The interplay between Mobilome and Resistome in *Staphylococcus aureus*

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Abstract

Antibiotic resistance genes (ARGs) in *Staphylococcus aureus* can disseminate vertically through successful clones, but also horizontally through the transfer of genes conveyed by mobile genetic elements (MGEs). The underexplored MGE/ARG associations in S. *aureus* favor the emergence of multidrug-resistant clones, posing a significant threat to human and animal health.

This study investigated the interplay between the mobilome, encompassing MGEs, and the resistome, the collection of ARGs, in more than 10,000 *S. aureus* genomes from human and animal sources. The analysis revealed a remarkable diversity of MGEs and ARGs, with plasmids and transposons being the main carriers of resistance genes. Numerous MGE/ARG associations were identified, suggesting that MGEs play a critical role in the dissemination of resistance. A high degree of similarity was observed in MGE/ARG associations between human and animal isolates, highlighting the potential for unrestricted spread of ARGs between hosts. While clonal expansion is a major driver of resistance dissemination in *S. aureus*, our results showed that MGEs and their associated ARGs can spread across different strain types (STs), favoring the evolution of these clones and their adaptation in selective environments. The high variability of MGE/ARG associations within individual STs and their spread across several STs highlight the crucial role of MGEs in shaping the *S. aureus* resistome.

Overall, this study provides valuable insights into the complex interplay between MGEs and ARGs in *S. aureus*, emphasizing the need to elucidate the mechanisms governing the epidemic success of MGEs, particularly those implicated in ARG transfer.

Importance

The research presented in this article highlights the crucial importance of understanding the interactions between mobile genetic elements (MGEs) and antibiotic resistance genes (ARGs) carried by *Staphylococcus aureus*, a versatile bacterium that can be both a harmless commensal and a dangerous pathogen for humans and animals. *S. aureus* strains represent a major threat due to their ability to rapidly acquire and disseminate ARGs. By analyzing a large dataset of *S. aureus* genomes, we

39 highlighted the substantial role of MGEs, in particular plasmids and transposons, in the dissemination
40 of ARGs within and between *S. aureus* populations, bypassing the host barrier. Given that multidrug-
41 resistant *S. aureus* strains are classified as a high-priority pathogen by global health organizations, this
42 knowledge is crucial for understanding the complex dynamics of transmission of antibiotic resistance
43 in this species.

44 # Introduction

45 *Staphylococcus aureus* is a versatile bacterium that can be a commensal microorganism and a lethal
46 pathogen for both humans and animals. The large range of symptoms caused by *S. aureus* in each host
47 is the result of the intricate interplay between complex factors, including host health status, genetic
48 composition of the *S. aureus* strain and the site of infection (1–3). The overuse and misuse of
49 antibiotics in both human healthcare and veterinary medicine have promoted the emergence of
50 numerous antibiotic-resistance genes (ARGs) and the dissemination of multidrug-resistant clones (4).
51 As a result, this species has been classified by the WHO (World Health Organization) as high-priority
52 for the development of new antibiotic targets, and by the WOAH (World Organization for Animal
53 Health) on the surveillance list of multi-resistant pathogens. Studies on antimicrobial resistance (AMR)
54 in *S. aureus* have primarily focused on methicillin-resistance, due to the presence of the *mecA/mecC*
55 genes, which confer resistance to all beta-lactam antibiotics. Consequently, *S. aureus* strains are
56 commonly classified as methicillin-resistant (MRSA) or methicillin-susceptible (MSSA) isolates (5).
57 However, *S. aureus* can acquire multiple additional ARGs conferring resistance to all known antibiotic
58 families, shaping the resistome of each isolate (6). In 2018, a review drew up an inventory of 46 ARGs
59 shared between *S. aureus* isolates of human and animal sources, suggesting potential interspecies
60 transmissions (7).

61 In contrast to a highly clonal core genome, up to 25% of the *S. aureus* genome is composed of accessory
62 genes, primarily encompassing mobile genetic elements (MGEs) that contribute significantly to the
63 adaptability and survival of these bacteria in various environmental conditions by spreading ARGs
64 mainly occurs through horizontal gene transfer (HGT) (8, 9). MGEs are DNA fragments that can
65 promote intra- or intercellular transfer of genetic material, and play a crucial role in the dissemination
66 of ARGs. The staphylococcal mobilome (set of MGEs) exhibits a remarkable variability (8, 10–13).
67 *S. aureus* MGEs include (i) plasmids (extrachromosomal genetic elements that can be conjugative,
68 mobilizable, or non-mobilizable in *S. aureus*) (12), (ii) integrative and conjugative elements (ICEs)
69 (MGEs that integrate into the bacterial chromosome and have the potential to excise and transfer

70 themselves to other bacteria via conjugation) (14, 15), (iii) insertion sequences (IS) and transposons
71 (Tn) (chromosomally-integrated MGEs that are often associated with other MGEs, in single or multiple
72 copies) (13), (iv) prophages (MGEs usually integrated into the host's chromosome, since they can
73 repress the phage's lytic functions) (16), and (v) genomic islands (such as the staphylococcal
74 chromosomal cassettes (SCC*mec*) specific to *mec*-carrying staphylococci) (13).

75 It is usually admitted that *S. aureus* disseminate through clonal expansion, spreading resistance genes
76 vertically through waves of successful lineages. While the role of MGEs, particularly plasmids, has been
77 extensively studied in Enterobacterales, few studies have addressed the diverse MGEs and associated
78 ARGs carried by *S. aureus* (8, 9, 13, 17). Likewise, no large-scale analyses have been conducted to
79 localize ARGs across *S. aureus* genomes from diverse sources and hosts. To fill in this knowledge gap,
80 this study aimed at (i) identifying the most prevalent MGEs and ARGs in 10,063 *S. aureus* genomes
81 from the NCBI public database, (ii) highlighting MGE/ARG associations and (iii) evaluating the role of
82 MGEs in the emergence and spread of antibiotic resistance in *S. aureus*.

83 Results

84 Diversity of human and animal *S. aureus* genomes

85 A total of 9,408 human and 655 animal *S. aureus* genomes were analyzed. Animal *S. aureus* genomes
86 came from 15 different hosts, mainly livestock (n=527, see porcine, bovine, avian, ovine and caprine
87 origins in Table S1). Data originated from all continents, with a significant proportion of *S. aureus* of
88 human source (Hm-SA) isolated from North America and Europe, and of *S. aureus* of animal source
89 (An-SA) isolated from Europe and Asia (Figure 1, Table S1). The core genome of all *S. aureus* strains
90 consisted of 1,716 genes, including 86 genes unique to An-SA and 43 genes unique to Hm-SA. A total
91 of 433 distinct sequence types (STs) were identified, but only 21 were found in >1% of either Hm-SA
92 and/or An-SA were identified. Among the 433 STs, 362 (three present in > 1% of Hm-SA) were unique
93 to Hm-SA, 34 (two present in > 1% of An-SA) to An-SA, and 37 (16 present in >1% of Hm-SA and An-SA)
94 were shared between both groups, highlighting the source-specificity of STs (Figure S1A).

95 The most frequently identified STs were (i) the two major livestock associated ST398 (n=216, mainly in
96 Europe) and pig-associated ST9 (n=125, mainly in Asia) (Figures 1A & S1B) in An-SA and (ii) ST5
97 (n=2,138) and ST8 (n=1,719) in Hm-SA (Figures 1B and S1B).

98

99 Mobile genetic elements arsenal in *S. aureus* genomes

100 Analysis of accessory genomes highlighted a remarkable diversity of MGEs including ICEs, transposons
101 and plasmids regardless of their human or animal sources (Figure 1, Table 1). A total of 114,845 MGEs,
102 or 59,768, if excluding IS, were detected (Tables 1 & S1), with IS elements, prophages, plasmids and
103 SCC*mec* being the most prevalent, followed by transposons and ICEs (Table 1). Composite transposons
104 (CTn) were the least common MGE detected in *S. aureus* genomes. Transposons and ICEs were found
105 in *S. aureus* genomes irrespective of their origin. In contrast, IS elements and plasmids exhibited
106 greater host specificity, since only 33% and 23% were respectively shared between Hm-SA and An-SA
107 strains (Table 1).

108 The MGE content varied significantly depending on STs. Plasmids, IS and SCC were present in all major
109 STs (found in >1% of isolates), regardless of their sources. However, specific MGEs could be absent
110 from certain STs, such as transposons that were not identified in ST22 genomes (Figure S2A & B). The
111 mobilome was also diverse among isolates of a same ST, particularly in their plasmid and transposon
112 content, as observed for An-SA ST398 and Hm-SA ST8 (Figure 1).

113 A wide diversity was also observed for each MGE (Figure 2). Among plasmids, Rep1 was predominant
114 in both An-SA (43%) and Hm-SA (29%) genomes, while others segregated depending on the source,
115 like RepA_N and RepL in Hm-SA (16%) versus Rep_trans in An-SA (24%) (Figure 2). Plasmids also
116 frequently harbored multiple *rep* genes (37% of all Hm-SA plasmids possessing multiple *rep* genes and
117 23% in An-SA). For transposons, the Tn*554* family was prevalent (30%) in Hm-SA, the Tn*558* family was
118 widespread (27%) in An-SA and the Tn*552* was equally distributed (about 20% in Hm-SA and An-SA)
119 (Figure 2). Concerning ICEs, the ICE*6013* family prevailed in Hm-SA (44% of genomes versus 26% in An-

120 SA), whereas the Tn*916* family exhibited a higher prevalence in An-SA (38%, and 12% for Hm-SA)
121 (Figure 2). For SCC*mec*, type II(2A) and type IVa(2B) were frequent in Hm-SA (27% and 19%,
122 respectively), while type XII(9C2) was the most prevalent (21.5%) in An-SA (Figure 3A). Among
123 prophages, the most common were phi2958PVL and P282 families, present in more than 33% of Hm-
124 SA genomes, while the prophage StauST398 was the most abundant in An-SA (28%) (Figure 3B). For IS,
125 the most common families were IS*Sau6*, IS*Sau3* and IS*1272*, regardless of the source (Figure 3C). IS*Sau4*
126 was very frequent in Hm-SA (41%) and almost absent in An-SA (0.9%) (Figure 3C). Contrarily, IS*256* was
127 widespread in An-SA (36%) but rarely found in Hm-SA (9%) (Figure 3C). Finally, as observed for ISs, the
128 CTn containing IS*Sau6* was the most prevalent, identified in over 23% of *S. aureus* genomes, regardless
129 of their source (Figure 3D). The CTn with IS*Sau4* was abundant in Hm-SA genomes (11.5%) but rare in
130 An-SA genomes (0.5%).

