Fecal Carriage of *Staphylococcus aureus* in the Hospital and Community Setting: A Systematic Review

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**Background and rationale:** *Staphylococcus aureus* fecal carriage has been identified as a potential source for nosocomial transmission and a risk factor for disease development. This systematic review determined the overall *S. aureus* [including methicillin susceptible and resistant *S. aureus* (MSSA and MRSA)] fecal carriage rates within the community and healthcare settings.

**Methodology:** Peer-reviewed articles indexed in Medline, Scopus, Academic Search Premier, Africa-Wide Information, CINAHL, and Web of Science were identified using applicable and controlled vocabulary through to 11 November 2015. Eligible studies were ascertained by three independent reviewers. Random-effects meta-analyses of proportions were performed to determine *S. aureus*, MSSA and MRSA fecal carriage rates reported by eligible studies.

**Results:** Twenty six studies were included in this review. The pooled estimates for *S. aureus*, MSSA and MRSA fecal carriage were 26% (95% confidence interval (CI): 16.8–36.3%), 86% (95% confidence interval (CI): 65.9–97.9%) and 10% (95% CI: 0.7–27.0%), respectively. Fecal *S. aureus* carriage rates increased on average from 10 to 65% during the first 8 weeks of life, followed by an average carriage rate of 64% at 6 months and 46% at 1 year of life. Genotyping techniques were employed mainly in studies conducted in developed countries and comprised largely of gel-based techniques. Six studies reported on the role of *S. aureus* fecal strains in diarrhea (*n* = 2) and the risk for acquiring infections (*n* = 4). Eight of the 26 studies included in this review performed antibiotic susceptibility testing of *S. aureus* fecal isolates.

**Conclusion:** This study provides evidence that screening for *S. aureus* fecal carriage, at least in populations at high risk, could be an effective measure for the prevention of *S. aureus* transmission and infection in the healthcare and community setting. More well-structured studies need to be conducted and sequence-based genotyping techniques should be employed for the comparison of isolates on a global scale in both developing and developed countries.

**Keywords:** carriage, community, fecal, *Staphylococcus aureus*, systematic review
INTRODUCTION

Staphylococcus aureus is a commensal Gram-positive bacterium, which under certain circumstances may be responsible for pyogenic or toxigenic infections, such as skin and soft tissue infections, toxic shock syndrome and pneumonia (Tong et al., 2015). Its carriage is considered as an important risk factor for subsequent development of hospital and community-acquired infections (Ellis et al., 2004; Wertheim et al., 2004; Maier et al., 2005; Dukic et al., 2013; Levy et al., 2013). The anterior nares is recognized as the primary site for S. aureus colonization (Kluytmans et al., 1997; van Belkum et al., 2009; Sollid et al., 2014). Other anatomical niches for S. aureus include the skin (Popov et al., 2014), oropharynx (Mertz et al., 2007; Petersen et al., 2013), intestinal tract (Acton et al., 2009), and the vagina (Bourgeois-Nicolaos et al., 2010).

The importance of fecal carriage of S. aureus has been recognized more than five decades ago in a study which demonstrated that rectal S. aureus carriage preceded those from the nose and throat in new-borns (Hurst, 1960). Thereafter, several studies have provided evidence on the clinical importance of fecal carriage of S. aureus [in particular methicillin-resistant S. aureus (MRSA)] in the hospital setting (Acton et al., 2009). For example, it has been shown that hospitalized patients with both S. aureus fecal and nasal colonization are significantly more likely to have positive skin cultures compared to patients with nasal carriage only (Bhalla et al., 2007). In addition, S. aureus fecal carriage may serve as an important source for environmental contamination, which can potentially facilitate nosocomial transmission within the healthcare setting (Bhalla et al., 2007). Furthermore, antibiotic-associated diarrhea attributed to MRSA has also been reported (Lo and Borchardt, 2009; Sizemore et al., 2012; Avery et al., 2015); and patients with MRSA colonized diarrheal stools impact significantly on environmental contamination (Boyce et al., 2007).

Despite the potential role and significance of the sole fecal carriage of S. aureus (Lee et al., 1997; Squier et al., 2002; Bhalla et al., 2007) and the transmission dynamics of S. aureus in infection, a limited number of studies have focused on fecal S. aureus carriage in the hospital and community setting (Acton et al., 2009). This systematic literature review is therefore aimed to determine the overall rate of S. aureus [including methicillin susceptible and resistant S. aureus (MSSA and MRSA)] fecal carriage amongst individuals in the community and healthcare settings.

METHODOLOGY

This review followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Moher et al., 2009). The PRISMA check-list for this review is provided in a Supplementary Table (Table S1).

Literature Search Strategy

Peer-reviewed articles (written in English and French) published through to 11 November 2015 on S. aureus fecal carriage within the community and healthcare settings were evaluated using four electronic databases and a combination of keywords (Table 1). We also explored for additional articles by checking the references cited in the primary eligible studies included in this systematic review.

Study Selection and Data Extraction

Potentially relevant articles (selected based on their titles and abstracts) were assessed for eligibility (Table 2) by three independent authors. All potentially eligible articles were screened for “ predatory journals” using “Beall’s list” (Beall, 2015; Shen and Björk, 2015; Siebert et al., 2015). The corresponding authors of potentially relevant articles were contacted to determine the healthcare exposure status of participants so as to assess their eligibility for inclusion in this systematic review (Table 2). Data extraction was performed independently by two authors using a standardized data extraction form. Disagreements and inconsistencies were resolved by consensus. The following information was extracted from each eligible study: study population, number of participants screened for fecal carriage, participant characteristics (age, health status, exposure to health care settings), sample collection details (sample type, age at which samples were collected, collection site), laboratory techniques (S. aureus and MRSA screening methods, genotyping techniques, virulence profile assessment), as well as S. aureus and MRSA detection rates.

