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Gut dysbiosis promotes dissemination of antimicrobial resistance genes

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INTRODUCTION & AIM

The global spread of antimicrobial resistance (AMR) genes (ARGs) poses a major challenge to bacterial infection treatment. Antimicrobial use, while targeting pathogens, also disrupts commensal gut bacteria, with effects varying by antimicrobial type. The impact of gut dysbiosis on ARG mobility from foodborne bacteria, especially with or without food matrix microbes, remains unclear.

METHOD

Using a murine model, we investigated ARG dissemination via mobile plasmids. Mice were pre-treated with streptomycin, ampicillin, or sulfamethazine to induce varying levels of gut dysbiosis. They were then inoculated with beta-lactam-resistant *Salmonella* Heidelberg (donor) and beta-lactam-susceptible *Salmonella* Typhimurium (recipient) with or without additional food matrix microbes. Fecal samples were cultured to detect ARG transfer among *Salmonella*, *E. coli*, and other gut bacteria, confirmed through whole genome sequencing. Changes in gut microbiota were assessed using 16S rRNA sequencing.

Fig. 1. Design of animal experiments

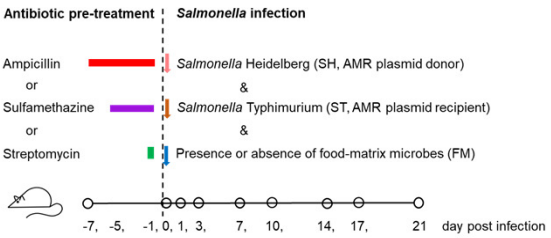


Fig. 2. Principal coordinate analysis on Bray-Curtis dissimilarity of mouse gut microbiota from individual mice in various treatment groups on different day post infection (DPI).

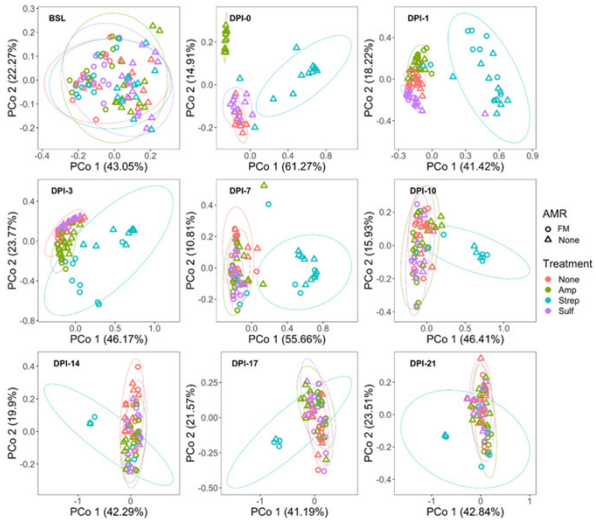
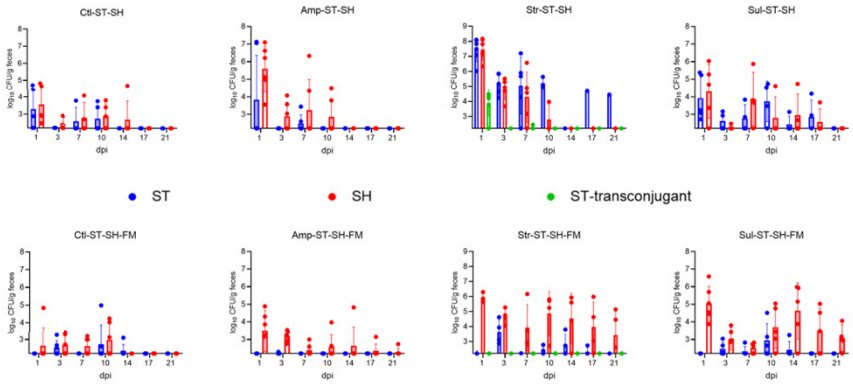


Fig. 3. Enumeration of *S.* Heidelberg (SH), *S.* Typhimurium (ST), and ST-transconjugant from mice on different day post infection (dpi).



RESULTS & DISCUSSION

Without background food matrix microbes, streptomycin caused severe dysbiosis, enhancing AMR plasmid transfer from *S.* Heidelberg to *S.* Typhimurium and *E. coli*. Ampicillin induced moderate disruption, allowing *S.* Heidelberg colonization and plasmid transfer to *E. coli*. Sulfamethazine caused mild disruption, hindering both Salmonella colonization and plasmid transfer. In contrast, food matrix microbes reduced AMR plasmid transfer, except in streptomycin pre-treated mice, where Enterobacteriaceae enrichment enabled plasmid transfer to *Escherichia*, *Enterobacter*, *Citrobacter*, and *Proteus*.

Table 1. Transconjugants isolated from mice with streptomycin pre-treatment and inoculation of food matrix microbes

Transconjugants isolated	ARGs on pIncA/C	ARGs on chromosome	Accession number[a]
Citrobacter brackii	*aph(3)-Ia, aph(3)-Ib, aph(6)-Id, blaTEM, blaCMY, dfrA1, floR, sul1, sul2, tet(A)*	bla_{CMY}, *mdfA*, *qnrB10*	SRR30190323
Enterobacter ludwigii	same as above	*oqxA*, *oqxB*, bla_{ACT}, *fosA2*, *mdfA*	SRR30190329 - 32
Escherichia coli	same as above	*mdfA*	SRR30190327, 28
Proteus mirabilis	same as above	*cat*, *aadA1*, *dfrA1*, *tetJ*	SRR30190324 - 26

CONCLUSION

Pre-existing gut microbiome disturbance from antimicrobials significantly affects ARG dissemination. These findings support more judicious antimicrobial use to mitigate resistance spread.

Canadian Food Inspection Agency
Agence canadienne d'inspection des aliments