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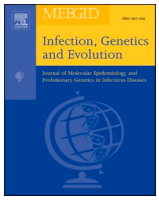

Review

Comparative review of the nasal carriage and genetic characteristics of *Staphylococcus aureus* in healthy livestock: Insight into zoonotic and anthroponotic clones

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ABSTRACT

Given the central role of livestock in understanding the genomic epidemiology of *S. aureus*, the present study systematically reviewed and synthesized data on the nasal *S. aureus* carriage, resistance patterns to critical antimicrobial agents, virulence factors and genetic lineages among healthy livestock. Bibliographical databases were searched for published studies from May 2003 to May 2022 on nasal *S. aureus* carriage, their phenotypic and genetic characteristics among healthy pigs (A), sheep and goats (B), cattle (C), poultry (D), camels (E) and buffaloes (F). Special focus was given to the prevalence of nasal MRSA, MRSA-CC398, MRSA-CC9, *mecC*-MRSA, MSSA-CC398, and resistance to linezolid (LZD^R), chloramphenicol (CLO^R) and tetracycline (TET^R) in *S. aureus* isolates. Of the 5492 studies identified, 146 comprised groups A(83)/B(18)/C(33)/D(4)/E(5)/F(3), and were found eligible. The overall pooled nasal prevalence of MRSA in healthy livestock was 13.8% (95% CI: 13.5–14.1) among a pooled 48,154 livestock population. Specifically, the pooled prevalence in groups A to F were: 16.0% (95% CI: 15.6–16.4), 3.7% (95% CI: 2.9–4.6), 13.6% (95% CI: 12.8–14.4), 5.8% (95% CI: 5.1–6.5), 7.1% (95% CI: 6.1–10.7), and 2.8% (95% CI: 1.5–4.8), respectively. These values varied considerably by continent. Varied pooled prevalences of CC398 lineage with respect to MRSA isolates were obtained, with the highest from pigs and cattle (>70%). Moreover, other classical animal-adapted MRSA as well as MSSA-CC398-t1928 were reported. TET^R-MSSA was lowest in cattle (18.9%) and highest in pigs (80.7%). LZD^R-*S. aureus* was reported in 8 studies (mediated by *optrA* and *cfr*), mainly in pigs ($n = 4$), while CLO^R-*S. aureus* was reported in 32 studies. The virulence genes *luk-S/F-PV, tst, etd, sea, see* were sparsely reported, and only in non-CC398-MRSA lineages. Certain *S. aureus* clones and critical AMR appeared to have predominance in some livestock, as in the case of pigs that are high nasal carriers of MRSA-CC398 and -CC9, and MSSA-CC398. These findings highlight the need for adequate prevention against the transmission of zoonotic *S. aureus* lineages to humans.

1. Introduction

Staphylococcus aureus (*S. aureus*) is one of the well-established nosocomial, community and livestock-associated bacterial pathogens in human and animal populations (Rao et al., 2022). *S. aureus* represents a major carrier of emerging and re-emerging antimicrobial resistance (AMR) determinants of global health concerns. The spread of AMR is multifactorial and significantly increases the severity of zoonotic-foodborne and other clinical infections in humans and animals (Howard and Scott 2nd, 2005; Smith and Coast, 2013; Centers for Disease Control and Prevention, Antibiotic Resistance Threats in the United States, 2013; Verraes et al., 2013; Hashempour-Baltork et al., 2019).

S. aureus has been recognized as the most invasive species of the *Staphylococcus* genus and a causative agent of diverse infectious diseases of humans and animals, often mediated by important virulence factors in form of staphylococcal superantigens (Hu et al., 2021). Of special relevance are the following virulence genes: *eta, etb, etd* (encode exfoliatins A, B, D; associated to scalded skin syndrome), *luk-S/F-PV*

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(encodes Panton Valentine Leucocidin, associated to abscesses); *tst* (encodes the toxin of toxic shock syndrome), and *sea, seb, sec, sed,* etc. (encode different exterotoxins, associated to food poisoning) (Tam and Torres, 2019; Hu et al., 2021).

Penicillin was the first mass-produced antibiotic for human use which previously was highly effective against *S. aureus* infections. However, most human *S. aureus* strains are now resistant to penicillin (Ebmeyer et al., 2021). The AMR gene that encodes penicillin resistance, *blaZ,* can also be found on mobile genetic elements (MGEs) (Partridge et al., 2018; Ebmeyer et al., 2021). MGEs constitute about 25% of the *S. aureus* genome, which can also encode several other putative virulence and AMR determinants (Lindsay and Holden, 2004) favouring co-selection processes. Hence, MGEs have a relevant role in *S. aureus* adaptability and survival (Malachowa and DeLeo, 2010). The methicillin-resistance trait (mediated by *mecA* and in some cases by *mecC* genes, carried in the SCC*mec* mobile elements) is the most challenging form for *S. aureus* that has become a global health issue. The methicillin-resistant *S. aureus* (MRSA) has been classified into 3 overlapping epidemiological groups, based on their frequently adapted niche and associated clonal complexes viz.; healthcare-associated (HA-MRSA), community-associated (CA-MRSA) and livestock-associated MRSA (LA-MRSA) (Kateete et al., 2019: Zarazaga et al., 2018).

Linezolid, a member of the oxazolidones, is one of the critically important antimicrobial agents against MRSA infections (Timmermans et al., 2021). Linezolid resistance (LZD^R) is a high-priority phenomenon in clinical infectious disease and epidemiology. The LZD^R occurs by (a) point mutations in the domain V of the 23S rRNA gene (predominantly G2576T and G2505A) or amino acid changes in ribosomal proteins L3, L4 and L22; and (b) acquisition of transferable genes (*cfr, cfrB, cfrC, cfrD, optrA* and *poxtA*) often found on plasmids (Prystowsky et al., 2001; Long et al., 2006; Wang et al., 2015; Antonelli et al., 2018; Mališová et al., 2021). It is worth mentioning that *cfr,* which codes for a methyltransferase that modifies position A2503 of the 23S rRNA, was first discovered in an *S. sciuri* strain from a calf in the year 2000 (Long et al., 2006). The *cfr* gene confers cross-resistance to lincosamides, streptogramin A, phenicols, linezolid, and pleuromutilins (Schwarz et al., 2000; Long et al., 2006).

Chloramphenicol, an extensively used antimicrobial agent against many infectious diseases of humans and animals gradually lost its effectiveness as a result of the development of AMR by some gram-positive cocci, such as *S. aureus* (Dinos et al., 2016; Udo et al., 2021). Most often, chloramphenicol resistance (CLO^R) in *S. aureus* is based on enzymatic inactivation by chloramphenicol acetyltransferase (*catA,* and related genes as *catpC194*, *catpC221* and *catpC223*), due to an efflux mechanism by florfenicol exporter (*fexA and fexB*), or by containing the gene *cfr* (which also mediates LZD^R) (Schwarz et al., 2004; Udo et al., 2021). The widespread and long-term use of chloramphenicol for livestock has selected chloramphenicol-resistant bacteria (Lees et al., 2021).

Based on available phenotypic and molecular data, *S. aureus* has been shown to exhibit host specificity (Haag et al., 2019). Particularly, adaptation could occur quickly and frequently, in various genetic lineages and many livestock species (Lozano et al., 2016). Pigs are considered major hosts for zoonotic *S. aureus* transmission to humans (Haag et al., 2019). However, colonization and 'host-jump' events to other hosts other than pigs such as dairy animals also occur (Bos et al., 2016).

