Outbreak of sexually transmitted, extensively drug-resistant \textit{Shigella sonnei} in the UK, 2021–22: a descriptive epidemiological study

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Summary

**Background** Shigellosis, traditionally a foodborne and waterborne infection, causes substantial morbidity globally. It is now a leading cause of sexually transmitted gastroenteritis among gay, bisexual, and other men who have sex with men (MSM). We describe an ongoing outbreak of extensively drug-resistant (XDR) \textit{Shigella sonnei} in the UK.

**Methods** Routine laboratory surveillance (Second Generation Surveillance System, Gastrointestinal Data Warehouse) identified an exceedance of \textit{S sonnei} clade 5 in England, first detected in September, 2021. Cases within this clade were subsequently reported from Scotland, Wales, and Northern Ireland. Confirmed cases in this outbreak were defined as individuals diagnosed with \textit{S sonnei} clade 5 in the UK, with a specimen date between Sept 1, 2021, and Feb 9, 2022, who were genomically confirmed as part of a ten-single nucleotide polymorphism (SNP) linkage cluster. We used whole-genome sequencing with SNP typing to identify genomic clusters and antimicrobial-resistance determinants, analysing cases across the UK. We collected demographic, epidemiological, and clinical data from people infected with \textit{S sonnei} clade 5 in England using questionnaires (standard and bespoke outbreak questionnaires). We used descriptive summary statistics to characterise cases.

**Findings** 72 cases (70 [97%] male, median age 34 years [IQR 27–39]) belonging to the ten-SNP single linkage cluster of \textit{S sonnei} clade 5 were identified between Sept 4, 2021, and Feb 9, 2022. Isolates were predominantly XDR, with 66 (92%) of 72 harbouring \textit{bla}_{\text{CTX-M-27}}, a plasmid-mediated gene for production of extended-spectrum \(\beta\)-lactamases (ESBLs). Of 33 cases with clinical data, 19 (58%) received antibiotics and eight (24%) were hospitalised. 21 (78%) of 27 cases with completed bespoke outbreak questionnaires were HIV-negative MSM taking HIV pre-exposure prophylaxis (PrEP) who reported sexual contacts in the UK and Europe within the incubation period.

**Interpretation** We highlight the rapid dissemination of XDR ESBL-producing \textit{S sonnei} in sexual networks of MSM. We recommend strengthening shigella testing where clinically indicated, antimicrobial-resistance surveillance, and integrated health promotion messaging among all MSM, including PrEP users, to reduce the burden of shigellosis.

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**Introduction** Shigella spp are Gram-negative bacteria transmitted through faecal–oral contact that cause acute bacillary dysentery; they are highly infectious with a low infective dose. Symptoms range from mild, self-limiting diarrhoea and abdominal cramps to severe colitis, bacteremia, intestinal perforation, and peritonitis; however, infection can be asymptomatic. Shigellosis is an important cause of morbidity and mortality globally and is a leading cause of death from infectious intestinal disease among young children in low-income and middle-income countries. Although shigellosis in high-income settings has been associated with travel to endemic regions or the consumption of contaminated food, infections are increasingly associated with sexual transmission among gay, bisexual, and other men who have sex with men (MSM). In 2019, more than half of all cases of shigellosis among adults in England were attributed to sexual transmission among MSM. Evidence suggests that faecal–oral transmission of Shigella spp is sustained in some sexual networks of MSM via group sex, multiple new partners met through geospatial apps, and sexualised drug use (herein referred to as chemsex).

Although most cases of shigellosis are self-limiting and only require supportive care, antibiotics are used to treat cases with prolonged symptoms, severe colitis, or complications such as sepsis. Globally, indiscriminate antimicrobial use contributes to increasing antimicrobial resistance in all bacteria, including \textit{Shigella} spp. WHO guidance for the treatment of shigellosis recommends ciprofloxacin as a first-line treatment, with azithromycin, ceftioxone, or pivmecillinam listed as second-line
Evidence before this study
Sexually transmitted shigellosis is endemic among men who have sex with men (MSM). Endemicity is sustained by continued replacement of species (Shigella flexneri, Shigella sonnei) and strains (serotypes or clades), and the emergence and expansion of resistance to multiple classes of antimicrobials threatens clinical management and infection control. We searched PubMed and MEDLINE up to May, 2022, using the search terms “MSM”, “Shigella”, “Shigellosis”, “antibiotic resistance”, “XDR”, and “outbreak”. Before the COVID-19 pandemic, sexually transmitted S sonnei in Europe was multidrug resistant but susceptible to third-generation cephalosporins such as ceftriaxone, which was the recommended treatment for severe infections in UK clinical guidelines.

