# Mapping the distribution of AMR in *Shigella sonnei*

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## INTRODUCTION

- The rise of antimicrobial resistance (AMR) in *Shigella sonnei*, a key pathogen in shigellosis that contributes to an estimated 188 million infections and approximately 160,000 deaths, is a formidable global health challenge[1].
- Genomic sequencing efforts have previously identified an assembly of antibiotic (AB) resistance determinants, particularly against azithromycin and ciprofloxacin[2,3].
- The presence of concurrent antimicrobial resistance genes (ARGs) to multiple ABs heightens the potential risk of acquisition of widespread resistance following antibiotic treatment.
- Therefore, identifying multi-drug resistance ARG casettes is critical to preparing for future challenges in the treatment of this widespread problem pathogen.

## METHODS

- A comprehensive collection of 3,884 S. *sonnei* isolates spanning 2004 to 2020 was used to examine ARG abundance correlations and the AMR landscape.
- We integrated phylogenetic, epidemiological, and genomic analyses, uncovering ARGs prevalent in specific high-risk patient groups.

## RESULTS

- Genomic analyses revealed high resistance levels in isolates against trimethoprim (98.31%), streptomycin (95.85%), streptothricin (95.81%), and sulfonamide (80.66%) including in MSM groups (Figure 1),and mutations in the quinolone resistance-determining regions (QRDR), conferring resistance to crucial antibiotics like ciprofloxacin.