S. aureus/MRSA has also shown economic importance in livestock production and this fact is mainly represented by the emergence and spread of certain AMR and clones (livestock-associated) that drastically reduce animal production (Lozano et al., 2016). Methicillin-resistant *S. aureus* (MRSA) of clonal complex 398 (CC398) was first described in pigs and humans having close contact with them in 2005 and was classified as an LA-MRSA lineage (Voss et al., 2005; Armand-Lefevre et al., 2005; Zarazaga et al., 2018). In the following years, MRSA-CC398 has been detected in different types of farm animals (Goerge et al., 2017), and also in wild animals, although pigs continue to be the primary host, and the pig-farm environment (Ruiz-Ripa et al., 2019; Zarazaga et al., 2018). Hence, MRSA-CC398 lineage is increasingly recognized as an occupational pathogen among livestock industry workers such as farmers, slaughterhouse workers and veterinarians (Abdullahi et al., 2021). Conversely, methicillin-susceptible *S. aureus*-CC398 (MSSA-CC398) is recently being detected as an emerging clone that has been implicated in human invasive infections in some countries, and mainly isolates of *spa*-type t571 are considered livestock-independent (Mama et al., 2021a). Other relevant livestock-adapted lineages include MRSA-CC9 (in most Asian countries) (Zarazaga et al., 2018). On the other hand, in a recent study on the multiclonal origin of *S. aureus* in bovines, MRSA-CC97 was found to be the predominant in Europe and America, while MRSA-CC188 in Asia (Yebra et al., 2022).

Nasal *S. aureus*/MRSA carriage in livestock could be a good indicator of colonization and potential infection for in-contact people by direct and/or indirect transmission within their shared environment (zoonosis); especially when clonally related *S. aureus* strains between livestock and famers are identified through the quantification of single nucleotide (SNPS) polymorphism difference of their core genomes (Randad et al., 2021). Given the central role of livestock in understanding the genomic epidemiology of *S. aureus* and the spread of AMR, the present study sought to determine the nasal *S. aureus*/MRSA carriage pattern and pooled prevalence among various livestock species. We have also comparatively reviewed the susceptibility pattern of the *S. aureus* isolates to penicillin, tetracycline, chloramphenicol and linezolid; virulence determinant and major genetic lineages related to livestock and human-adapted clones, over the past twenty years.

2. Methods

2.1. Study design

This was a systematic review executed on cross-sectional, prospective and cohort studies that reported *S. aureus* and/or MRSA from the nasal samples of healthy pigs, sheep, goats, cattle, poultry, camels and buffaloes. Ethical approval was not necessary for this study, as all the data used were secondary and adequately referenced. This study was conducted following the latest guidelines provided by the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) (http://prisma-statement.org/PRISMAstatement/checklist.aspx. Of which all the relevant checklists were adequately filled (Supplementary Table S1). For the purpose of this systematic review, special focus was given to data available on MRSA and information about certain CCs such as MRSA-CC1, MRSA-CC5, MRSA-CC9, MRSA-CC130, MRSA-CC97, MRSA-CC398, MRSA-CC425, MSSA-CC9 and MSSA-CC398 identified from nasal samples of healthy pigs, sheep, goats, cattle, poultry, camels and buffaloes. Also, data about penicillin-susceptibility (PEN^S), as well as about linezolid (LZD^R), chloramphenicol (CLO^R), and tetracycline (TET^R) resistance in *S. aureus* and virulence determinants (and genes) were extracted for all eligible articles.

2.2. Articles search strategy

This study did not limit the bibliographic (database) search by geographical regions, continents or countries, as it was world-over. The entire literature search strategy, selection of suitable published articles (in English), data extraction, statistical analyses and presentation of results and findings were performed as per the PRISMA guidelines. Published articles that provided data of any or a combination of *S. aureus,* MSSA, and/or MRSA were reviewed from Google scholar, Ajol, Embase, ScieLo, Web of Science, PubMed, Scopus. Original research and short communications (brief reports) were searched in these databases. Studies (articles) were searched, identified, reviewed and processed using keys words generated from the medical subject headings (MeSH), article titles and/or abstracts. For this purpose, the following MeSH keywords were used: "nasal *S. aureus* carriage in pigs", "nasal *S. aureus* carriage in swine", "nasal *S. aureus* carriage in hogs", "nasal *S. aureus*

carriage in sheep", "nasal *S. aureus* carriage in goats", "nasal *S. aureus* carriage in cattle or cow or bovine", "nasal *S. aureus* carriage in poultry or chicken", "nasal *S. aureus* carriage in camel", "nasal *S. aureus* carriage in buffaloes", "nasal Methicillin-Resistant *Staphylococcus aureus* in swine", "nasal Methicillin-Resistant *Staphylococcus aureus* in hogs", "nasal Methicillin-Resistant *Staphylococcus aureus* in pigs", "nasal Methicillin-Resistant *Staphylococcus aureus* in healthy sheep", "nasal Methicillin-Resistant *Staphylococcus aureus* in goats", "nasal Methicillin-Resistant *Staphylococcus aureus* in cattle or cow or bovine", "nasal Methicillin-Resistant *Staphylococcus aureus* in poultry or chicken", "nasal Methicillin-Resistant *Staphylococcus aureus* in camels", "nasal Methicillin-Resistant *Staphylococcus aureus* in buffaloes". All eligible studies were scrutinized to identify potential studies from their references' lists.

2.3. Inclusion criteria

All studies that provided suitable, appropriate and sufficient data according to the parameters here established [detection, and prevalence of nasal *S. aureus,* MRSA and/or MSSA carriage in healthy pigs (A), sheep and goats (B), cattle (C), poultry (D), camels (E) and buffaloes (F) (in the farms)] were scrutinized, selected and extensively reviewed for inclusion. Data from these eligible articles were extracted and used to determine the pooled prevalences of *S. aureus* and MRSA nasal carriages in healthy livestock (studies with sample size >10). To avoid bias from data selections and extraction, the pooled frequencies were computed from cross-sectional, prospective and cohort studies which categorically reported the number of single MRSA isolate per animal and number of animals studied at a given time (point frequency). Livestock was considered healthy if no history of recent or ongoing disease or illness was reported in the study under review. Also, no abnormalities were detected and reported on the animal by the study upon physical examination. The MRSA status of the livestock was based on the phenotypic detection of cefoxitin resistance, PBP2a agglutination, and/or molecular detection of *mecA* by polymerase chain reaction tests.

Concerning the genetic lineages of *S. aureus*, data from both original and brief communication studies on the molecular typing of isolates from healthy pigs, sheep, goats, cattle, poultry, camels and buffaloes, regardless of the study being cross-sectional or not, were comprehensively reviewed and extracted.

2.4. Exclusion criteria

(i) Studies with overlapping or duplicate publications with no clear differences; (ii) literature reviews and abstracts from conference proceedings; (iii) studies on diseased livestock or samples collected at veterinary clinics and animal hospitals, (iv) studies on samples other than nasal swabs, were excluded, (v) donkeys and horses (equids) were not included in this study due to uncertainty on whether they are strict livestock, pets, or recreational animals.