Operational Definitions of Terms Used in this Systematic Review

Community Setting

Healthy participants

- Participants reported to be healthy at the time of screening for S. aureus or MRSA fecal carriage without any exposure to healthcare settings during the year preceding screening (McKinnell et al., 2013);
TABLE 2 | Eligibility criteria.

| Inclusion criteria for systematic review | Exclusion criteria for systematic review |
|-----------------------------------------|-----------------------------------------|
| • Studies published from 1920 to 11 November 2015 were included in the search. | • Studies screening for S. aureus or MRSA from samples other than feces/rectal/swabs/anal swabs. |
| • Studies reporting on S. aureus or MRSA carriage from fecal/rectal/anal specimens from humans. | • Fecal samples studied for parasites or bacteria other than S. aureus. |
| • Studies providing information on the prevalence of S. aureus or MRSA fecal carriage. | • Articles reporting on the number of S. aureus or MRSA isolates detected from fecal specimens or on the number of fecal specimens positive for S. aureus or MRSA, but not providing information on the number of participants testing positive for S. aureus or MRSA fecal carriage. |
| • Healthcare exposure data should include information on whether or not participants were: 1. Hospitalized in the 12 months prior to screening nursing home residents, health care workers, or patients transferred from other hospitals or wards (McKinnell et al., 2013). 2. Screened for S. aureus or MRSA fecal carriage within > or ≤ 48 hours of healthcare contact (Folden et al., 2005; Millar et al., 2007; Otter and French, 2011). | • Studies not providing the necessary healthcare exposure data for participants (via the published article or via correspondence with the authors), in order to categorize participants into Healthy participants, Out-patients, In-patients and Healthcare personnel. |
| • Studies published in either English or French. | • Articles published in predatory journals (Beall, 2015). |
| • Studies not obtainable from the electronic databases, the review should include information on whether or not participants were: | • Articles not obtainable from the electronic databases, the University of Cape Town (UCT) library or the UCT inter-library loans. |

Inclusion criteria for meta-analysis of proportions

- Overall fecal carriage prevalence for S. aureus and/or MRSA must be available.

Exclusion criteria for meta-analysis of proportions

- Studies providing fecal carriage rates for participants for which fecal carriage rates have previously been reported.
- Studies not providing information on the age at which participants were screened.
- Studies screening a pre-selected group of participants based on microbiological assessments.
- Studies for which MRSA was not confirmed using molecular methods.

Pregnant women visiting obstetric clinics;
- New-borns and mothers at maternity wards during the time of delivery;
- Mothers and infants reported as healthy at the time of screening for S. aureus or MRSA fecal carriage, but exposed to the delivery unit or maternity ward during the year preceding screening.

Out-patients

Patients screened for S. aureus or MRSA fecal carriage with ≤48 h of healthcare contact (Folden et al., 2005; Millar et al., 2007; Otter and French, 2011). Patients should not have had contact with healthcare settings in the year preceding the study.

Healthcare Setting

In-patients

Patients screened for S. aureus or MRSA fecal carriage with >48 h of healthcare contact. Patients screened within ≤48 h after admission should be those transferred from another hospital/ward which will allow for >48 h of hospital contact.

Healthcare personnel

Participants screened for S. aureus or MRSA fecal carriage working at a healthcare setting with or without any illness.

Developed and Developing Countries

Countries were categorized as developed or developing countries based on data from the International Monetary Fund (http://www.imf.org/external/pubs/ft/weo/2015/01/weodata/groups.htm).

Antibiotic Susceptibility Results

The percentage of isolates (obtained from participants with S. aureus or MRSA fecal carriage) resistant to each of the antibiotics assayed was calculated from studies that provided adequate data on antibiotic susceptibility test results. Our review noted susceptibility test results whether or not the respective studies incorporated published guidelines [such as Clinical Laboratory Standards Institute (CLSI), National Committee on Clinical Laboratory Standards (NCCLS), European Committee on Antimicrobial Susceptibility Testing (EUCAST), Antibiotic Committee of the French Society of Microbiology (CA-SFM), or the Swedish Reference Group for Antibiotics (SRGA) guidelines] in assessing the antibiotic resistance profiles.

Statistical Analysis and Data Visualization

The S. aureus, MRSA and MSSA fecal carriage rates for studies included in this systematic review were calculated as follows:

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S.\text{ aureus} \text{ fecal carriage rate (\%)} = \frac{\text{Participants positive for S. aureus fecal carriage}}{\text{Participants screened for S. aureus fecal carriage}} \\
\text{MRSA fecal carriage rate (\%)} = \frac{\text{Participants positive for MRSA fecal carriage}}{\text{Participants screened for S. aureus or MRSA fecal carriage}} \\
\text{MSSA fecal carriage rate (\%)} = \frac{\text{Participants positive for MRSA fecal carriage} - \text{Participants positive for MRSA fecal carriage}}{\text{Participants screened for S. aureus fecal carriage}}
\]
Individual reports assessing the same participants for *S. aureus*, MSSA or MRSA fecal carriage were considered as a single report. Calculated fecal *S. aureus* carriage rates were used to derive longitudinal data of individual studies, as well as the average carriage rate amongst these studies, at each time-point. Meta-analyses of proportions were performed to determine the overall *S. aureus*, MSSA and MRSA fecal carriage rates (pooled estimates) among individuals in the community and healthcare settings. Meta-analyses of proportions for MRSA and MSSA did not include studies for which MRSA was not confirmed using molecular methods. For all meta-analyses of proportions, studies screening for MRSA amongst pre-selected vancomycin resistant enterococci (VRE) fecal carriers were excluded. Similarly, meta-analyses of proportions did not include studies that screened for MRSA fecal carriage solely from pre-selected MRSA carriers (MRSA identified from other body sites). Meta-analyses were performed using StatsDirect statistical software version 3.0.165 [England: StatsDirect Ltd. 2016] for studies adhering to the inclusion criteria summarized in Table 2. The StatsDirect statistical software version 3.0.165 [England: StatsDirect Ltd. 2016] was also applied to assess the heterogeneity between the studies included in the meta-analyses (Cochran Q-test) (Cochran, 1954) and to determine the inconsistency across the studies included (I² statistic) (Higgins et al., 2003). The criterion for statistical significance for the test for heterogeneity was set at alpha = 0.05. The risk of publication bias was assessed and visualized by a Funnel plot (Egger et al., 1997; Sterne et al., 2011).

