Nasal *Staphylococcus aureus* and *S. pseudintermedius* carriage in healthy dogs and cats: a systematic review of their antibiotic resistance, virulence and genetic lineages of zoonotic relevance

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Abstract

The molecular ecology of *Staphylococcus aureus*, *Staphylococcus pseudintermedius* and their methicillin-resistant strains in healthy dogs and cats could serve as good models to understand the concept of bacterial zoonosis due to animal companionship. This study aims to provide insights into pooled prevalence, genetic lineages, virulence and antimicrobial resistance (AMR) among healthy dogs and cats. Original research and brief communication articles published from 2001 to 2021 that reported the nasal detection of *S. aureus* and *S. pseudintermedius* in healthy dogs and cats in the community, homes and outside veterinary clinics were examined and analysed. Forty-nine studies were eligible and included in this systematic review. The pooled prevalence of nasal carriage of *S. aureus*/methicillin-resistant *S. aureus* (MRSA) in healthy dogs and cats were 10.9% (95% CI: 10.1–11.9)/2.8% (95% CI: 2.4–3.2) and 3.2% (95% CI: 1.9–4.8)/0.5% (95% CI: 0.0–1.1), respectively. Conversely, the pooled prevalence of *S. pseudintermedius*/methicillin-resistant *S. pseudintermedius* (MRSP) in healthy dogs and cats were 18.3% (95% CI: 17.1–19.7)/3.1% (95% CI: 2.5–3.7) and 1.3% (95% CI: 0.6–2.4)/1.2% (95% CI: 0.6–2.3), respectively. Although highly diverse genetic lineages of *S. aureus* were detected in healthy dogs and cats, MSSA-CC1/CC5/CC22/CC45/CC121/CC398 and MRSA-CC5/CC93/CC22/CC30 were mostly reported in dogs; and MSSA-CC5/CC8/CC15/CC48 and MRSA-CC22/CC30/CC80 in cats. Of note, MSSA-CC398 isolates (*spa*-types t034 and t5883) were detected in dogs. Genetic lineages often associated with MSSP/MRSP were ST20/ST71, highlighting the frequent detection of the epidemic European MRSP-ST71 clone in dogs. *S. aureus* isolates carrying the *luk-S/F-PV*, *tst*, *eta*, *etb* and *etd* genes were seldomly detected in dogs, and *luk-S/F-PV* was the unique virulence factor reported in isolates of cats. *S. pseudintermedius* isolates harbouring the *luk-S/F-I*, *seint* and *expA* genes were frequently found, especially in dogs. High and diverse rates of AMR were noted, especially among MRSA/MRSP isolates. There is a need for additional studies on
the molecular characterization of isolates from countries with under-studied nasal staphylococci isolates.

**KEYWORDS**
healthy cats, healthy dogs, MRSA, MRSP, MRSP-ST71, MSSA-CC398, nasal carriage, *Staphylococcus aureus*, *Staphylococcus pseudintermedius*, zoonosis

**INTRODUCTION**

*Staphylococcus aureus* (*S. aureus*) and *Staphylococcus pseudintermedius* (*S. pseudintermedius*) are considered part of the nasal microbiota of healthy humans and dogs/cats, respectively, but can also become opportunistic pathogens (Abdullahi, Lozano, et al., 2021; Ruiz-Ripa et al., 2021). In the nasal cavities of these pets, *S. pseudintermedius* is more frequently detected than *S. aureus* (Bannoehr & Guardabassi, 2012; Ruiz-Ripa et al., 2021). *S. pseudintermedius* is a significant aetiological agent of pyoderma, soft tissue, urinary tract and ear infections in dogs (Bannoehr & Guardabassi, 2012; Lynch & Helbig, 2021). Although humans are not the natural host of *S. pseudintermedius*, this microorganism could cause infections in persons with close contact with infected/colonized dogs (zoonotic transmission) (Carroll et al., 2021; Lozano et al., 2017).

*S. pseudintermedius*, described in Devriese et al. (2005), belongs to the *Staphylococcus intermedius* group (SIG) which encompasses four additional species, viz; *S. intermedius*, *S. delphini*, *S. cornubiensis* and *S. ursi* (Carroll et al., 2021). The last two species have been very recently described (Murray et al., 2018; Perreten et al., 2020). *S. pseudintermedius* is the most common skin commensal in dogs (Bannoehr & Guardabassi, 2012; Ma, Worthing, Ward, et al., 2020), but it is less prevalent in cats due to differences in skin cell adherence factors (Bierowiec et al., 2021; Mališová et al., 2019). This species can also be isolated in healthy donkeys or wild boar, among others (Gharsa, Slama, et al., 2015; Mama et al., 2019). In the earlier 2000s, *S. pseudintermedius* could not be accurately distinguished from *S. intermedius* using biochemical methods. Therefore, it was often incorrectly identified as *S. intermedius* (Börjesson et al., 2015).

Methicillin-resistant *S. aureus* (MRSA) represents a major challenge in human and animal infection control. Methicillin-resistant *S. pseudintermedius* (MRSP) has also become a global health problem in veterinary medicine and both *S. aureus*/MRSA and *S. pseudintermedius*/MRSP are of zoonotic relevance. The *meca* or *mecC* genes are responsible for methicillin resistance and confer reduced affinity for beta-lactam antimicrobials, and *meca* is found in most MRSA/MRSP isolates.

*Staphylococcus aureus*/MRSA nasal carriage in dogs and cats could be an indicator of increased risk of colonization/infection for persons in-contact with these animals by virtue of transmission processes in their shared household (Gómez-Sanz, Torres, Lozano, et al., 2013). Available molecular typing data revealed that companion animals could be carriers of *S. aureus*/MRSA human-associated clonal lineages of livestock-associated (LA) MRSA clones, which suggests reverse zoonosis and jump among hosts (Gómez-Sanz, Torres, Lozano, et al., 2013). In addition to MRSA, available literature has also highlighted MRSP as one of the most concerning multidrug-resistant staphylococci in pets’ health. There have been increasing reports of MRSP colonization and infection with high multidrug resistance in dogs and cats (Bierowiec et al., 2021; Lord et al., 2022; Papić et al., 2021).

It is crucial to have close surveillance on MRSP and MRSA in companion animals in place to determine their burden and direct adequate infection control in veterinary hospitals and the human–pet interface. While the molecular epidemiology of clinical MRSA and MRSP isolates in small animals has often been explored, very few have assessed the nasal carriage of *S. aureus* and *S. pseudintermedius* in healthy dogs and cats. Regarding *S. pseudintermedius*, molecular analysis has revealed that the global MRSP population are very diverse and have been identified in pets (Pires Dos Santos et al., 2016). Using MultiLocus Sequence Typing (MLST), studies have demonstrated between-country variations in common sequence types (STs) (Perreten et al., 2010; Pires Dos Santos et al., 2016). For *S. aureus* in pets, the mainly reported genetic lineages of MRSA in dogs and cats often depend on the geographical location, health status of pets and occupation of pets’ owners. For instance, community-associated MRSA (eg. CC22, CC30, CC5) and LA-MRSA (eg. CC398) clones have been widely reported (Aires-de-Sousa, 2017; Chueahiran et al., 2021; Gómez-Sanz, Torres, Lozano, et al., 2013; Ma, Worthing, Gottlieb, et al., 2020; Quitoco et al., 2013).