131

132 *S. aureus* antibiotic resistance genes content

133 Seventy-eight different ARGs were identified, of which 50 were shared by both Hm-SA and An-SA
134 genomes, 27 were unique to Hm-SA, and one (*optrA*) was unique to An-SA (Figure 4, Table S1).
135 *S. aureus* genomes harbored an average of six or five different ARGs per An-SA or Hm-SA genomes,
136 respectively, with a maximum of 17 per Hm-SA and 15 per An-SA (Table S1). In An-SA isolates, the
137 *lnu*(B) gene was consistently found in tandem with the *lsa*(E) gene (>99%) (Figure S3). Similarly, in Hm-
138 SA some ARGs were frequently collocated (>90%) as *ant(9)-Ia* and *erm(A)*, *ant(6)-Ia* and *aph(3')-III*, and
139 *mph(C)* and *msr(A)* (Figure S3).

140 The *blaZ* and *mecA* genes, conferring resistance to beta-lactam antibiotics, were commonly found
141 regardless of the source and often co-harbored (n=417 in An-SA and n=5,913 in Hm-SA) (Figures 4 &
142 S3). The *aac(6')-aph(2'')* (aminoglycoside), *tet(M)* and *tet(L)* (tetracyclines), *dfrG* (trimethoprim), *lnu(B)*
143 *and lsa(E)* (lincosamides) and *fexA* (phenicol) genes were more prevalent (present in >25% of genomes)
144 in An-SA, while the *ant(9)-Ia* and *aph(3')-III* (aminoglycosides) and *erm(A)* (macrolides) genes were

145 more common in Hm-SA (Figure 4). Of note, the *aac(6')-aph(2'')* gene was found in 83% of the equine
146 *S. aureus*, while it was present in less than 60% of the genomes of other animal hosts (Figure 4). Among
147 animals, pig isolates presented the largest number of resistance genes, with 11 genes belonging to
148 seven different families present in more than 40% of the genomes (Figure 4). In contrast, in bovine,
149 only *blaZ* and *mecA* were present in more than 40% of the genomes (Figure 4). Certain ARGs exhibited
150 restricted distribution patterns, as *vga(E)* present only in human-derived ST398 *S. aureus* strains or
151 *vga(A)LC* and *apmA* identified in animal-derived ST398/ST9 strains. The ARG/ST associations were
152 source-specific, except for *str*, *spd*, *ampA*, *erm(T)*, *dfrK* and *vga(E)*, which were predominantly (>80%)
153 identified in ST398 genomes in both Hm-SA and An-SA (Figures S2C & D).

154

155 ## Association of mobile genetic elements with antibiotic resistance genes in *S. aureus*

156 A Pearson correlation analysis revealed a strong positive correlation between the number of ARGs and
157 the number of MGEs (excluding IS) in *S. aureus* genomes (r=0.57, p<0.0001, r=0.39, p<0.0001, for Hm-
158 SA and An-SA, respectively). This correlation was particularly high for transposons, with R-values of
159 0.45 (p<0.0001) for Hm-SA and 0.60 (p<0.0001) for An-SA strains, but also for SCC elements (r=0.45,
160 p<0.0001; r=0.48, p<0.0001) and plasmids (r=0.24, p<0.0001; r=0.46, p<0.0001).

161 The majority of ARGs (78% in Hm-SA, 75% in An-SA) were associated with MGEs (Figure5, Table S2).
162 Plasmids (47% in An-SA and 42% in Hm-SA) were the predominant MGE harboring ARGs, followed by
163 SCC elements (22% in Hm-SA and 11% in An-SA) and transposons (18% in Hm-SA and 12% in An-SA)
164 (Figure 5, Table S2). The diversity of MGE/ARG co-occurrences was high since 21 and 12 different
165 combinations of MGE/ARG were identified in Hm-SA and An-SA, respectively (Figure 5). The *spd*,
166 *cat(pC221)*, *qacG*, *str*, *tet(T)* and *vga(A)LC* genes were exclusively found on plasmids, while *ant(9)-Ia*,
167 *erm(A)*, *fexA*, *vga(A)V* and *vga(E)* were primarily associated with transposons, regardless of the
168 *S. aureus* source (Figure 5). Several genes were associated with various types of MGEs, like *erm(B)* and
169 *dfrK* which were frequently carried by plasmids or transposons and by putative plasmid/transposon

170 tandem (Figure 5). *S. aureus* MGEs could be nested within each other, like plasmids or ICEs harboring
171 transposons, or SCC*mec* elements hosting a diverse array of other MGEs (Figure 5).

172 *Plasmid/ARG associations.* Each ARG was primarily associated with a specific Rep family (Figure 6).
173 Rep1 and RepA_N were the dominant plasmid families associated with ARGs, either alone or in
174 combination with other Rep (80%, 496/619 in Hm-SA; 78%, 164/210 in An-SA) (Figure 6). Within these,
175 Rep1/*aadD* (8%, n=1,603/20,299) in Hm-SA and Rep1/*tet(L)* (6.5%, n=133/2,038) in An-SA, emerged as
176 the most common. An-SA displayed two prevalent plasmid/multi-ARGs co-occurrences (Figure 7A). The
177 first involved seven ARGs *aac(6')-aph(2'')*, *aadD*, *ant(6)-Ia*, *erm(C)*, *lnu(B)*, *lsa(E)* and *tet(L)* carried by a
178 Rep1 plasmid (n=42). The second involved the *aadD*, *tet(L)* and *tet(T)* genes carried by an Inc18/Rep1
179 plasmid (n=13). In Hm-SA, the two most widespread associations were Inc18/Rep1/RepA_N (n=401)
180 and Inc18/RepA_N (n=363), each associated with the same six ARGs *ant(6)-Ia*, *aph(3')-III*, *blaZ, mph(C),*
181 *msr(A) and sat-4* (Figure 7B).

182 *Transposon/ARG associations.* Each ARG was associated with one type of transposon and identical
183 transposon/ARG associations were identified in both human and animal genomes (Figure 6). The
184 Tn*554/ant(9)-Ia*, Tn*554/erm(A)* and Tn*558/fexA* associations were the most frequently detected in
185 Hm-SA and An-SA, respectively (Figure 6). Apart from *erm(A)* and *ant(9)-Ia* found on Tn*554* and Tn*6133*
186 or *erm(B)* associated with Tn*551* and Tn*917* (Figure 6), ARGs were found only on one type of
187 transposon. Some ARGs, such as *blaZ*, were also found associated with both transposons and ICEs
188 (Table S2). A strong co-occurrence between certain genes and transposons was observed, as for *lnu(G)*,
189 *vga(A)V*, *vga(E)* or *fexA* genes that were predominantly associated with transposons (Figure 6).
190 Transposon also harbored multiple ARGs. Notably, the Tn*554/erm(A)/ant(9)-Ia* association emerged
191 as the most frequent MGE/multi-ARGs association in Hm-SA (n=3,643) and the second most common
192 in An-SA (n=25) (Figure 7). Additionally, the Tn*6133/erm(A)/ant(9)-Ia/vga(E)* co-occurrence was
193 identified in both Hm-SA (n=25) and An-SA (n=11) genomes (Figure 7).

194 *Integrative and conjugative element/ARG associations.* Overall, a minority (<9% of MGE/ARG
195 associations) of ARGs were associated with ICEs, but associations were diverse (Table S2). The most
196 widespread element was Tn*916/tet(M)* (Figure 6). This gene was itself usually located on ICEs
197 (96%/100% in Hm-SA/An-SA) (Figure 6) and sometimes associated with other genes like *dfrG* (Figure
198 7).

199 *Staphylococcal chromosomal cassette/ARG associations.* The *mecA* gene was carried by several
200 types of SCC*mec* cassettes, while *mecC* was exclusively associated with the type XI(8E) element. In
201 addition to *mec* genes, 23 different ARGs were found on SCC*mec* elements and formed 97 SCC*mec*/ARG
202 associations in Hm-SA genomes, while nine different ARGs were found forming 12 different
203 SCC*mec*/ARG associations in An-SA strains (Table S2). In Hm-SA, the most common genes were *ant(9)-*
204 *Ia* and *erm(A)* genes carried by a type II(2A) SCC*mec* element (1,513 for *ant(9)-Ia* and 1,473 for *erm(A)*)
205 and in An-SA genomes *blaZ* was always associated with type XI(8E) cassette carrying *mecC* (n=10)
206 (Table S2). The SCC*mec*/multi-ARGs associations, like type Vc/*mecA*/*tet(K)* and type IVa/*mecA*/*dfrC*,
207 were found in both humans (n=27 and and animals even though their proportions differed depending
208 on the source (n=27 and 41 in Hm-SA, n=8 and 3 in An-SA) (Figure 7, Table S2).

209 *Prophage/ARG associations.* ARGs were rarely associated with prophages (0.3% in Hm-SA, 0.1% An-
210 SA genomes). In Hm-SA genomes, the most common prophage/ARG associations were
211 phi2958PVL/*dfrG* (n=27) and SPbeta_like/*aac(6')-aph(2'')* (n=23) (Table S2). This prophage was found
212 associated with 17 different ARGs (Table S2). Prophage/ARG occurrences were not exclusive, i.e. *blaZ*
213 could be associated with 10 different types of prophages. In An-SA genomes, only two associations
214 were identified, i.e. *aac(6')-aph(2'')*, *aph(3')-III* and *ant(6)-Ia* carried by a SPbeta-like prophage, and
215 *dfrG* associated with YMC/09/04/R1988.

