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

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

45 # Introduction

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

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

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

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

84 Results

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

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

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

99

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

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

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

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

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

132

133 ## *S. aureus* antibiotic resistance genes content

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

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

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

155

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

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

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

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

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

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

195 *Integrative and conjugative element/ARG associations.* Overall, a minority (<9% of MGE/ARG
196 associations) of ARGs were associated with ICEs, but associations were diverse (Table S2). The most
197 widespread element was Tn*916*/*tet(M)* (Figure 6). This gene was itself usually located on ICEs
198 (96%/100% in Hm-SA/An-SA) (Figure 6) and sometimes associated with other genes like *dfrG* (Figure
199 7).

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

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

217 *Composite transposon/ARG associations.* These MGEs were only associated with about 5% of ARGs
218 in both Hm-SA and An-SA (Table S2). IS*Sau6* was the most common CTn associated with several ARGs
219 (24 different ARGs in Hm-SA and 15 in An-SA genomes) (Table S2). The most frequently identified co-

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

223

224 Discussion

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

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

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

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

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

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

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

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

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

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

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

335

336 Materials and methods

337 Genome characterization and phylogenetic analysis

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

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

356

357 Identification and characterization of detected mobile genetic elements

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

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

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

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

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

388

389 Identification of associations between antibiotic resistance genes and mobile genetic 390 elements

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

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

400

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408 data.

409 # Table

410 **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%)	

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

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659

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

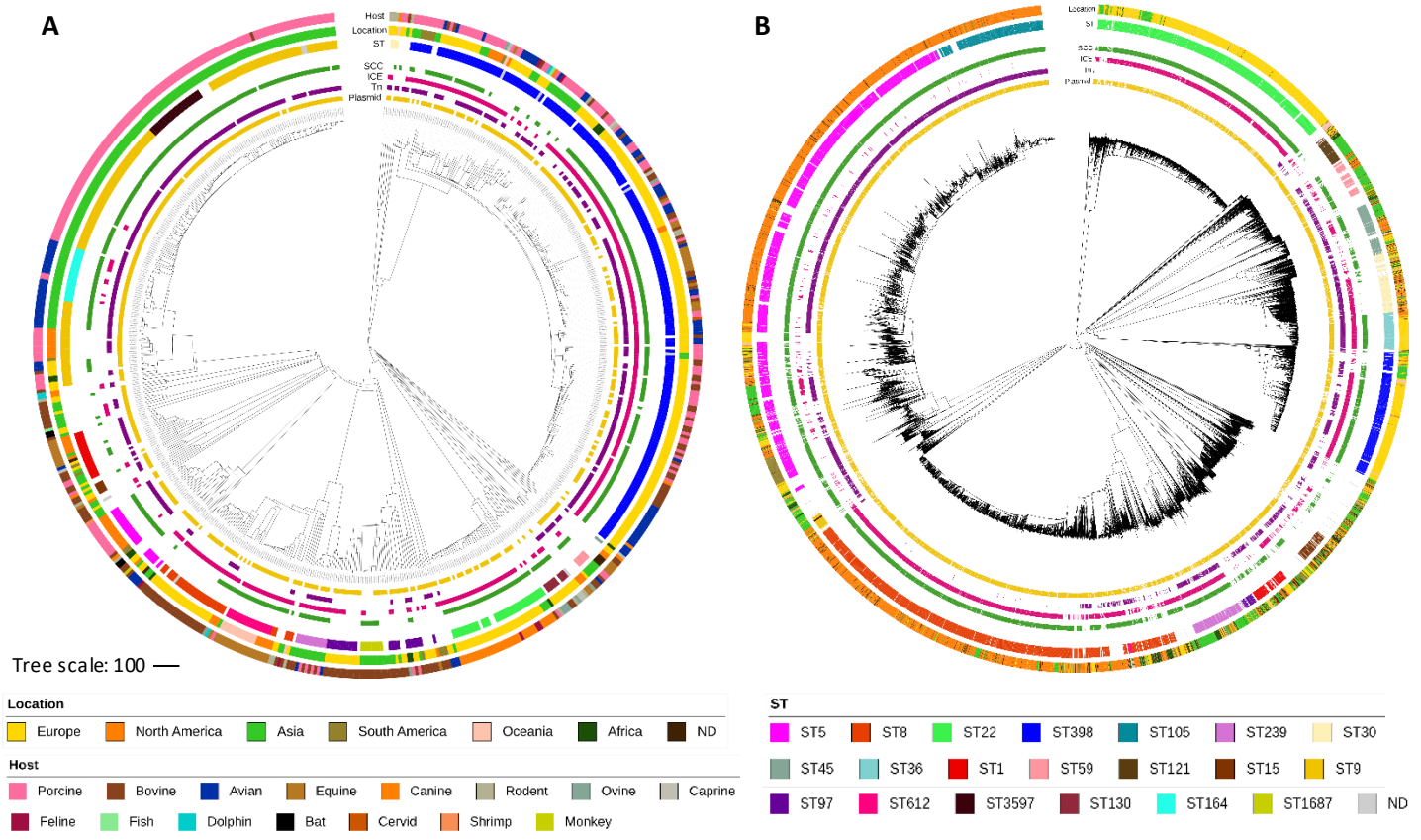
A
Host
Location
ST
SCC
ICE
Tn
Plasmid
Tree scale: 100
B
Location
ST
SCC
ICE
Tn
Plasmid
Location
Europe
North America
Asia
South America
Oceania
Africa
ND
Host
Porcine
Bovine
Avian
Equine
Canine
Rodent
Ovine
Caprine
Feline
Fish
Dolphin
Bat
Cervid
Shrimp
Monkey
ST
ST5
ST8
ST22
ST398
ST105
ST239
ST30
ST45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