A recent global health research strategy emphasized the imperative need for an integrated surveillance system in the ‘One Health’ context of antimicrobial resistance (AMR) profiles of zoonotic bacteria including *Staphylococcus* spp (Dafale et al., 2020). Given the significant role of animals in the transmission of *Staphylococcus*...
sp. across other ecosystems (human and environment), the present study was designed to investigate the pattern and pooled prevalence of *S. aureus*, MRSA, *S. pseudintermedius* and MRSP in healthy dogs and cats and to provide a comprehensive review, analysing extracted data on their AMR, virulence and genetic lineages in the past two decades over the world.

**METHODOLOGY**

**Study design**

This systematic review was developed and executed on cross-sectional studies that reported *S. aureus*, *S. pseudintermedius*, MRSA and/or MRSP in the nasal cavities of healthy dogs and cats. This study did not require formal ethical approval, as the data used were obtained from previously published findings. This systematic review was based on the guidelines of Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) ([http://prisma-statement.org/PRISMAstatement/checklist.aspx](http://prisma-statement.org/PRISMAstatement/checklist.aspx), accessed on 1 October 2021). All literature describing canine and feline isolates formerly identified as *S. intermedius* will be referred to as *S. pseudintermedius*, unless otherwise shown by genomic investigation. Special focus was given to MRSA, MRSA-CC398, MRSA-CC22, MRSA-CC1, MRSA-CC5 and MSSA-CC398 among dogs/cats. Also, data about the AMR phenotypes and virulence genes were extracted.

**Articles search strategy**

This was a systematic and synthesizing review on nasal carriage of healthy dogs and cats by *S. aureus*, *S. pseudintermedius*, MRSA and/or MRSP. The entire literature search strategy, the selection of suitable published articles, the data extraction, the presentation of results and the statistical analyses were performed following the PRISMA guidelines. Published articles covering any or a combination of *S. aureus*, *S. pseudintermedius* and their meticillin-susceptible/resistant strains were reviewed using PubMed/MeLine, Scopus, Google scholar, Ajol, Embase, ScieLo and Web of Science databases. Original researches and brief communications (reports) published (in English) from 1 January 2001 to 1 October 2021 were searched in these databases. Studies were searched and identified using the medical subject headings (MeSH) or article titles or abstracts. For that, the following MeSH key words combination were used: “nasal *S. aureus* carriage in dogs”, “nasal *S. aureus* carriage in cats”, “Methicillin-Resistant *Staphylococcus aureus* in dogs”, “Methicillin-Resistant *Staphylococcus aureus* in cats”, “nasal MRSA in healthy dogs”, “nasal MSSA in healthy dogs”, “nasal MRSA in healthy cats”, “nasal MSSA in healthy cats”, “Methicillin-Resistant *Staphylococcus pseudintermedius* in healthy cats”, “Methicillin-Resistant *Staphylococcus pseudintermedius* in healthy dogs”, “nasal MRSP in healthy dogs”, “nasal MRSP in healthy cats”, “nasal *Staphylococcus pseudintermedius* in healthy dogs” and “nasal *Staphylococcus pseudintermedius* in healthy cats”. All eligible studies were scrutinized to identify potential articles from their reference lists. This study did not limit the search by any geographical location.

**Inclusion criteria**

Articles with appropriate and sufficient data about the prevalence of *S. aureus*, *S. pseudintermedius*, MRSA and/ or MRSP nasal carriage, in healthy dogs/cats (pets in the community, outside veterinary clinics) were selected and extensively reviewed. Data from these studies were extracted and utilized to determine the pooled prevalences of *S. aureus*, *S. pseudintermedius*, MRSA and MRSP nasal carriages in healthy dogs and cats (studies with sample size higher than 10). To avoid error from data selections, the pooled prevalence values were computed from only studies with a cross-sectional design. A dog or cat was considered healthy if there was no reported history of current disease or illness and no abnormalities detected on full physical examination in the eligible study. The MRSA or MRSP status was defined by the identification of resistance by phenotypic methods (using oxacillin or cefoxitin, according to the susceptibility method used and the microorganism) and/or meca positivity by polymerase chain reaction (PCR) or agglutination tests.

All original or brief communication studies on the molecular typing of *S. aureus*, *S. pseudintermedius*, MRSA and/or MRSP in healthy dogs and cats regardless of whether they were cross-sectional or not were considered and included in the systematic review of genetic lineages of data of the isolates. Also, this was regardless of the number of animals tested in contrast to the criterion for determination of pooled prevalence (i.e. a sample size of >10). The search also included *S. intermedius* as well for the dates prior to the accurate discrimination of *S. intermedius* and *S. pseudintermedius*.

**Exclusion criteria**

(i) Studies that contained duplicate data or were overlapping articles; (ii) reviews and conference abstracts; (iii) cross-sectional studies that included fewer than 10 dogs
or cats; (iv) studies on sick or healthy dogs and cats in the veterinary clinics and hospitals, (v) studies on dogs or cats owned by a veterinarian, (iv) studies on wound scrapings, buccal, tracheal, skin, ear, faecal and other animal samples were excluded.

Data extraction process

Where possible and appropriate, authors; year of study; study design; study setting or location; the number of *S. aureus*, *S. pseudintermedius*, MRSP, MRSA, MSSP, and/or MSSA isolates; type of specimen; laboratory method employed for detection; antimicrobial susceptibility phenotypes and corresponding genotypes and molecular types were reviewed and extracted. When there was disagreement, the relevant paper was reviewed, and the differences were resolved by the authors’ consensus. Finally, 49 full-text articles were included. These directly focused on the distribution pattern of the *S. aureus*, MRSA, *S. pseudintermedius*, MRSP, genetic lineages, AMR phenotypes and genotypes, and/or virulence genes in nasal cavities of healthy dogs and cats.

Statistical analysis

The pooled prevalence of nasal carriage of *S. aureus*, MRSA, *S. pseudintermedius* and MRSP was calculated. MedCalc version 20.013 was used for all statistical analyses. Where possible, analyses of pooled prevalence and corresponding 95% confidence intervals (CI) were carried out using the random-effects model. The pooled prevalence was computed by combining the results of the positive cases and the total number of animals. Where possible, analyses of pooled prevalence and corresponding 95% confidence intervals (CI) were carried out using the random-effects model. The pooled prevalence of nasal carriage of *S. pseudintermedius* and MRSP was calculated.

MAIN FINDINGS AND DISCUSSION

Studies characteristics

Out of the 49 eligible and analysed studies (Figure 1), 47 studies were on *S. aureus* and/or *S. pseudintermedius*. Three nasal carriage in healthy dogs and cats, respectively (Table S1). Of these, three studies on healthy dogs or cats reported *S. intermedius* instead of *S. pseudintermedius* (Chasioti et al., 2019; Elnageh et al., 2021; Epstein et al., 2009); however, due to suspected misidentification, all the *S. intermedius* isolates for dogs/cats were considered as *S. pseudintermedius* for this systematic review. It is important to remark that some studies simultaneously investigated staphylococci in both dogs and cats. Table S1 shows the characteristics and data of the eligible studies, countries of the studies, type of pets (divided into dogs and cats), number of pets tested, number of *S. aureus*, *S. pseudintermedius* and MRSA/MRSP obtained from the studies, and the AMR phenotypes and genes, as well as the virulence factors detected from *S. aureus* and/or *S. pseudintermedius* isolates.