216 *Composite transposon/ARG associations.* These MGEs were only associated with about 5% of ARGs
217 in both Hm-SA and An-SA (Table S2). IS*Sau6* was the most common CTn associated with several ARGs
218 (24 different ARGs in Hm-SA and 15 in An-SA genomes) (Table S2). The most frequently identified co-

219 occurrences were IS*Sau6*/*mecA*, harbored by a SCC*mec* element, in An-SA strains (n=103), but also
220 abundant in Hm-SA (n=534), even if IS*Sau6*/*aadD*, also located on SCC*mec*, was most widespread in
221 Hm-SA (n=547).

222

223 Discussion

224 Although MGEs are recognized key players in the dissemination of AMR, the association between
225 MGEs and ARGs has been understudied in Gram-positive bacteria, particularly in *S. aureus*. While
226 previous studies focused either on MGEs and/or ARGs (8, 9, 18, 19), our large-scale analysis of over
227 10,000 publicly available *S. aureus* genomes from both animal and human sources is, to our
228 knowledge, the first to reveal the intricate interplay between mobilome and resistome. Our analysis
229 highlighted a remarkable diversity of STs (n=433), MGEs (n=278) and ARGs (n=78) in *S. aureus,* as well
230 as the routes of their dissemination within the species. Our study, like all studies based on publicly
231 available genomes, has some limitations imposed by the bias in sequenced genomes deposited in the
232 NCBI database. Due to sequencing costs, only strains harboring the most critical resistance genes for
233 human and animal health were analyzed. This resulted in an over-representation of MRSA strains (80%
234 Hm-SA and 71% An-SA) and the under-representation of An-SA, except for *mecA*-positive ST398 and
235 ST9 isolates of porcine origin (n=143/655 An-SA, 22%) and MRSA of bovine-origin (n=81/655 An-SA,
236 12%). Additionally, our analyses included both complete and draft genomes, which may have resulted
237 in the exclusion of elements spanning several contigs. However, since our study aimed to capture the
238 diversity of MGEs and ARGs rather than quantify them, this bias did not significantly interfere with our
239 analyses.

240 Our study showed a wide distribution and a large diversity of ARGs in *S. aureus* of human and animal
241 origin, even larger than the one reported in the review by Schwartz *et al.* (7), and capable of conferring
242 resistance to all antibiotic families known to treat staphylococcal infections. The most widespread
243 genes were *blaZ* and *mecA*, as also pointed out in a recent study of AMR in publicly available *S. aureus*

244 genomes (20). A recent study on the resistome/mobilome association in ESKAPE pathogens highlighted
245 the overall high prevalence of genes conferring resistance to aminoglycosides, chloramphenicol,
246 trimethoprim and tetracyclines (21). Specific genes conferring resistance to these antibiotic families
247 were also particularly frequent in our study dedicated to *S. aureus*, and their wide dissemination is
248 consistent with antibiotic use in both human and veterinary medicine. Globally, our study revealed a
249 higher diversity of ARGs in Hm-SA and a larger set of human-specific genes. This could be explained by
250 the larger number of genomes analyzed, but also by the higher exposure of humans to antibiotic
251 selection in various environments (hospitals, farm environments or food). Only one gene, *optrA*, was
252 specific to An-SA. This gene, first discovered in human and animal enterococci on a conjugative plasmid
253 (22), and then observed in *Staphylococcus sciuri* of porcine origin (23), is conferring resistance to
254 phenicols. It was found on *S. aureus* chromosome near the SCC*mec*, but also on a plasmid with the *cfr*
255 gene (23). In our study, *optrA* was identified on the chromosome and not associated with an MGE:
256 nevertheless, it was located <10kb from the *fexA* gene carried by Tn*558*, an MGE/ARG association
257 already found on the plasmid carrying *cfr* in other staphylococci (24, 25). Besides these host
258 specificities, a large set of genes, among which *aph(3')-III*, *dfrC*, *fusA*, *tet(T)*, *apmA* and *vga(E)*, were
259 shared between An-SA and Hm-SA. This suggests that numerous ARGs have no host boundaries and
260 can be disseminated from human *S. aureus* to animals and vice versa.

261 The *S. aureus* mobilome was largely composed of IS and phages, which rarely carried ARGs, followed
262 by plasmids and transposons that were identified as the main carriers of ARGs for this species. Our
263 study also highlighted that plasmids exhibited the highest diversity among MGE, with 297 different *rep*
264 genes combinations often forming mosaic plasmids with multiple *rep* genes (37% in Hm-SA and 23% in
265 An-SA) (12, 26). Previous studies mainly reported the association of only two *rep* genes, belonging to
266 the same or two different plasmid families (27, 28). However, our work demonstrates that as many as
267 eight different *rep* genes can be found in a single plasmid. Unlike plasmids circulating in
268 Enterobacterales, those identified in *S. aureus* present few Rep proteins incompatibilities. This
269 facilitates the formation of mosaic plasmids, enabling *S. aureus* to adapt more effectively to diverse

270 hosts and environmental conditions (27, 29–31). Furthermore, the presence of numerous insertion
271 sequences (IS elements) and the rolling-circle replication (RCR) system of small plasmids (<10 kb) favors
272 the recombination and fusion of several small plasmids, resulting in unique large hybrids carrying
273 multiple *rep* genes (27, 32).

274 The prevailing view for a long time held that *S. aureus* possessed very few plasmids, and horizontal
275 gene transfer was believed to occur primarily through transduction. However, studies on Gram-
276 positive bacteria showed that plasmids can be mobilized by using the conjugation system of other
277 plasmids or ICEs present in the strain (33–35). A study in *Bacillus subtilis* showed that plasmids can be
278 mobilized by the *ori*T of ICE*Bs1,* an ICE of the Tn*916* family (34, 35). In *S. aureus*, plasmids can be
279 mobilized if they possess a relaxase or by forming co-integrates that are subsequently resolved by
280 "conduction" (36, 37). O'Brien *et al.* (38) showed that the conjugative plasmid pWBG749 could
281 mobilize the transfer of numerous small plasmids carrying an *ori*T similar to its own (38, 39). Thus,
282 plasmids carrying ARGs, even non-conjugative ones, could be easily transferred between cells,
283 highlighting their central role in the dissemination of these genes (15).

284 Often misclassified in the literature as transposons or plasmids (40), ICEs are also capable of HGT.
285 Studies on enterococci and streptococci showed that these MGEs play a crucial role in the
286 dissemination of ARGs (41). The well-known Tn*916* family was found in many Firmicutes, always
287 carrying the *tet(M)* gene (42–44). This element exhibits a similar backbone sequence between
288 *S. aureus* and streptococci (43). Within *S. aureus*, it was first described in the Mu50 strain and named
289 Tn*5801* (45). Our study identified another ICE, ICE*6013*, as the most prevalent family typically
290 harboring few resistance genes itself. However, it can carry other MGEs like Tn*552*, often associated
291 with the *blaZ gene*. This association of multiple MGEs with ARG was first identified in *S. aureus* ST239
292 (14). Despite sharing some protein similarities with the ICE*Bs1* of *Bacillus subtilis*, ICE*6013* belongs to
293 a distinct family (14). Other MGEs were also found nested within each other, like transposons found
294 within plasmids and SCC*mec* cassettes. For instance, Tn*554/ant(9)-Ia/erm(A)* was found on both Rep1

295 plasmids and SCC*mec* type II(2A) cassettes. The interweaving of MGEs significantly amplifies the
296 potential for dissemination of ARGs (14, 40).

297 Beyond revealing the remarkable diversity of ARGs and MGEs in *S. aureus*, our study importantly
298 evidenced numerous associations between these elements. The high degree of similarities between
299 MGE/ARG associations observed in An-SA and Hm-SA strongly suggested unrestricted dissemination
300 of MGEs across hosts. This finding implies that An-SA could serve as a reservoir for Hm-SA and vice
301 versa. Our results identified a few dominant STs within Hm-SA or An-SA populations, typically
302 harboring the same set of ARG/MGE associations. This observation highlights clonal expansion as a
303 major driver of dissemination in *S. aureus*. This is the case for *S. aureus* ST22, initially identified in
304 United Kingdom hospitals (46), which has become a globally disseminated epidemic clone and has
305 spread across Europe and worldwide, impacting both healthcare settings and the community,
306 including domestic animals like dogs and cats (47, 48). Due to its pandemic character, very few
307 variations were observed in ST22 MGE content in genomes available in public databases. Although our
308 study did not capture evidence of such events, the reported presence of a plasmid carrying via Tn*558*
309 the *cfr* and *fexA* genes in Irish ST22 isolates (25) demonstrates the potential for horizontal transfer
310 even within this otherwise stable clonal lineage. Besides this specific example of a rare event, our
311 results also evidenced more frequent transfers. Notably, within the same ST, the observed diversity of
312 MGEs and ARGs demonstrates that the mobilome and resistome are sources of significant genomic
313 plasticity, despite core genome similarity. Furthermore, our analysis revealed an intense spread of
314 certain MGE/ARG associations across diverse STs (Figure 6). For instance, the Rep1/*aadD* association
315 was found in all five most prevalent STs. Additionally, the Tn*916*/*tet(M)* is primarily associated with
316 ST398 in An-SA (80% of identified *tet(M)* genes are in ST398), while in Hm-SA, it was found in both
317 ST398 (40%) and ST239 (20%). This suggests potential host adaptation, in line with recent studies
318 demonstrating the role of *tet(M)*-carrying Tn*916* transposon, facilitating the jump from An-SA to Hm-
319 SA (49). Despite lacking their own transfer systems and residing primarily within chromosomes,
320 transposons also contribute to *S. aureus* genome plasticity and resistome dissemination among STs.

