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# Landscape of mobile genetic elements in *Staphylococcus aureus* of animal origin and their antibiotic resistance genes content

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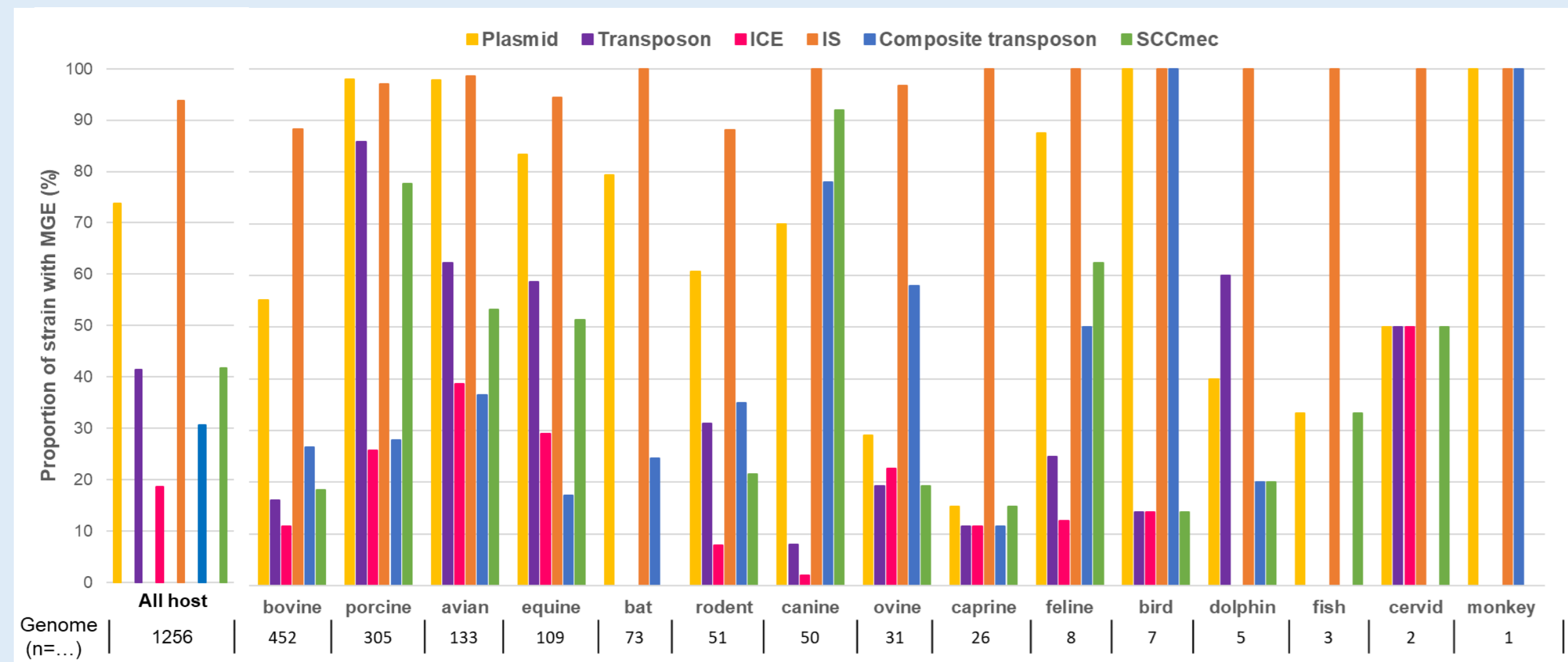
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*Staphylococcus aureus* is a major human and animal commensal and opportunistic pathogen that has developed resistance to many antibiotics. Its ability to acquire antibiotic resistance genes (ARGs) is closely associated with the large proportion of mobile genetic elements (MGEs) present in its genome (between 15 and 20%) and its capacity to exchange genetic material with its environment. Currently, little is known about the diversity of ARG-carrying MGEs in *S. aureus* of animal origin and their impact in the spread of antibiotic resistance. To provide an exhaustive overview of the associations between MGEs, ARGs and hosts in these bacteria, an *in silico* analysis was carried out on 1256 *S. aureus* genomes of animal origin publicly available on NCBI and responding to assembly quality criteria, using the ResFinder (1) and MeFinder (2) tools.