RESULTS

Study Selection and Characteristics

*S. aureus* Study Selection

Figure 1 outlines the study selection process and the broad reasons for exclusion. The search strategy identified 2522 records. An additional record was identified from the reference list of one of the eligible articles included in the review. A total of 124 potentially eligible reports were identified, of which 69 fulfilled the primary inclusion criteria (Figure 1). The vast majority (80%; 55/69) of these potentially eligible articles did not provide information on healthcare exposure during the year preceding screening and/or did not indicate the duration for which patients were admitted prior to the time of screening. Following correspondence with authors, seven articles were excluded as these reports did not fulfill our inclusion criteria. Moreover, 36 articles were excluded due to lack of required information from corresponding authors or as a result of unavailable author contact information. Consequently, only 26 (11 and 15 reports based on their full texts and information obtained from the authors, respectively) of the 69 studies could be included in our systematic review. The main findings reported by each of the 26 eligible studies are summarized in detail in Tables 3, 4. Select studies that screened for *S. aureus* fecal carriage from both community and healthcare settings are also reported accordingly in Tables 3, 4.

Characteristics of Reports from Community and Healthcare Settings

Reports on *S. aureus* fecal carriage

A total of 19 reports investigated fecal *S. aureus* carriage within the community setting, of which five and 14 studies reported on fecal carriage rates from outpatients and healthy participants, respectively (Table 3). Moreover, the majority (64%; 9/14) of reports on fecal *S. aureus* carriage rates from healthy participants were of longitudinal design and investigated infants up until one year of age (Table 3). Of the five reports on fecal carriage rates from outpatients, a single study performed a longitudinal analysis of *S. aureus* fecal carriage (Efuntoye and Adetosoye, 2003) and another investigated infants during the first year of life (Shehabi et al., 2013). Study sizes for the community setting ranged between 21 and 1761 participants (Table 3).

Fecal *S. aureus* carriage within the healthcare setting was noted in 12 reports (Table 4). Of these, 10 were from inpatients and two from healthcare personnel. All reports on inpatients were of cross-sectional design and the majority (60%; 6/10) did not provide information on the age of the participants. In addition, the two studies on healthcare personnel were cross-sectional in design and carried out in the United States of America (USA) (Carmeli et al., 1998; Andrews et al., 2009). Study sizes for healthcare-based reports ranged between 37 and 2727 participants (Table 4).

Reports on methicillin susceptible and resistant *S. aureus* fecal carriage

Six of the 19 reports on *S. aureus* fecal carriage from the community setting provided MRSA fecal carriage rates confirmed by molecular methods (Table 3). Five of these studies (conducted in developed countries) reported both *S. aureus* and MRSA fecal carriage rates which allowed for the calculation of MSSA fecal carriage rates. Only one study within the healthcare setting (conducted in the USA) confirmed fecal MRSA carriage by screening specimens using a molecular approach (Andrews et al., 2009).

Pooled Estimates of *S. aureus* Fecal Carriage Rates Assessed by Meta-Analyses

Studies included in all of the proportional meta-analyses were heterogeneous, as determined by the Cochrane Q test and I² statistic (Figures 2–4). We could not determine pooled MSSA or MRSA fecal carriage rates within the healthcare setting as only a single study was considered eligible for this analysis.

The pooled random-effects estimate for *S. aureus* fecal carriage within the community and healthcare settings was 26% (95% CI = 16.8–36.3; Figure 5). Sub-analyses of *S. aureus* fecal carriage within the community and healthcare settings resulted in pooled random-effects estimates of 31% (95% CI = 17.8–46.3) and 5% (95% CI = 1.7–8.9), respectively.

MSSA fecal carriage was estimated at 86% (95% CI = 65.9–97.9) using the random-effects model (Figure 6). Within the community setting, the random effects estimate for MSSA fecal
The pooled random-effects estimates for MRSA fecal carriage were 10% (95% CI = 0.7–27.0; Figure 7); and 10% (95% CI = 0.4–28.9) within the community setting.

**S. aureus** Fecal Carriage Rates According to the Age of Participants

The report on this section is not based on meta-analysis. *S. aureus* fecal carriage rates within the community setting were higher during the first year of life (Figure 8). On average, reports from longitudinal studies revealed an increase in *S. aureus* fecal carriage rates from approximately 10–65% during the first 8 weeks of life (Figure 8). At 6 months of age, the average fecal carriage rate was 64%, thereafter it decreased to approximately 46% at 1 year of life. A longitudinal investigation of fecal MRSA carriage rates from healthy participants from the USA showed an increase in fecal MRSA carriage from 0 to 9% during the first 2 weeks of life (Gries et al., 2009). The highest MRSA fecal carriage rate (23%) reported was from Spanish infants screened at ≤ 1 year of life (Benito et al., 2015).

**Assessment of Antibiotic Susceptibility of Fecal S. aureus Isolates**

Eight of the 26 eligible studies (31%) included in this review assayed for antibiotic susceptibility of fecal *S. aureus* or MRSA isolates (Table 5). Overall, *S. aureus* or MRSA isolates were
### TABLE 3 | Characteristics of eligible studies analysing fecal carriage of *Staphylococcus aureus* or MRSA from the community.

