Emergence of extensively drug-resistant *Shigella flexneri* serotype 2a associated with sexual transmission among gay, bisexual, and other men who have sex with men, in England.

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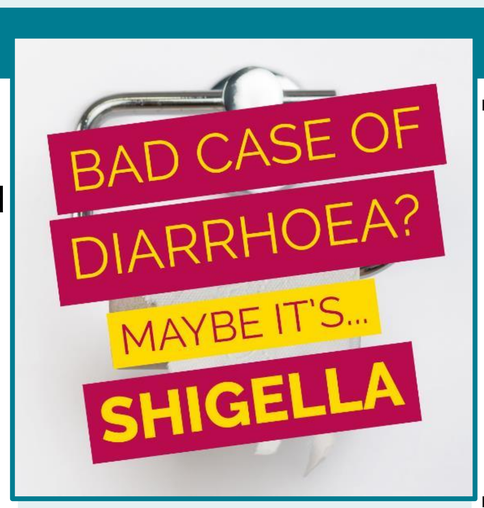
1. Introduction

- Shigellosis, bacillary dysentery spread through faecal-oral contact, was traditionally travel-associated in England but sexual transmission of *Shigella flexneri* and *Shigella sonnei* among gay, bisexual and other men who have sex with men (MSM) is now common.
- When needed, ciprofloxacin is the primary treatment for shigellosis, with azithromycin and ceftriaxone second line.
- Emergence of extensively drug-resistant (XDR) *S. sonnei* in September 2021 harbouring plasmid-encoded $bla_{\text{CTX-M-27}}$, conferring resistance to ceftriaxone, raised concerns over further spread of this gene.
- Using national surveillance, we identified and characterised *S. flexneri* harbouring $bla_{\text{CTX-M-27}}$ in England.



Shigella awareness Social Media campaign post; a joint campaign between UKHSA (formerly PHE) and HIV Prevention England (HPE), aiming to raise awareness of shigellosis among gay and bisexual men in 2021. Available through the HPE website.

2. Methods

- *Shigella* spp. isolates referred to the Gastrointestinal Bacterial Reference Unit at UKHSA undergo whole genome sequencing, enabling antimicrobial resistance (AMR) determination using genetic markers. Isolates were defined as multidrug-resistant (MDR) when resistant to over three of the antimicrobial classes fluoroquinolones, β-lactam antibiotics, tetracyclines, 3rd generation cephalosporins, trimethoprim, aminoglycosides, macrolides, and sulphonamides; and XDR when resistant to all but two.
- *S. flexneri* isolates, referred between 01 September 2015 and 12 June 2022, harbouring $bla_{\text{CTX-M-27}}$ were identified and phylogenetically characterised.
- Long-read sequencing elucidated the genomic location of $bla_{\text{CTX-M-27}}$
- Laboratory data, integrated with available demographic and clinical information from patient questionnaires, was summarised using descriptive statistics.