321 Our findings revealed the presence of transposons in diverse STs, like Tn*554/ant(9)-Ia/erm(A)* which
322 was identified in more than 12 STs, and Tn*558/fexA* found in 10 An-SA STs. This widespread distribution
323 across different epidemic clones highlights the horizontal propagation of these elements, suggesting
324 their important role in shaping the resistome and, more broadly the genomes of *S. aureus*.

325 In conclusion, this study revealed the remarkable abundance and diversity of MGEs and ARGs within
326 *S. aureus* genomes, primarily associated with plasmids and transposons. While it is known that
327 *S. aureus* disseminate through clonal waves, our results showed that these clones can also evolve
328 through horizontal acquisition of MGE/ARG associations that are promoting the dissemination of
329 resistance genes. This study provides additional evidence that An-SA can serve as reservoirs for Hm-
330 SA and vice versa, and that the mobilome's only limitation is its transfer efficiency. Plasmids in *S.*
331 *aureus*, as primary reservoirs of ARGs, are key players of AMR dissemination. This highlights the critical
332 need to elucidate the mechanisms governing the epidemic success of MGEs, particularly those
333 implicated in ARG transfer.

334

335 Materials and methods

336 Genome characterization and phylogenetic analysis

337 Genome assemblies (complete and draft genomes) of *S. aureus* of animal (n=1,436) and human
338 sources (n=11,888) were downloaded from the NCBI public database in October 2021. Quality and
339 completeness of assemblies were evaluated using QUAST v.5.0.2 (50) and BUSCO v.5.2.1 (51) (Figure
340 S4). All contigs <1000 bp were removed from the analysis. Genomes were characterized according to
341 their ST using MLST v.2.1.1 (52). Transposons, ICE, IS and CTn were identified using
342 MobileElementFinder v.1.0.3 (80% coverage and 70% identity) (53). Plasmid replicons (*rep* coding
343 gene) were detected using PlasmidFinder v.2.1.6 software (databases: v.2021-11-29) (60% coverage
344 and 90% identity) (54, 55). SCCs were identified using SCC*mec*Finder v.1.2.1 (database extended, 60%

345 coverage and 90% identity) (54, 56, 57). ARGs were identified using ResFinder v.4.1.7 (database:
346 v.2021-09-22) (60% coverage and 80% identity) (54, 58) and RGI-CARD (Comprehensive Antibiotic
347 Resistance Database) (59) (percentage length of the reference sequence >200). Co-occurrence was
348 considered when several ARGs were identified within the same strain. A phylogenetic tree was
349 constructed using pyMLST v.2.1.3 with default parameters (60). A neighbor-joining tree based on the
350 *S. aureus* core genome was constructed using cgMLST software (https://www.cgmlst.org/ncs) (61). To
351 avoid duplicates, only one genome with identical MGE and ARG content, geographical origin, collection
352 year and NCBI bioProject was selected in each group determined by cgMLST with a maximum distance
353 of 10 different alleles (Figure S4). Following this selection, a total of 9,408 genomes of Hm-SA and 655
354 genomes of An-SA, carrying at least one ARG and one MGE (except IS) were included in this study.

355

356 ## Identification and characterization of detected mobile genetic elements

357 *Plasmids identification*. PlasForest (54, 62, 63), RFPlasmid for *Staphylococcus* species (64), Plasmer
358 (65) and Plasflow (66) were used with default parameters to identify whether contigs were plasmidic
359 or chromosomal. A contig was considered plasmidic if predicted by at least thre e software. Due to the
360 fragmented nature of draft genomes, some plasmids were split into multiple contigs during assembly.
361 To identify contigs belonging to the same plasmid, those identified as plasmidic were analyzed using
362 BLASTN. Contigs were considered part of the same plasmid if they shared more than 60% identity and
363 coverage with the same reference plasmid sequence. Some previously unclassified contigs were
364 identified as plasmidic due to their similarity to known plasmids. Plasmids were classified according to
365 the active protein domain of the Rep protein that was encoded by *rep* gene. All *rep* genes identified
366 on chromosomal contigs were excluded from the analysis.

367 *Composite transposons identification.* A CTn was predicted when two IS were at a specified distance
368 from each other. The threshold value was 12kb according to the length of the largest CTn identified in
369 *S. aureus* (8).

370 *Staphylococcal Chromosomal Cassettes identification.* Boundaries of SCC was fixed with *orfX* gene
371 and the end was adjusted based on the size of the cassette type (https://www.sccmec.org/). SCCs
372 found scattered across multiple contigs were adjusted based on gene order (synteny) to define their
373 limits. SCC*mec*Finder v.1.2.1 did not determine the cassette type for some SCC elements, considered
374 as "indeterminate". SCC lacking *mecA* or *mecC* genes were classified "SCC" instead of SCC*mec*.

375 *Prophages identification.* These elements were identified using PHASTEST, last accessed October
376 2023 (67–69). Only prophages with a "complete" score were retained. Prophages were named
377 according to the bacteriophage exhibiting the closest similarity, determined by both sequence identity
378 and the number of common genes.

379 *Integrative and Conjugative Elements identification.* In addition to MobileElementFinder v.1.0.3
380 detection, a BLASTP analysis was performed against a custom database created from literature and
381 ICEBerg 2.0 database (15, 45, 70, 71). This database included conserved components of the two main
382 ICE families, Tn*916* and ICE*6013*, identified based on a previous study (70) (Figure S5A). Only conserved
383 elements meeting the following criteria were considered as ICEs: proximity between elements,
384 number of conserved elements on the same contig and integrity of the gene (Figure S5B). ICEs
385 boundaries were extended by 10kb at each end of the ICE, reflecting the average size of Staphylococci
386 ICE (approximately 30kb).

387

388 Identification of associations between antibiotic resistance genes and mobile genetic 389 elements

390 To assess the correlation between the number of ARGs and the number of each MGE within a genome,
391 the Pearson correlation coefficient was calculated using GraphPad Prism 9.5.1 (GraphPad Software
392 Inc., CA, USA). MGE/ARG associations were identified through co-localization analysis when the MGE
393 region entirely overlapped the ARG region. This rule was applied only for transposons, ICE, SCC,

394 prophages and CTn. For plasmids, an ARG was considered associated when it was localized on a
395 plasmidic contig (see above). For plasmidic contig lacking *rep* gene, associated ARGs were considered
396 carried by a plasmid of non-determinate (ND) type. Unclassified contigs identified as associated with
397 SCC, prophage, ICE were reclassified as chromosomal. When multiple ARGs were found within the
398 same MGE from a single strain, the MGE was considered to harbor multiple ARGs.

399

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407 data.

408 # Table

409 **Table 1**. Prevalence of mobile genetic elements (MGEs) identified in *S. aureus* genomes of animal (An-SA) and human (Hm-SA) origin.

	Plasmid		Transposon		ICE		SCC		Phage		IS		CTn		All MGEs		All MGEs (except IS)	
Sources	**Hm**	**An**	**Hm**	**An**	**Hm**	**An**	**Hm**	**An**	**Hm**	**An**	**Hm**	**An**	**Hm**	**An**	**Hm**	**An**	**Hm**	**An**
Quantity of MGEs identified	12,084	929	6,581	499	5,287	436	471	7,518	867	19,124	2,873	52,204	5,585	387	108,383	6,462	56,179	3,589
Mean of MGEs per strain	1.5	1.7	1.4	1.2	1.1	1.2	1	1	2.1	1.6	5.6	4.5	1.7	1.9	11.5	9.9	6.0	5.5
Maximum of MGEs per strain	8	6	7	3	4	3	1	1	6	5	58	41	17	11	78	57	23	16
Strains containing MGEs (%tot genomes)*	8,064 (86%)	532 (81%)	4,707 (50%)	420 (64%)	4,751 (50%)	363 (55%)	7,518 (80%)	471 (72%)	9,090 (97%)	554 (85%)	9,286 (99%)	636 (97%)	3,368 (36%)	206 (31%)	9,408 (100%)	655 (100%)	9,408 (100%)	655 (100%)
MGEs specific to sources	203	25	2	0	0	0	12	1	30	4	35	8	10	2	292	40	257	32
MGEs shared between sources (%MGEs shared)**	69 (23%)		9 (82%)		3 (100%)		18 (58%)		51 (60%)		21 (33%)		10 (45%)		181 (35%)		160 (36%)	

410 *ICE: Integrative and Conjugative Element; SCC: Staphylococcal chromosomal cassette; IS: Insertion Sequence; CTn: Composite transposon.*
411 ** Number of MGE/total number of genomes (in %)*
412 ***Number of MGE shared between sources/total number of type of MGEs (in %)*

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658

Figures

Figure 1. Genomic diversity of *S. aureus* genomes of animal (An-SA) (A) and human (Hm-SA) (B) sources. The phylogenetic trees represent 655 An-SA and 9,408 Hm-SA. This tree based on cgMLST distance was constructed using Neighbor-Joining method and visualized using iTOL v6 (https://itol.embl.de). From outer circle to inner circle, host, location, sequence type (ST), Staphylococcal Chromosomal Cassette (SCC) (green), Integrative and Conjugative Element (ICE) (pink), transposon (Tn) (purple) and plasmid (yellow) were represented. The correspondence between colors and each type of host, location, or ST were indicated below the figure. Only STs with a frequency >1% in Hm-SA and/or in An-SA, were represented. Genomes with no associated ST and/or no location were annotated as "not determined" (ND). As they were present in up to 90% of the analyzed genomes, IS and prophages were not represented.

Figure 2. Diversity and occurrence of the most prevalent mobile genetic elements (MGEs) families (plasmids, transposons and integrative and conjugative elements (ICEs)) among *S. aureus* of human (Hm-SA, black) and animal (An-SA, white) origins. Bar chart of the percentage of genomes carrying MGE which corresponds to the number of genome containing at least one MGE out of the total number of genomes analyzed (Hm-SA n=9,408 and An-SA n=655). Only types of MGEs identified in >1% of Hm-SA and/or An-SA genomes are represented in the x-axis.