Figure 1.

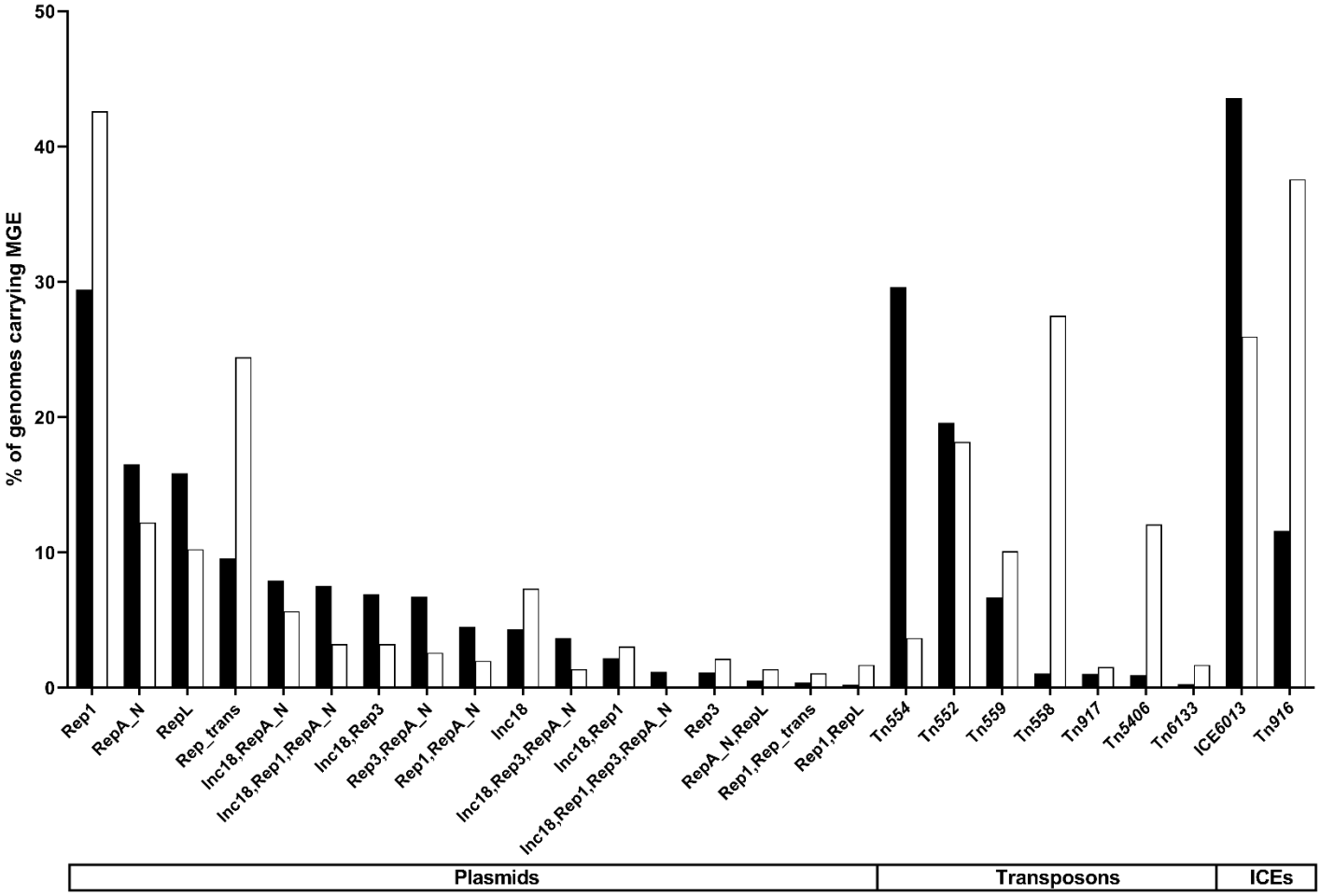
% of genomes carrying MGE
50
40
30
20
10
0
Rep1
RepA_N
RepL
Rep_trans
Inc18,RepA_N
Inc18,Rep1,RepA_N
Inc18,Rep3
Rep3,RepA_N
Rep1,RepA_N
Inc18
Inc18,Rep3,RepA_N
Inc18,Rep1
Inc18,Rep1,Rep3,RepA_N
Rep3
RepA_N,RepL
Rep1,Rep_trans
Rep1,RepL
Tn554
Tn552
Tn559
Tn558
Tn917
Tn5406
Tn6133
ICE6013
Tn916
Plasmids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