| Study population setting | Participants screened for fecal carriage (n) | Participant characteristics | Sample collection | Laboratory technique(s) | S. aureus detection | MRSA detection | Genotyping | Virulence profile analysis | % (n/N) | & (n/N) | References |
|--------------------------|---------------------------------------------|-----------------------------|--------------------|-------------------------|---------------------|------------------|------------|-----------------------------|--------|--------|--------------------------|
| Italy                    | 100 Birth to 12 months                      | Healthy                     | At time of delivery | Rectal swabs, Feces    | 3 days              | Delivery unit    | Phenotypic | NP             | RAPD  | 5 (5/100)²   | NA           | Lindberg et al., 2010 |
|                          |                                             |                             |                    |                         | 1 week              | Home             | Phenotypic | NP             | &     | 15 (15/100)²  | 24 (24/100)² |                        |
|                          |                                             |                             |                    |                         | 2 weeks             | Home             | Phenotypic | NP             | &     | 34 (34/100)²  | 45 (45/100)² |                        |
|                          |                                             |                             |                    |                         | 4 weeks             | Home             | Phenotypic | NP             | &     | 52 (52/100)²  | 66 (66/100)² |                        |
|                          |                                             |                             |                    |                         | 8 weeks             | Home             | Phenotypic | NP             | &     | 31 (27/86)²  | NA           |                        |
|                          |                                             |                             |                    |                         | 6 months            | Home             | Phenotypic | NP             | &     | 66 (66/100)²  | NA           |                        |
|                          |                                             |                             |                    |                         | 1 year              | Home             | Phenotypic | NP             | &     | 15 (15/100)²  | 24 (24/100)² |                        |
|                          |                                             |                             |                    |                         | Overall prevalence  | Home             | Phenotypic | NP             | &     | 34 (13/38)³  | Onanuga and Temedie, 2011 |
| Mozambique               | 121 ≤14 days to 1 year Healthy               | NR                          | Feces              | ≤14 days to 1 year     | Home               | Molecular       | NP         | NP             | &     | 77 (92/120) | NA           | González et al., 2013 |
| Nigeria                  | 120 15–35 years Healthy No                   | Faces                       | 15 to 35 years     | Provided by participants | Phenotypic         | Phenotypic       | NP         | &              |   32 (38/120) | 34 (13/38)³ | Onanuga and Temedie, 2011 |
| Spain                    | 21 7–35 days Healthy                         | Faces                       | At time of delivery | Rectal swabs, Feces    | 1 week              | Home             | Phenotypic and Molecular | &     | 10 (2/21)  | 14 (3/21)  | Benito et al., 2015 |
|                          |                                             |                             |                    |                         | 2 weeks             | Home             | Phenotypic and Molecular | &     | 48 (10/21) | 57 (12/21) |                        |
|                          |                                             |                             |                    |                         | 5 weeks             | Home             | Phenotypic and Molecular | &     | 57 (12/21) | 42 (5/12)  |                        |

(Continued)
TABLE 3 | Continued

| Study population setting | Participants screened for fecal \( ^y \) carriage (n) | Participant characteristics | Sample collection | Laboratory technique(s) | S. aureus detection & MRSA detection | References |
|--------------------------|--------------------------------------------------------|-----------------------------|-------------------|-------------------------|--------------------------------------|------------|
|                          | Age range | Health status | Exposure to healthcare setting 12 months prior to screening \( ^{1} \) | Sample type | Age at which samples were collected | Site at which samples were collected | S. aureus detection | MRSA detection | Genotyping | Virulence profile analysis | % (n/N) | (n/N) |
| Spain                    | 100       | 2–89 years | Healthy No \( ^{4} \) | Feces | 2–89 years | NR | Phenotypic and Molecular | Phenotypic and Molecular | spa typing | agr typing | MLST | SE | PVL | ET | TSST | AUR | BAP | CNA |
|                          |           |              |                          |                |               |               | 15 (15/100) | 0 (0/15) | Benito et al., 2013 |
| Spain                    | 50        | 7–23 months | Healthy At time of delivery \( ^{6} \) | Feces | 7–23 months | Nurseries | Phenotypic and Molecular | Phenotypic and Molecular | NP | NP | 6 (3/50) | 0 (0/3) | Dominguez et al., 2002 |
| Sweden                   | 100       | Birth to 12 months | Healthy At time of delivery | Rectal swabs | 3 days | Delivery unit | Phenotypic | NP | RAPD | SE | TSST | 16 (16/100) | 48 (48/100) | 56 (56/100) | 64 (64/100) | 72 (72/100) | 68 (68/100) | 55 (55/100) | 78 (78/100) | Lindberg et al., 2010 |
| Sweden                   | 64        | Birth to 8 weeks | Healthy At time of delivery | Rectal swabs | 3 days | Delivery unit | Phenotypic | NP | NP | SE | TSST | 13 (8/64) | 39 (25/64) | 53 (33/62) | 59 (37/63) | 71 (44/62) | 73 (47/64) | Lundell et al., 2009 |

(Continued)
| Study population setting | Participants screened for fecal carriage (n) | Participant characteristics | Sample collection | Laboratory technique(s) | S. aureus detection | MRSA detection | References |
|--------------------------|---------------------------------------------|----------------------------|-------------------|-------------------------|--------------------|-----------------|------------|
| Sweden                   | 50 Birth to 12 months                       | Healthy                    | At time of delivery | Rectal swabs            | Delivery unit       | Phenotypic NP   | Lindberg et al., 2004a |
|                          |                                             |                            | 3 days             | 1 week                  | Home               | RAPD PFGE ET TSST |            |
|                          |                                             |                            | 2 weeks            | 4 weeks                 |                    |                 |            |
|                          |                                             |                            | 8 weeks            |                        |                    |                 |            |
|                          |                                             |                            | Overall            |                        |                    |                 |            |
|                          |                                             |                            | prevalence         |                        |                    |                 |            |
| 37                       |Apparently Allergic and non-allergic mothers| At time of delivery       | Feces              | 1 week after delivery or at a later stage | Home               |                   |            |
| Sweden                   | 81 Birth to 12 months                       | Healthy                    | At time of delivery | Rectal swabs            | Delivery unit at 3 days and home at 1 week to 1 year | Phenotypic RAPD ET TSST | Lindberg et al., 2004b |
|                          |                                             |                            | 3 days             | 1 week                  |                    |                 |            |
|                          |                                             |                            | 2 weeks            | 4 weeks                 |                    |                 |            |
|                          |                                             |                            | 8 weeks            |                        |                    |                 |            |
|                          |                                             |                            | 6 months           |                        |                    |                 |            |
|                          |                                             |                            | 1 year             |                        |                    |                 |            |
|                          |                                             |                            | Overall prevalence |                        |                    |                 |            |
| Sweden                   | 49 Birth to 12 months                       | Healthy                    | At time of delivery | Rectal swabs Feces     | Delivery unit Home | Phenotypic NP RAPD ET TSST | Lindberg et al., 2000 |
|                          |                                             |                            | 3 days             | 1 week                  |                    |                 |            |
|                          |                                             |                            | 2 weeks            | 4 weeks                 |                    |                 |            |
|                          |                                             |                            | 8 weeks            |                        |                    |                 |            |
|                          |                                             |                            | 6 months           |                        |                    |                 |            |
|                          |                                             |                            | 1 year             |                        |                    |                 |            |
|                          |                                             |                            | Overall prevalence |                        |                    |                 |            |
TABLE 3 | Continued