Figure 3. Occurrence and diversity of Staphylococcal Chromosomal Cassettes (SCC) (A), prophages (B), insertion sequence (IS) (C) and composite transposons (CTn) (D) detected families in *S. aureus* of human (Hm-SA, black) and animal (An-SA, white) sources. Bar chart of the percentage of genomes carrying MGE which corresponds to the number of genomes carrying at least one MGE out of the total

number of genomes analyzed (Hm-SA n=9,408 and An-SA n=655). For SCC and CTn only MGEs identified in >1% of Hm-SA and/or An-SA genomes were represented. For prophages and IS only MGEs identified in >5% of Hm-SA and/or An-SA genomes were depicted.

Figure 4. Occurrence of antibiotic resistance genes (ARGs) in *S. aureus* genomes. *S. aureus* hosts were indicated on the left of the Heatmap, detected ARGs on the bottom and the total number of genomes analyzed for each host on the right. Hosts grouped under the label 'others' correspond to dolphins (n=4), bats (n=4), fishes (n=2), cervid (n=1), shrimp (n=1) and monkey (n=1). The bar at the bottom of the Heatmap corresponds to the families of antibiotics with TMP for trimethoprim and 'others' for nucleoside (*sat-4*) and mupirocin (*mupA)* families. The percentages of genomes containing ARGs were obtained by dividing the number of genomes possessing the resistance gene by the total number of genomes on the top right of the Heatmap. These percentages are represented by different shades of red color, as shown at the bottom of the Heatmap. Only ARGs with a frequency >0.1% in Hm-SA and/or in An-SA, were represented. Genes exclusively present in Hm-SA are indicated by an asterisk.

Figure 5. Associations of antibiotic resistance genes (ARGs) and mobile genetic elements (MGEs) in *S. aureus* genomes of animal (An-SA) (A) and human (Hm-SA) sources (B). Bar chart representing the percentage of associations between ARGs and MGEs, with each association assigned a color and indicated in the legend. When an ARG is not associated, the percentage is represented in gray. Only the ARGs with a frequency >0.1% in Hm-SA and/or An-SA, were depicted. The percentage of ARG corresponds to the number of ARG associated with MGE or a combination of MGEs divided by the total number of this ARG, identified in An-SA or Hm-SA. Tn: transposon; ICE: Integrative and Conjugative Element; SCC: Staphylococcal chromosomal cassette; CTn: composite transposon.

48 **Figure 6. Co-occurrences of antibiotic resistance genes (ARGs) with plasmids, transposons and**
49 **integrative and conjugative elements (ICEs) in *S. aureus* genomes of animal (An-SA) (A) and human**
50 **(Hm-SA) (B) sources depending on sequence type (ST).** Each ARG, MGE and ST were represented by a
51 node that is linked by a flow when associated. The color of the ARG nodes corresponds to the type of
52 MGE with which it is associated: pink for ICE, yellow for plasmid, purple for transposon and brown for
53 plasmid and transposon. The thickness of the flow is proportional to the percentage of ARG associated
54 with the MGE and the percentage of MGE associated with ST. This percentage is calculated by dividing
55 the number of ARG associated with the MGE by the total number of these ARGs identified in An-SA or
56 Hm-SA. Only ARGs with a frequency >0.1% in Hm-SA and/or in An-SA, and association frequencies of
57 MGE/ARG >10% were represented. For the MGE/ST association, only the 6 most abundant STs in both
58 Hm-SA and/or in An-SA were represented. The maximum thickness of the flow corresponds to 100%,
59 as demonstrated by Tn*916/tet(M)* for (A) and Inc18,Rep1/*tet(T)* for (B). Sankey diagrams were created
60 using SankeyMATIC (http://sankeymatic.com).

61

62 **Figure 7. Co-occurrences between multiple antibiotic resistance genes (ARGs) and mobile genetic**
63 **elements (MGEs) in *S. aureus* of animal (An-SA) (A) and human (Hm-SA) (B) sources.** Associations
64 were represented by links that indicate that ARGs were found within the same genome on the same
65 MGE. The thickness of the line is proportional to the number of genomes carrying this co-occurrence.
66 The thickest lines correspond to Rep1/*aac(6')-aph(2'')/aadD/ant(6)-Ia/erm(C)/lnu(B)/lsa(E)/tet(L)*
67 association identified in 42 An-SA genomes and Tn*554/ant(9)-Ia/erm(A)* co-occurrence in 3,643 Hm-
68 SA genomes. Only associations found in at least two An-SA genomes, or 10 Hm-SA genomes were
69 shown. SCC: Staphylococcal chromosomal cassette; CTn: Composite transposon; ICE: Integrative and
70 Conjugative Element.

71

72

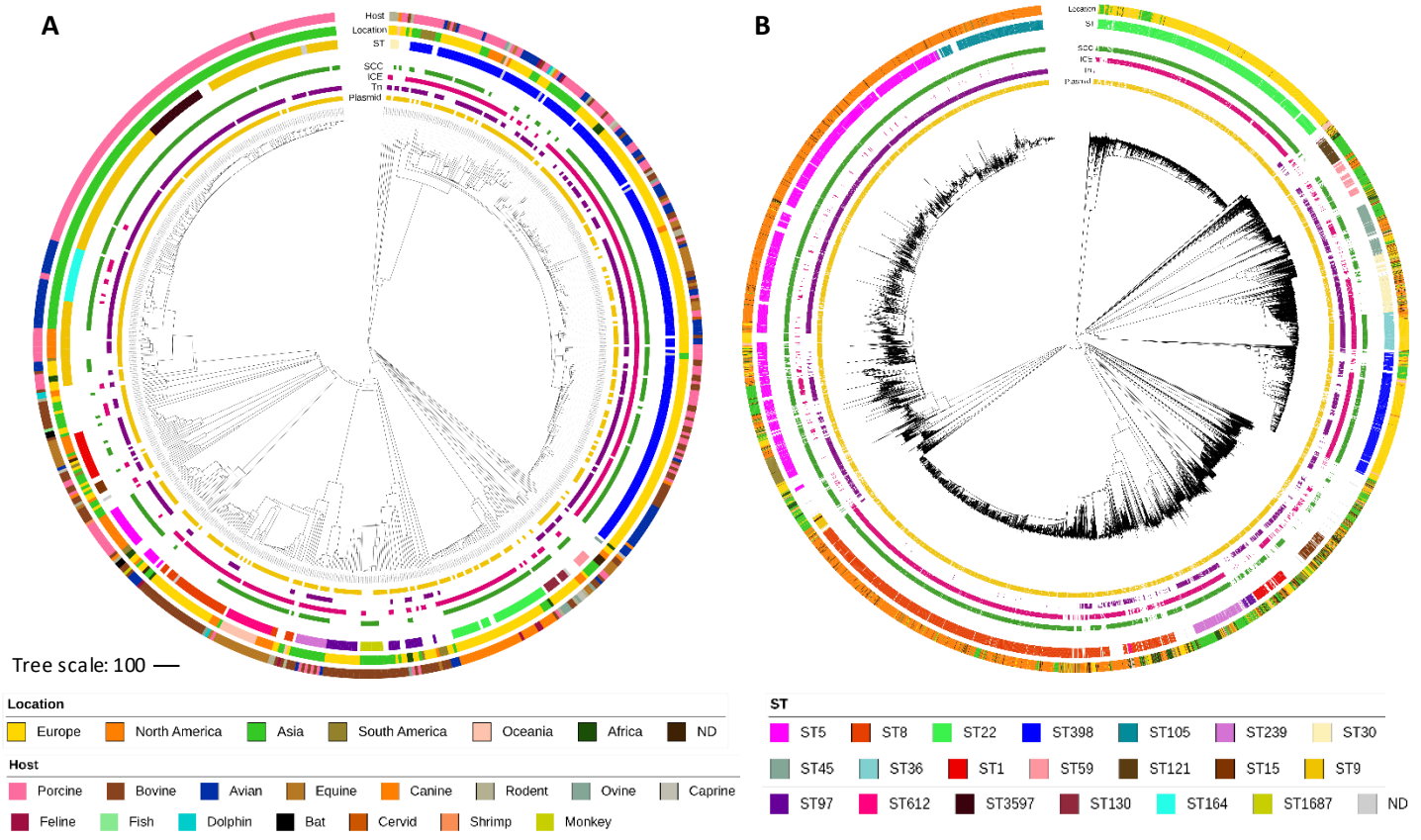
A
Host
Location
ST
SCC
ICE
Tn
Plasmid
Tree scale: 100
B
Location
ST
SCC
ICE
Tn
Plasmid
Location
Europe
North America
Asia
South America
Oceania
Africa
ND
Host
Porcine
Bovine
Avian
Equine
Canine
Rodent
Ovine
Caprine
Feline
Fish
Dolphin
Bat
Cervid
Shrimp
Monkey
ST
ST5
ST8
ST22
ST398
ST105
ST239
ST30
ST45
ST36
ST1
ST59
ST121
ST15
ST9
ST97
ST612
ST3597
ST130
ST164
ST1687
ND

Figure 1.