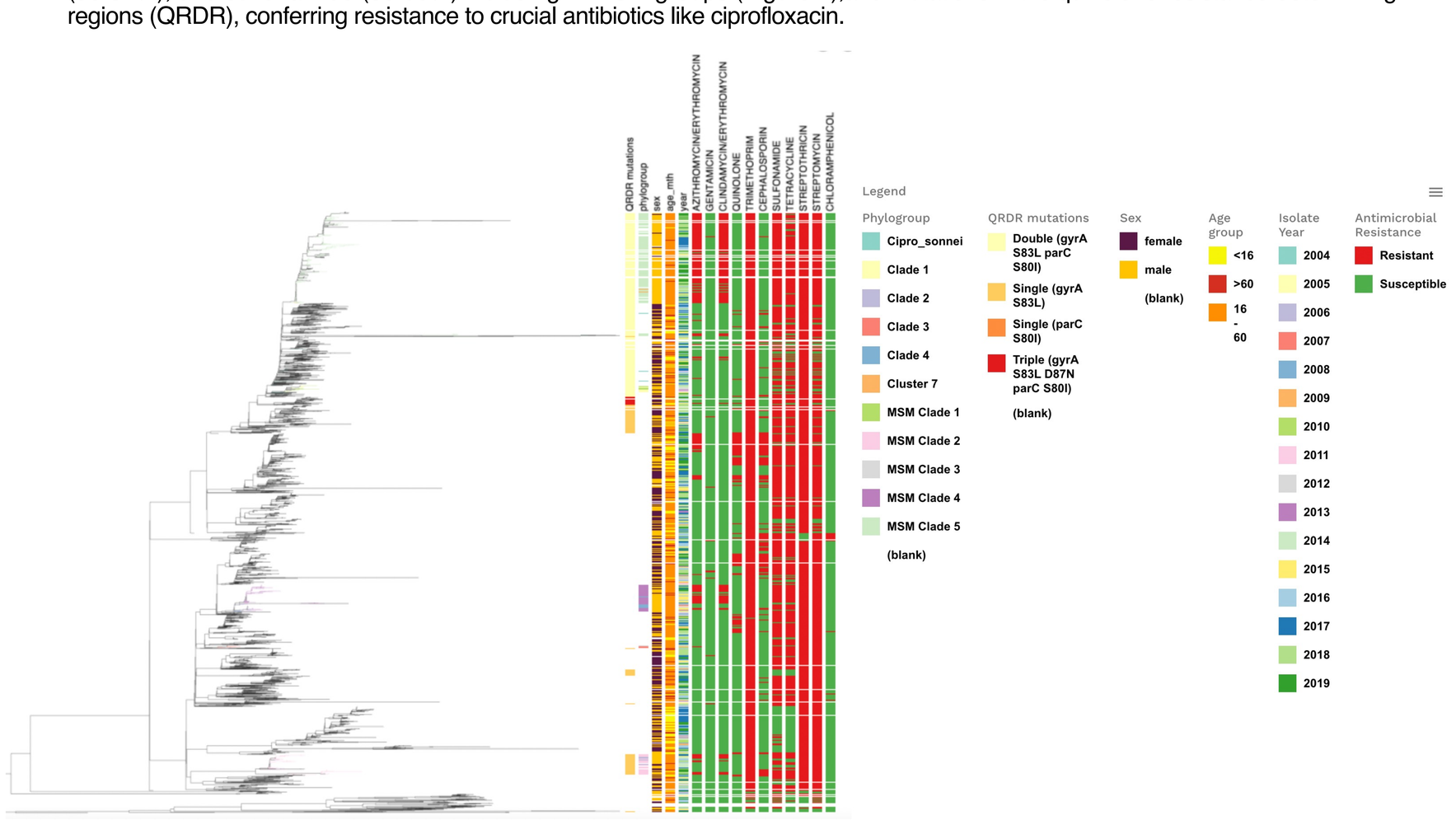


Figure 1. A maximum likelihood phylogenetic tree showing population structure, other metadata shows antimicrobial resistance profiles by antimicrobial class, presence of QRDR mutations and MSM clusters. The phylogenetic tree was created from SNP variants called from short reads mapped against the *S. sonnei* 53G closed reference genome using a GTR-gamma model in IQ-tree. Mutations in QRDR of gyrA and parC genes were detected using Mykrobe.

## DISCUSSION

- We discovered 5 ARG co-abundant clusters, including azithromycin resistance genes *ermB* and *mphA*, previously reported in non-travel cases[3].
- ARGs in cluster E confers resistance to macrolides, ampicilin, aminoglycosides, trimethoprim and sulphonamides, D to trimethoprim, chloramphenicol, C to tetracyclines and suphonamides, B to beta-lactams, and A to quinolones and beta-lactams.
- The co-abundance within cluster E, C, and D aligns with the resistance traits in previously reported MGEs such as pSS046_spA, the SRL-MDRE chromosomal island, and pKSR100, all of which showcase similar AMR combinations[4]. This resemblance indicates a common mechanism for the evolution and spread of multi-drug resistance.
- We identified new ARGs(*aph6-Id, aph3-Ib* resistant to aminoglycosides*, sat2* and *dfrA1* resistant to streptothricin and trimethoprim) integrating into these known clusters suggesting an ongoing evolution and adaptation of the bacteria, potentially giving rise to more robust forms of resistance.

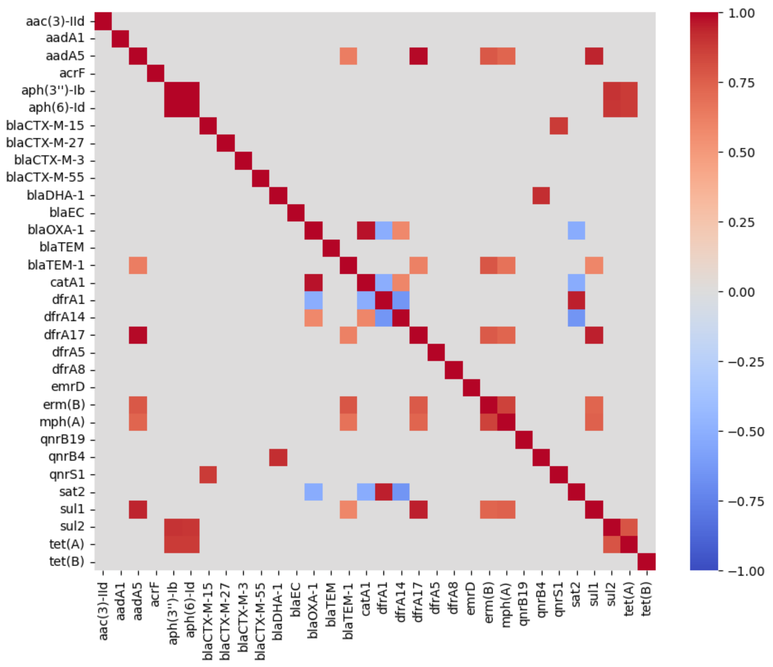


Figure 2: Heatmap of ARG co-occurrence in *3,884 Shigella sonnei* Isolates. Correlation between ARGS was calculated using Pearson correlation($p \leq 0.05$, $r \geq 0.6$). Red indicates a positive correlation, blue indicates a negative correlation, and intensity of the color denotes the strength of correlation.