2.5. Statistical analysis

The pooled prevalences of nasal carriage of *S. aureus* and MRSA from the entire and individual livestock species were carefully computed. Comprehensive Meta-analysis software (version 4.0, NJ, USA) was used for all statistical analyses. Pooled prevalences and their corresponding confidence intervals (CI) at 95% were carried out using the random-effects model. The pooled prevalence was computed by combining the results of the number of positive cases divided by the valid number of animals (studied) obtained from eligible cross-sectional studies. This involved dividing total positives (e.g., of MRSA) by the entire population of healthy livestock from eligible studies.

3. Results and discussion

3.1. Studies characteristics

Of the 5492 studies identified, 146 comprised groups A (83 studies) /B (18) /C (33) /D (4) /E (5) /F (3) and were eligible (Supplementary Fig. S1). However, 143 studies with 48,154 animals of groups A(82) /B (16) /C(33) /D(4) /E(5) /F(3) were comparatively reviewed and utilized to compute the pooled prevalence of nasal MRSA carriage across the livestock groups (Table 1). The other 3 studies solely reported the prevalence of *S. aureus* without data on MRSA (Mørk et al., 2012; Buyukcangaz et al., 2013; Vautor et al., 2005). It is important to remark that some studies simultaneously investigated staphylococci in various livestock species.

Supplementary Table S2 shows the characteristics and data of the eligible studies, countries of the studies, type of livestock, number of animals tested, number of *S. aureus* and MRSA reported from the studies, the antimicrobial resistance phenotypes and/or genes associated with tetracycline resistance. In addition, data related to penicillin susceptibility among MSSA isolates were presented.

It was not possible to report the accurate pooled prevalence of *S. aureus* among the livestock groups because most studies (especially in pigs and cattle) only focused on MRSA detection, and it was not reported how many *S. aureus* in these studies were MSSA.

3.2. Nasal carriage of MRSA in healthy livestock

The prevalence of MRSA has extensively been documented in livestock, however, several studies from various countries have reported the absence of nasal MRSA colonization in some livestock species (Supplementary Table S2). The overall pooled prevalence of MRSA nasal isolates in livestock was 13.8% (95% CI: 13.5–14.1). MRSA pooled prevalence by livestock species was highest among pigs, 16.0% (95% CI: 15.6–16.4) and cattle, 13.6% (95% CI: 12.8–14.4), but lowest in poultry and buffaloes (5.8% and 2.8%, respectively) (Table 1). These values widely varied by continent and were highest in Europe (pigs: 24.3%; cattle: 19.4%), and lowest in pigs from Africa (5%), and cattle from America (0%) (Fig. 1). It is important to remark that only two studies on healthy pigs from the Oceania continent (Australia) were available with individual MRSA prevalences of 0.9% in 2014 (Groves et al., 2014), and 75.2% in 2020 (Sahibzada et al., 2020). The observed variations in pooled MRSA prevalence in the continents could be due to differences in pig herds but also could reflect the extent of prophylactic and therapeutic use of antimicrobial agents at the time of the studies, which may correlate with the incidence rate of the emergent AMR *S. aureus* clones (including MRSA) in pigs and the environment. Also, variations in nasal MRSA carriage could be due to differences in applied methodologies, or antibiotic use legislations in livestock agribusiness across the countries of study and the level of intensive livestock species farming (as in the case of intensive pig farming in Europe and America) (Van et al., 2020).

3.3. Penicillin susceptibility and tetracycline resistance in MSSA nasal isolates of livestock

From our systematic review, the pooled prevalence of PEN^S-MSSA was lowest in isolates from healthy pigs (12.5%) and highest in those from healthy sheep and goats (64.5%) (Fig. 2). It would be interesting to track the evolution of MSSA-PEN^S in humans and the potential relationship with these isolates in animals. Most of the PEN^S-MSSA isolates were of the genetic lineages ST9 and CC398 (from pigs); CC8, CC133, CC398, CC522 (from goats); CC5, ST6, ST15, ST152, ST291 (a double loci variant of ST398) (from cattle); ST6, ST8, ST88, ST3583, ST6504, ST6506, ST7345 (from camels); and ST152 (from poultry) (Supplementary Table S2). Some antibiotics are categorized as highly important, while others are considered critically important (World Health Organization, 2017). Among the former, penicillin is a typical example

Table 1
Global pooled prevalence of MRSA nasal carriages among the five studied livestock groups.

Livestock groups	Total number of evaluated studies[a]	Number of MRSA studies included	Total number		Pooled MRSA carriage rate (%)	Prevalence range	95% CI
			Animals	MRSA			
A: Pigs	83	82	32,373	5183	16.0	0.0–99.0	15.6–16.4
B: Sheep and goats	18	16	2174	80	3.7	0.0–26.5	2.9–4.6
C: Cattle	33	33	7751	1053	13.6	0.0–51.6	12.8–14.4
D: Poultry	4	4	4708	272	5.8	0.0–30.0	5.1–6.5
E: Camels	5	5	686	49	7.1	0.0–8.8	6.1–10.7
F: Buffaloes	3	3	462	13	2.8	0.7–27.3	1.5–4.8
Total Livestock	146	143	48,154	6650	13.8	0.0–99.0	13.5–14.1

[a] Studies that analyse either *S. aureus*, MRSA or both.

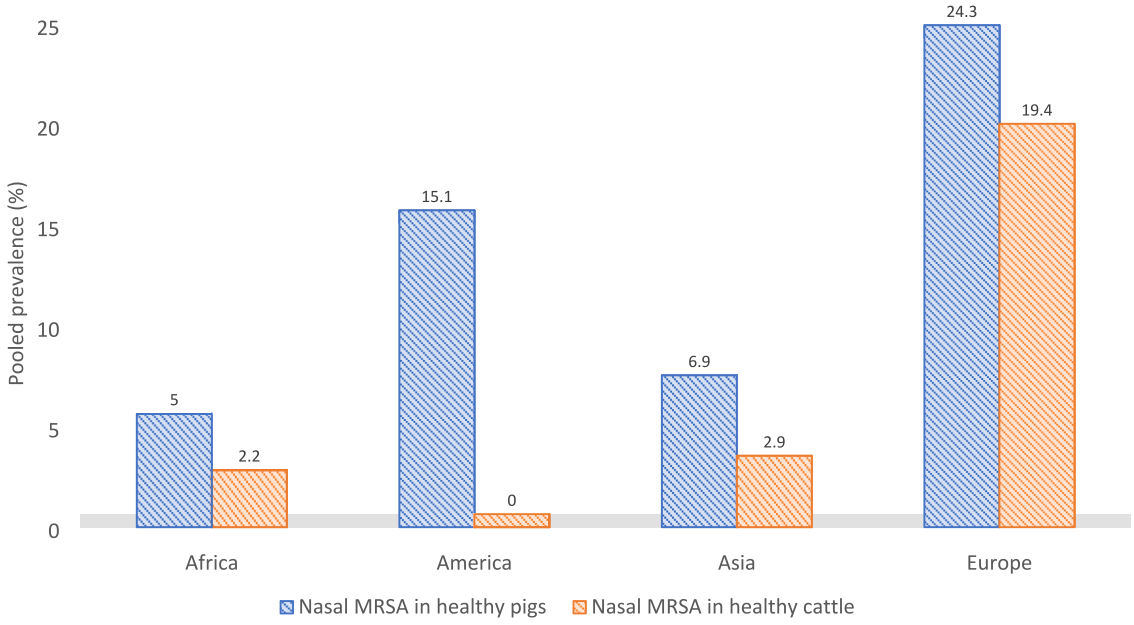

Fig. 1. Pooled prevalences of nasal MRSA carriages among healthy pigs and cattle by continents.
Note: The number of studies in each continent in MRSA nasal carriage on pigs and cattle, respectively, were as follows: Africa (pigs: 9; cattle: 9); America (pigs: 15; cattle: 3); Asia (pigs: 22; cattle: 12) and Europe (pigs: 31; cattle: 9).