Added value of this study
In this study, we characterise the emergence and expansion of an extensively drug-resistant (XDR) strain of S sonnei, which is currently being transmitted among MSM in the UK, Europe, and the USA. This strain contains a plasmid-encoded extended-spectrum β-lactamase (ESBL) gene (blaCTX-M) conferring resistance to all first-line treatments. Enhanced surveillance of confirmed cases documented clinical severity, possible treatment failure, and sporadic transmission outside sexual networks in the outbreak of XDR S sonnei in the UK. These parameters should be monitored when responding to outbreaks of antimicrobial-resistant sexually transmitted shigellosis. We also identified a potential shift in the epidemiology of sexually transmitted shigellosis, with most cases being in HIV-negative MSM using pre-exposure prophylaxis (PrEP), by contrast with previous evidence suggesting that the infection is mostly transmitted in networks of those living with HIV.

Implications of all the available evidence
Our findings contribute to understanding the emergence and dissemination of plasmid-mediated ESBL-producing S sonnei, which is being sexually transmitted among MSM. We identify the need for a global effort for surveillance of antimicrobial-resistant shigellosis and appropriate clinical management, especially in light of documented clinical severity, treatment failure, and sporadic transmission to immunocompromised individuals. We outline a strategy for the treatment of severe XDR shigellosis, including pivmecillinam and fosfomycin. Finally, we identify the urgent need to integrate health promotion for the prevention of shigellosis and other enteric sexually transmitted infections within the routine delivery of PrEP.

Methods
Laboratory and genomic surveillance
Shigella spp are notifiable organisms in the UK. Since 2004, national surveillance in England, Wales, and Northern Ireland has been undertaken through an automated laboratory notification system called the Second Generation Surveillance System, which electronically captures positive Shigella spp laboratory
results (PCR or culture). These laboratories locally undertake phenotypic antibiotic susceptibility testing for a limited range of antibiotics (using European Committee on Antimicrobial Susceptibility Testing or Clinical and Laboratory Standards Institute criteria. Approximately two thirds of isolates are voluntarily referred by the diagnostic laboratories to the Gastrointestinal Bacterial Reference Unit (GBRU), UK Health Security Agency (UKHSA; London, UK), and undergo species and clade identification, single nucleotide polymorphism (SNP) typing, and antimicrobial-resistance profiling using whole-genome sequencing (WGS) methods that have been previously described.12 Scotland has an equivalent surveillance system for Shigella spp, and sequence data are run through the UKHSA pipeline. A threshold of ten SNP differences across the core genome of any two isolates is the current standard for defining likely transmission clusters in routine public health surveillance of Shigella spp at UKHSA.13 Microbiological data are routinely linked to demographic data, including date of birth and sex, and stored in a local database, Gastrointestinal Data Warehouse.

Genomic surveillance identified an exceedance of S sonnei clade 5 t10.377 cases in England, first detected in September, 2021. Anecdotal reports of hospitalisation of severe cases of S sonnei in London in November and December, 2021, suggested an outbreak and prompted investigations through a multidisciplinary Outbreak Control Team. The Outbreak Control Team was responsible for investigating the epidemiological, microbiological, and phylogenetic features of cases, and translating this information into optimal clinical management and public health control measures. Confirmed cases in this outbreak were defined as individuals diagnosed with S sonnei clade 5 in the UK, with a specimen date between Sept 1, 2021, and Feb 9, 2022, who were genomically confirmed as part of a single ten-SNP linkage cluster. Data for these analyses for England, Wales, and Northern Ireland were extracted from Gastrointestinal Data Warehouse on Feb 28, 2022. Data for Scotland were extracted from Electronic Communication of Surveillance in Scotland on Feb 28, 2022.

Long-read sequencing was undertaken using Oxford Nanopore Technology for nine strains to characterise and determine the genomic locus of key resistance determinants, such as blaCTX-M, as previously described.17 Full nanopore sequencing and bioinformatics methodologies can be found in appendix p 1.