## IS and plasmids are the most represented MGEs in *S. aureus* of animal origin

Histogram representing the distribution of MGE in *S. aureus* of animal origin



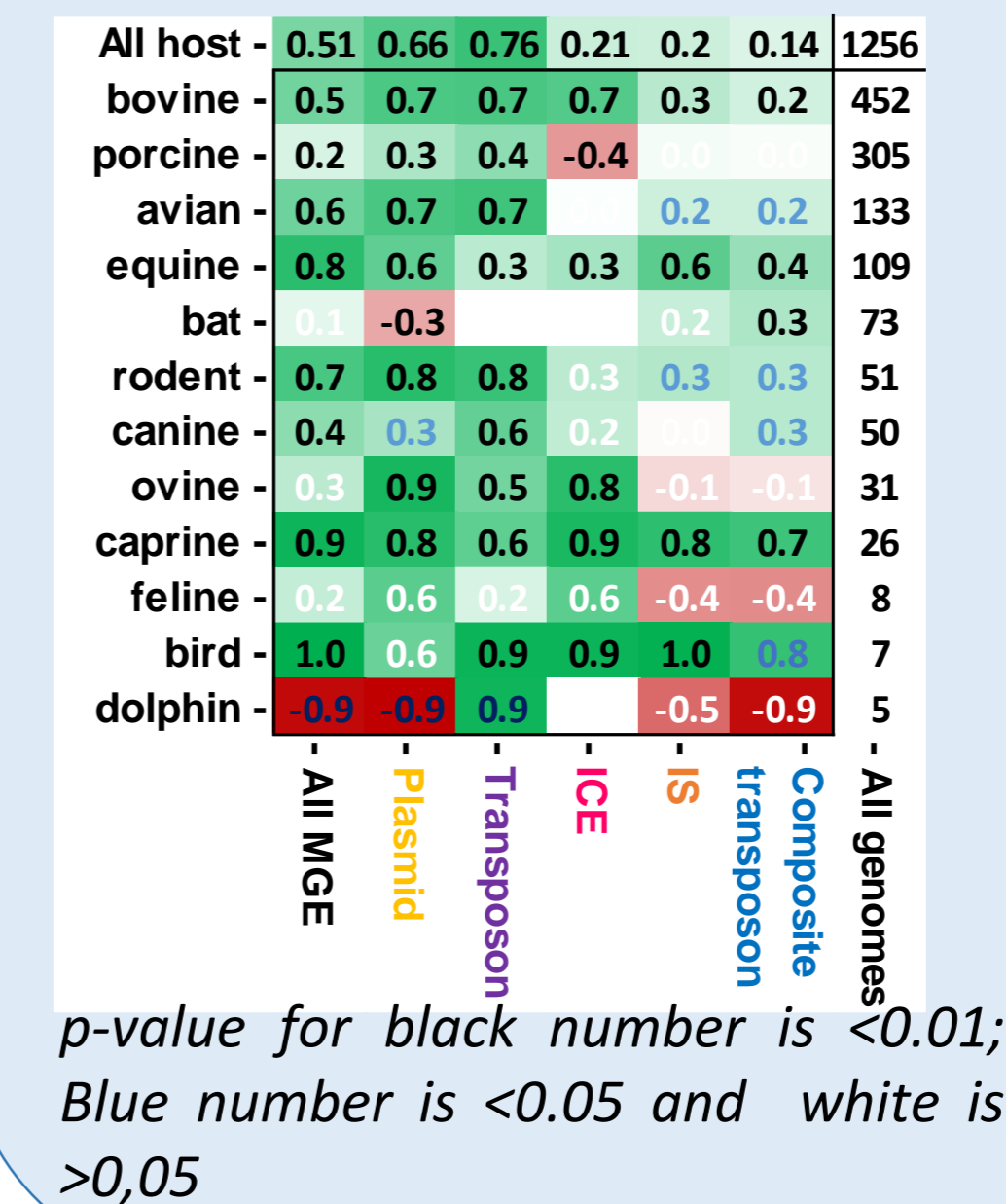
The genomes analyzed come from 15 different hosts, in a non-homogeneous manner depending on the NCBI genomes availability. 45 ARGs and 134 MGEs (including 58 plasmids, 31 insertion sequences (IS), 13 composite transposons, 9 transposons, 8 integrative and conjugative elements (ICE) and 15 SCCmec cassettes) were identified.