(World Health Organization, 2017). Some decades ago, penicillin was often the first-line antimicrobial for *S. aureus* infection in the general human population (except for those with allergies), until the widespread of penicillin resistant staphylococci (Blumenthal et al., 2019). However, new data suggest that penicillin susceptibility might have an important therapeutic relevance (Cheng et al., 2016). An increased rate of penicillin susceptibility phenotype among some MSSA human isolates from clinical invasive infections has been detected, especially among *scn*-negative isolates (animal-adapted) and MSSA-CC398 isolates (Mama et al., 2021b).

From our analysis, TET^R-MSSA was highest in pig isolates (80.7%) (Fig. 2) than in those of other animals. The high pooled prevalence of TET^R-MSSA and the low PEN^S-MSSA in pigs highlight the possible acquisition of these phenotypes due to the highest use of antimicrobial agents in the swine breeding processes compared to other livestock species (Nobre et al., 2021). Tetracycline is highly used in pigs and it has been suggested that TET^R in MSSA was highest in pigs due to the potential acquisition of tetracycline resistance genes from tetracycline-transposon carrying-MRSA (*tetM*) found within the same ecological niche with MSSA (Matuszewska et al., 2022; de Vries et al., 2009). Based on findings from this systematic review, *tetM*-mediated tetracycline resistance in MSSA was reported in 5 studies (3 from pigs, 1 from cattle and 1 from goats) (Supplementary Table S2). Tetracycline resistance (TET^R) is a phenotypic marker for MRSA, and it is associated with livestock-associated MRSA clones, especially with CC398 (Ceballos et al., 2022); nevertheless, the situation is not clear among MSSA isolates (Little et al., 2021).

3.4. Chloramphenicol and linezolid resistance in S. aureus nasal isolates of livestock

As livestock has originally been considered as important reservoirs and vehicles of emergence and re-emergence of resistance to critical antimicrobial agents, it is necessary to review the frequency of detection of LZD^R in various animal species on the eligible studies. Based on our analysis, LZD^R was reported in 8 studies, mainly in pigs ($n = 4$), although only in three of them the mechanism of resistance was determined (all of pig origin, mediated by *optrA* or *cfr* genes) (Supplemenatry Table 3); moreover, CLO^R was reported in 30 studies, although the mechanism of resistance was determined only in 4 of them (*fexA* or *cat* genes) (Supplementary Table 3). Also, the simultaneous detection of LZD^R and CLO^R in MRSA isolates in pig herds was reported in three of the eligible studies from China (Guo et al., 2018; Li et al., 2018: Peeters et al., 2015). None of these studies reported any point mutation in the domain V region of the 23S rRNA nor amino acid changes in ribosomal proteins L3, L4 and L22 of *S. aureus*. These studies indicate that LZD^R in nasal *S. aureus* isolates from healthy livestock is uncommon, while CLO^R is occasionally detected in both MRSA and MSSA in livestock.

Linezolid is considered a critically important antimicrobial agent for the treatment of multiple drug-resistant staphylococcal infections in

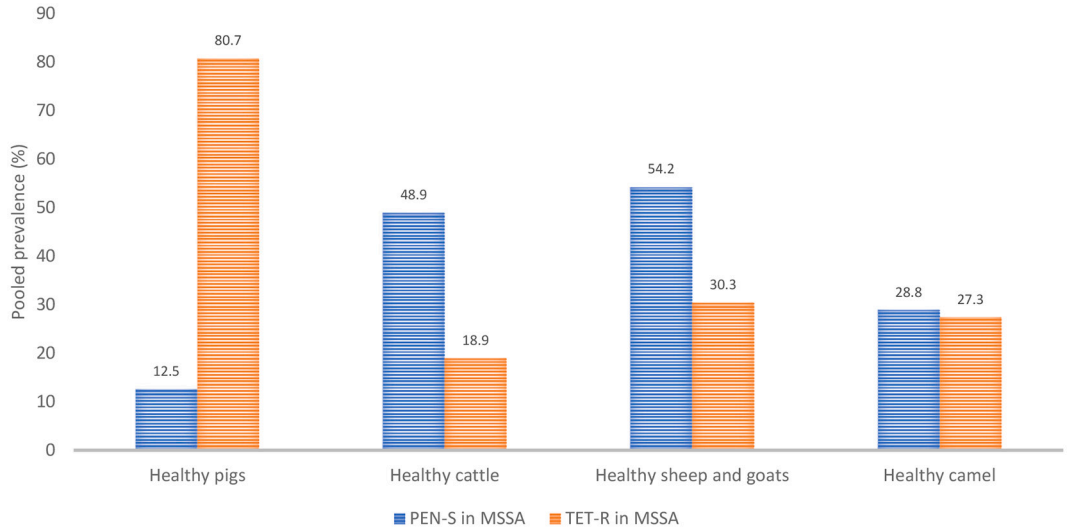

Fig. 2. The pooled prevalence of antimicrobial profiles related to tetracycline-resistant (TET^R) and penicillin-susceptible (PEN^S) among MSSA strains in healthy livestock.

NB: (a) The number of total isolates, animals and number of studies in healthy pigs; cattle; sheep/goats; and camel used for PEN^S in MSSA were as following: (53, 425, 12); (24, 49, 9), (77, 142, 8); and (19, 66, 4), respectively. Whereas the number of total isolates, animals and number of studies in healthy pigs; cattle; sheep/goats; and camel used for TET^{-R} in MSSA were as follows: (498, 617, 14); (11, 58, 10), (43, 142, 8); and (18, 66, 4), respectively. (b) Pooled prevalences were extracted and computed from data on supplementary Table S1.

humans and animals. In several European countries, the use of critically important antimicrobials in animals has been restricted due to the emergence of novel AMR of public health concerns (European Commission, 2022). In the past, extensive chloramphenicol usage has co-selected resistance to other antimicrobial agents, especially linezolid (Lees et al., 2021). It was not until recently that the use of antimicrobial agents as prophylactics in feeds was prohibited by the European Union in 2022 (European Commission, 2022). Although chloramphenicol is not a critical antimicrobial agent, it was only included in this systematic review, as it is a potential marker for LZD^R.

3.5. Genetic lineages associated with zoonotic S. aureus nasal isolates

S. aureus clonal complexes (CCs) are defined as a cluster of strain types that share alleles at ≥6 of the 7 MLST genes within a single category suggesting their maintenance in a population of *S. aureus* solely within the group (Omuse et al., 2016). The CC398 has been referred to as the major LA-MRSA lineage in Europe (Butaye et al., 2016; Ye et al., 2016), but CCs, such as the CC5 and CC9 have also been reported (Cui et al., 2009; Frana et al., 2013; Hau et al., 2018). It is worth mentioning that other genetic lineages related to LA-MRSA have also been detected in livestock and they are gaining huge interest in the public health sector. Although some of these CCs have been associated with pig farming (e.g., CC1 and CC97), others have been found in bovine (CC130 and CC425) and poultry (CC5) (Monaco et al., 2013). Nevertheless, most of these CCs have been detected in different animal hosts (Monaco et al., 2013) and their potential transmission across many livestock species has been suggested (Larsen et al., 2017).