| Study population setting | Participants screened for fecal carriage (n) | Participant characteristics | Sample collection | Laboratory technique(s) | S. aureus detection | MRSA detection | References |
|--------------------------|---------------------------------------------|-----------------------------|-------------------|-------------------------|---------------------|----------------|------------|
|                          | Age range | Health status | Exposure to healthcare setting 12 months prior to screening | Sample type | Age at which samples were collected | Site at which samples were collected | S. aureus detection | MRSA detection | Genotyping | Virulence profile analysis | % (n/N) | & (n/N) |
| United Kingdom           | 30        | 2–7 months     | NR                 | Feces       | 2 weeks 10 weeks 7 months Overall prevalence | Home | Phenotypic NP NP SE TSST | 37 (11/30) 40 (12/30) 40 (12/30) | NA | Harrison et al., 2009 |
| United States of America | 147       | > 18 years     | Healthy pregnant women at 35-37 weeks of pregnancy | Rectal swabs | > 18 years Obstetric clinics | Phenotypic and Molecular SCCmec typing PFGE | 4 (6/147) φ 0 (0/6) | Andrews et al., 2009 |
| United States of America | 38        | 1 day to 2 weeks | Healthy at time of delivery | Feces | 1–2 days 2 weeks Overall prevalence | New-born unit | Phenotypic and Molecular PFGE PVL | 0 (0/38) 26 (6/23) 33 (2/6) 26 (6/23) 33 (2/6) | Gries et al., 2009 |
| CATEGORY: OUTPATIENTS    | India     | 100 | 16–88 years | Patients at admission No long hospital stay or admission to other hospitals | Feces | 16–88 years Hospital | Phenotypic NP NP NP | 0 (0/100) NA | Daeo et al., 2014 |
| Jordan                  | 216       | ≤ 28 days to 1 year | NR | No | Feces | 28 days to 1 year Clinic | Phenotypic SCCmec typing ET PVL SE TSST | 17 (37/216) 59 (22/37) | Shehabi et al., 2013 | (Continued) |
| Study population setting | Participants screened for fecal carriage (n) | Participant characteristics | Sample collection | Laboratory technique(s) | S. aureus detection | MRSA detection | References |
|--------------------------|---------------------------------------------|-----------------------------|-------------------|-------------------------|---------------------|----------------|------------|
|                          | Participants | Age range | Health status | Exposure to healthcare setting 12 months prior to screening | Sample type | Age at which samples were collected | Site at which samples were collected | S. aureus detection | MRSA detection | Genotyping | Virulence profile analysis | % (n/N) | & (n/N) |
| Nigeria                  | 1761          | ≤5 years | Diarrhoeic children | No* | Feces | <1 year | Hospital | Phenotypic | Phenotypic NP | ET | 3 (11/416) | NR | Eluntoye and Adetosoye, 2003 |
|                          |               | 1.1–2.0 years | | | | 2.1–3.0 years | | | | 4 (12/309) | NR | |
|                          |               | 3.1–4.0 years | | | | 4.1–5.0 years | | | | 5 (15/252) | NR | |
|                          |               | Overall prevalence | | | | | | | | 5 (21/421) | NR | |
|                          |               | | | | | | | | | 4 (72/1761) | NR | |
| Saudi Arabia             | 58            | NR | Patients at admission (<48 h)* with diarrhea or abdominal pain | No* | Feces | NR | Hospital | Phenotypic | Phenotypic NP | NP | NA | 9 (5/58) | Babay and Somily, 2009 |
| United States of America | 150           | Birth to 18 years | Children requiring abscess drainage (n = 60) | No* | Rectal swabs | Birth to 18 years | Hospital | Phenotypic and Molecular | MLVA SCCmec typing | PVL | 47 (28/60) | NR | Faden et al., 2010 |
|                          |               | | | | | | | | | 1 (1/90) | NR | |

*Fecal samples, rectal swabs, anal swabs, peri-rectal or peri-anal swabs.
†Hospitals, long-term care facility, nursing homes, maternity wards.
§Resistant to cefoxitin.
Information obtained from the author.
Phenotypic identification: culture characteristics on mannitol salt agar, Baird-Parker agar, Chapman agar, Staphylococcus medium 110, positive results for Gram stain, catalase, coagulase and DNase Tests; agr, Accessory gene regulator; AUR, Aureolysin; BAP, biofilm-associated protein; CAN, collagen-binding protein; ET, Exfoliative toxins; MLVA, Multiple-locus variable-number tandem repeat analysis; MRSA, methicillin resistant Staphylococcus aureus; NR, Not reported; NP, Not performed; NA, Not applicable; PFGE, pulsed-field gel electrophoresis; PVL, Panton-Valentine Leukocidin; RAPD, random amplified polymorphic DNA; SCCmec, staphylococcal cassette chromosome mec; SE, Staphylococcal enterotoxins; spa, Staphylococcus aureus protein A; TSST, Toxic shock syndrome toxin.
## TABLE 4 | Characteristics of eligible studies analysing fecal carriage of *Staphylococcus aureus* or MRSA from the healthcare setting.

