NIHR | Health Protection Research Unit in Gastrointestinal Infections at University of Liverpool

The evolution and international spread of extensively drug-resistant *Shigella sonnei*

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Abstract

Shigella sonnei causes shigellosis, a severe gastrointestinal illness that is sexually transmissible among men who have sex with men (MSM). Multidrug resistance in *S. sonnei* is common and can include resistance to the WHO recommended treatment options, azithromycin, and ciprofloxacin. Recently, an MSM-associated outbreak of extended-spectrum β-lactamase producing, extensively drug resistant *S. sonnei* was reported in the United Kingdom. Here, we aimed to identify the genetic basis, evolutionary history, and international dissemination of the outbreak strain. Our genomic epidemiological analyses of 3,304 isolates from the United Kingdom, Australia, Belgium, France, and the United States of America revealed an internationally connected outbreak carrying a low-fitness cost resistance plasmid, previously observed in travel associated sublineages of *S. flexneri*. Our results highlight the persistent threat of horizontally transmitted antimicrobial resistance and the value of continuing to work towards early and open international sharing of genomic surveillance data.

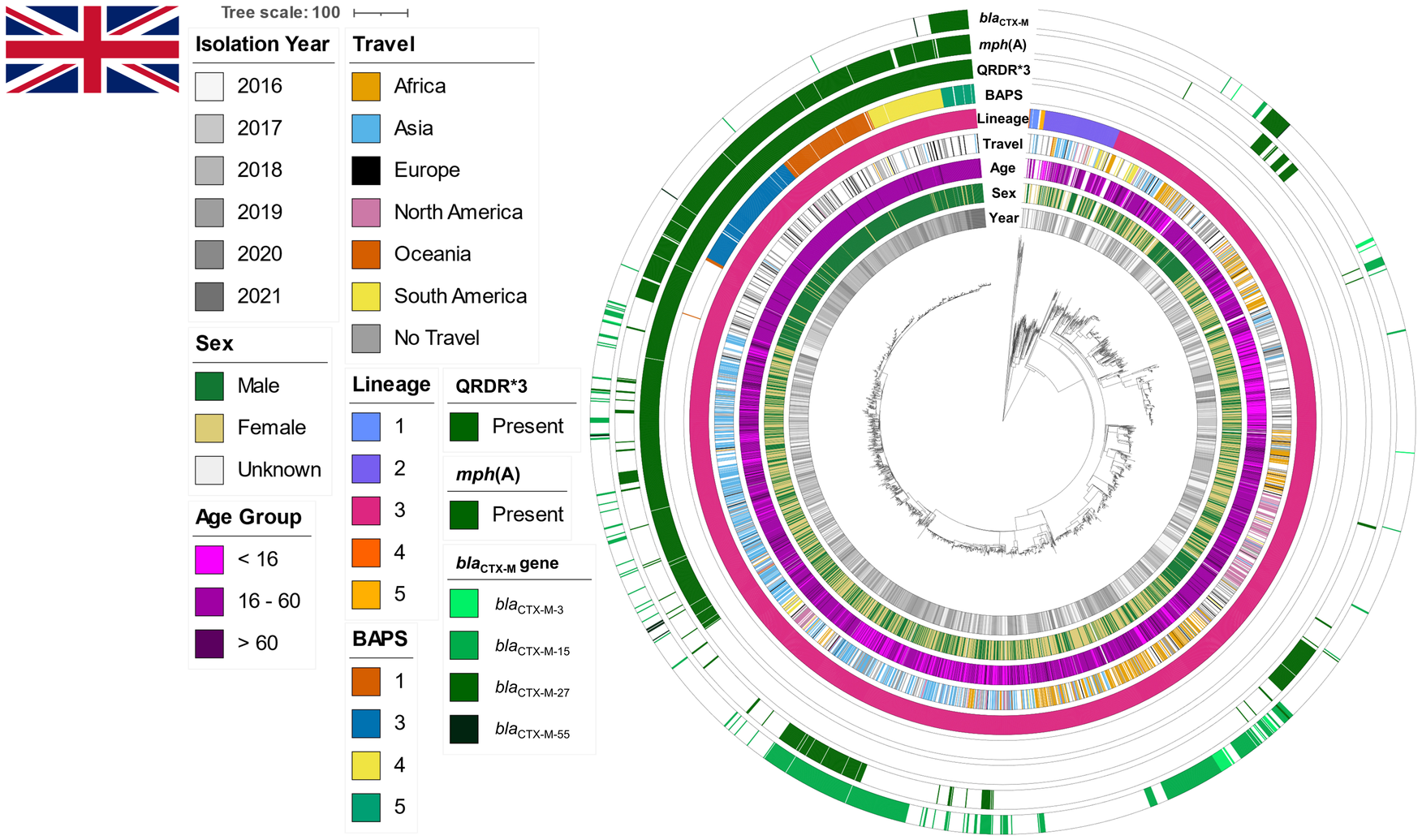

Figure 1. The emergence of an XDR *S. sonnei* outbreak in the United Kingdom. A cgMLST dendrogram (midpoint rooted) of clinical isolates from the UK (n=2,820) and genomic subtype references (n=120) with the scale bar indicating distance in cgMLST alleles. Metadata tracks show patient and genomic features for isolates coloured according to the inlaid keys. Specifically, from inner to outer, the patient data comprises: year of isolation, patient sex, age group, and travel history (for UK isolates only), with missing/unavailable/not determined data shown as white. Genomic features then show: isolate lineage, BAPS clusters (for isolates belonging to the t10.377 cluster only), and the presence of mutations in the Quinolone Resistance Determining Region (QRDR*3 denotes all three canonical mutations; *gyrA*_D87G, *gyrA*_S83L and *parC*_S80I) and *mph*(A), and bla_{CTX-M} genes, where white indicates absence of the gene.