The pooled prevalence of nasal carriage of *S. aureus*, *S. pseudintermedius*, MRSA and MRSP in healthy dogs and cats

The pooled prevalence of nasal carriage of *S. aureus* in healthy dogs and cats was 10.9% (95% CI: 10.1–11.9) and 3.2% (95% CI: 1.9–4.8) respectively (Table 1). Although, relatively low when compared to the pooled prevalence of nasal *S. aureus* carriage in healthy humans (15.9%) and nasotracheal carriage in healthy wild animals (18.5%) (Abdullahi, Fernández-Fernández, et al., 2021; Abdullahi, Lozano, et al., 2021), the pooled prevalence of nasal *S. aureus* carriage in healthy dogs was higher than in cats. The reason for this observation is not fully understood as both dogs and cats frequently come in close contact with humans in the household environment, showing a similar risk of *S. aureus* acquisition from humans.

From our analysis, the pooled prevalence of nasal carriage of *S. pseudintermedius* in dogs and cats was 18.3% (95% CI: 17.1–19.7) and 1.3% (95% CI: 0.6–2.4), respectively (Table 1). *S. pseudintermedius* carriage is frequently higher in healthy dogs than in healthy cats. Moreover, comparing *S. pseudintermedius* and *S. aureus* carriage, *S. pseudintermedius* carriage is also higher than *S. aureus* in these animals. *S. pseudintermedius* is considered an opportunistic pathogen that could cause severe and necrotizing infections of the skin, ears, bones and post-surgical abscesses (Bannoehr & Guardabassi, 2012). Moreover, *S. pseudintermedius* could also be found in humans acquired by zoonotic transmission from colonized dogs (Carroll et al., 2021; Lozano et al., 2017; Somayaji et al., 2016) and may be misdiagnosed as *S. aureus* in human infections (Börjesson et al., 2015). To the best of our knowledge, no study determined the pooled prevalence of *S. pseudintermedius* nasal carriage in healthy dogs. Differences were observed in the prevalence of *S. pseudintermedius* nasal carriage among the eligible studies; for instance, some reported a very high prevalence (74.7%) (Garbacz et al., 2013). This difference in prevalence is multifactorial,
it could be related to the environment of the dogs, and owners’ and animals’ health statuses.

In relation to MRSA, the growing concern about the spread of MRSA in communities has led to the establishment of recommendations for surveillance, including research into the rate of colonization in healthy dogs, including stray dogs present in public areas. The pooled prevalence of canine MRSA nasal carriage (2.8% [95% CI: 2.4–3.2]) was relatively higher than that of the feline carriage (0.5% [95% CI: 0.0–1.1]) (Table 1). The exposure of pets to their living environment or persistently colonized humans or other animals can be considered a risk factor for colonization with MRSA strains; thus, it is essential to identify community and environmental reservoirs and sources of MRSA in healthy dogs and cats (Mohamed et al., 2020). MRSA nasal carriage in healthy cats was detected by five studies in Libya, the United States, Brazil, the United Kingdom and Saudi Arabia (Elmoslemany et al., 2021; Elnageh et al., 2021; Gingrich et al., 2011; Loeffler et al., 2011; Quitoco et al., 2013) (Table S1).

Moreover, nasal MRSA in healthy dogs has been studied and detected in all continents (Table S1). From our analysis, the pooled prevalence of nasal carriage of MRSP in dogs and cats was 3.1% (95% CI: 2.5–3.7) and 1.2% (95% CI: 0.6–2.3) respectively (Table 1).

The complex relationships between bacterial species from different hosts facilitate genetic flow, extending AMR between humans, animals and the environment, resulting in public health concerns. Of this, methicillin resistance is one of the major and significant AMR of zoonotic importance. A companion animal may play an important role in the maintenance and transmission of MRSP or MRSA in the household (Gómez-Sanz, Torres, Lozano, et al., 2013).

It is important to remark that there was a variation in the pooled prevalence of S. aureus/S. pseudintermedius and MRSA/MRSP across the continents (Figure 2). Nevertheless, when interpreting these data, it should be noted that they may be influenced by regional or local epidemiologies of S. aureus/S. pseudintermedius. Particularly, the pooled MRSA and MRSP prevalence were highest in Africa and Asia respectively. In these cases, these variations could also be due to differences in used methodologies,
and other potential reasons such as pets care (especially animal hygiene), environmental sanitation or antibiotic use in animals and humans in these continents (Collignon & Voss, 2015; Fletcher, 2015; Valiakos et al., 2020).

Antibiotic resistance phenotypes and genotypes of *S. aureus* and *S. pseudintermedius* detected from nasal cavities of healthy dogs and cats

In the studies included in this systematic review, it appeared that both MRSA and MSSA had resistance against non-beta-lactam antimicrobials, such as fluoroquinolones, aminoglycosides, tetracyclines, sulphonamides, macrolides, and/or lincosamides (Tables 2 and 3). Based on the WHO classification of antimicrobials into highly important versus critically important classes of antimicrobial agents (World Health Organization, 2017), some antibiotics of zoonotic relevance in each class are discussed below.

Regarding methicillin resistance, out of the 21 studies that reported nasal MRSA in healthy dogs or cats, 17 investigated and detected the *mecA* gene. However, none reported the *mecC* gene (Tables 2 and 3). In dogs, *S. aureus* isolates were frequently resistant to tetracycline, aminoglycosides, rifampicin, sulphonamides and/or chloramphenicol (Table 2). *S. pseudintermedius* strains presented wider AMR patterns (phenotype and genotype) than those reported in nasal *S. aureus* of healthy dogs. In a recent study, *S. pseudintermedius* from dogs showed more frequently a MDR phenotype (45.5%) than *S. aureus* (40.9%) in a collection of isolates obtained between 2007 and 2016 (Lord et al., 2022).

Aside from the cefoxitin/oxacillin resistance detected in MRSA and MRSP, sulfamethoxazole-trimethoprim and ciprofloxacin resistances were the most predominant in healthy cats (reported in 4 and 3 out of 5 studies respectively). Other antibiotic resistances detected included erythromycin and clindamycin (inducible), amikacin, enrofloxacin and tetracycline (Table 3). Remarkably, Gómez-Sanz, Torres, Lozano, et al. (2013) detected the resistance genes *tet(M)*, *erm(B)*, *aphA*, *aadE* and *sat4* in MSSP isolates from healthy cats in Spain. Moreover, Rynhoud et al. (2021) detected some genes responsible for sulfamethoxazole-trimethoprim and aminoglycoside resistance in MRSP (*dfrG* and *aac(6’)-aph(2’)*, *aadD*, *ant6-Ia*, and/or *aph3-III* respectively). A wide variation in *S. aureus* resistance patterns was detected in many studies, but penicillin and ciprofloxacin resistances were frequently detected in *S. aureus* and *S. pseudintermedius* that colonize healthy cats (Table 3). MDR phenotype has also been reported to be common among *S. pseudintermedius* strains from diseased pets (100.0%) than healthy ones (73.0%) (Rynhoud et al., 2021).
Focusing on some antimicrobials of great importance for human and animal health (or for epidemiological purposes), tetracycline resistance was reported in healthy cats in only one study related to MSSA isolates in Saudi Arabia (Elmoslemany et al., 2021). In contrast, tetracycline resistance was detected in nasal MRSA and MSSA isolates from healthy dogs in 12 studies (Table 2). Specifically, out of the 61 pooled MRSA isolates from nasal cavities of healthy dogs, 24 (39.3%) were tetracycline resistant. However, eight (8.9%) out of the 89 pooled MSSA isolates from eligible studies were tetracycline resistant (data obtained from Table 2). The lineages MSSA- ST1212/t582, MSSA- ST121/t159 and MRSA- ST59 were detected among tetracycline-resistant isolates (Gharsa, Ben Slama, et al., 2015; Gómez-Sanz, Torres, Lozano, et al., 2013; Wan et al., 2012). The elevated frequency of tetracycline resistance found may be related to the frequent use of this antimicrobial agent (first-line) in dogs and cats. This phenotype of resistance has been proposed as a good marker of MRSA isolates belonging to clonal lineages associated with livestock animals, especially CC398 (Benito et al., 2014; Ceballos et al., 2020).