Figure 2.

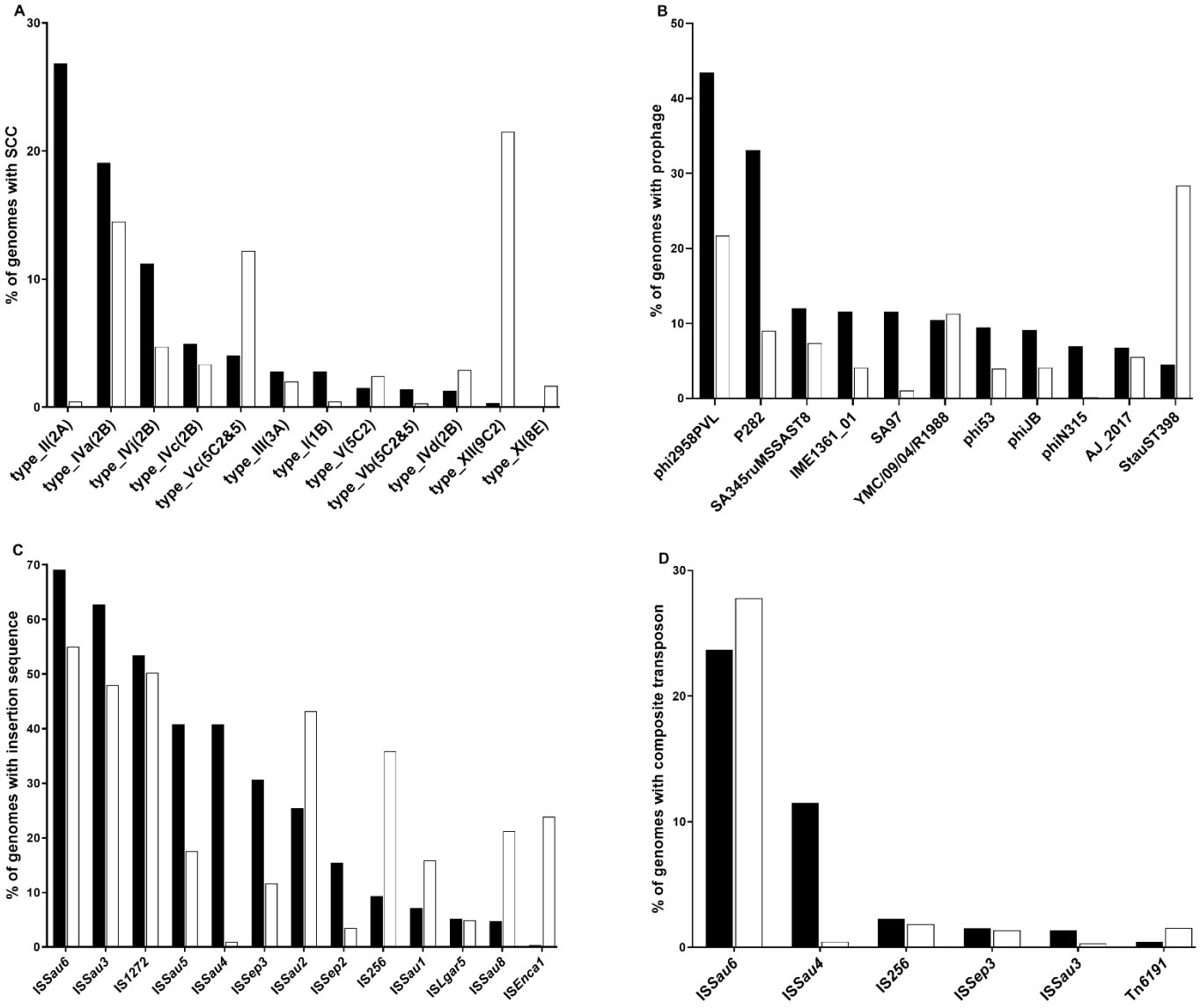
A
% of genomes with SCC
30
20
10
0
type_II(2A)
type_IVa(2B)
type_IVj(2B)
type_IVc(2B)
type_Vc(5C2&5)
type_III(3A)
type_I(1B)
type_V(5C2)
type_Vb(5C2&5)
type_IVd(2B)
type_XII(9C2)
type_XI(8E)
B
% of genomes with prophage
50
40
30
20
10
0
phi2958PVL
P282
SA345ruMSSAST8
IME1361_01
SA97
YMC/09/04/R1988
phi53
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.