The CC398 lineage is of particular interest among the clinically relevant CCs of *S. aureus*. MRSA-CC398 isolates were only described as frequent colonizers of livestock until 2007 when the narrative changed (Laumay et al., 2021). This was because sporadic cases of *S. aureus*-CC398 infection were reported in humans who had contact with livestock (MRSA variant), and now, this CC398 genetic lineage has increasingly been identified as the cause of severe and invasive infections in people with no history of direct contact with animals (MSSA variant, livestock-independent) (Laumay et al., 2021; Mama et al., 2021a). These observations suggest that MRSA-CC398 and MSSA-CC398 clones have been spreading in both community and hospital settings (Laumay et al., 2021). Thus, the genomic epidemiology of *S. aureus* of the CC398 lineage could contribute to future studies that attempt to detect the origins of microbes and infection in humans, animals, and the environment (One Health domain). It is worth mentioning that recently available data indicate that the evolution of MSSA-CC398 clades is driven by the acquisition of prophages (such as φsa3), while MRSA-CC398 by the acquisition of SCC*mec* and other mobile genetic elements such as *Tn*916 carrying *tetM* gene (Laumay et al., 2019; Sieber et al., 2020; Matuszewska et al., 2022).

As expected, the pooled prevalence of lineage CC398 among nasal MRSA isolates was exceedingly high in pigs, cattle and poultry (>70%), but not reported in camels, sheep, goats and buffaloes (Table 2).

MRSA-CC9 lineage was detected predominantly among healthy pigs (pooled prevalence 13.0%) and in buffaloes (pooled prevalence 100%) (Table 2). However, a single study on buffaloes reported CC9 and was detected in all three MRSA nasal isolates (Badua et al., 2020).

The variation in the detection rate of the MRSA-CC9 and MRSA-CC398 lineages from the different livestock species reflects the differences in host adaption to these CCs, and the level and types of intensive livestock farming across the world (Fig. 3). It is important to mention that not all studies reported the *spa* types of the nasal MRSA-CC398 isolates in healthy livestock. Of the 22 studies that reported the *spa* types of 10,003 isolates of MRSA-CC398 in pigs, it appeared that *spa* types t034 (40.5%) and t011 (37.5%) were the most frequent (Fig. 4). Also, reported *spa* types of MRSA-CC398 isolates in pigs in lower frequencies include t108 (2.5%), t1451 (1.5%), t1456 (1.5%) and others such as t1255, t1184, t899, t1197, t1594, t2346, t12359, t12359 and t18103 *etc*. (Supplementary Table S2). Of the 101 MRSA-CC398 isolates from cattle, *spa* types t011 (66.3%) and t034 (11.9%) were the most frequent (Fig. 4). Other reported *spa* types in lower frequencies among the MRSA-CC398 isolates from cattle include t899 (7.9%), t1451 (2.9%) and t1456 (2.9%) (Fig. 4). However, the eight MRSA-CC398 isolates detected in poultry were of the *spa* type t1451 (Persoons et al., 2009).

Although most MRSA-CC398 were reported from studies in Europe and MRSA-CC9 from studies in Asia, both CCs have been detected (in low frequencies) in pigs from both continents, especially in studies from recent years. Moreover, MRSA-CC398 has been widely reported from nasal samples of healthy pigs in the American continent (Supplementary Table S2), and it was also reported in Australia in 2020 (Sahibzada et al.,

Table 2
Pooled prevalence and corresponding *spa* types of MSSA and MRSA clonal complexes from nasal cavities of the livestock groups.

Animal category	MSSA							MRSA						
	No. of studies	No. of CC9 isolates	No. of CC398 isolates	No. of MSSA	Pooled prevalence (%) CC9	95% CI	Pooled prevalence (%) CC398	95% CI	No. of studies	No. of CC9 isolates	No. of CC398 isolates	No. of MRSA	Pooled prevalence (%) CC9	95% CI	Pooled prevalence (%) CC398	95% CI
Healthy pigs	11	205	194	587	34.9	31.1–38.9	33	29.3–37	49	430	2478	3301	13.0	11.9–14.2	75.1	73.6–76.5
Healthy sheep and goats	7	0	8	117	0	NA	6.8	2.4–11.9	3	0	0	5	0	NA	0	NA
Healthy cattle	4	0	0	37	0	NA	0	NA	8	0	749	763	0	NA	98.2	96.9–98.9
Healthy poultry	1	0	0	1	0	NA	0	NA	2	0	8	9	0	NA	88.9	51.7–99.7
Healthy camels	3	0	0	39	0	NA	0	NA	0	NT	NT	NT	0	NA	0	NA
Healthy buffaloes	0	NT	NT	NT	0	NA	0	NA	1	3	0	3	100	NA	0	NA

NB: (a) No study was conducted on genetic lineages of MRSA from camels, (b) only two studies reported genetic lineage of MRSA in poultry and one MRSA study in buffalo (c) pooled prevalences extracted and computed from data from Supplementary Table S1.

2020). This observation may be due to the increased international travel and trade (including livestock) within these continents (Ruiz-Ripa et al., 2021; Sasaki et al., 2020; Back et al., 2020; Peeters et al., 2015). In contrast to this, MRSA-CC9 has not been reported in Africa, but MRSA-CC398 *spa*-type t011 has been reported in one study in Cameroon and South Africa (Founou et al., 2019). Perhaps this under-reporting or misdiagnosis could be due to the paucity of comprehensive genetic studies on *S. aureus* or the absence of factors that could support the maintenance and transmission of these lineages in livestock (Lawal et al., 2022).

Aside the MRSA-CC398 and MRSA-CC9, both *mec*A-mediated, there are other MRSA strains that contain the mechanism *mec*C, which was first isolated from bovine mastitis samples in UK (García-Álvarez et al., 2011). Later, it was detected in human samples from some European countries (Lozano et al., 2020). The *mecC* gene, previously referred to as $mecA_{LGA251,}$ is carried by the mobile genetic element *SCCmec* type XI (Shore et al., 2011). The CCs often associated with *mecC*-MRSA is the CC130, others include CC49, CC425, CC599, CC1943, CC2616, CC2620, and CC2361 (Larsen et al., 2022a, 2022b; Sahin-Tóth et al., 2022). However, *mecC*-MRSA was reported in only one of the eligible studies on cattle in the Netherlands, showing in this case a low prevalence of nasal carriage (0.15%), with the CC425 lineage (Graveland et al., 2010). The *mecC*-MRSA isolates have frequently been reported in wild animals (Gómez et al., 2015, 2016; Larsen et al., 2022a, 2022b) and bovine milk samples. Moreover, in healthy pigs, MRSA-CC5 strains (animal--dependent clone) were detected from nasal samples (range: 3.2 to 100%) in Canada, Japan, and the USA (Narvaez-Bravo et al., 2016, Sato et al., 2015, Gordoncillo et al., 2012; Khanna et al., 2008). It is worth mentioning that the study that detected ST5 in all the MRSA from pigs were on only two isolates (Gordoncillo et al., 2012).

