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Trends in shigellosis notifications in England, January 2016 to March 2023

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Abstract

We reviewed all diagnoses of *Shigella* species notified to the UK Health Security Agency from January 2016 to March 2023. An overall increase in notifications of shigellosis was seen between 2016 (n = 415/quarter) and 2023 (n = 1 029/quarter). However, notifications dramatically declined between March 2020 and September 2021 during the COVID-19 pandemic (n = 208/quarter) highlighting the impact of travel and social distancing restrictions on transmission. *S. sonnei* diagnoses were more affected by lockdown restrictions than *S. flexneri*, most likely due to a combination of species-specific characteristics and host attributes. Azithromycin resistance continued to be associated with epidemics of sexually transmissible S. *flexneri* (adult males = 45.6% vs. adult females = 8.7%) and *S. sonnei* (adult males = 59.5% vs. adult females = 14.6%). We detected resistance to ciprofloxacin in *S. sonnei* from adult male cases not reporting travel at a higher frequency (79.4%) than in travel-associated cases (61.7%). Extensively drug-resistant *Shigella* species associated with sexual transmission among men almost exclusively had ESBL encoded by $bla_{\text{CTX-M-27}}$, whereas those associated with returning travellers had $bla_{\text{CTX-M-15}}$. Given the increasing incidence of infections and AMR, we recommend that enhanced surveillance is used to better understand the impact of travel and sexual transmission on the acquisition and spread of MDR and XDR Shigella species.

Key results

- Except for the years covered by the COVID-19 pandemic, there was a steady increase in shigellosis notifications from January 2016 to March 2023.
- During the pandemic, notifications dramatically declined and then gradually increased as lockdown restrictions were relaxed.
- *S. sonnei* diagnoses were more influenced by lockdown restrictions than *S. flexneri*, suggesting that returning travellers may seed domestic transmission of *S. sonnei.*
- Azithromycin resistance continued to be a factor in epidemics of sexually transmissible *S. flexneri* and *S. sonnei.*
- Resistance to ciprofloxacin in *S. sonnei* from adult male cases not reporting travel was higher than from travel-associated cases.
- Extensively-drug resistant *Shigella* species associated with sexual transmission among men almost exclusively had $bla_{\text{CTX-M-27}}$, whereas those associated with returning travellers had $bla_{\text{CTX-M-15}}$.
- Enhanced collection of travel and sexual transmission data will improve understanding of this clinically significant pathogen.

Introduction

Shigellosis, previously known as bacillary dysentery, is a gastrointestinal illness characterized by diarrhoea containing blood and/or mucus, and sometimes stomach cramps, fever, and vomiting. Although most people recover without treatment within a few days, others require hospitalization to treat dehydration, blood stream infections, and/or other complications [1]. Globally, most cases of shigellosis are caused by *Shigella sonnei or S. flexneri*, although *S. boydii* and *S. dysenteriae* also contribute to the burden of gastrointestinal disease in endemic regions and may cause infectious gastrointestinal disease in travellers returning from the Indian sub-continent and Africa [2, 3].

Shigella species are patho-adapted to infect the colonic mucosa of the human gut, and there is no animal reservoir. The infectious dose is low (10–100 bacteria) and the incubation period is usually 24–48 hours. Due to the low infectious dose, shigellosis is highly transmissible, and transmission is maintained primarily by direct person to person contact but can occur indirectly via the ingestion of food or water contaminated by human faeces. There is evidence

that some individuals continue to be carriers for weeks or even months after their symptoms have resolved [4]. Historically in England, sporadic cases of shigellosis were associated with travellers returning from endemic regions (e.g., Africa, Asia, and Latin America) [5–7]. Outbreaks mostly occurred amongst children in school and nursery school settings, although foodborne outbreaks have been described [8–10]. More recently, domestic transmission has been sustained by sexual transmission among gay, bisexual, and other men who have sex with men (GBMSM) [3, 11, 12].