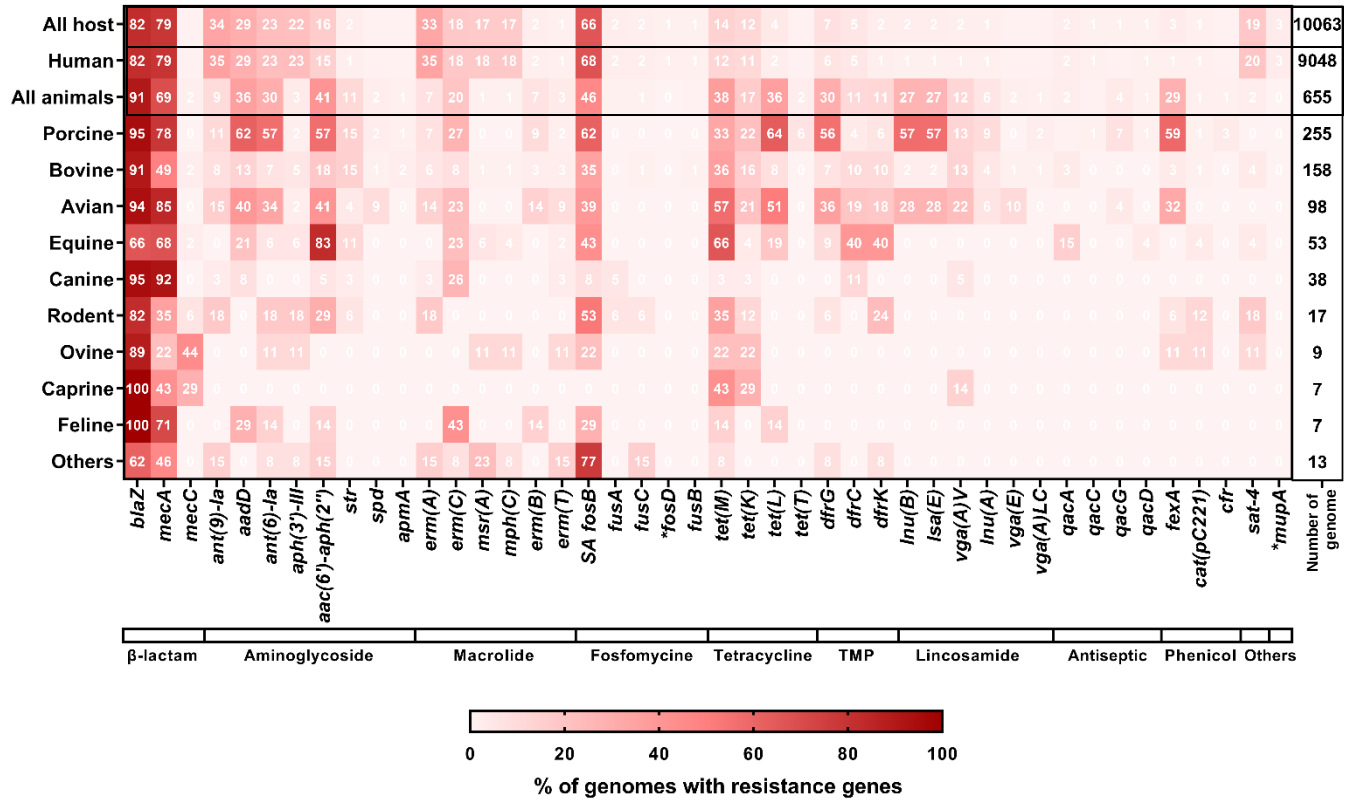
All host
Human
All animals
Porcine
Bovine
Avian
Equine
Canine
Rodent
Ovine
Caprine
Feline
Others
blaZ
mecA
mecC
ant(9)-Ia
aadD
ant(6)-Ia
aph(3')-III
aac(6')-aph(2'')
str
spd
apmA
erm(A)
erm(C)
msr(A)
mph(C)
erm(B)
erm(T)
SA fosB
fusA
fusC
*fosD
fusB
tet(M)
tet(K)
tet(L)
tet(T)
dfrG
dfrC
dfrK
lnu(B)
lsa(E)
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.