In healthy dogs, four studies also reported varying ciprofloxacin resistance among nasal S. aureus isolates, with a range of 40.7%–100.0% (Abdel-Moein et al., 2012; Coelho et al., 2011; Myaing et al., 2016; Wedley et al., 2014). Of the four studies, the pooled prevalence of ciprofloxacin resistance in S. aureus nasal isolates from healthy dogs was 53.9% (55 out of 102 isolates). Ciprofloxacin resistance was reported in S. aureus isolates in two studies of healthy cats (Elnageh et al., 2021; Gharsa, Ben Slama, et al., 2015). None of the S. aureus studies reported the molecular mechanisms implicated. In the case of S. pseudintermedius, the GyrA [Ser84Leu, Glu714Lys, Ser84Leu] and GrlA [Ser80Ile] amino acid substitutions were reported from MRSP isolates of healthy dogs in one unique study (Gómez-Sanz et al., 2011); these mutations are associated with decreased susceptibility to ciprofloxacin and other fluoroquinolones in staphylococci (Rynhoud et al., 2021).

In healthy dogs, four studies reported gentamicin resistance in S. aureus strains from healthy dogs, many studies reported the detection of erythromycin resistance (Table 2). Similarly, two studies reported the erythromycin-clindamycin inducible resistance phenotype in nasal S. pseudintermedius isolates from healthy dogs and cats (Gómez-Sanz, Torres, Lozano, et al., 2013; Van Balen et al., 2017).

Recently, an increasing penicillin susceptibility rate is being detected among invasive MSSA human isolates, opening therapeutic opportunities for these infections; this phenotype has been frequently found among scn-negative or CC398 isolates suggesting a potential animal association (Mama, Aspiroz, Lozano, et al., 2021). In this review, penicillin susceptibility was reported in 79.2% (n = 19) of the MSSA isolates detected from healthy dogs by Gómez-Sanz, Torres, Benito, et al. (2013), and seven of these isolates (36.8%) belonged to the CC398 clone.

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Nine studies of healthy dogs or cats reported gentamicin resistance in S. aureus (Table 2), but only one of these studies indicated the bifunctional gene, aac(6’)-aph(2’”) as the mechanism implicated (Coelho et al., 2011).
| Reference                | Country         | Sample size | No. of *S. aureus* (%)/*MRSA* (%) | No. of *S. pseudintermedius* (%)/*MRSP* (%) | Antimicrobial resistance phenotype | Antimicrobial resistance genes |
|--------------------------|-----------------|-------------|-----------------------------------|-------------------------------------------|-----------------------------------|---------------------------------|
| Katakweba et al. (2016)  | Tanzania        | 100         | 11 (11.0)/0 (0.0)                 | ND                                        | SA: AMP, TET                      | NT                              |
| Wachtmeister (2018)      | Uganda          | 39          | 5 (12.8)/2 (5.1)                  | 10 (25.6)/0 (0.0)                         | SA: ERY, FOX, TET                 | MRSA: *mecA*                     |
| Mustapha et al. (2016)   | Nigeria         | 211         | 78 (36.9)/50 (23.7)               | ND                                        | SA: CLI, ERY, FOX, OXA, TET       | MRSA: *mecA*                     |
| Daodu et al. (2016)      | Nigeria         | 173         | 31 (14.0)/NT                      | ND                                        | SA: AMP, GEN, STR, SXT            | NT                              |
| Moses et al. (2020)      | Nigeria         | 35          | ND                                 | 25 (71.4)/18 (51.1)                       | SP: AMP, CHL, CIP, LEV, OFL, OXA  | MRSP: *mecA*                     |
| Abdel-Moein et al. (2012)| Egypt           | 48          | 1 (2.1)/1 (2.1)                   | NT                                        | SA: CLI, CIP, FOX, GEN, OXA, RIF, SXT | MRSA: *mecA*                     |
| Gharsa et al. (2013)     | Tunisia         | 100         | ND                                 | 55 (55.0)/0 (0.0)                         | SP: CHL, CIP, CLI, ERY, KAN, PEN, SXT, TET | MRSP: *mecA*                     |
| Gharsa, Ben Slama, et al. (2015) | Tunisia | 100         | 4 (4.0)/0 (0.0)                   | ND                                        | SA: ERY, PEN, TET                 | MRSP: *mecA*                     |
| Quitoco et al. (2013)    | Brazil          | 70          | NR/0 (0.0)                         | NR/1 (1.4)                               | MRSP: CLI, CHL, FOX, ERY, GEN, OXA, PEN, TET | MRSP: *mecA*                     |
| Fabri et al. (2021)      | Brazil          | 241         | 38 (15.8)/3 (1.2)                 | ND                                        | SA: FOX, OXA                      | MRSA: *mecA*                     |
| Penna et al. (2021)      | Brazil          | 88          | NT/3 (3.4)                         | NT                                        | MRSA: CHL, ENR                    | MRSA: *mecA*                     |
| Rubin and Chirino-Trejo (2011) | Canada   | 175         | ND                                 | 75 (42.9)/0 (0.0)                         | SP: PEN, ERY, CLI, TET           | NT                              |
| Van Balen et al. (2017)  | USA             | 113         | 7 (8)/0 (0.0)                     | NT                                        | AMP, ERY, CLI<sup>abd</sup>       | ND                              |
| Han et al. (2015)        | South Korea     | 92          | NT                                 | 32 (34.8)/22 (23.9)                       | MRSP: OXA                        | MRSP: *mecA*                     |
| Wan et al. (2012)        | Taiwan          | 776         | 20 (2.6)/1 (0.13)                 | NT                                        | SA: CHL, CLI, ERY, FOX, GEN, OXA, TET | MRSA: *mecA*                     |