A network analysis of the co-connectedness of ARGs (Figure 3) identified 5 discrete networks of ARGs which suggest they are commonly acquired as a single unit. These 5 clusters were A) *qnrS1 and blaX-M15*, B) *blaDHA-1 and qrnB4*, C) *tetA, sul2, aph6-Id and aph3-Ib*, D) *sat2, dfrA14, blaOXA-1, dfrA1 and catA1*, E) *aadA5, mphA, sul1, dfrA1, ermB, blaTEM-1.*

An analysis of co-abundance between ARGs identified significant positive correlation between specific ARGs indicating co-acquisition (Figure 2). ARGs families where this was observed included *aph3-Ib aph6-Id, blaTEM, catA1*, various *dfrA* alleles, *emrB, mphA, qnr, sat2, sul1 and tetA*. Negative correlation, perhaps indicating antagonistic relationships between ARGs, were observed between *sat2* and *blaOXA, catrA1 and dfrA14.*

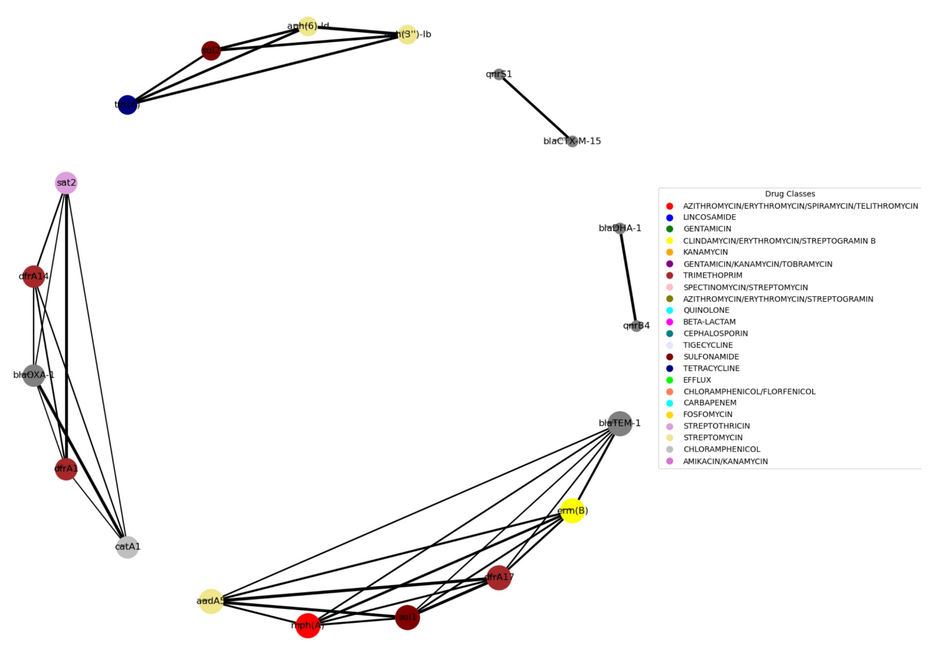


Figure 3: the network plot illustrates the interconnectedness of ARGS, with nodes representing genes and edges indicating significant co-occurrence($p \leq 0.05$, $r \geq 0.6$). Node size corresponds to the degree of connectivity, edge thickness corresponds to strength of correlation and color coding with resistance drug classes.

## REFERENCES

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## CONCLUSION

- Our study reveals complex networks of gene co-occurrence in *S. sonnei,* indicating a risk for collateral resistance. The emergence of new ARGs highlight an evolving resistance scenario. The high resistance levels particularly in high-risk groups emphasize the critical need for intensive surveillance to manage the spread of AMR in this pathogen.