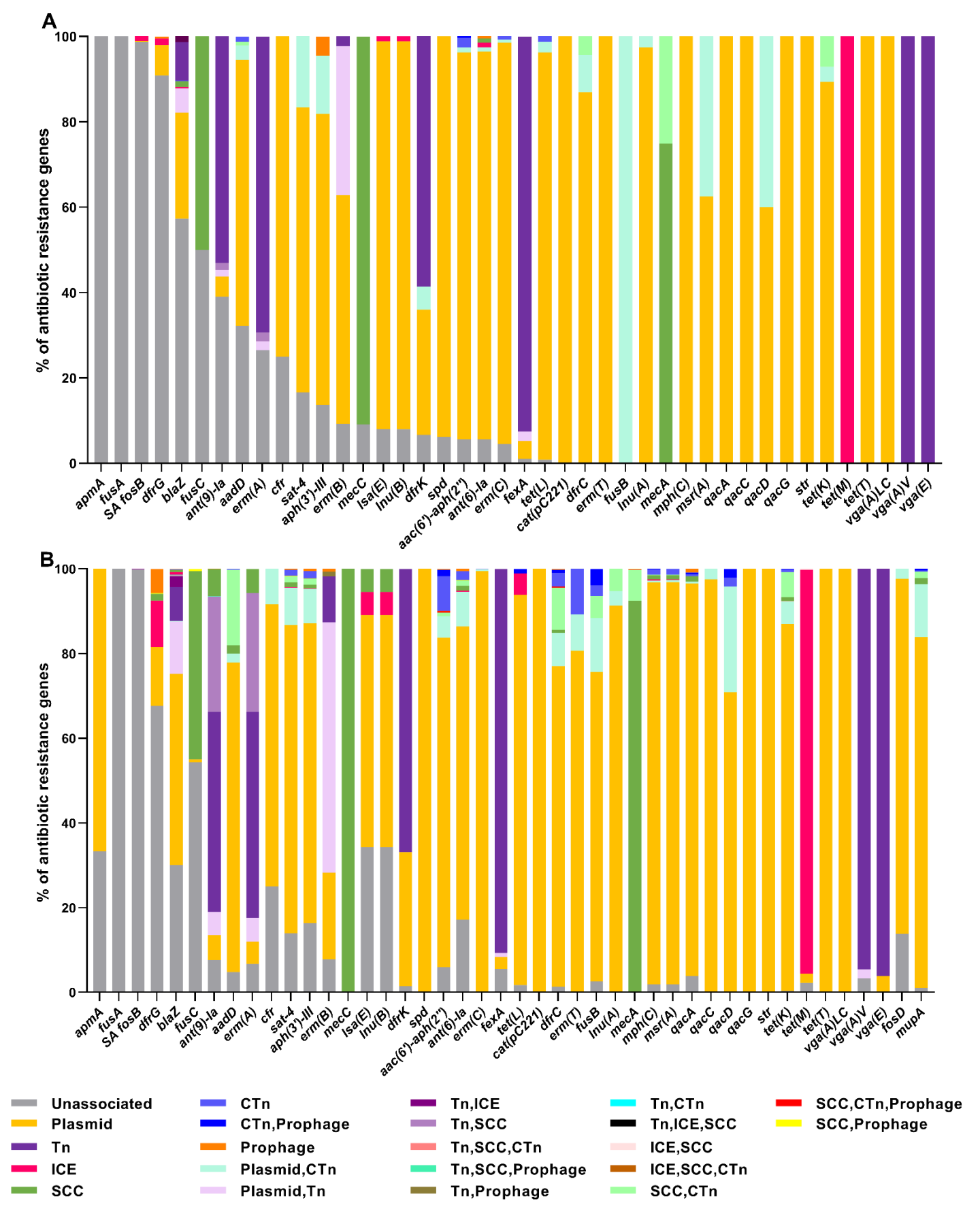
A
% of antibiotic resistance genes
0
20
40
60
80
100
apmA
fusA
SA fosB
dfrG
blaZ
fusC
ant(9)-Ia
aadD
erm(A)
cfr
sat-4
aph(3')-III
erm(B)
mecC
lsa(E)
lnu(B)
dfrK
spd
aac(6')-aph(2'')
ant(6)-Ia
erm(C)
fexA
tet(L)
cat(pC221)
dfrC
erm(T)
fusB
lnu(A)
mecA
mph(C)
msr(A)
qacA
qacC
qacD
qacG
str
tet(K)
tet(M)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