Epidemiological surveillance
In January and February, 2022, trained public health scientists approached confirmed cases reported from England for interviews to obtain demographic, epidemiological, and clinical data. While initial cases had information collected using standard health protection questionnaires (appendix p 11), the finding of suspected sexual transmission prompted the Outbreak Control Team to design and implement bespoke outbreak questionnaires (appendix pp 3–11). Their structure and content were informed by findings from previous outbreak investigations.18 These questionnaires captured demographic (sexual orientation, ethnicity, postcode), clinical (symptoms, symptom duration, hospitalisation, attendance to emergency services, antibiotic use, treatment failure), and epidemiological (exposures, travel and sexual history) data. Possible treatment failure was defined as symptom duration of at least 7 days in patients who received antibiotics. Following questionnaire completion, and based on individual needs, interviewers delivered health promotion messages focused on STI prevention, access to HIV pre-exposure prophylaxis (PrEp), retention in HIV care, or harm reduction for chemsex. These data were entered into a Microsoft Access database, and integrated with laboratory data, cleaned, and summarised using descriptive statistics (including proportions and median and IQR) in Stata 15.0.

Ethics
The UKHSA has approval to handle data obtained through laboratory surveillance under Regulation 3 of the Health Service (Control of Patient Information) Regulations 2002. Questionnaires were administered via interviews with cases in the context of this outbreak response, and although participation was voluntary following a verbal explanation of the context and activity, informed consent was not required as UKHSA has the authority to handle patient data for public health monitoring and infection control under Section 251 of the UK National Health Service Act 2006.

Role of the funding source
The sponsor of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
Outbreak investigation
A total of 72 confirmed cases were identified in the UK between Sept 4, 2021, and Feb 9, 2022, based on the faecal specimen date (figure 1). Of 72 confirmed cases, 70 (97%) were male, with a median age of 34 years (IQR 27–39); all were adults (≥16 years). 65 (90%) cases resided in England; four cases were residents in Scotland, two in Northern Ireland, and one in Wales. Of those residing in England, the highest proportion of confirmed cases were living in London (38 [58%] of 65).

Alongside the six cases reported from England with a completed standard questionnaire, of 39 cases approached, a further 27 cases had a completed outbreak questionnaire. Therefore, 33 (51%) of 65 cases in England had either a completed standard or outbreak questionnaire. Cases with questionnaire data described their ethnicity most
frequently as White (30 [91%] of 33). Most cases with questionnaire data identified as gay men (28 [85%] of 33). The most common symptoms were diarrhoea (33 [100%] of 33), abdominal cramps (32 [97%] of 33), blood in stools (23 [70%] of 33), and fever (19 [58%] of 33). Symptoms lasted for a median of 12 days (IQR 6–14). Of 33 cases with questionnaire data available, 18 (55%) attended general practice, 16 (48%) attended emergency services, and eight (24%) were hospitalised for a median of 5 days (IQR 3–6).

19 (58%) of 33 cases received antibiotics, the most common agent being ciprofloxacin (n=8). Azithromycin, ertapenem, metronidazole, and fosfomycin were the next most common agents (n=2 each), followed by single reports of vancomycin, rifaximin, amoxicillin, clindamycin, doxycycline, and erythromycin use. Among 19 cases receiving antibiotics, possible treatment failure to first-line antibiotics was identified in at least seven cases (37%, 95% CI 16–62), leading to persistence of symptoms following antimicrobial treatment.

Of the 27 cases with an outbreak questionnaire, 25 (93%) were HIV negative and 21 (78%) were taking HIV PrEP; 11 (41%) reported bacterial STIs (gonorrhoea, chlamydia, Mycoplasma genitalium, and syphilis) in the past year that required antimicrobial treatment. Sexual transmission was the likely route of acquisition in all but two cases (one male and one female); both cases identified as heterosexual, had a history of immunosuppression, and were hospitalised due to severity of symptoms.

Most cases with an outbreak questionnaire reported engaging in one or more sequential oral and anal sexual acts in the week before symptom onset (22 [81%] of 27), usually with new or one-off partners (19 [86%] of 22). Contexts for exposure included group sex in private parties, sex on premises in commercial venues (dark rooms in nightclubs, cruise ships), and sex with new partners coordinated through geospatial online-dating apps. Chemsex was reported by four (15%) of 27 cases with an outbreak questionnaire. Although most acquired the infection in cities in England, a minority reported sex while travelling to other countries in Europe (Spain: n=2, France: n=1, Greece: n=1) during the incubation period. Interviews revealed a lack of or limited understanding among cases about the infectious nature of Shigella spp and the risk of acquisition via sexual contact with both symptomatic and asymptomatic cases; cases also reported limited awareness of shigellosis as an STI among health-care professionals involved in managing their illness.