(Continues)
| Reference                  | Country      | Sample size | No. of S. aureus (%) / MRSA (%) | No. of S. pseudintermedius (%) / MRSP (%) | Antimicrobial resistance phenotype | Antimicrobial resistance genes                                                                 |
|----------------------------|--------------|-------------|---------------------------------|-------------------------------------------|-----------------------------------|---------------------------------------------------------------------------------------------|
| Boost et al. (2007)        | Hong Kong    | 815         | 73 (8.9)/6 (0.74)               | NT                                        | SA: CLI, CHL, ERY, GEN, OXA, PEN, SXT, TET                                              |
| Epstein et al. (2009)      | Hong Kong    | 35          | 0 (0.0)/0 (0.0)                 | NR/6 (17.1)                               | MRSP: FOX, GEN, PEN                                                                        |
| Myaing et al. (2016)       | Myanmar      | 65          | NR/31 (47.7)                    | NT                                        | MRSA: AMP, CLI, CIP, ERY, LZD, RIF, SXT, TET                                             |
| Rahman et al. (2018)       | Bangladesh   | 36          | 9 (25.0)/4 (11.1)               | NT                                        | SA: OXA                                                                                  |
| Decline et al. (2020)      | Indonesia    | 50          | 24 (48.0)/14 (28.0)             | NT                                        | SA: AMK, CLI, ERY, FOX, OXA, PEN, SXT, TET                                              |
| Sekhar et al. (2017)       | India        | 40          | 14 (35.0)/5 (12.5)              | NR                                        | SA: PEN, FOX                                                                             |
| Rynhoud et al. (2021)      | Australia    | 61          | 0 (0.0)/0 (0.0)                 | NT/7 (11.5)                               | MRSP: CLI, CHL, ERY, ENR, GEN, SXT, TET                                                  |
| Gómez-Sanz et al. (2011)   | Spain        | 196         | NR                              | NR/9 (4.6)                                | MRSP: CLI, ERY, FOX, CIP, GEN, KAN, OXA, STR, SXT, TET                                  |
| Gómez-Sanz, Torres, Benito, et al. (2013) | Spain | 54          | 5 (9.2)/0 (0.0)                 | 14 (25.9)/2 (3.7)                         | SA: ERY, CLI, PEN SP: CIP, FUS, GEN, OXA, PEN, TET                                       |
|                            |              |             |                                 |                                           | SR: blaZ, erm(A) SP: mecA, aac(6’)-aph(2’), aphA-3, aadE, blaz, dfr(G), erm(B), GyrA [Ser84Leu, Glu714Lys, Ser84Leu] and GrlA [Ser80Ile], tet(K), sat4 |

**TABLE 2** (Continued)
| Reference                  | Country       | Sample size | No. of S. aureus (%) / MRSA (%) | No. of S. pseudintermedius (%) / MRSP (%) | Antimicrobial resistance phenotype | Antimicrobial resistance genes |
|----------------------------|---------------|-------------|---------------------------------|----------------------------------------|-----------------------------------|--------------------------------|
| Gómez-Sanz, Torres, Lozano, et al. (2013) | Spain         | 98          | 24/0 (0.0)                      | 22 (22.4)/8 (8.2)                      | SA: CLI<sup>ind</sup>, ERI, PEN, STR, TET | SA: blaZ, erm(C), erm(A), str, tet<sup>K</sup> |
|                            |               |             |                                 |                                        | SP: CLI<sup>ind</sup>, CHL, ERY, KAN, PEN, STR, TET | SP: aphA3, aadE, blaZ, erm(B), sat4, tet(<i>L</i>), tet(M) |
| Loeffler et al. (2010)     | UK            | 129         | NR/10 (7.8)                     | ND                                     | MRSA: FOX                          | MRSA: mecA                       |
| Loeffler et al. (2011)     | UK            | 302         | NR/2 (0.66)                     | NT                                     | MRSA: FOX                          | MRSA: mecA                       |
| Schmidt et al. (2014)      | UK            | 73          | 6 (8.2)/0 (0.0)                 | 32 (43.8)/0 (0.0)                      | SA: FUS, GEN, TET                   | NT                             |
|                            |               |             |                                 |                                        | SP: CIP, FUS, GEN, TET              |                                |
| Wedley et al. (2014)       | UK            | 724         | 54 (7.5)/7 (0.9)                | 80 (11.0)/0 (0.0)                      | SA: CIP, FOX, GEN, RIF, TET         | MRSA: mecA, erm(C)               |
|                            |               |             |                                 |                                        | SP: CIP, GEN, SXT, TET              |                                |
| Coelho et al. (2011)       | Portugal      | 54          | NR/16 (29.6)                    | NR                                     | MRSA: CIP, CLI, ERY, GEN, KAN, TOB  | MRSA: mecA, aac(6')-aph(2''), ant(4')-Ia, aph(3')-III, ermB, ermC, msrA, tet(M) |
|                            |               |             |                                 |                                        |                                   |                                |
| Chasioti et al. (2019)     | Greece        | 33          | 2 (6.1)/0 (0.0)                 | 0 (0.0)/0 (0.0)                        | SA: ERY, PEN                        | NT                             |
|                            |               |             |                                 |                                        |                                   |                                |
| Loncaric et al. (2019)     | Austria       | 152         | NT                              | NR/2 (1.3)                            | MRSP: AMK, CLI, CIP, ERY, GEN, OXA, SXT, TET | MRSP: mecA, aac(6')-aph(2''), dfRG, erm(B), aac(6')-Ie. tet(K) |
|                            |               |             |                                 |                                        |                                   |                                |
| Bean & Wigmore, 2016       | Australia     | 117         | 7 (5.9)/0 (0.0)                 | 52 (44.4)/1 (0.85)                     | SA: PEN                            | MRSP: mecA                       |
|                            |               |             |                                 |                                        | SP: PEN, TET, OXA                   |                                |

(Continues)
Regarding *S. pseudintermedius*, nine studies reported the detection of gentamicin resistance in isolates from healthy dogs (Table 2), however, only four showed the molecular mechanism implicated for this resistance. Different aminoglycoside resistance genes have been detected in the eligible studies (\( \text{aac(6')-aph(2'\prime)} \), \( \text{aph(3')-III} \), \( \text{aadD} \), \( \text{ant6-Ia} \)) (Gómez-Sanz, Torres, Benito, et al., 2013; Gómez-Sanz et al., 2011; Loncaric et al., 2019; Rynhoud et al., 2021).

### Genetic lineages associated with *S. aureus* isolates from the nasal cavities of healthy dogs and cats

In relation to nasal MSSA isolates from healthy dogs, the lineages CC1, CC5, CC22, CC45, CC121 and CC398 were predominant, although CC15, CC30, CC88, CC97 and CC133 were also reported; these lineages are generally associated with both humans and animals. Moreover, the lineages CC22 and CC30, that were identified among canine MRSA isolates, are known human-associated clones (Table 4). On the other hand, the lineages CC5, CC15, CC45 and CC8 were found in MSSA isolates of healthy cats, and CC22, CC80 and CC30 among feline MRSA isolates (Table 4).