| Study population setting | Participants screened for fecal carriage (n) | Participant characteristics | Sample collection | Laboratory technique(s) | S. aureus detection | MRSA detection | Reference |
|--------------------------|---------------------------------------------|-----------------------------|-------------------|-------------------------|---------------------|----------------|-----------|
|                          | Age range Heat status | Exposure to healthcare setting 12 months prior to screening | Sample type | Age at which samples were collected | Site at which samples were collected | S. aureus detection | MRSA detection | Genotyping | Virulence profile analysis | % (n/N) & (n/N) | |
|                          |               |                          | Sample type | Age at which samples were collected | Site at which samples were collected | S. aureus detection | MRSA detection | Genotyping | Virulence profile analysis | % (n/N) & (n/N) | |
| **CATEGORY: IN-PATIENTS** |                                             |                                            |                    |                          |                               |                |              |              |                           |              | |
| France                   | 748 Mean age: 55 years±12 Liver cirrhosis | Hospitalized for minimum of 2 weeks | Feces | Mean age: 55 years±12 | Hospital | Phenotypic | Phenotypic | NP | NP | NR | 12 (93/748) | Campillo et al., 2001 |
| France                   | 327 NR Chronic liver disease, post-surgical patients, patients with alcohol withdrawal and digestive tract diseases | Patients transferred from other hospitals | Feces | NR | Hospital | Phenotypic and Molecular | Phenotypic | PFGE | NP | NR | 11 (36/327) | Dupeyron et al., 2002 |
| Germany                  | 2727 NR Nosocomial diarrhea | ≥ 72 h at the time of study | Feces | NR | Hospital | Phenotypic | Phenotypic | NP | SE | 7 (198/2727) | Flemming and Ackermann, 2007 |
| Germany                  | 131 NR | NR | Inpatients positive for MRSA | Rectal swabs | NR | Hospital | Phenotypic and Molecular | Phenotypic and Molecular | PFGE | SE | NR | 47 (61/131) | Klotz et al., 2005 |
| Jordan                   | 214 ≤28 days to 1 year | NR | Feces | ≤28 days to 1 year | NICU | Phenotypic | Phenotypic | SCCmeC typing | ET PVL SE TSST | 2 (5/214) | 20 (1/5) | Sheltali et al., 2013 |
| Saudi Arabia | 122 NR | NR | ≥72 h at the time of study | Feces | NR | Hospital | Phenotypic | Phenotypic | NP | NP | NA | 7 (9/122) | Babay and Soni, 2009 |
| United States of America | 810 (2000-01) NR Cancer | Inpatients | Rectal swabs | NR | Hospital | Phenotypic and Phenotypic | spa typing MLST | PVL | NA | 0.6 (5/810) | Srinivasan et al., 2010 |
|                          | 925 (2008-07) | | | | | | | | 2.9 | (27/925) | |

(Continued)
### TABLE 4 | Continued

| Study population setting | Participants screened for fecal carriage (n) | Participant characteristics | Sample collection | Laboratory technique(s) | S. aureus MRSA detection | Reference |
|--------------------------|---------------------------------------------|-----------------------------|-------------------|-------------------------|-------------------------|-----------|
| **Participant characteristics** | | | | S. aureus detection | Genotyping | Virulence profile analysis |
| | Age range | Health status | Exposure to healthcare setting 12 months prior to screening | Sample type | Age at which samples were collected | Site at which samples were collected |
| United States of America | 161 | 57–103 years | Fecal and urinary incontinence, pressure ulcers, diabetes, COPD, heart failure | Rectal swabs | 57–103 years | Long-term care wards |
| | 57–103 years | Fecal and urinary incontinence, pressure ulcers, diabetes, COPD, heart failure | Rectal swabs | 57–103 years | Long-term care wards |
| United States of America | 161 | 57–103 years | Fecal and urinary incontinence, pressure ulcers, diabetes, COPD, heart failure | Rectal swabs | 57–103 years | Long-term care wards |
| United States of America | 37 | 48–91 years | Chronic renal failure, Inpatients positive for VRE | Feces | 48 to 91 years | Hospital |
| United States of America | 114 | NR | Skilled-care patients admitted for long-term care | Rectal swabs | Hospital |
| United States of America | 62 | >18 years | Healthy pregnant women at 35–37 weeks of pregnancy | Rectal swabs | Obstetric clinics |
| United States of America | 55 | 36 years±11 | Nurses (n = 29), Physicians (n = 15), Others (n = 9), Unknown (n = 2) (mean patient contact years: 13 years±19) | Fecal swabs | 36 years±11 | NR |

**CATEGORY: HEALTHCARE PERSONNEL**

- **United States of America**: 62
  - 18 years: Healthy pregnant women at 35–37 weeks of pregnancy
  - Rectal swabs: Obstetric clinics
  - Phenotypic: PFGE
  - SCCmec: PVL

- **United States of America**: 55
  - 36 years±11: Nurses (n = 29), Physicians (n = 15), Others (n = 9), Unknown (n = 2) (mean patient contact years: 13 years±19)
  - Fecal swabs: Phenotypic

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**Notes:**

- | Fecal samples, rectal swabs, anal swabs, perirectal or peri-anal swabs.
- | Hospital, long-term care facility, nursing homes, maternity wards.
- | Information obtained from the author.
- Phenotypic identification: culture characteristics on mannitol salt agar, Baird-Parker agar, Triplicase soy agar, Chapman agar, Staphylococcus medium 110, positive results for Gram stain, catalase, coagulase and DNase Tests.
- MRSA, methicillin-resistant Staphylococcus aureus; NICU, Neonatal intensive care unit; NR, Not reported; NP, Not performed; NA, Not applicable; PFGE, pulsed-field gel electrophoresis; PVL, Panton-Valentine Leukocidin; SCCmec, staphylococcal cassette chromosome mec; SE, Staphylococcus enterotoxins; spa, Staphylococcus aureus protein A; TSST, Toxic shock syndrome toxin; VRE, Vancomycin-resistant enterococci.
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FIGURE 2 | Bias assessment (Funnel) plot for studies assessing Staphylococcus aureus fecal carriage rates.

FIGURE 3 | Bias assessment (Funnel) plot for studies assessing Methicillin susceptible Staphylococcus aureus fecal carriage rates.

FIGURE 4 | Bias assessment (Funnel) plot for studies assessing Methicillin resistant Staphylococcus aureus fecal carriage rates.

screened with 32 different antibiotics across the respective studies using disk diffusion, agar dilution, or the Vitek Legacy System. The use of published guidelines for susceptibility testing were reported by six of the eight studies (Table 5). Susceptibility testing to erythromycin was performed most frequently (88%; 7/8), followed by chloramphenicol, clindamycin, ciprofloxacin, gentamicin, penicillin and vancomycin (75%; 6/8) (Table 5). Vancomycin intermediate or resistant S. aureus (VISA/VRSA) were not identified in five of the six studies that screened for vancomycin resistance (Table 5). Only the study by Onanuga and Temedie (2011) reported fecal VRSA carriage of 37% (14/38).