All cases were genotypically multidrug resistant or XDR, with resistance to a wide range of antimicrobial classes. Phenotypic testing was conducted by diagnostic laboratories and confirmed resistance to amoxicillin, ceftriaxone, amikacin, gentamicin, tobramycin, azithromycin, tetracycline, fluoroquinolone, and cotrimoxazole; ESBL activity was confirmed with synergy testing with clavulanic acid. Isolates were susceptible to ertapenem, meropenem, temocillin, and fosfomycin. Where antimicrobial-resistance information was available (n=66), all outbreak isolates exhibited genomic antimicrobial-resistance determinants for amino glycosides (strA: strB, aadA-5), sulfonamides (sul-1, sul-2), trimethoprim (dfrA-1, dfrA-17), fluoroquinolones (gyrA S83L,D87L; parC S80I; qnrB-19), and macrolides (mph-A, ermB). In addition, 66 (92%) of 72 outbreak isolates harbour ed blaCTX-M-27, which is known to confer resistance to ceftriaxone; isolates belonging to this ten-SNP single linkage cluster detected before September, 2021, only sporadically expressed
**Outbreak control measures**

In January and February, 2022, the Outbreak Control Team undertook extensive communications with the target population through press briefings, social media posts, and awareness raising through charities and sexual health professionals, alerting them to the common symptoms, and asking them to inform their general practitioner about recent sexual contacts. Advice on sexual hygiene, hand washing, and avoiding sexual contact for 1 week after complete resolution of symptoms was emphasised. Feedback from communications on social media and target groups suggested an overall lack of awareness of shigellosis among MSM.

Hospital and primary-care physicians were alerted to this XDR *Shigella sonnei* outbreak through professional bodies. Recommended actions included taking sexual history in adult men presenting with diarrhoeal illness and requesting microbiological testing of faecal specimens for MSM. Clinicians were alerted to likely failure of first-line agents used in sepsis protocols in the UK (usually a β-lactam with β-lactam inhibitor combination and an aminoglycoside). As options for licensed oral therapeutics were extremely limited, the recommendations included pivmecillinam (400 mg four times a day orally for adults) and fosfomycin (3 g on day 1, day 3, and day 5 orally for adults) for cases with prolonged symptoms or as oral step-down after intravenous treatment. A suitable oral antibiotic, chloramphenicol, is not easily available in primary care and is an expensive option in the UK. Carbapenems were recommended for treatment of hospitalised, suspected or confirmed cases with severe infection or complications for 3–5 days (depending on clinical condition and type of complication) with suitable oral step-down treatment as appropriate. Intravenous options were limited to carbapenems, and colistin in case of β-lactam allergy, for complicated cases. Specialist hospital and primary-care physicians were alerted to this XDR *Shigella sonnei* outbreak through professional bodies.

**Figure 2:** Phylogenetic tree of strains isolated from confirmed cases within this *Shigella sonnei* clade 5 outbreak with epidemiological exposure data (*n*=73) and presence of *bla*<sub>CTX-M-27</sub>.
sexual health professional organisations (British HIV Association and British Association of Sexual Health and HIV) developed educational materials,22 which were cascaded to relevant health-care practitioners, and national guidelines are being developed to manage enteric STIs.

International alerts, coordinated by WHO and the European Centre for Disease Prevention and Control (ECDC), highlighted the rise in XDR S

sonnei notifications, and WGS data were shared with other countries. Austria, Spain, Norway, Ireland, Belgium, Denmark, France, Germany, and the USA all confirmed they had detected isolates of XDR S sonnei phylogenetically linked to this outbreak cluster.23,24 Members of the Outbreak Control Team in the UK contributed to the rapid risk assessment for XDR S sonnei published by ECDC and WHO.21,24

Discussion

We report an ongoing outbreak of XDR S sonnei among MSM in the UK. Similar to previous outbreaks of sexually transmitted shigellosis, acquisition of a plasmid-encoded antimicrobial-resistance determinant was a defining feature, although most of these previous outbreaks were short-lived and none of the strains were XDR.25,26 This outbreak strain is resistant to seven different classes of antibiotics, and oral treatment options are extremely limited. In addition, there have been reports of clinical severity including hospitalisation and possible treatment failure.