Out of the 5 groups of livestock in this systematic review, MSSA-CC9 was only reported in pigs (8.1%, 95% CI: 6.3–10.4). Of the 7 studies that report MSSA-CC9 in pigs, 3 were from European countries, 3 from Asia and 1 from the USA (Supplementary Table S2). MSSA-CC9 (*scn*-negative) clade is occasionally detected in food-producing animals, suggesting that this lineage has no categorical geographical predominance. However, further studies on factors responsible for host adaptation could provide better understand their epidemiolocal relevance in pig herds.

Concerning MSSA isolates, the MSSA-CC398 has gained a lot of attention in recent times, as several surveillance programs (mainly in Europe) consistently reported a rise in its incidence and has been implicated in severe infections, mainly in bone and joint infections and bloodstream infection with *spa* type t571 and presence of *scn* gene. This genetic lineage is the most frequently implicated MSSA-CC398 subclade in human infections (Mama et al., 2021a; Diene et al., 2017; Senneville et al., 2014). From our data analyses, the pooled prevalence of this lineage (MSSA-CC398) in pigs and sheep/goats were 33.0%, and 6.8%, respectively (Table 2). Among the 3 studies that reported the *spa* types of forty MSSA-CC398 isolates from healthy pigs (Mroczkowska et al., 2017; Osadebe et al., 2013; Guardabassi et al., 2007), *spa* type t034 (67.5%) appeared to be the most frequent; the IEC typing data was available only from the study of Mroczkowska et al. (2017) that showed that all the MSSA-CC398-t034 were *scn*-negative. However, other *spa* types such as t1580, t1928, t4387 and t4389 were reported in one of the studies. All the MSSA-CC398 isolates were *scn*-negative except one (MSSA-CC398-t1928) which was IEC-type B (Mroczkowska et al., 2017), contrary to the subclade implicated in invasive human infections (t571-IEC-positive) (Mama et al., 2021a).

Since MSSA-CC398 (*scn*-positive and t571) has been considered a livestock-independent subclade, few data are available on their prevalence and genetic characteristics in animals. Most isolates of available animal MSSA-CC398 data were of the *spa*-types t034, t108, and t899, which are not related to the major human *spa*-type t571 (Tegegne et al., 2022). Recently, some studies argued whether the MSSA-CC398 is a true

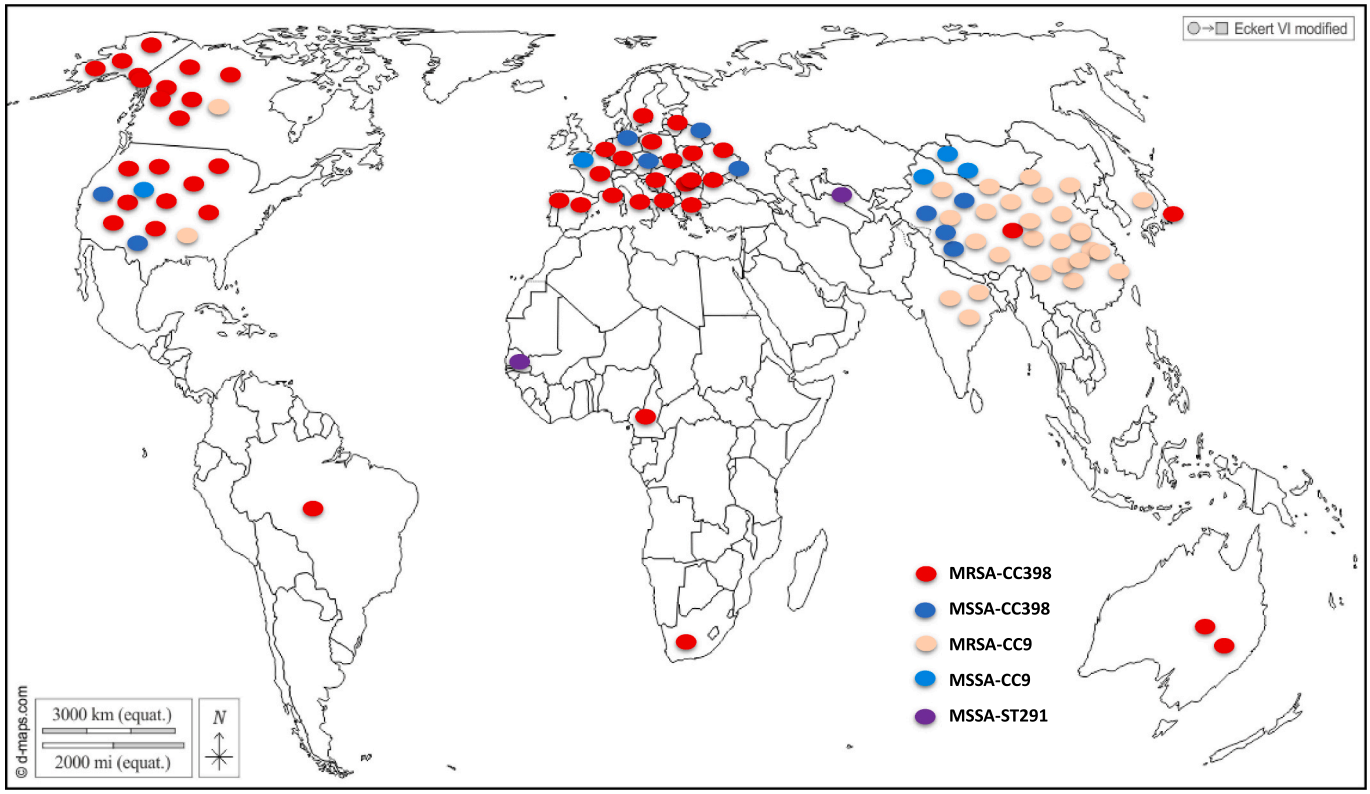

Fig. 3. Geographical distribution of the major LA-MRSA and MSSA clonal complexes reported from nasal cavities of healthy livestock.