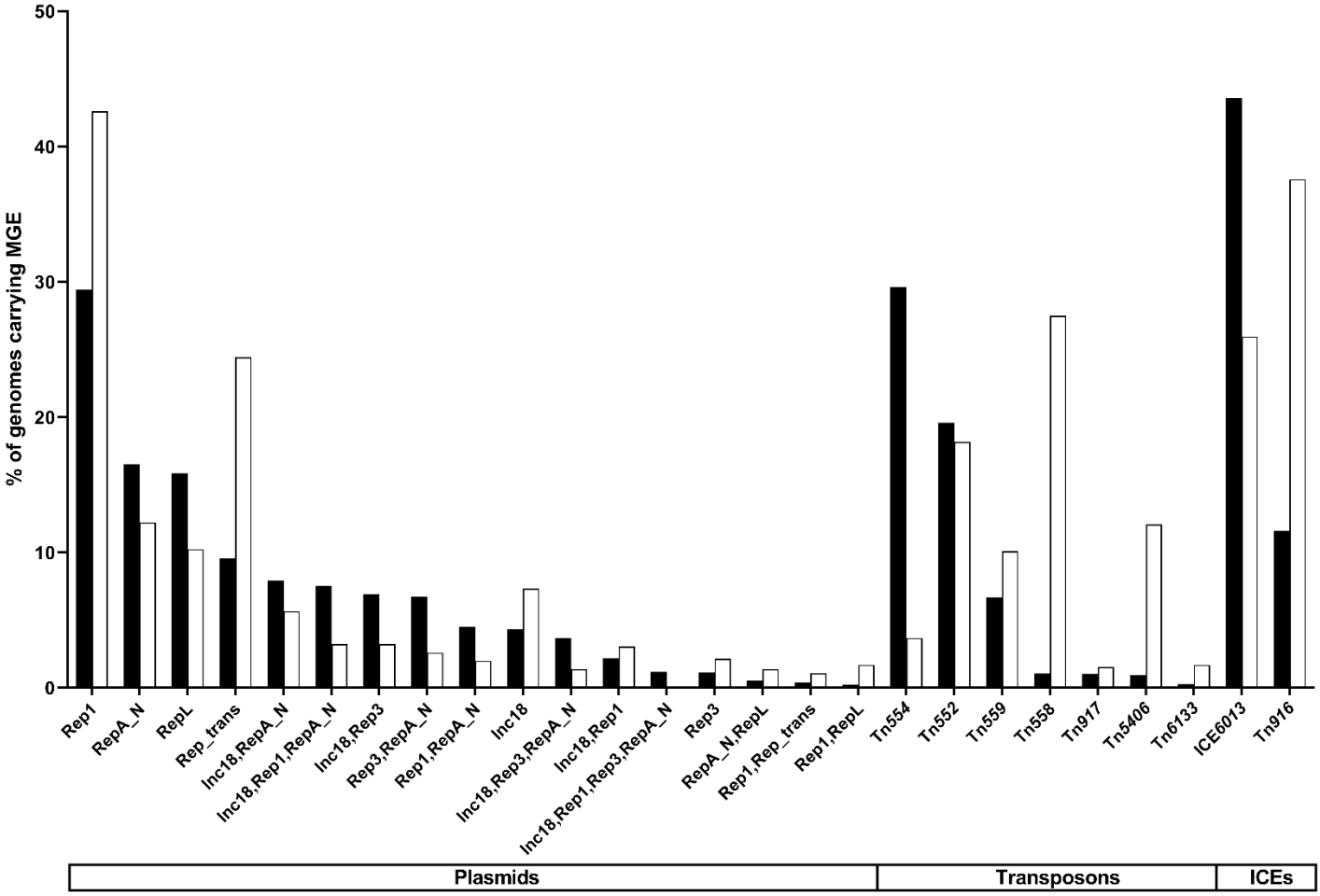
% of genomes carrying MGE
50
40
30
20
10
0
Rep1
RepA_N
RepL
Rep_trans
Inc18,RepA_N
Inc18,Rep1,RepA_N
Inc18,Rep3
Rep3,RepA_N
Rep1,RepA_N
Inc18
Inc18,Rep3,RepA_N
Inc18,Rep1
Inc18,Rep1,Rep3,RepA_N
Rep3
RepA_N,RepL
Rep1,Rep_trans
Rep1,RepL
Tn554
Tn552
Tn559
Tn558
Tn917
Tn5406
Tn6133
ICE6013
Tn916
Plasmids
Transposons
ICEs

Figure 2.

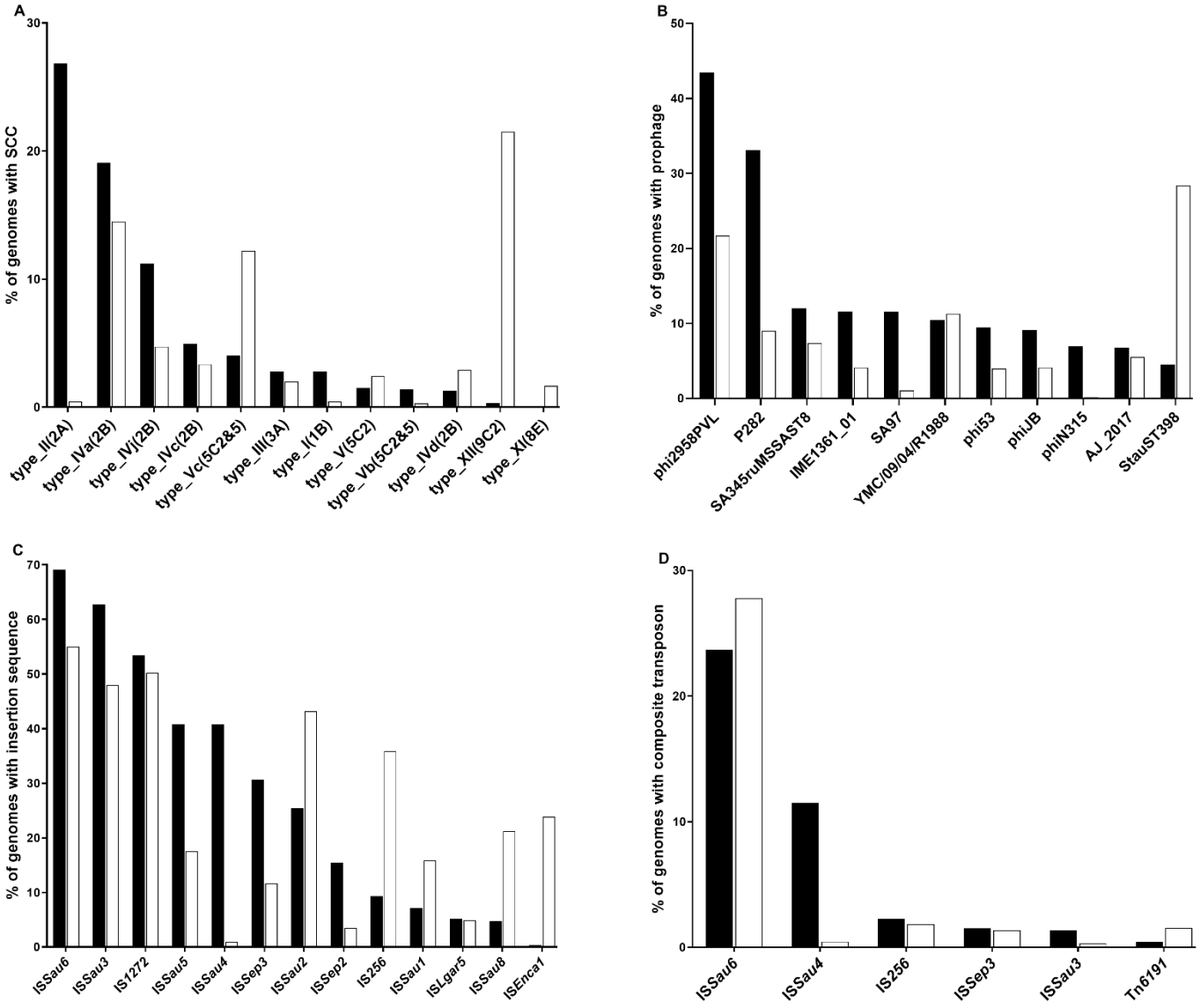
A
% of genomes with SCC
30
20
10
0
type_II(2A)
type_IVa(2B)
type_IVj(2B)
type_IVc(2B)
type_Vc(5C2&5)
type_III(3A)
type_I(1B)
type_V(5C2)
type_Vb(5C2&5)
type_IVd(2B)
type_XII(9C2)
type_XI(8E)
B
% of genomes with prophage
50
40
30
20
10
0
phi2958PVL
P282
SA345ruMSSAST8
IME1361_01
SA97
YMC/09/04/R1988
phi53
phiJB
phiN315
AJ_2017
StauST398
C
% of genomes with insertion sequence
70
60
50
40
30
20
10
0
ISSau6
ISSau3
IS1272
ISSau5
ISSau4
ISSep3
ISSau2
ISSep2
IS256
ISSau1
ISLgar5
ISSau8
ISEnca1
D
% of genomes with composite transposon
30
20
10
0
ISSau6
ISSau4
IS256
ISSep3
ISSau3
Tn6191

Figure 3.