IS and plasmids are the most frequently found MGEs (>90% and 72%, respectively) in *S. aureus* of animal origin, regardless of the host.

Plasmids and IS could play a major role in the dissemination of antibiotic resistance in *S. aureus* of animal origin. Are they the MGEs most associated with ARGs?

## ARG/plasmids and ARG/transposons are positively correlated

Heatmap of ARG and MGE correlation

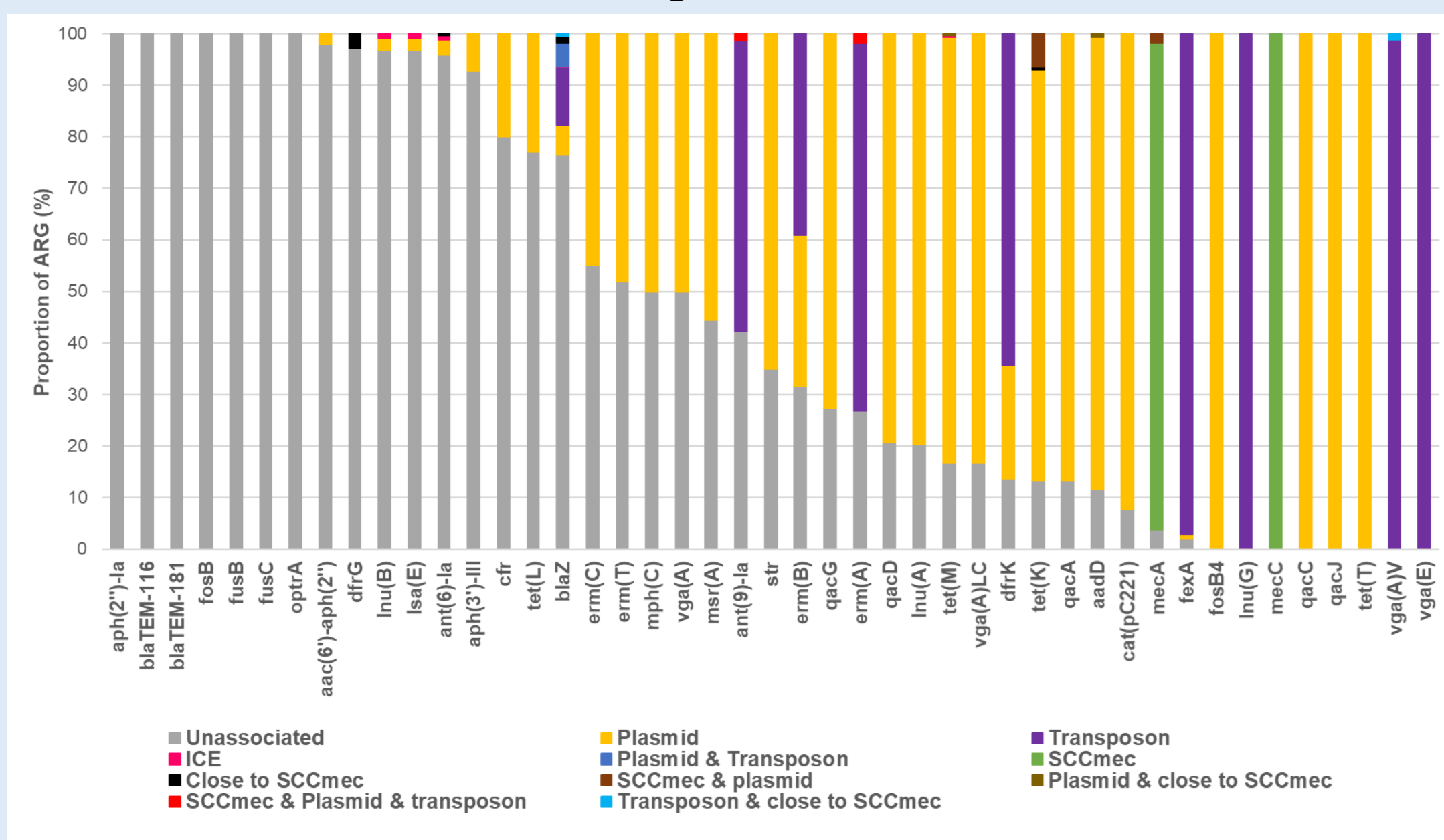


In most cases, positive correlations between ARGs and MGEs are observed. ARGs are positively associated with plasmids and transposons, while this is not the case with IS and composite transposons