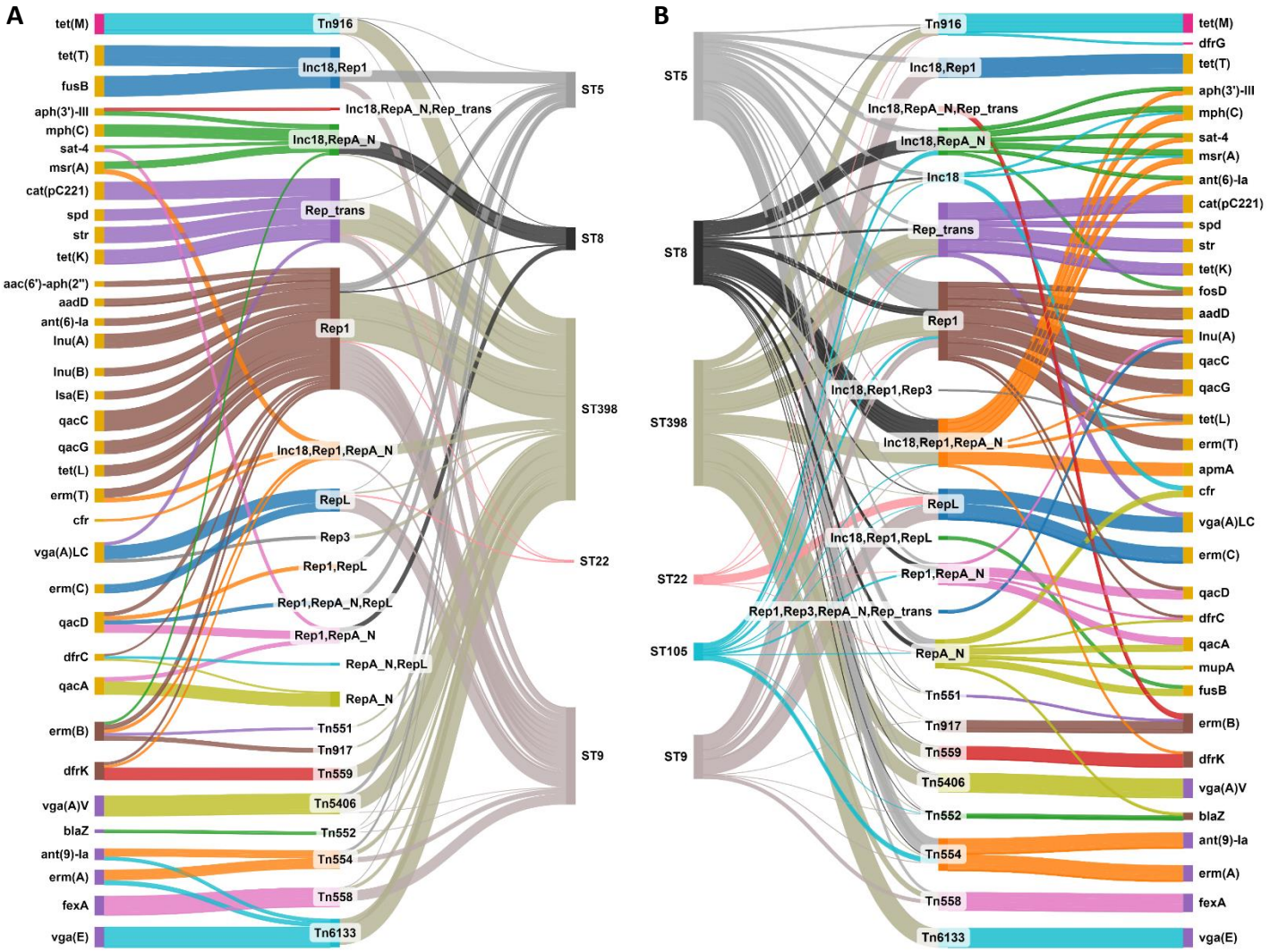
A
tet(M)
tet(T)
fusB
aph(3')-III
mph(C)
sat-4
msr(A)
cat(pC221)
spd
str
tet(K)
aac(6')-aph(2'')
aadD
ant(6)-Ia
lnu(A)
lnu(B)
lsa(E)
qacC
qacG
tet(L)
erm(T)
cfr
vga(A)LC
erm(C)
qacD
dfrC
qacA
erm(B)
dfrK
vga(A)V
blaZ
ant(9)-Ia
erm(A)
fexA
vga(E)
Tn916
Inc18,Rep1
Inc18,RepA_N,Rep_trans
Inc18,RepA_N
Rep_trans
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.