CC398 is a relevant clonal lineage due to its possible relationship with farm animals or veterinary farmers. In recent years, two CC398 clades have been proposed, one animal subclade more associated with MRSA and one human subclade related to MSSA. The CC398 lineage was reported in healthy dogs in only one study performed in Spain (Gómez-Sanz, Torres, Benito, et al., 2013), in which all isolates were MSSA. The MSSA-ST398 lineage represented 29.2% of the total *S. aureus* isolates recovered from the dogs in this study and no data about the possible contact with livestock were available for these animals. These MSSA-ST398 isolates presented the *spa*-types t034, t108 and t5883 (Table 4). Despite the methicillin susceptibility of these strains (that could suggest the human-related livestock-independent subclade), the detection of the *spa*-type t034 and the absence of the IEC system (*scn*-marker) infer an animal (or livestock) origin (Mama, Aspiroz, Ruiz-Ripa, et al., 2021). MSSA-CC398 isolates have also been detected in wild birds (such as storks), also in Spain, but the isolates presented the *spa*-types t571 and t6606; and were *scn*-positive (Gómez et al., 2016).

Regarding CC133, it is a well-known small ruminant-associated lineage (Guinane et al., 2010), that has been detected as a predominant *S. aureus* lineage in cats in Japan (Sasaki et al., 2012), and in a collection of large felines from a Danish Zoo (Espinosa-Gongora et al., 2012).

Among other STs isolated from dogs, ST1/CC1 was the most frequently reported in most eligible dogs’ studies. It is a
# Table 3: Antimicrobial resistance phenotypes and genotypes of *Staphylococcus pseudintermedius* and *S. aureus* isolates from the nasal cavities of healthy cats

| Reference                        | Country     | Sample size | No. of *S. aureus* (%)/MRSA (%) | No. of *S. pseudintermedius* (%)/MRSP (%) | Antimicrobial resistance phenotype | Antimicrobial resistance genes |
|----------------------------------|-------------|-------------|----------------------------------|-------------------------------------------|-----------------------------------|-------------------------------|
| Elnageh et al. (2021)            | Libya       | 62          | 3 (4.8)/1 (1.6)                  | NT                                        | NT                               | MRSA: meca                      |
| Gharsa, Ben Slama, et al. (2015) | Tunisia     | 34          | 2 (5.9)/0 (0.0)                  | ND                                       | SA: CLI, CIP, ERY, GEN, PEN       | MRSA: blaZ                      |
| Quitoco et al. (2013)            | Brazil      | 60          | NR/1 (1.7)                       | NR/0 (0.0)                               | MRSA: FOX, OXA                   | MRSA: meca                      |
| Gingrich et al. (2011)           | USA         | 200         | NR/1 (0.5)                       | NR/0 (0.0)                               | NT                               | NT                            |
| Elmoslemany et al. (2021)        | Saudi Arabia| 209         | 5 (2.4)/1 (0.48)                 | 1 (0.48)/0 (0.0)                         | SA: ERY, FOX, GEN, PEN, TET      | MRSA: meca                      |
| Gómez-Sanz, Torres, Benito, et al. (2013) | Spain     | 12          | 3 (25.0)/0 (0.0)                 | 1 (8.3)/0 (0.0)                           | SA: PEN                         | SP: blaZ                        |
|                                   |             |             |                                  |                                           | SP: CLI ind, CHL, ERY, PEN, STR, TET | SP: aphA3, aadE, blaZ, catpC221, erm(B), tet(M), sat4 |
| Loeffler et al. (2011)           | UK          | 216         | NT/1 (0.46)                      | NT                                        | MRSA: FOX                       | MRSA: meca                      |
| Chasioti et al. (2019)           | Greece      | 22          | 0 (0.0)/0 (0.0)                  | 3 (13.6)/0 (0.0)                         | SP: PEN                         | NT                            |
| Rynhoud et al. (2021)            | Australia   | 127         | 0 (0.0)/0 (0.0)                  | NT/9 (7.1)                               | MRSP: CLI, CHL, ENR, ERY, GEN, SXT, TET | MRSP: mecA, mecA. aac(6′)-aph(2″), aadD, ant6-la, aph3-III, blaZ, cat-pC221, dfrG, ermB, ermC, sat4A, tet(M) |
| Ma, Worthing, Gottlieb, et al. (2020) | Australia | 80          | 0 (0.0)/0 (0.0)                  | 0 (0.0)/0 (0.0)                           | NT                              | NT                            |

Abbreviations: NT, not tested; ND, not detected; NR, not reported in detail.; SA, *S. aureus*; SP, *S. pseudintermedius*; MRSA, methicillin-resistant *S. aureus*; MRSP, methicillin-resistant *S. pseudintermedius*; ind, inducible.; AMK, amikacin; CHL, chloramphenicol; CLI, clindamycin; CIP, ciprofloxacin; ENR, enrofloxacin; ERY, erythromycin; FOX, cefoxitin; GEN, gentamicin; PEN, penicillin; RIF, rifampicin; SXT, trimethoprim/sulfamethoxazole; TET, tetracycline.
| Reference | Country | No. of S. aureus/no. of MRSA | Molecular typing of MSSA (no. of isolates, when available) | Molecular typing of MRSA isolates (no. of isolates, when available) |
|-----------|---------|----------------------------|--------------------------------------------------|--------------------------------------------------|
| **Healthy dog population** | | | | |
| Gharsa, Ben Slama, et al. (2015) | Tunisia | 4/0 | t701 (2), t582, t178/t701 (2) | ST2121, ST6 (2), ST188, MT6 (2) |
| | | | | CC5 (2), CC15, CC30, CC5 (2) |
| Katakweba et al. (2016) | Tanzania | 11/0 | t314/t064, t223, t267, t1476, t508/t127 (4) | ST1 (4), ST121, ST15, ST18, ST2, ST97, ST1 (4) |
| | | | | NR |
| Van Balen et al. (2017) | USA | 7/0 | NT | USA600 (3), USA300 (2), USA100 (1), group C (1) |
| | | | | NT |
| Coelho et al. (2011) | Portugal | NR/16 | NR | NR |
| | | | | t032 (7), t747 (6), t432 (2), t127 (1) |
| Loeffler et al. (2011) | UK | 0/2 | NT | NT |
| | | | | t032 (5), t022 (1), t3213 (1) |
| Wedley et al. (2014) | UK | 758/7 | t2133, t304, t026, t660, t012, t019, t1010, t474, t27, t272, t287, t160, t002, t409, t688 | NT |
| | | | | NT |
| Gómez-Sanz, Torres, Benito, et al. (2013) | Spain | 24/0 | t034 (4), t5883 (2), t108 (1), t166, t002, t77, t8765, t40, t015, t8764 | ST398 (7), ST133, ST2329, ST1, ST5, ST146, ST188, ST1655, ST15, ST78, ST45, ST217 |
| | | | | CC398 (7), CC133, CC5, CC88, CC45, CC22 |
| Gómez-Sanz, Torres, Lozano, et al. (2013) | Spain | 5/0 | t021, t073, t159, t151 (2) | ST45, ST121 (3) |
| | | | | CC45, CC121 (3) |
| Ma, Worthing, Gottlieb, et al. (2020) | Australia | NR/5 | NT | NT |
| | | | | t127 (1), t202 (2), other two are non-typeable |
| **Healthy cat population** | | | | |
| Gharsa, Ben Slama, et al. (2015) | Tunisia | 2/0 | t279, t701 | ST15, ST6 |
| | | | | CC5, CC15 |
| Quitoco et al. (2013) | Brazil | NR/1 | NT | NT |
| | | | | NT |
| Elmoslemany et al. (2021) | Saudi Arabia | 5/1 | NT | NT |
| | | | | NT |
| Rynhoud et al. (2021) | Australia | NT/9 | NT | NT |
| | | | | NT |
| Loeffler et al. (2011) | UK | 0/2 | NT | NT |
| | | | | NT |
| Gómez-Sanz, Torres, Lozano, et al. (2013) | Spain | 3/0 | t073, t002, t711 | ST45, ST5, ST2176 |
| | | | | CC45, CC5, CC8 |

Abbreviations: CC, clonal complex; ND, not detected; NR, not reported in detail; NT, not tested; ST, sequence type.
lineage that has no host specificity, as it has also been associated with rabbits, horses, cattle and swine (Alba et al., 2015; Feltrin et al., 2016; Islam et al., 2017; Silva et al., 2020). Conversely, MRSA-CC1 has often been linked to hospital-associated outbreaks, especially in the intensive care unit (Monecke et al., 2020). The role of pets in the dissemination of *S. aureus* CC1 isolates should be evaluated in the future.