Plasmids and transposons are closely linked to antibiotic gene resistance. Are they key players in their dissemination?

## Plasmids and transposons are the main vehicles of ARGs

Histogram representing the proportion of ARGs associated with MGEs in *S. aureus* of animal origin



46% of the genes are associated with at least one MGE in 285 different ARG/MGE combinations.

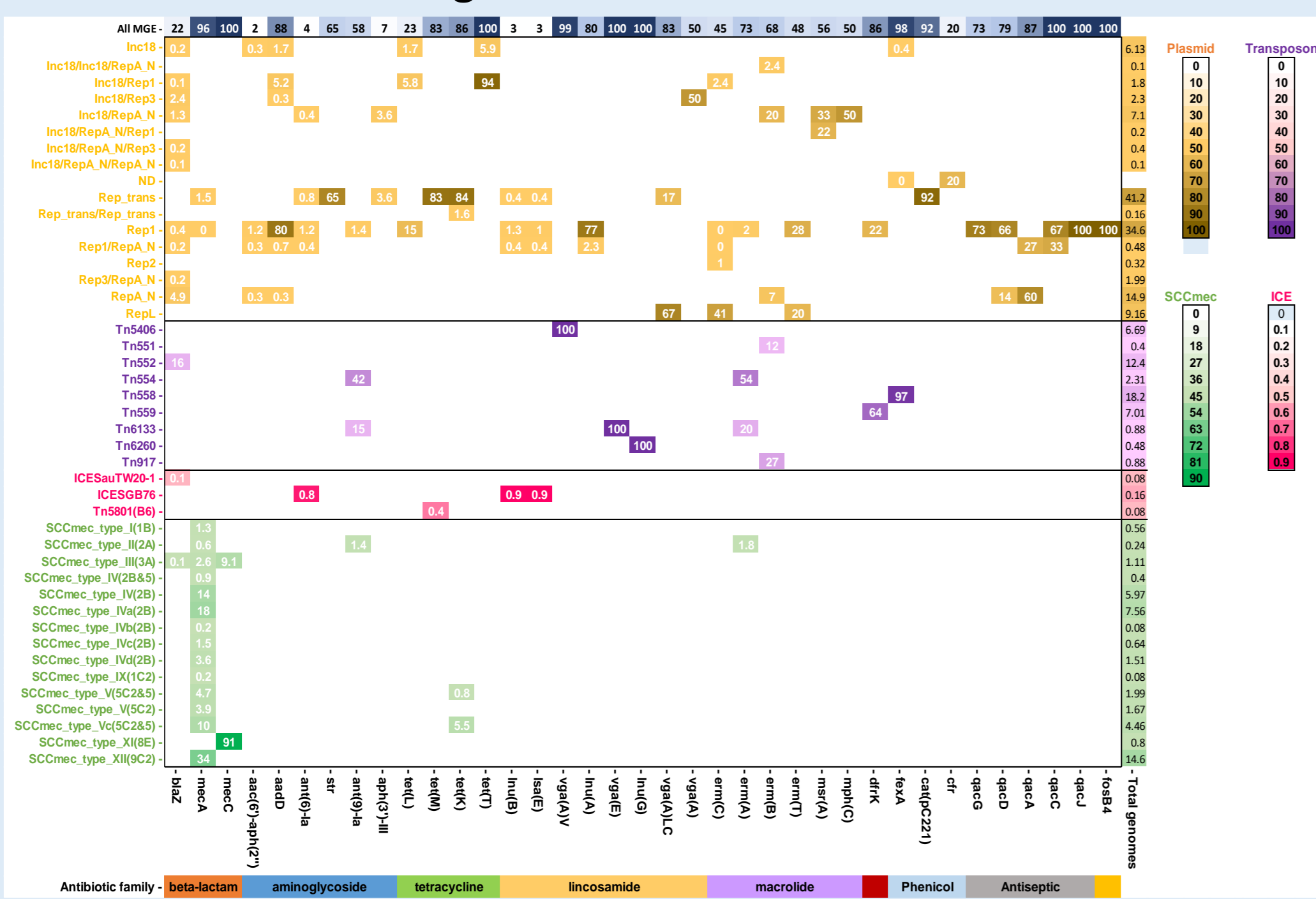
- 87% of ARGs are carried by plasmids,
- 24% are carried by transposons,
- 44% of resistance genes are found only on plasmids,
- 31% of genes are found on more than one type of MGE and *blaZ* is involved in 7 different combinations.