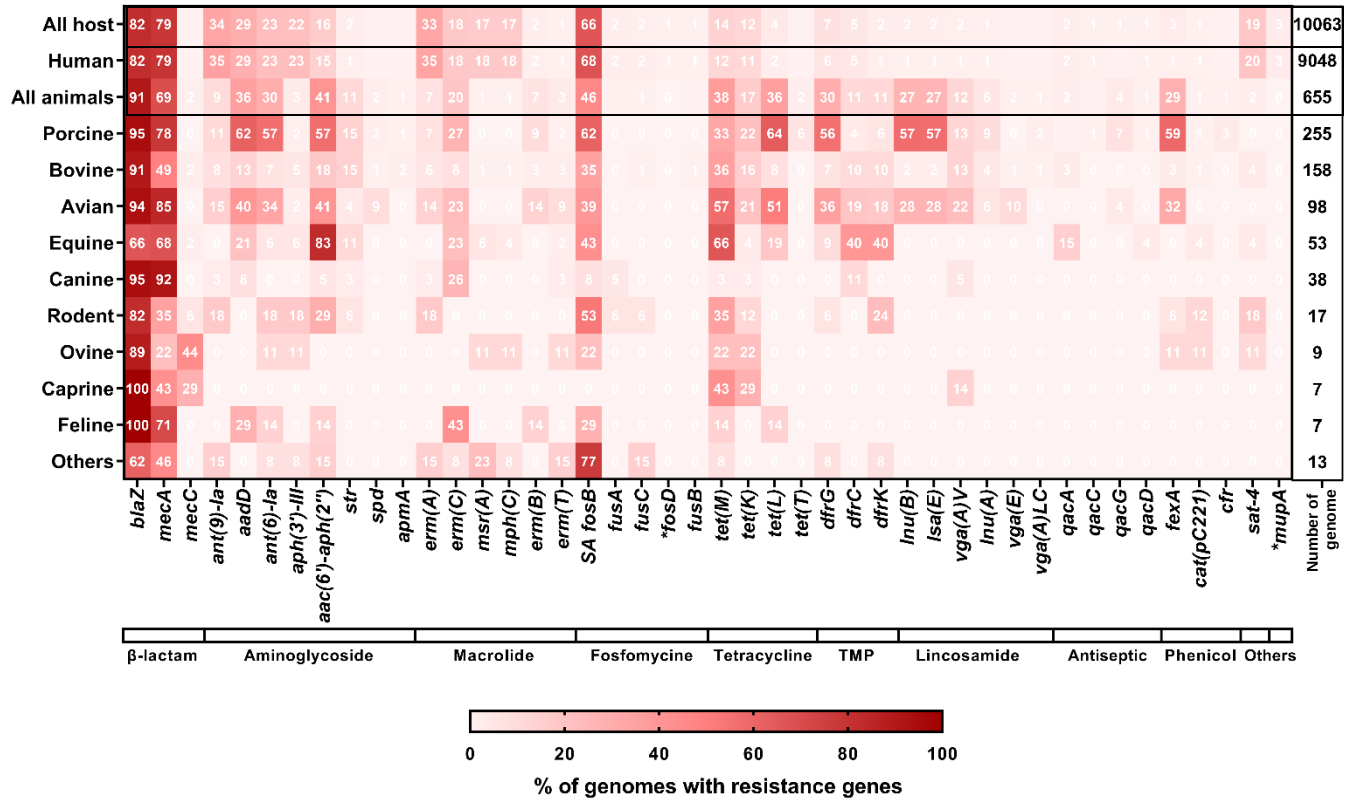
All host
Human
All animals
Porcine
Bovine
Avian
Equine
Canine
Rodent
Ovine
Caprine
Feline
Others
blaZ
mecA
mecC
ant(9)-Ia
aadD
ant(6)-Ia
aph(3')-III
aac(6')-aph(2'')
str
spd
apmA
erm(A)
erm(C)
msr(A)
mph(C)
erm(B)
erm(T)
SA fosB
fusA
fusC
*fosD
fusB
tet(M)
tet(K)
tet(L)
tet(T)
dfrG
dfrC
dfrK
lnu(B)
lsa(E)
vga(A)V
lnu(A)
vga(E)
vga(A)LC
qacA
qacC
qacG
qacD
fexA
cat(pC221)
cfr
sat-4
*mupA
Number of genome
β-lactam
Aminoglycoside
Macrolide
Fosfomycine
Tetracycline
TMP
Lincosamide
Antiseptic
Phenicol
Others
0
20
40
60
80
100
% of genomes with resistance genes

Figure 4.

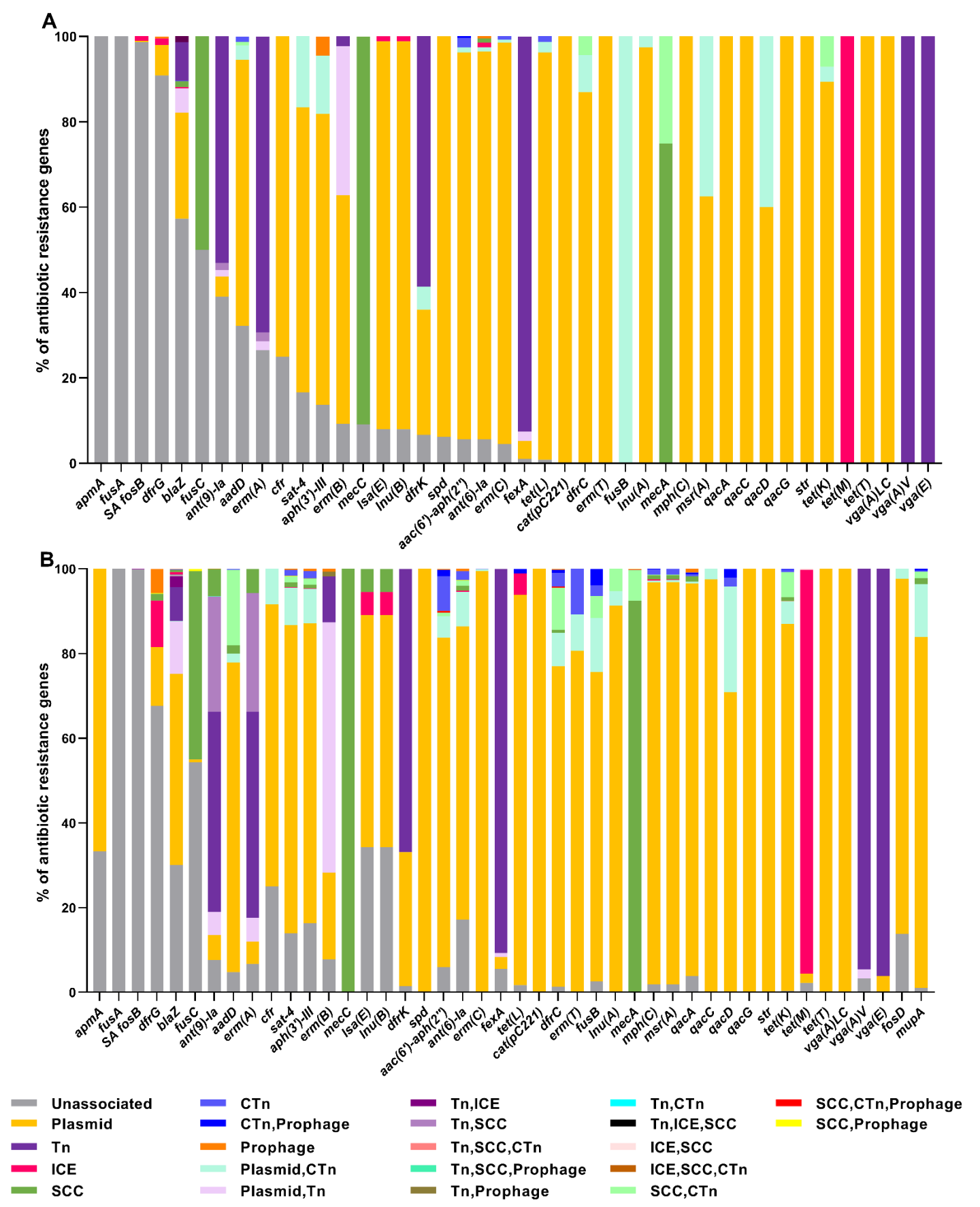
A
% of antibiotic resistance genes
0
20
40
60
80
100
apmA
fusA
SA fosB
dfrG
blaZ
fusC
ant(9)-Ia
aadD
erm(A)
cfr
sat-4
aph(3')-III
erm(B)
mecC
lsa(E)
lnu(B)
dfrK
spd
aac(6')-aph(2'')
ant(6)-Ia
erm(C)
fexA
tet(L)
cat(pC221)
dfrC
erm(T)
fusB
lnu(A)
mecA
mph(C)
msr(A)
qacA
qacC
qacD
qacG
str
tet(K)
tet(M)
tet(T)
vga(A)LC
vga(A)V
vga(E)
B
% of antibiotic resistance genes
0
20
40
60
80
100
apmA
fusA
SA fosB
dfrG
blaZ
fusC
ant(9)-Ia
aadD
erm(A)
cfr
sat-4
aph(3')-III
erm(B)
mecC
lsa(E)
lnu(B)
dfrK
spd
aac(6')-aph(2'')
ant(6)-Ia
erm(C)
fexA
tet(L)
cat(pC221)
dfrC
erm(T)
fusB
lnu(A)
mecA
mph(C)
msr(A)
qacA
qacC
qacD
qacG
str
tet(K)
tet(M)
tet(T)
vga(A)LC
vga(A)V
vga(E)
fosD
mupA
Unassociated
Plasmid
Tn
ICE
SCC
CTn
CTn,Prophage
Prophage
Plasmid,CTn
Plasmid,Tn
Tn,ICE
Tn,SCC
Tn,SCC,CTn
Tn,SCC,Prophage
Tn,Prophage
Tn,CTn
Tn,ICE,SCC
ICE,SCC
ICE,SCC,CTn
SCC,CTn
SCC,CTn,Prophage
SCC,Prophage

Figure 5.