Genotyping of S. aureus Isolated from Fecal Specimens
Techniques used to genotype S. aureus isolated from fecal specimens included multiple-locus variable-number tandem repeat analysis (MLVA), pulsed-field gel electrophoresis (PFGE), random amplified polymorphic DNA (RAPD) analysis, staphylococcal cassette chromosome mec (SCCmec), accessory gene regulator (agr) and Staphylococcus aureus protein A (spa) typing (Tables 3, 4). Genotyping was performed in slightly more reports from the healthcare setting (67%; 8/12) compared to the community (58%; 11/19). Gel-based methods (PFGE, RAPD and MLVA) were employed in 58% (7/12) and 42% (8/19) of studies in the healthcare and community settings, respectively. In addition, similar rates (26% vs. 25%) in the use of sequence-based methods (spa typing, SCCmec typing and MLST) for genotyping of S. aureus strains were reported from community and healthcare settings. Only a single study conducted in a developing country (Jordan) performed genotyping of the S. aureus strains (Shehabi et al., 2013).

Assessment of the Detection of S. aureus Virulence Genes
Virulence genes screened included the aureolysin enzyme, biofilm-associated protein, collagen-binding protein, exfoliative toxins (ETs), staphylococcal enterotoxins (SEs), toxic shock syndrome toxin (TSST), and Panton-Valentine leukocidin (PVL) (Tables 3, 4). More community–based investigations screened for S. aureus virulence genes compared to reports from the healthcare setting. Thus, 53% (10/19), 37% (7/19), and 37% (7/19) of studies conducted in the community setting reported on TSSTs, SEs, ETs, respectively, using PCR, reverse passive latex agglutination tests or enzyme-linked immunosorbent assays. Approximately one third of the studies conducted in the community setting (6/19) reported on PCR detection of the PVL genes. In studies conducted in the healthcare setting; 8% (1/12), 25% (3/12.), 8% (1/12), and 25% (3/12) reported on TSSTs, SEs, ETs, and PVL, respectively.

S. aureus and MRSA Fecal Carriage as Risk Factors for Disease Development
Two studies included in this review identified enterotoxin producing S. aureus strains from fecal specimens of patients with diarrhea (Efuntoye and Adetosoye, 2003; Flemming and Ackermann, 2007). Another study reported that all patients colonized with MRSA in both the nares and rectum (8/8) developed an infection (Srinivasan et al., 2010). In addition, two of the nine patients, colonized with MRSA in the rectum only, were concurrently or subsequently infected. Spa typing on a
subset of colonizing isolates from the nares and rectum noted that the majority (69%; 9/13) were clonally related to infecting isolates (Srinivasan et al., 2010). In support of the potential of fecal carriage for infection, it has also been shown that *S. aureus* detection occurs more frequently from rectal specimens of children with skin and soft tissue abscesses (47%; 28/60) compared with the control group (1%; 1/90) \((P = 0.0001)\) (Faden et al., 2010).

**DISCUSSION**

Our results clearly showed that fecal *S. aureus* carriage from healthy infants is high during the first year of life. Specifically, *S. aureus* fecal carriage rates increased during the first 8 weeks of life followed by a gradual decrease towards 1 year of life. The reasons for this abrupt increase in fecal carriage very early in life (especially from healthy infants) is not yet clear,
however a potential explanation may be early life care-giving practices, particularly breastfeeding. For example, colostrum contains the highest levels of human milk oligosaccharides (HMOs) (Bode, 2012), which have been suggested to stimulate S. aureus growth (Hunt et al., 2012). Moreover, S. aureus strains may be transmitted from parents via skin contact (Lindberg et al., 2004a) or from the mother via breastfeeding (Kawada et al., 2003; Lindberg et al., 2004a; Benito et al., 2015). Furthermore, staphylococci from the maternal GIT or skin surrounding the areola may be transferred to breast milk during lactation (Thum et al., 2012; Fernández et al., 2013). Higher S. aureus fecal carriage rates have also been noted from breast-fed in comparison to formula-fed or mixed-fed infants (González et al., 2013; Salminen et al., 2015). The observed change in the dynamics of S. aureus fecal carriage after 8 weeks of life may be explained by the increase in anaerobic bacteria from around 1 week of life (Bezirtzoglou, 1997; Adlerberth et al., 2006; Adlerberth and Wold, 2009; Jost et al., 2012), as well as the introduction of formula feeding (González et al., 2013) and solid foods (Bergström et al., 2014; Voreades et al., 2014). Infant fecal bacterial profiles have also been shown to change during the course of the lactation period (Cabrera-Rubio et al., 2012; González et al., 2013).

This systematic review does not only provide insight into the dynamics of fecal S. aureus carriage rates during the first year of life; but also highlights that S. aureus and MRSA fecal carriage is a potential risk factor for subsequent infections. Vancomycin is
### TABLE 5 | Antibiotic resistance profiles across participants screened for fecal S. aureus or MRSA.

| Study                  | Guidelines applied | Techniques applied | Total number of S. aureus or MRSA isolates screened for resistance | Antibiotic resistance profiles of fecal S. aureus or MRSA isolates (%) |
|------------------------|--------------------|--------------------|---------------------------------------------------------------------|---------------------------------------------------------------------|
|                        |                    |                    |                                                                     | Antibiotics                                      |
|                        |                    |                    |                                                                     | Aminoglycosides | β-lactam/β-lactamase inhibitors | Cephalosporin | Fluoroquinolones | Glycopeptides | Liposides | Lipopeptides | Macrolides | Oxazolidinones | Penicillins | Phenicols | Pseudomonic acid | Pyrimidines | Pyrimidines/Sulfonamides | Streptogramins | Steroids | Tetracyclines |
| Domínguez et al., 2002 | NR                 | Agar dilution method | 3                                                                   | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 67 | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Efuntoye and Adetosoye, 2003 | NCCLS             | Disk diffusion method | 72                                                                  | 22 | 0 | 0 | 9 | 99 | 99 | 67 | 78 | 78 | 0 | 0 | 0 | 1 | 2 |
| Lindberg et al., 2004b | SRGA               | Disk diffusion method | 116                                                                 | 0 | 0 | 0 | 1 | 3 | 3 | 78 | 0 | 0 | 0 | 1 | 2 |
| Flemming and Ackermann, 2007 | NR               | Disk diffusion method | 198                                                                 |                |                |                |                |                |                |                |                |                |                |                |                |                |                |                |                |                |                |
| Srinivasan et al., 2010 | CLSI              | Vitek Legacy System | 31*                                                                | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 67 | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Onanuga and Tamede, 2011 | CLSI              | Disk diffusion and agar dilution method | 38                                                                  | 5 | 0 | 18 | 34 | 24 | 8 | 8 | 37 | 34 | 68 | 34 | 37 | 0 | 61 |
| Benito et al., 2013    | CLSI CA-SFM        | Disk diffusion method | 15                                                                  | 0 | 0 | 0 | 7 | 0 | 0 | 0 | 0 | 20 | 0 | 60 | 0 | 7 | 0 | 0 | 0 | 0 | 0 | 0 |
| Benito et al., 2015    | CLSI EUCAST        | Disk diffusion method | 25                                                                  | 36 | 0 | 16 | 36 | 40 | 4 | 0 | 32 | 36 | 0 | 40 | 40 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 |