The distribution of ARG/plasmid associations is homogeneous contrary to ARG/transposon associations which, are more specific to one antibiotic group and to one gene. Each transposon is associated with one gene, except Tn554 and Tn6133 which carries 2 and 3 genes, respectively (*ant(9)-la*, *erm(A)* and *vga(E)* for Tn6133). The most represented ARG/transposon association is *fexA*/Tn558.

SCCmec cassettes are mainly associated with *mecA* and *mecC*. Each type of SCCmec cassette is linked to the *mecA* gene except type XI(8E) which is found only with *mecC*. There is one exception: a SCCmec type III (3A) cassette carries both *mecC* and *mecA*. Some SCCmec are associated with other ARGs like *tet(K)*, *erm(A)* and *ant(9)-la*.

The ICESGB76 is co-localized with 3 genes of 2 antibiotic groups (aminoglycoside and lincosamide). Only, 37.5% of ICE are associated with one ARG. To date, this MGE is one of the least characterized in *S. aureus*. Further study of this MGE should reveal a larger number of ARG/ICE associations.

Heatmap depicting the associations between ARGs and MGEs in *S. aureus* of animal origin

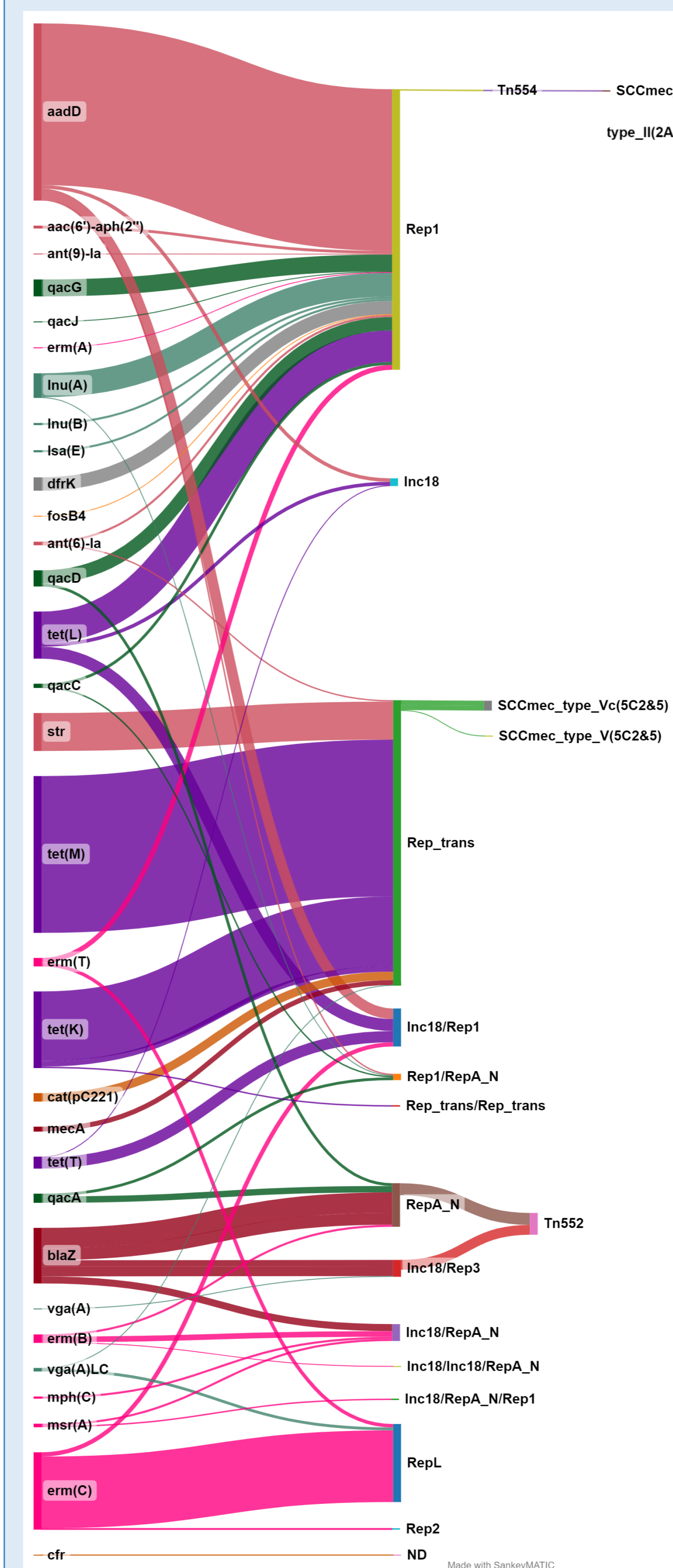


The number of each ARG associated with each MGE relative to the total number of each ARG (in %) are represented. *dfkK*: trimethoprim resistant gene and *fosB4*: fosfomycin resistant gene. The plasmids (yellow) are identified with the Rep protein domain family.

This exhaustive map of associations between resistance genes and MGEs highlights the great diversity and the predominance of certain ARG/plasmid and ARG/transposon associations in *S. aureus* of animal origin.

## Plasmids are ARGs spreaders

Sankey diagram depicting ARGs/plasmids associations plus their association with other MGEs



ARGs are mainly associated with Rep1 and Rep\_trans family plasmids. All antibiotic groups are associated with the Rep1 family plasmid. Each gene is mainly associated to one type of plasmid: tetracycline groups (*tet(M)* and *tet(K)*) with Rep\_trans plasmids; macrolide group (*erm(C)* and *erm(T)*) with Repl plasmids.