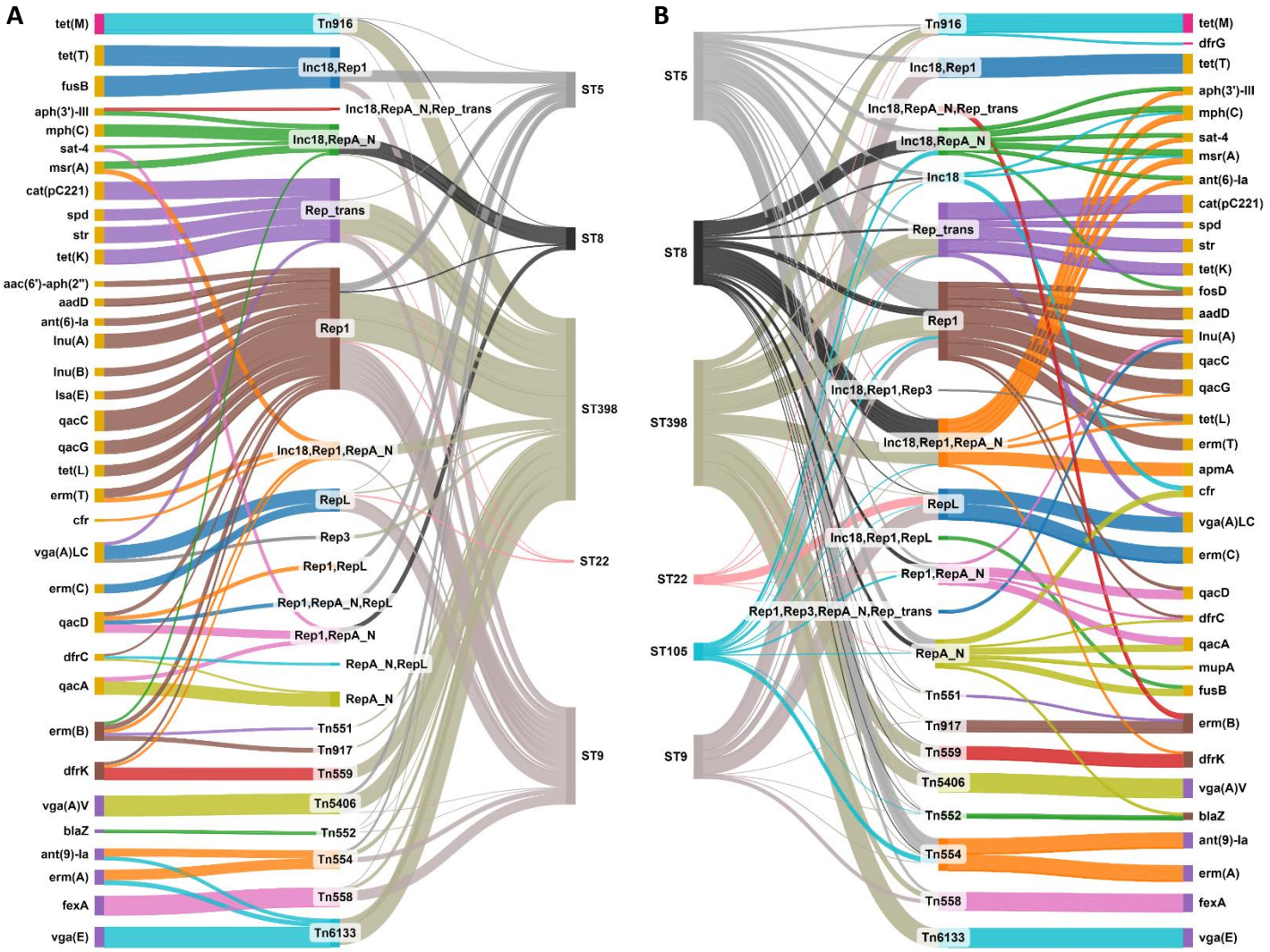
A
tet(M)
tet(T)
fusB
aph(3')-III
mph(C)
sat-4
msr(A)
cat(pC221)
spd
str
tet(K)
aac(6')-aph(2'')
aadD
ant(6)-Ia
lnu(A)
lnu(B)
lsa(E)
qacC
qacG
tet(L)
erm(T)
cfr
vga(A)LC
erm(C)
qacD
dfrC
qacA
erm(B)
dfrK
vga(A)V
blaZ
ant(9)-Ia
erm(A)
fexA
vga(E)
Tn916
Inc18,Rep1
Inc18,RepA_N,Rep_trans
Inc18,RepA_N
Rep_trans
Rep1
Inc18,Rep1,RepA_N
RepL
Rep3
Rep1,RepL
Rep1,RepA_N,RepL
Rep1,RepA_N
RepA_N,RepL
RepA_N
Tn551
Tn917
Tn559
Tn5406
Tn552
Tn554
Tn558
Tn6133
ST5
ST8
ST398
ST22
ST9
B
ST5
ST8
ST398
ST22
ST105
ST9
Tn916
Inc18,Rep1
Inc18,RepA_N,Rep_trans
Inc18,RepA_N
Inc18
Rep_trans
Rep1
Inc18,Rep1,Rep3
Inc18,Rep1,RepA_N
RepL
Inc18,Rep1,RepL
Rep1,RepA_N
Rep1,Rep3,RepA_N,Rep_trans
RepA_N
Tn551
Tn917
Tn559
Tn5406
Tn552
Tn554
Tn558
Tn6133
tet(M)
dfrG
tet(T)
aph(3')-III
mph(C)
sat-4
msr(A)
ant(6)-Ia
cat(pC221)
spd
str
tet(K)
fosD
aadD
lnu(A)
qacC
qacG
tet(L)
erm(T)
apmA
cfr
vga(A)LC
erm(C)
qacD
dfrC
qacA
mupA
fusB
erm(B)
dfrK
vga(A)V
blaZ
ant(9)-Ia
erm(A)
fexA
vga(E)

Figure 6.

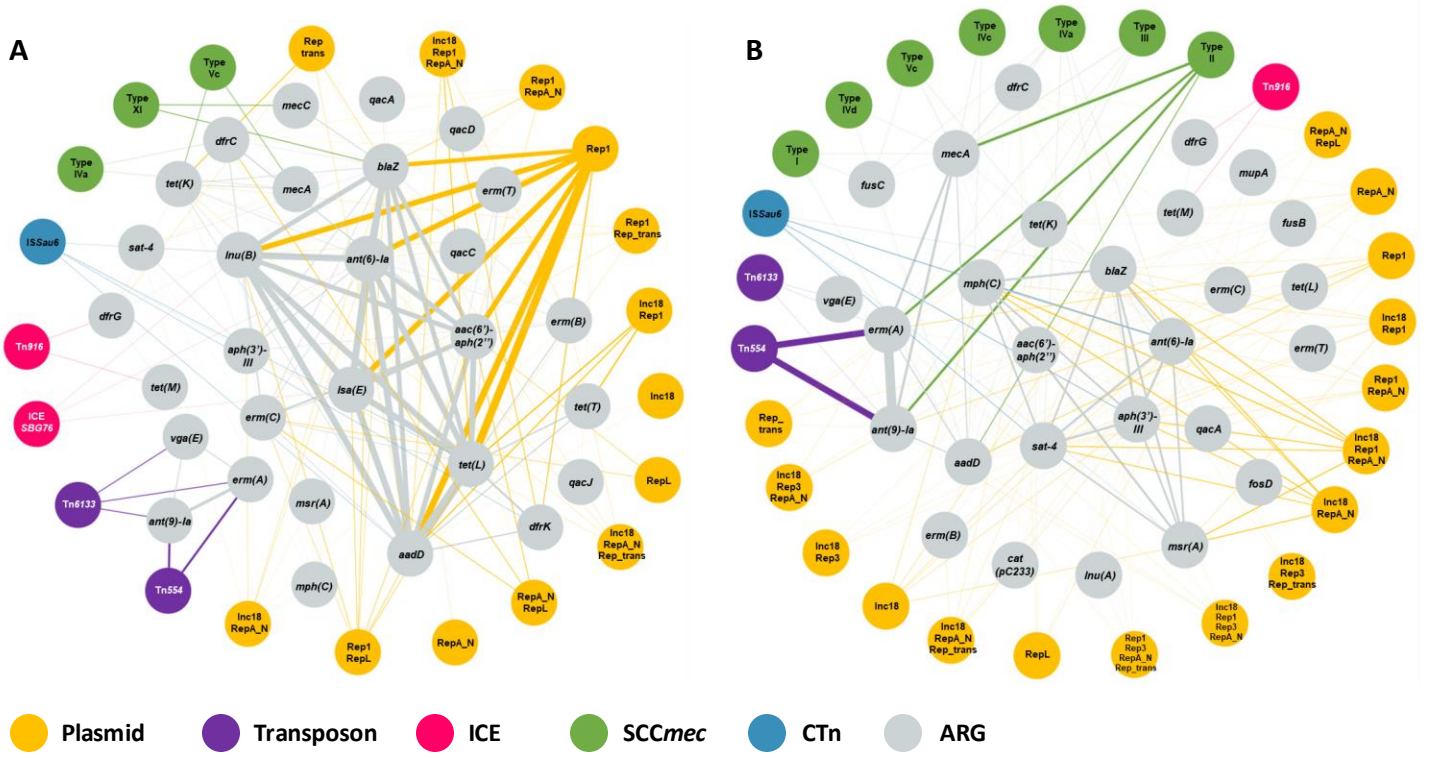
A
Rep trans
Inc18 Rep1 RepA_N
Type Vc
Rep1 RepA_N
Type XI
mecC
qacA
qacD
dfrC
Rep1
Type IVa
tet(K)
mecA
blaZ
erm(T)
Rep1 Rep_trans
ISSau6
sat-4
lnu(B)
ant(6)-Ia
qacC
Inc18 Rep1
dfrG
erm(B)
Tn916
aph(3')-III
aac(6')-aph(2'')
tet(M)
lsa(E)
Inc18
tet(T)
ICE SBQ76
erm(C)
vga(E)
tet(L)
RepL
qacJ
erm(A)
Tn6133
msr(A)
ant(9)-Ia
dfrK
Inc18 RepA_N Rep_trans
aadD
Tn554
mph(C)
RepA_N RepL
Inc18 RepA_N
Rep1 RepL
RepA_N
B
Type IVc
Type IVa
Type III
Type II
Type Vc
dfrC
Tn916
Type IVd
RepA_N RepL
Type I
mecA
dfrG
mupA
fusC
RepA_N
ISSau6
tet(K)
tet(M)
fusB
Rep1
Tn6133
mph(C)
blaZ
erm(C)
tet(L)
vga(E)
Inc18 Rep1
erm(A)
Tn554
aac(6')-aph(2'')
ant(6)-Ia
erm(T)
Rep1 RepA_N
Rep_ trans
ant(9)-Ia
aph(3')-III
qacA
sat-4
Inc18 Rep1 RepA_N
aadD
Inc18 Rep3 RepA_N
fosD
Inc18 RepA_N
erm(B)
msr(A)
Inc18 Rep3
cat (pC233)
lnu(A)
Inc18 Rep3 Rep_trans
Inc18
Inc18 Rep1 Rep3 RepA_N
Inc18 RepA_N Rep_trans
RepL
Rep1 Rep3 RepA_N Rep_trans
Plasmid
Transposon
ICE
SCC*mec*
CTn
ARG

Figure 7.