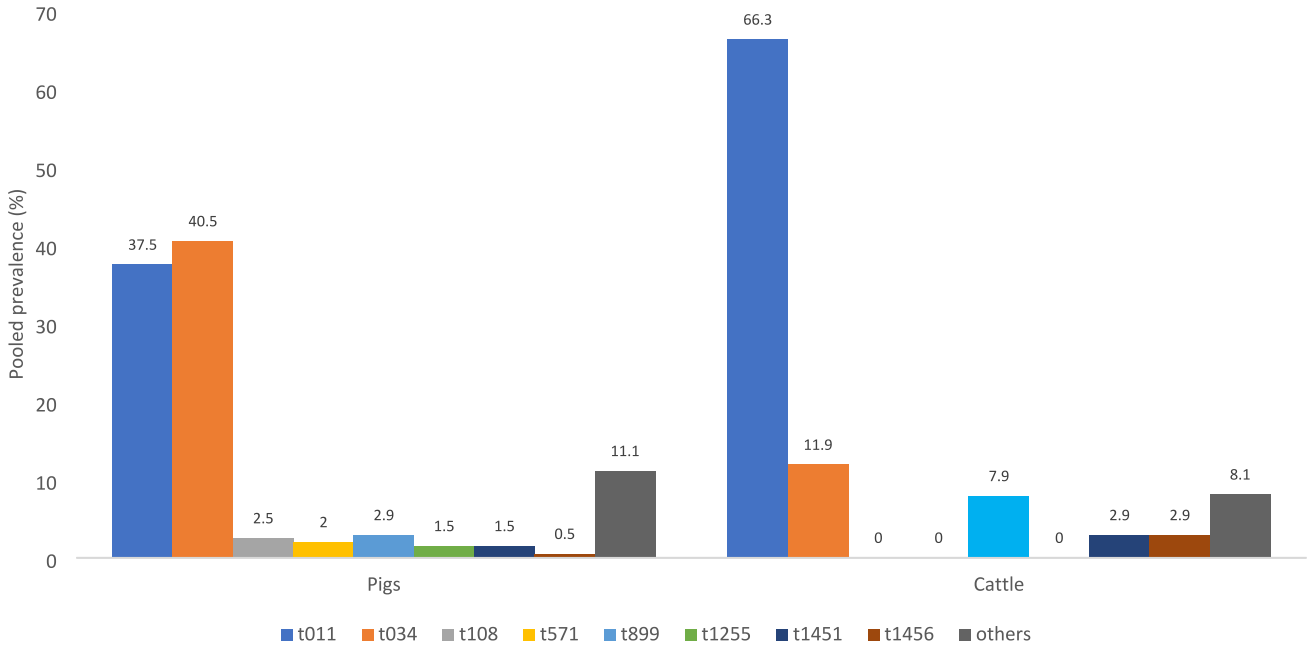

Fig. 4. Distribution pattern of *spa* types of nasal MRSA isolates from healthy pigs and cattle.
NB: (a) The number of total isolates and number of studies in healthy pigs and cattle used for the pooled percentages of *spa* types in MRSA were (1222,22) and (101, 4), respectively. Data were extracted and computed from data in Supplementary Table S1.

animal-independent subclade, as some of the MSSA-CC398 from animals were *scn*-negative (Tegegne et al., 2022). Nevertheless, MSSA-CC398-t571 isolates have also been detected in migratory birds (Gómez et al., 2016).

3.6. Genetic lineages associated with human-adapted S. aureus nasal clones from livestock

The detection of MRSA clones carrying the *scn* gene (a human-adaptation marker) in healthy livestock indicates the potential circulation of these clones among farmers and animals (Laumay et al., 2021).

Although there is often minimal contact between livestock and humans in well-organized farms with efficient biosecurity, some human-adapted *S. aureus* clones could be in circulation in livestock herds.

Aside from the well-known human-adapted MSSA-CC398-t571, an MSSA-CC398 of the *spa* type t1928 and IEC-type B has been reported in a pig in Poland (Mroczkowska et al., 2017). Interestingly, another MSSA-CC398-t1928 isolate from the same study had no *scn* gene (Mroczkowska et al., 2017). Also, in the study of Nemeghaire et al. (2014) in Belgium, one MRSA-CC239-t037-IEC-type B while another MRSA-CC239-t388-*scn*-negative strain was detected in cattle. These data highlight the intra-clonal variability (different *spa* types) of the IEC among *S. aureus* and suggest the potential of *S. aureus* from livestock to acquire prophage and become a challenging zoonotic pathogen. Based on the available IEC typing data of *S. aureus* in healthy livestock, it appears that the majority of the *scn*-positive isolates were of the IEC -type B (Table 4). However, it appears that human-adapted MRSA and MSSA isolates are rare in livestock (Table 4).

Moreover, CA-MRSA-CC1, a common IEC-type B (*scn and sak* positive) strain (Earls et al., 2021) was reported in pigs in Korea (7.1%), Switzerland (3.2%) and Argentina (all the two MRSA isolates [100%]) (Giacoboni et al., 2020; Back et al., 2020; Overesch et al., 2011). Also, it was reported in MRSA isolates from the nasal samples of cattle in Switzerland (one of the 4 MRSA isolates [25.0%]) and Italy (1.9%) (Zoppi et al., 2021; Huber et al., 2010) (Supplementary Table S2).

3.7. Virulence determinants among S. aureus from nasal cavities of livestock

There are many virulence determinants in *S. aureus*, however, some are particularly relevant in clinical infectious diseases in humans and animals, among them, *luk-S/F-PV, tst, eta, etb, etd*, and the enterotoxins encoding genes.

Out of the 16 studies that reported the detection of key virulence factors (Table 3), interestingly, only 6 were on MRSA. Concerning PVL-producing MRSA, one CC1 pig isolate was identified in a study in China (Guo et al., 2018), and in another study, two MRSA-ST1 pig isolates were reported in Korea (Back et al., 2020). Also, in Nigeria, all the MRSA isolates from cattle were PVL-positive (19 out of 50 isolates) (Igbinosa et al., 2016). One *eta*-carrying MRSA-CC97 out of 37 isolates was reported from a pig in Spain (Gómez-Sanz et al., 2013), while *tst*-carrying MRSA-ST5 was reported (one out of 29 isolates) in a pig in Korea (Back et al., 2019). Finally, in an Australian study, most of the MRSA-ST93 strains (n = 227, 68.9%) from pigs were *luk-S/F-PV*-positive (Sahibzada et al., 2020). These findings support the claim that the most predominant LA-MRSA (i.e., CC398 and CC9) are less likely to carry these virulent factors.

Concerning the detection of virulence factors in MSSA isolates on livestock, PVL-producing isolates were mostly associated to the lineages CC15, CC152, CC7, CC8 (t008) and ST39 (t007) from pigs. Moreover, it is worth mentioning that a PVL-producing MSSA-CC398-t034 was reported in a pig in the USA (Osadebe et al., 2013). Also, PVL-carrying MSSA of the lineages ST152 were reported from cattle and poultry while MSSA-CC8 and MSSA-CC80 were from sheep (Table 3). It is also worth mentioning that the *tst*-carrying MSSA-ST291 (a double locus of ST398) have been reported in cattle from Senegal (Mama et al., 2019a, 2019b) and *tst*-positive MSSA-ST508 in goats from Ghana (Egyir et al., 2020). Aside from these, it is important to mention that MSSA-ST15 carrying *eta* and other MSSA-ST15 and MSSA-ST6 carrying enterotoxin encoding genes (*sea* and *see*) were reported in Senegalese cattle (Mama et al., 2019a, 2019b). All these put together highlight the potential of livestock to carry exfoliating and toxin-producing *S. aureus* in their nasal cavities and implicating possible zoonotic transmission to farmers and

Table 3
Genetic lineages, antimicrobial resistance, virulence genes and IEC system in MRSA and MSSA isolates detected in nasal *S. aureus* carriage in healthy livestock.