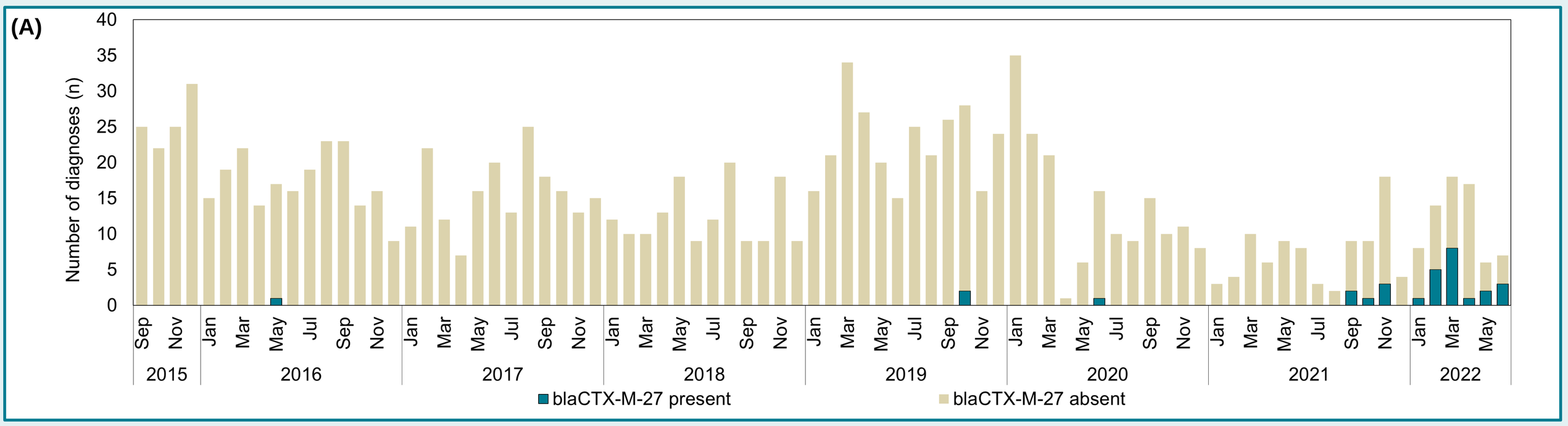
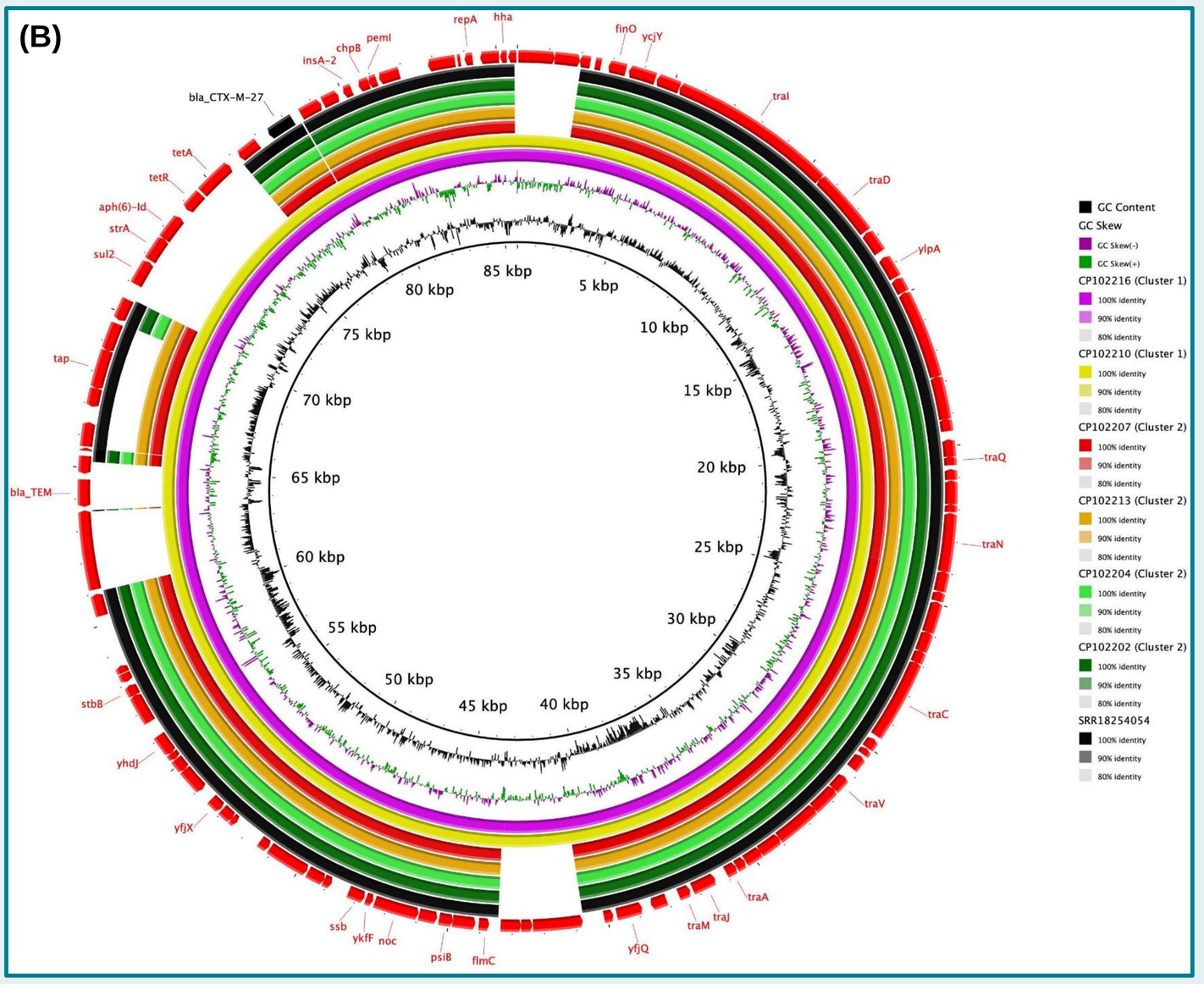


Figure: (A) *S. flexneri* serotype 2a diagnoses by presence or absence of $bla_{\text{CTX-M-27}}$ and specimen date in England, September 2015 to June 2022. **(B)** Comparison of IncFII plasmids isolated from seven *S. flexneri* 2a cases (reference included) in England compared with an IncFII plasmid from a case of the XDR *S. sonnei* Clade 5 (SRR18254054).

3. Results

- A sustained increase in *S. flexneri* 2a harbouring $bla_{\text{CTX-M-27}}$ (n=26) occurred from September 2021, having been sporadically reported only 4 times in the preceding six years (alongside sporadic occurrences of other serotypes 1c (n=3), 1a (n=2) and 3a (n=2)) (Figure A).
- Phylogenetic analysis characterised separate $bla_{\text{CTX-M-27}}$ acquisition events within *S. flexneri* 2a, establishing an XDR (n=8) and a MDR (n=18) cluster.
- All 26 cases were adult men, and of those with a patient questionnaire, most identified as MSM (77%; 10/13). Antimicrobial treatment was received for 54% (7/13) of individuals, and 31% (4/13) were hospitalised.
- The $bla_{\text{CTX-M-27}}$ genetic marker was encoded on an IncFII plasmid; comparison to the XDR *S. sonnei* outbreak plasmid showed high similarity, with 82% and 99% nucleotide similarity for the XDR (Cluster 1) and MDR (Cluster 2) plasmids, respectively (Figure B).



4. Conclusions

- We report emergence of XDR and MDR *S. flexneri* 2a clusters harbouring $bla_{\text{CTX-M-27}}$, among MSM in England.
- Epidemiological and plasmid similarities with the XDR *S. sonnei* outbreak support horizontal acquisition events, emphasising the importance of mobilisable AMR and need for genomic-based surveillance and research.

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Reference: Thorley *et al*., 2023. 'Emergence of extensively drug-resistant and multidrug-resistant Shigella flexneri serotype 2a associated with sexual transmission among gay, bisexual, and other men who have sex with men, in England: a descriptive epidemiological study.' Lancet Infectious Diseases. https://doi.org/10.1016/S1473-3099(22)00807-6.

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