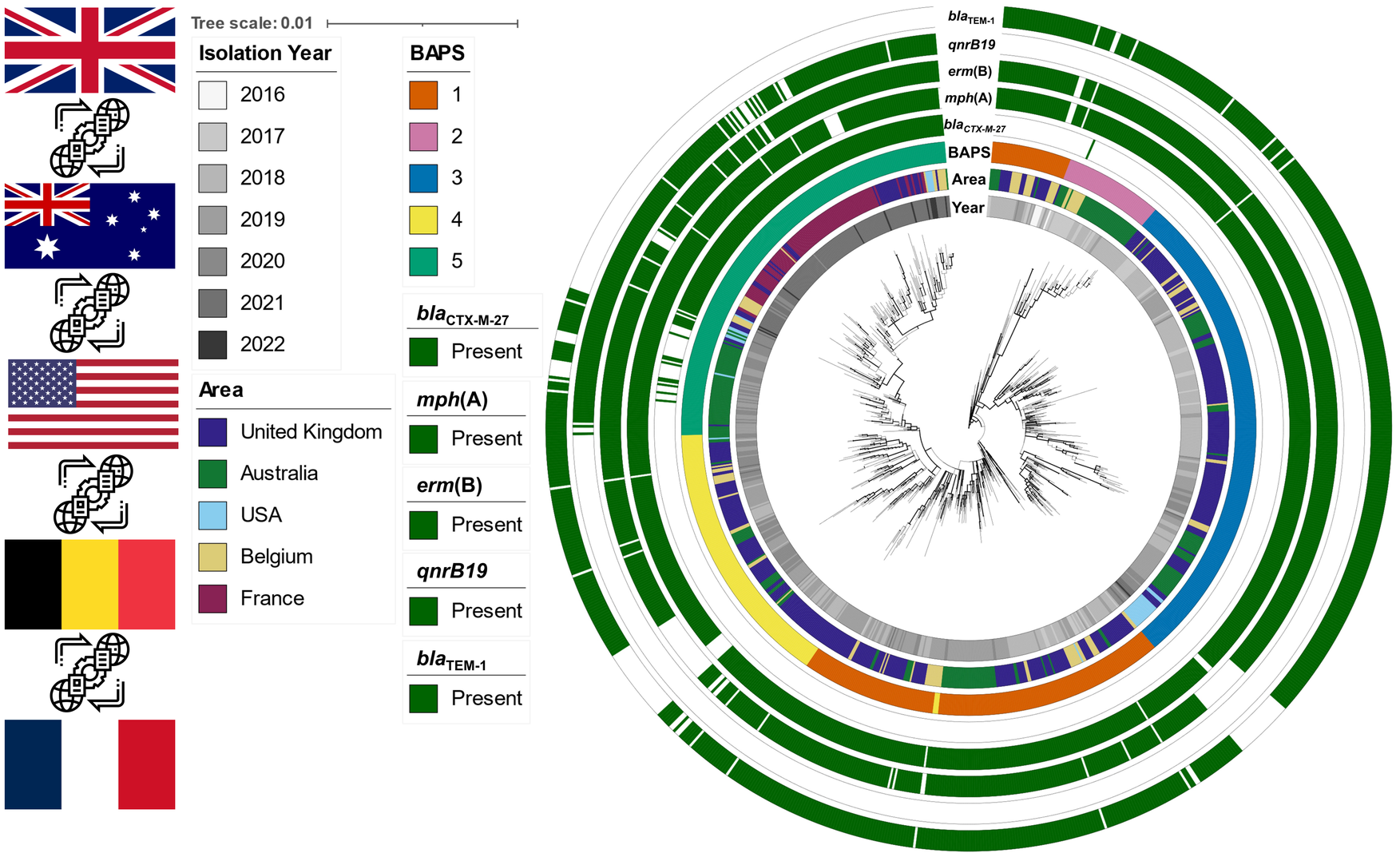

Figure 2. The evolution and international spread of MSM-associated *XDR S. sonnei*. A midpoint rooted maximum likelihood phylogenetic tree shows the distribution of UK isolates (belonging to both CipR.MSM5 and the t10.377 outbreak cluster, n=468) and relevant related international isolates belonging to CipR.MSM5 (Supplementary Figure 1, n=475). Metadata tracks show year and country (area) of isolation, BAPS subtype, and the presence of selected AMR genes according to the inlaid keys. The scalebar is provided by IQTree,[50] and represents expected number of substitutions per site across a 1,717 bp alignment. Bold branches represent a bootstrap value of ≥ 70 out of 100.

Introduction

- *Shigella sonnei (S. sonnei)* causes shigellosis, a sexually transmissible illness.
- Ciprofloxacin and azithromycin resistant *S. sonnei* recently acquired resistance to ceftriaxone by acquiring a plasmid-borne $bla_{CTX-M-27}$ gene.
- Our work aimed to investigate the evolution and spread of this extensively drug-resistant (XDR) *S. sonnei.*

Emergence of XDR *S. sonnei* in the United Kingdom

- $bla_{CTX-M-27}$-containing isolates are in the BAPS 5 group of the phylogenetic tree.
- Males aged 16 – 60 who had not reported international travel represented 84% (405/482) of CipR.MSM5, genotype 3.6.1.1.2 isolates in the UK, associated with sexual transmission.

International spread of XDR *S. sonnei*

- XDR *S. sonnei* in the BAPS 5 group have spread across the UK, Australia, USA, Belgium and France.
- These XDR *S. sonnei* have retained *mph*(A), *erm*(B) and *qnrB19,* but lost bla_{TEM-1}.
- This analysis suggests the CipR.MSM5 isolates carrying $bla_{CTX-M-27}$ were circulating intercontinentally across regions historically considered low-risk for shigellosis.

Conclusion

- It is clear that the emergence of a concerning antimicrobial resistance phenotype can lead to rapid global dissemination.
- This study highlights the importance of international cooperation and collaboration in genomic surveillance.

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