The ST22 lineage is found in many of the MRSA isolates from dogs and it is known as a human epidemic clone (EMRSA-15) (Katakweba et al., 2016). The EMRSA-15 (ST22) is predominantly a pandemic MRSA isolated both in hospital and community settings. It was estimated that ∼98% of all ST22 isolates reported in the literature have been associated with humans (Roberts et al., 2018). However, this ST has previously been isolated from dogs in other geographical regions, supporting the notion that this *S. aureus* lineage may have adapted to the canine host (Katakweba et al., 2016). Nevertheless, this clone may be of human origin and transmitted to dogs in the household environment. The other predominant lineage detected among MRSA from dogs was ST36, which is one of the three pandemic lineages that have been described within CC30 causing epidemic waves (Di Gregorio et al., 2021). Moreover, MRSA isolates of the genetic lineages ST5 and ST93 were also reported in nasal strains from healthy dogs in Australia (Ma, Worthing, Ward, et al., 2020).

In cats, MRSA isolates belonging to ST80, ST30, ST496, ST749, ST71, ST316, ST84 and CC22 genetic lineages were identified in four of the eligible studies (Elmoslemany et al., 2021; Loeffler et al., 2011; Quitoco et al., 2013; Rynhoud et al., 2021). In relation to nasal MSSA of healthy cats’ samples, only two eligible studies carried out the molecular typing of isolates with the detection of lineages CC5, CC15, CC45 and CC8 (Gharsa, Ben Slama, et al., 2015; Gómez-Sanz, Torres, Benito, et al., 2013) (Table 4). It is interesting to note that the genetic lineage CC22, often considered HA-MRSA, and a frequent lineage in dogs was in addition detected in one study on healthy cats (Loefller et al., 2011).

The definition of community- and hospital-associated strains is no longer a strict one, as CA-MRSA strains have been described to be responsible for outbreaks in hospital settings, while HA-MRSA strains have been reported spreading in the community (Bal et al., 2016; Coll et al., 2017). However, it is crucial to delineate the pattern of predominant transmission and degree of spillover from community to hospital and vice-versa. The ability of MRSA-ST80 to disseminate at the community level has been reported (Drougka et al., 2016; Mairi et al., 2020). Furthermore, the transmission of MRSA-ST80 among different host species in the context of households and veterinary practices has been described by Drougka et al. (2016), who reported that dogs and cats can be the reservoir of MRSA-ST80 which can cause severe infection in humans. The so-called paediatric clone, CC5, has globally been associated with community outbreaks (McManus et al., 2021).

**Genetic lineages associated with *S. pseudointermedius* isolates from the nasal cavities of healthy dogs and cats**

Out of the eight studies with molecular typing on *S. pseudointermedius* in healthy dogs, a great diversity of lineages was reported among MSSP isolates, and no specific predominance was observed (Table 5). As observed in the current review, high MLST clonal diversity is a common characteristic of MSSP (Pires Dos Santos et al., 2016). The diverse global population structures of *S. pseudintermedius* are evident in the world map comparing shared STs (Perreten et al., 2010).

Moreover, diverse lineages were also detected among MRSP of healthy dogs, although ST71 lineage was predominant (14.6% of isolates), detected in studies carried out in Spain, Brazil and Australia (Table 5). MRSP isolates of the lineage ST71 have largely been associated with sick dogs. Although the ST71 was considered a major MRSP-clone in Europe, recent studies have reported a downward trend in the prevalence of the MRSP-ST71 lineage among companion animals in France, Netherlands and Finland (Bergot et al., 2018; Duim et al., 2016; Grönthal et al., 2017). In relation to MRSP-ST71 from nasal swabs of healthy cats and dogs, other non-European countries have reported this clone, such as Australia (Rynhoud et al., 2021). It could be that veterinary personnel acted as carriers and facilitated the transmission of the MRSP-ST71 clone between animals they handle, or pet owners who interact with other dogs in the community such as in dogs’ parks. The MRSP-ST71 has already been incriminated in potential zoonotic diseases (Kitagawa et al., 2021), reflecting the recent emergence of these important multidrug-resistant bacteria in animal and public health. Conversely, the other clone of high relevance, especially in the USA, MRSP-ST68, was not reported from nasal cavities of healthy dogs and cats in the studies included in this systematic review.

Although none of the MRSP isolates from cats was genetically characterized, an MSSP isolate was found to be ST142 by Gómez-Sanz, Torres, Lozano, et al. (2013) (Table 5). Although the MSSP-ST142 is a rarely reported lineage in cats, it has been detected in household dogs, and their owner; and could represent a case of transmission between dogs and cats in the same household.
### Table 5 Molecular typing reports of *Staphylococcus pseudintermedius* isolated from the nasal cavities of healthy dogs and cats

| Reference                                | Country     | No. of *S. pseudintermedius* / no. of MRSP | Molecular typing of MSSP (no. of isolates, when available) | Molecular typing of MRSP isolates (no. of isolates, when available) |
|------------------------------------------|-------------|-------------------------------------------|------------------------------------------------------------|---------------------------------------------------------------|
| **Healthy dog population**               |             |                                           | ST                                                         |                                                                 |
| Gharsa et al. (2013)                     | Tunisia     | 55/0                                      | ST20, ST44, ST69, ST70, ST78, ST100, ST108, ST160, ST161, ST162 | NT ND                                                          |
| Abouelkhair et al. (2018)                | Botswana    | 3/0                                       | ST887, ST888, ST889                                       | NT NT NT                                                       |
| Quitoco et al. (2013)                    | Brazil      | 0/1                                       | NT                                                        | NT ST71                                                        |
| Penna et al. (2021)                      | Brazil      | NT/3                                      | NT                                                        | NT ST30 (3)                                                    |
| Rynhoud et al. (2021)                    | Australia   | NT/7                                      | NT                                                        | NT ST496, ST749, ST71, ST316, ST84                              |
| Gómez-Sanz, Torres, Benito, et al. (2013)| Spain       | 14/2                                      | ST42, ST141, ST154, ST33, ST142, ST29, ST7, ST77          | NT ST71, ST92                                                   |
| Gómez-Sanz, Torres, Lozano, et al. (2013)| Spain       | 22/8                                      | ST20, ST31, ST44, ST160, ST181, ST182, ST183, ST184, ST185, ST186, ST187, ST188, ST190 | NT ST71 (2)                                                   |
| **Healthy cat population**               |             |                                           |                                                            |                                                                |
| Gómez-Sanz, Torres, Lozano, et al. (2013)| Spain       | 1/0                                       | ST142                                                     | NT ND                                                          |

Abbreviations: CC, clonal complex; ND, not detected; NR, not reported in detail; NT, not tested; ST, sequence type.
(Gómez-Sanz, Torres, Lozano, et al., 2013; Gómez-Sanz et al., 2019).