CA-SFM, Antibiogram Committee of the French Society of Microbiology; CLSI, Clinical Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility; NCCLS, National Committee on Clinical Laboratory Standards; SRGA, Swedish Reference Group for Antibiotics; NR, Not reported.

*Number of MRSA isolates (detected using oxacillin screening agar) screened for antibiotic resistance

Antibiotic resistance rates (%):  Q > 0–10;  > 10–20;  > 20–30;  > 30–40;  > 40–50;  > 50–60;  > 60–70;  > 70–80;  > 80–90;  > 90–100.
regarded as one of the drugs of choice for MRSA infections (Tarai et al., 2013); however the emergence of vancomycin resistant \textit{S. aureus} (VRSA) poses yet another threat to infection control (Hiramatsu, 1998; Spagnolo et al., 2014). The intestinal tract, in particular, may be a key potential reservoir for the emergence and transmission of VRSA isolates due to the intestinal coexistence (Ray et al., 2003), and potential transfer of the \textit{vanA} gene from VRE to MRSA (Courvalin, 2006). Although, 23\% of the studies included in this review screened for fecal carriage of VRSA within community and healthcare settings (Domínguez et al., 2002; Lindberg et al., 2004b; Srinivasan et al., 2010; Onanuga and Temedie, 2011; Benito et al., 2013, 2015); only a single study, performed in Nigeria, reported VRSA fecal carriage (Onanuga and Temedie, 2011). It is noteworthy, however, that this finding should be interpreted with caution as the disk diffusion method was used to screen for vancomycin resistance at 30 $\mu$g/ml, which is not recommended by the CLSI guidelines (Clinical Laboratory Standards Institute, 2012).

Healthcare associated fecal screening for \textit{S. aureus} and MRSA is of key importance in infection control (Campillo et al., 2001; Ray et al., 2003; Bhalla et al., 2007). For example, it has been shown that select staphylococcal enterotoxins (SEs) may contribute to the colonizing success of \textit{S. aureus} strains in the GIT (Nowrouzian et al., 2011), which could potentially facilitate in its transmission. Moreover, \textit{S. aureus} and MRSA fecal carriage may complicate de-colonization, with a potential to contribute to infections within the healthcare setting (Campillo et al., 2001; Dupeyron et al., 2002; Ray et al., 2003; Srinivasan et al., 2010). To prevent nosocomial transmission and infection, two recent studies (Roth et al., 2016; Senn et al., 2016) have also highlighted the importance of screening for \textit{S. aureus} fecal carriage on admission in the following risk groups: patients admitted to surgery or intensive care units with a history of MRSA colonization or infection; hospitalization during the past year; or direct transfer from another healthcare facility. Only a single study was considered eligible for inclusion in our meta-analyses of the proportions on MSSA and MRSA fecal carriage within the healthcare setting. Therefore we could not determine the fecal carriage rate for MSSA or MRSA within this setting.

A major limitation in this systematic review is the poor study design and limited data available from studies assessing the fecal carriage rates of \textit{S. aureus} and MRSA. For example, a large proportion of potentially eligible articles were excluded due to the lack of information regarding participants’ contact with healthcare facilities as well as the duration of hospital admission prior to \textit{S. aureus} and MRSA screening. This information is essential in comparing fecal carriage rates from community and healthcare settings. Furthermore, a number of studies could not be included in calculating the pooled estimates for MSSA and MRSA fecal carriage (from both community and healthcare settings) due to the lack of molecular techniques incorporated to confirm MRSA carriage. On the other hand, the extent in which our observations could have changed if unavailable articles were included is unclear. However, based on the rigorous appraisal of various studies in this systematic review, we conclude that the excluded articles are not likely to impact significantly on observations presented in the manuscript. In addition, more studies from both developed and developing countries are needed in order to determine \textit{S. aureus} and MRSA fecal carriage and transmission within and between the community and healthcare settings. In support of this, rural areas and low socioeconomic status have been shown to contribute to higher fecal transmission rates of \textit{S. aureus} and MRSA (Vale and Vítor, 2010). Finally, there is the need for more sequence-based genotyping data on \textit{S. aureus} and MRSA fecal carriage as the majority of studies from developed countries made use of gel-based methods which are not ideal when comparing isolates on a global level.

**CONCLUSION**

\textit{S. aureus}, MSSA and MRSA fecal carriage rates within both the community and healthcare setting are not negligible and estimated at 26, 86, and 10\%, respectively. Therefore, preventative strategies which include fecal \textit{S. aureus} screening of high risk patients are necessary for infection control within these settings. More studies are needed to determine the role of fecal \textit{S. aureus} carriage as a risk factor for disease development; as well as fecal carriage rates of MSSA, MRSA, and VRSA from both community and healthcare settings. Furthermore, well-structured research should be conducted and sequence-based genotyping techniques should be employed. The latter will allow for comparison of isolates on a global level in both developing and developed countries.

**AUTHOR CONTRIBUTIONS**

MK and SC initiated the project. SC, MRN, and MK searched the databases for potentially eligible articles based on their titles and abstracts. SC extracted the data and contacted authors of potentially eligible publications to obtain healthcare information on participants when this information was unclear or not provided by the articles. SC, MK, and AS reviewed the articles. SC, LT, and MK performed the statistical analysis and interpreted the results. SC, LT, AS, MPN, and MK wrote the manuscript. All the authors reviewed the final version of the manuscript prior to submission for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fmicb.2016.00449

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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