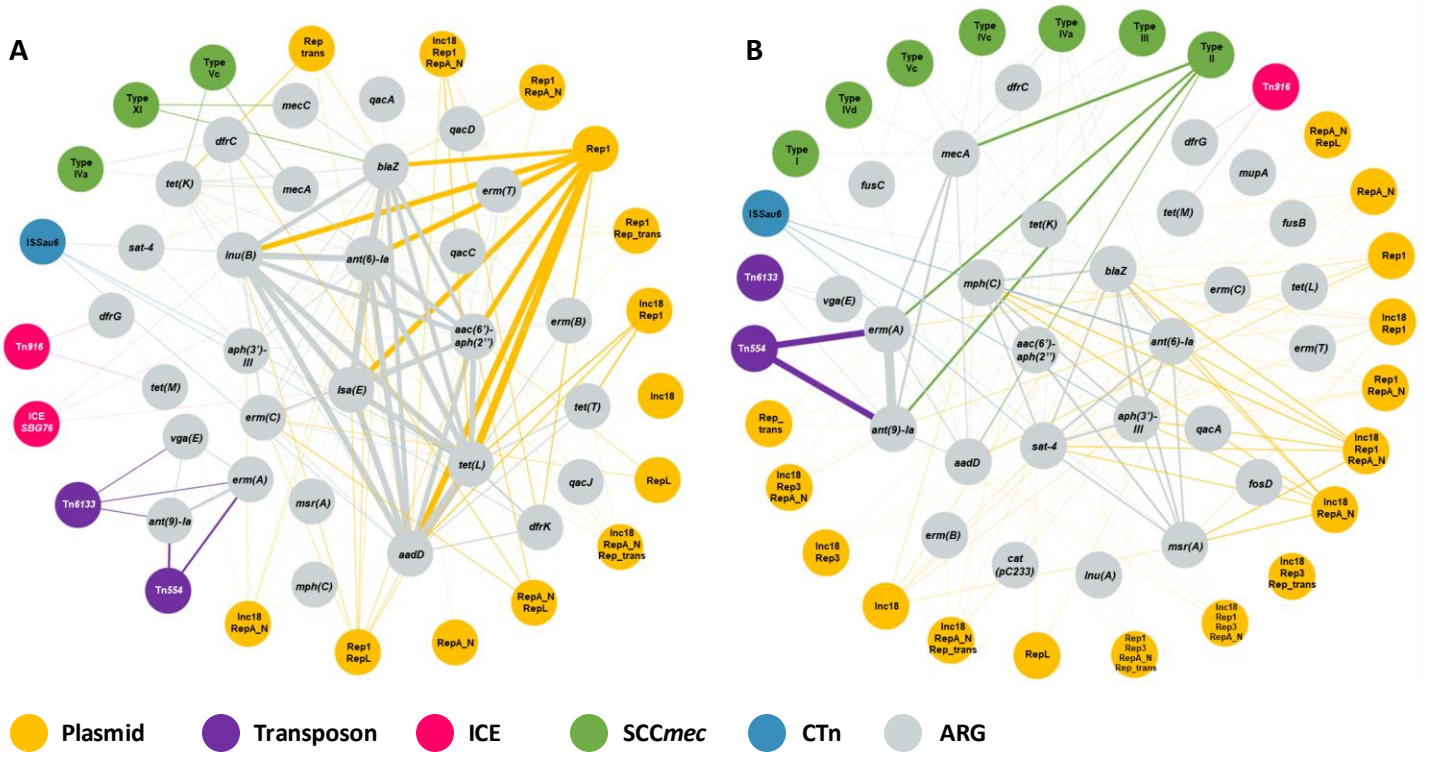
A
Rep trans
Inc18 Rep1 RepA_N
Type Vc
Rep1 RepA_N
Type XI
mecC
qacA
qacD
dfrC
Rep1
Type IVa
tet(K)
mecA
blaZ
erm(T)
Rep1 Rep_trans
ISSau6
sat-4
lnu(B)
ant(6)-Ia
qacC
Inc18 Rep1
dfrG
erm(B)
Tn916
aph(3')-III
aac(6')-aph(2'')
tet(M)
lsa(E)
Inc18
tet(T)
ICE SBQ76
erm(C)
vga(E)
tet(L)
RepL
qacJ
erm(A)
Tn6133
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.