Some ARGs associated to plasmids are also co-localized with one or two different MGE(s). The *ant(9)-la* and *erm(A)* genes are both co-localized on Tn554 and Rep1 plasmids suspected integrated in type II(2A) SCCmec cassette. The *blaZ* genes localized on plasmids are also found on Tn552. The *tet(K)* and *mecA* genes are carried by type V and Vc SCCmec cassette with potential integration of a Rep\_trans type plasmids inside the cassette.

ARG/plasmids association are mostly unique. Rep1, Rep\_trans and Repl plasmids seems to be the key players of antibioresistance spreading in *S. aureus* of animal origin.

ARG inducing resistance to the same antibiotic family are represented by the same color. The thickness of the flow is proportional to the amount of association.

This preliminary study highlights the diversity of MGEs and the predominance of ARG/plasmid associations. It suggests that *S. aureus* plasmids of animal origin play a key role in the spread of multidrug resistance, reinforcing the interest to deepen our knowledge and understanding of the dispersal mechanisms of this type MGE. Indeed, plasmids are well characterized in Enterobacteriales but poorly studied in *Staphylococcaceae* despite their major interest. A similar approach on the genomes of *S. aureus* of human origin will be carried out, in order to better understand the emergence, dissemination and potential reservoirs of multi-resistance in this major pathogen.

(1) ResFinder 4.0 for predictions of phenotypes from genotypes. Bortolai V. et al. Journal of Antimicrobial Chemotherapy, 75(12), 3491-3500, 2020  
 (2) Detection of mobile genetic elements associated with antibiotic resistance in Salmonella enterica using a newly developed web tool: MobileElementFinder. Johansson, Markus H K and al.. Journal of Antimicrobial Chemotherapy, 2020 Oct 3.