Rapid geographical dissemination of this strain of XDR S sonnei suggests that harbouring resistance genes might confer a selective advantage that, in part, facilitates transmission and persistence. The monophyletic nature of this cluster suggests transmission is occurring in a dense sexual network, which along with immunity and host behaviour, likely contributes to transmission and persistence. Circulation of multidrug-resistant ESBL-producing S sonnei in adult men has been reported previously.27 Before the COVID-19 pandemic, isolates of S sonnei clade 5 in the UK were multidrug resistant but only sporadically exhibited bla_{CTX-M-27}.19 When the clade 5 outbreak strain emerged and expanded in England in September, 2021, it consistently harboured bla_{CTX-M-27}, conferring phenotypic resistance to ceftriaxone.

Previous studies have shown rapid international transmission of antimicrobial-resistant shigellosis in sexual networks of MSM, which have increased connectivity and antimicrobial use compared with heterosexual networks.1 In this outbreak, enhanced surveillance and phylogenetic data suggested that person-to-person transmission occurred predominantly in sexual networks of MSM engaging in one or more sequential oral and anal sexual acts with multiple new partners in private or commercial venues. We identified repeated antimicrobial treatment for bacterial STIs, such as gonorrhoea and chlamydia, in the year before acquiring shigellosis, highlighting that continued exposure to antimicrobials might drive antimicrobial resistance in this population. Furthermore, enhanced surveillance identified potential transmission during international travel following the relaxation of COVID-19 control measures. These findings suggest how local trends in strain replacement driven by antimicrobial resistance could be rapidly translatable to the global scale through sexual network interconnectivity and international travel; we therefore advocate for continued antimicrobial stewardship in STI control and prevention messaging among at-risk populations.

Our study contributes to the available evidence highlighting that plasmid acquisition is probably an important mechanism for the emergence of ESBL-producing S sonnei.21,24 Our phylogenetic analyses identified that all isolates harbouring the plasmid encoding bla_{CTX-M-27} were located on the same branch of the tree, suggesting a single plasmid acquisition event in a common ancestor. Previous acquisition of this plasmid in S sonnei has been documented in Australia.27 This increase of plasmid-mediated ESBL-production is of particular concern due to its ability to spread to other Shigella spp, Enterobacteriaceae, and the wider gut microbiota, increasing the overall resistance pool in the population.11

Previous evidence has shown that sexually transmitted shigellosis can be transmitted sporadically outside sexual networks,27 enhanced surveillance for this outbreak provided further evidence of this. This outbreak included two severe cases in immunocompromised individuals not associated with sexual transmission, indicating that spillover events might be common but only identified when increased host susceptibility is present. Sporadic transmission outside sexual networks, leading to severe cases in immunocompromised individuals, highlights the wider public health risk of continued, uncontrolled transmission of XDR shigellosis. Our enhanced surveillance identified a case belonging to a high-risk occupational group who reported no recent sexual activity. Currently, there are no public health guidelines in the UK for S sonnei on mandatory microbiological clearance before returning to work, which further elevates the risk of transmission. Asymptomatic cases also contribute to onward transmission and add to the burden of infection.10,11

By contrast with previous evidence, which identified that cases of shigellosis were frequent among MSM living with HIV,4 most cases in this outbreak were HIV-negative MSM taking daily PrEP. In England, PrEP has been routinely commissioned since 2020 and is free of charge in sexual health services; UK national guidelines recommend quarterly STI and HIV testing for PrEP users.28 Our findings suggest that although general health promotion for the prevention of sexually transmitted shigellosis is needed, a concerted effort to integrate health promotion within PrEP care will also be required. Efforts to target wider needs, including harm
control team. HF, DR, IW, and GG provided clinical input. LB, RS, and PC provided data from Scotland, Wales, and Northern Ireland, respectively. The manuscript was prepared by HC, MP, CJ, and GG. All authors contributed to reviewing and editing the manuscript before publication. HC was responsible for the decision to submit for publication.

Declaration of interests
We declare no competing interests.

Data sharing
FASTQ sequences from the genomes used in this study were submitted to the National Center for Biotechnology Information under BioProject PRJNA33192 and are publicly available with no access restrictions. A table with accession numbers (Nanopore and Illumina reads) is available in appendix p 2.

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