyngeal carriage of *S. aureus* among healthy people, particularly highest rate of carriage observed in children aged between 6-15 years of age. In the current study, high rate of carriage of MERSA have been observed. In light of recent findings described, it seems prudent to continue to monitor the prevalence of MRSA in the community.

DECLARATIONS

Conflicts of interest

There are no conflicts of interests to declare.

AVAILABILITY OF DATA AND MATERIALS

All the datasets generated and analyzed during the review are included in this article.

AUTHOR'S CONTRIBUTION VAILABILITY OF DATA AND MATERIALS

EA, KD, AA and FW designed the study, extracted, critically reviewed, and analyzed data and wrote the first draft of the manuscript, and approved the manuscript.

FUNDING SOURCE

This manuscript was prepared independently without any funding support.

CONSENT FOR PUBLICATION

Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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