**Major virulence factors of *S. aureus* detected from nasal cavities of healthy dogs and cats**

Genes of several virulence factors including leukotoxins, enterotoxins and exfoliatins were reported in some of the reviewed and eligible studies of healthy dogs and cats (Table 6).

Eight MRSA strains carrying *luk*-S/F-PV, three MSSA *eta*-positive, two MSSA *etb*-positive and one MRSA *tst*-positive were reported in five studies on healthy dogs. However, only one MRSA *luk*-S/F-PV-positive strain (of the lineage ST80) was detected in one study on healthy cats (Elmoslemany et al., 2021). Previous results have shown that *luk*-S/F-PV (encoding the Panton-Valentine Leucocidin, PVL) is considered a stable genetic marker for CA-MRSA and has been associated with necrotic skin lesions and necrotic pneumonia (Kong et al., 2016; Labandeira-Rey et al., 2007; Shallercross et al., 2013). The *luk*-S/F-PV gene was detected in three studies on healthy dogs; in one of them, three PVL-positive MRSA-ST30 isolates were reported in Brazil (Penna et al., 2021). Another study from Australia demonstrated MRSA-*luk*-S/F-PV in 4 out of 5 strains (3 ST93 and 1 ST5) from healthy dogs (Ma, Worthing, Ward, et al., 2020). However, the genetic lineage of the MRSA-*luk*-S/F-PV-positive strain from the study of Wachtmeister (2018) was not determined. Moreover, one MRSA-*tst*-positive strain (*spa*-type 022) was detected in a healthy dog in the United Kingdom (Wedley et al., 2014).

**Major virulence factors of *S. pseudintermedius* detected from nasal cavities of healthy dogs and cats**

Most of the *S. pseudintermedius* isolates in which virulence was analysed, carried a diverse range of virulence factors that are responsible for host-specific clinical symptoms such as the pyodermic infection on dogs and cats (Table 7). The *lukS/F-I*, *siet*, *expA* genes were particularly often detected in nasal *S. pseudintermedius* isolates. MSSP-*lukS/F-I* positive isolates were reported in three studies involving dogs and cats (Gharsa et al., 2013; Gómez-Sanz, Torres, Benito, et al., 2013; Gómez-Sanz, Torres, Lozano, et al., 2013). Similarly, *siet*-carrying *S. pseudintermedius* isolates were detected in eight studies on healthy dogs and cats. Moreover, staphylococcal enterotoxins genes (*sea*, *seb*, *sec*, *sed*, *sei*, *sej*, *sek* and *ser*) were also reported in some studies (Table 7).
Biofilms produced by *S. pseudintermedius* play an important role in the pathophysiology of infection and colonization (Jain & Agarwal, 2009; Singh et al., 2013). Some studies reported that MRSP-ST71 can produce biofilms, suggesting the necessity of investigating the prevalence of biofilm-producing *S. pseudintermedius* and their implications on AMR in veterinary medical practices (Dicicco et al., 2012; Osland et al., 2012; Singh et al., 2013). The *icaA* and *icaD* genes responsible for biofilm production were detected among healthy dogs' isolates in one study (Han et al., 2015).

**Host adaptation system of *S. aureus* isolates from nasal cavities of healthy dogs and cats**

In relation to the host adaptation system of *S. aureus* for humans, the immune evasion cluster (IEC) harbours the gene *scn* (a marker of the IEC system) as well as different combinations of the *sak, chp* and *sea* (or *sep*) genes (Ahmadrajabi et al., 2017; Gómez et al., 2021). These genes encode staphylococcal complement inhibitor (encoded by *scn* gene), staphylocokinase (SAK), chemotaxis inhibitory protein (CHP) and staphylococcal enterotoxin A (SEA). It is important to remark that IEC genes are bacteriophage encoded (Ahmadrajabi et al., 2017) and their presence (with *scn* gene as a marker) is considered a human-adaptation marker (Gómez et al., 2021). The IEC system was rarely investigated on *S. aureus* isolates from healthy dogs and cats (just two of the eligible studies). In the study of Gómez-Sanz, Torres, Benito, et al. (2013) on dogs and cats, 54.2% of the *S. aureus* isolates (all MSSA) were *scn*-positive, and they presented the IEC-types B, C and E, and corresponded to the genetic lineages CC5, CC45, CC22 and CC88. These data infer that more than half of the MSSA isolates of dog origin contained the human-adaptation marker. In the other study on healthy dogs by Ma, Worthing, Gottlieb, et al. (2020), four out of the five MRSA strains (of the genetic lineages ST5 and ST93) were IEC type B, while the remaining one was IEC type A (ST1). A suitable explanation for these findings is that the isolates are most likely from community transmission and/or the dogs-owners. Also, all the five MRSA strains isolated...
from the nasal samples of healthy dogs in the study of Ma, Worthing, Gottlieb, et al. (2020) were scn-positive.

As a limitation of this study, analysis of global data was performed using studies from low-resources and developed countries, that used different techniques for bacterial isolation and identification. The studies’ methodologies differences might to some extent affect the prevalence values of S. aureus or S. pseudintermedius reported in healthy dogs and cats. Consequently, the pooled prevalence data obtained could be misreported (i.e. under-reported or over-reported).

CONCLUSION

It can be inferred that the nasal carriage of S. aureus and S. pseudintermedius in healthy dogs were moderate (10.9% and 18.3%) but low in healthy cats (3.2% and 1.2%). However, the nasal carriage of MRSA and MRSP in both healthy dogs and cats was low (<3.5%). Moreover, a high diversity of lineages and clones was detected in both staphylococcal species, especially among MSSP and MSSA. The MRSA strains recovered from healthy dogs and cats frequently belonged to human-associated genetic lineages which indicates the transmission of these clones within the household niche. Conversely, the MSSA strains corresponded to genetic lineages associated with both humans and animals. Both S. aureus and S. pseudintermedius showed high levels of AMR to commonly used human antibiotics. MRSP isolates from dogs and cats showed more frequently a MDR phenotype than MRSA. Moreover, some S. aureus isolates carried virulence factors of human health importance, as is the case of luk− S/F-PV, tst, eta, etb and etd. It is necessary to implement adequate epidemiological and microbiological surveillance on S. aureus/S. pseudintermedius and MRSA/MRSP in companion animals. Additional studies should include follow-up of molecular characterization of isolates from countries with under-studied nasal staphylococci isolates. By extension, studies should be more tailored towards the ‘One Health’ approach (humans-animals-and their shared environment).

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CONFLICT OF INTEREST

No conflict of interest declared.

DATA AVAILABILITY STATEMENT

The data extracted and utilized for this study have been thoroughly referenced. However, data related to the statistical analyses can be made available on request through the corresponding author (C.T.)

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**SUPPORTING INFORMATION**

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