Reference	Animal species (location)	Number of animals tested	No. of MRSA (%)	Virulence genes (number strains) of MRSA/ genetic lineage	No. of MSSA (%)	Virulence genes (number strains) of MSSA/ genetic lineage
Agabou et al. (2017)	Camel/Algeria	45	2 (4.4)	ND	22 (48.9)	*tst* (3)/NR *luk-SF-PV* (3)/CC80, CC152
Agabou et al. (2017)	Sheep/Algeria	43	5 (11.6)	ND	9 (20.9)	*tst* (7)/NR *luk-S/F-PV* (4)/CC80 *etd* (4)/NR
Agabou et al. (2017)	Cattle/Algeria	40	0 (0)	NT	6 (15)	*tst* (2)/NR *sea* (1)/NR *etd* (2)/NR
Mama et al. (2019a)	Poultry/ Senegal	199	0 (0)	NT	1 (0.5)	*luk-S/F-PV* (1)/ST152
Mama et al. (2019a)	Cattle/ Senegal	149	0 (0)	NT	6 (4.0)	*tst* (3)-*scn*-negative/ ST291 *luk-S/F-PV* (1)-*scn*-negative/ ST152 *eta* (1)-*scn*-negative/ST15 *sea, see* (1)-*scn*-negative/CC6
Khemiri et al. (2018)	Cattle/ Tunusia	26	1 (3.8)	NT	1 (3.8)	*sea (1)/NT*
Egyir et al. (2020)	Goat/ Ghana	56	0 (0)	NT	7 (12.5)	*tst* (1)-IEC-B/ST508 *tst* (6)/ST133-*scn*-negative
Momoh et al. (2018)	Pigs/ Nigeria	300	0 (0)	NT	16 (5.3)	*luk-S/F-PV* (5)-*scn*-positive/CC15 (1), CC152 (4)
Igbinosa et al. (2016)	Cattle/ Nigeria	50	19 (38)	*luk-S/F-PV* (19)/NT	0 (0)	NT
Osadebe et al. (2013)	Pigs/ USA	159	8 (5.0)	ND	77 (48.4)	*luk-S/F-PV* (7)/ t008 (5), t034 (1), t007 (1))
Wang et al. (2012)	Pigs/ China	173	14 (8.1)	*luk-S/F-PV* (14)-NT	39 (22.5)	*luk-S/F-PV* (24)-NT
Lee et al. (2020)	Cattle/ Korea	169	0 (0)	NT	1 (0.6)	*sea (1)*/t008/ ST2416
Yan et al. (2014)	Pigs/ China	590	38 (6.4)	ND	162 (27.5)	*luk-S/F-PV* (3)/ST7
Back et al. (2020)	Pigs/ Korea	1080	29 (2.7)	*tst* (1)/ST5 *luk-S/F-PV* (2)/ST1	NT	NT
Guo et al. (2018)	Pigs/ China	1458	48 (3.3)	*luk-S/F-PV* (1)/CC1	99 (6.8)	ND
Zhou et al. (2017)	Sheep/ China	74	0 (0)	NT	32 (43.2)	*tst* (4) *luk-S/F-PV* (3)
Sahibzada et al. (2020)	Pigs/ Australia	618	465 (75.2)	*luk-S/F-PV* (227)/ST93	0 (0)	NT
Mama et al. (2019b)	Lamb/ Spain	45	2 (4.4)	ND	9 (20)	*tst* (9)-*scn*-negative /ST133 *luk-S/F-PV* (2)-IEC-B/ ST8
Gómez-Saenz et al. (2010)	Pigs/ Spain	106	37 (34.9)	*eta* (1)/CC97	ND	NT

NT: Not tested; ND: Not detected; NR: Not reported in detail.

Table 4
Immune Evasion cluster (IEC) types of nasal *S. aureus* isolates from healthy livestock.

Reference	Livestock species/ Country/ Continent	Sample size	*S. aureus*/ MRSA	IEC type in MSSA	IEC type in MRSA
Egyir et al. (2020)	Pigs/ Ghana/ Africa	208	8/0	IEC-negative (8)/ST9 (7), ST97 (1)	NT
Founou et al. (2019)	Pigs/ South Africa/ Africa	144	22/4	NT	IEC-negative (4)/ST398
Momoh et al. (2018)	Pigs/ Nigeria/ Africa	300	16/0	a. *scn*-positive (13)/CC5 (t311, t002), CC15 (t084), CC8 (t304), CC152 (t355) b. IEC-negative (3)/ CC5 (t442), CC15 (t5691)	NT
Founou et al. (2019)	Pigs/ Cameroon/ Africa	72	13/1	NT	IEC-negative (1)/ST398
Slifierz et al. (2015)	Pigs/ Canada/ America	390	94/6	NT	IEC-negative (6)/ST398
Peeters et al. (2015)	Pigs/ Belgium/ Europe	328	215/215	NT	a. IEC-B (1)/ CC80 b. IEC-negative (214)/ ST398 ST9, ST239
Mroczkowska et al. (2017)	Pigs/ Poland/ Europe	1845	80/31	a. IEC-negative (48)/ CC398, CC9, CC12, CC30, CC22/ t034, t1580, t1928, t4387, t4389 b. IEC-B (1)/ CC398-t1928	IEC-negative (31)/ CC398, CC30/ t011, t034, t108, t1928, t4387
Mama et al. (2019a)	Cattle/Senegal/ Africa	149	6/0	IEC-negative (6)/ST6, ST15, ST291, ST152	NT
Mama et al. (2019b)	Cattle/ Spain/ Africa	72	1/0	IEC-negative (1)/ST45	NT
Nemeghaire et al. (2014)	Cattle/ Belgium/ Europe	432	81/81	NT	a. IEC-B (1)/ CC239 (t388) b. IEC-negative (80)/ CC398, CC8, CC239 (t037)
Egyir et al. (2020)	Goats/ Ghana/ Africa	56	7/0	a. IEC-negative (6)/ST133 b. IEC-B (1)/ ST508	NT
Mama et al. (2019b)	Goats/ Spain/ Europe	45	12/1	IEC-negative (6)/ST133, ST8, ST522	IEC-B (1)/ ST8
Mama et al. (2019a)	Poultry/Senegal/ Africa	199	1/0	IEC-negative (1)/ST152	NT
Silva et al. (2022)	Camel/ Spain/ Europe	86	5/0	IEC-negative (5)/ ST7345 (1), ST88 (3), ST8 (1)	NT

NT: Not tested.

animals, unsafe food products for consumption, especially if the toxin is present in high concentration (Zeaki et al., 2019).

Generally, these important virulence factors of *S. aureus* are scarcely reported in isolates of livestock. They are also lower in MRSA compared to MSSA isolates. As a rule, isolates belonging to MRSA-CC398 are devoid of these virulence factors.

4. Conclusion

Livestock, particularly pigs and cattle, are significantly high nasal carriers of major animal-adapted MRSA clones (CC398 and CC9), MSSA-CC398 and critical AMR (to LZD). Important geographical variations have been identified. Also, *S. aureus* CCs appeared to have adapted to a variety of livestock. Current data suggest that humans are major sources of *S. aureus* (*scn*-positive) but these human-adapted lineages have rarely been identified (in very low frequency) in animals. Hence, this anthroponosis needs to be fully monitored in livestock. These findings put together highlight the need for adequate prevention against the transmission of zoonotic *S. aureus* to humans, either via occupational exposure or consumption of contaminated animal products.

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CRediT authorship contribution statement

Idris Nasir Abdullahi: Conceptualization, Methodology, Validation, Software, Formal analysis, Data curation, Funding acquisition, Visualization, Writing – original draft, Writing – review & editing. **Carmen Lozano:** Validation, Formal analysis, Supervision, Writing – original draft, Writing – review & editing. **Andre Becker Simoes Saidenberg:** Validation, Formal analysis, Writing – original draft, Writing – review & editing. **Javier Latorre-Fernández:** Validation, Formal analysis, Writing – original draft, Writing – review & editing. **Myriam Zarazaga:** Validation, Formal analysis, Funding acquisition, Writing – original draft, Writing – review & editing. **Carmen Torres:** Conceptualization, Methodology, Validation, Formal analysis, Data curation, Supervision, Project administration, Funding acquisition, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

None of the coauthors have conflicts of interest in relation with this study.

Data availability

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.).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.meegid.2023.105408.

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