Sexually transmissible shigellosis among GBMSM is a public health concern. Surveillance data indicate that the burden of disease is high, clinical outcomes can be severe, and outbreaks have been caused by multidrug resistant (MDR) and extensively drug resistant (XDR) strains of *S. flexneri* and *S. sonnei* [13–15]. However, not all MDR and XDR cases of shigellosis are sexually transmitted, and previous studies in the UK and elsewhere have identified MDR and XDR *Shigella* in travellers returning from endemic regions [16, 17]. We reviewed all diagnoses of *Shigella* species notified to the UK Health Security Agency (UKHSA) from January 2016 to March 2023. The aim of this study was to describe the epidemiology, microbiology, and antimicrobial resistance profiles of travel-associated and sexually transmitted shigellosis in England.

Methods

Data collection

Faecal specimens from hospitalized patients and individuals in the community with gastrointestinal symptoms are sent to local hospital, private or regional laboratories in England for culture (https://www.gov.uk/government/publications/smi-b-30-investigation-of-faecal-specimens-for-enteric-pathogens). All *Shigella* isolated at these diagnostic laboratories are captured via the Second Generation Surveillance System (SGSS) (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/739854/PHE_Laboratory_Reporting_Guidelines.pdf). This dataset comprises comprehensive, national coverage of primary laboratory-based notifications of shigellosis.

UKHSA guidelines recommend that diagnostic laboratories submit isolates of presumptive *Shigella* to the Gastrointestinal Bacterial Reference Unit (GBRU) at UKHSA for confirmation by PCR and typing by whole genome sequencing (WGS). PCR and sequencing results are stored in the Gastro Data Warehouse (GDW) and linked to patient demographic data, including age, sex, area of residence, and travel history. Not all isolates of *Shigella* are referred to the GBRU, and therefore the data in GDW are a subset (approximately two-thirds) of diagnoses reported in SGSS. However, the sequencing data in GDW were used in this analysis for detailed analyses of molecular typing, strain differentiation and relatedness, and AMR profiling.

Data analysis

Microbiological typing data from all isolates of *Shigella* species submitted to the GBRU between January 2016 and March 2023 were extracted and analyzed (Supplementary Table). Travel-associated cases were defined as those reporting recent foreign travel to any country seven days prior to the onset of symptoms, based on information from laboratory reports. Travel history is poorly captured for cases of *Shigella* species; if no travel history is reported, it cannot be inferred that the case did not travel. Laboratory surveillance data lack information on patient sexual orientation. However, in line with previous work, we used a proxy indicator of cases that may be attributed to sexual transmission among GBMSM, defined as cases among adult males without a history of travel [18]. Patients aged <16 years were classified as children.

The analysis was undertaken in three stages. First, we analyzed the demographic data available in SGSS, specifically, age, sex, and travel history, over time. We then analyzed the demographic data available in GDW, specifically age, sex, and travel history over time, linked to the reference laboratory-confirmed cases of shigellosis in England for all *Shigella* species and then for each individual species of *Shigella.* Finally, we analyzed the sequencing data for genomic markers of resistance to azithromycin (defined here as the presence of *ermB* and/or *mphA*), ciprofloxacin (defined here as the presence of mutations in *gyrA*, *parC* and/or the presence of *qnr*), and the third generation cephalosporins (defined here by the presence any $bla_{\text{CTX-M}}$ variant) for all *Shigella* species and for each individual species of *Shigella.* We defined extensively-drug resistant isolates as those expressing genomic markers of resistance to azithromycin, ciprofloxacin and third-generation cephalosporins.

Data are presented quarterly; Quarter 1 (Q1) from January to March, Q2 from April to June, Q3 from July to September and Q4 from October to December.

Whole-genome sequencing

Since August 2015, microbiological typing, including confirmation of the species and the serotype, has been performed at UKHSA using WGS [6, 7]. DNA was extracted for sequencing on an Illumina HiSeq 2500 instrument. Identification to the species level was based on kmer identification [19]. Genome-derived serotyping and AMR determinant profiling were performed using the GeneFinder tool (https://github.com/phe-bioinformatics/gene_finder), run using the default parameters. For serotyping, a reference database containing the gene sequences encoding the 12 O-antigen synthesis or modification genes was constructed and then used to determine serotype as previously described [7].

For AMR determinant profiling, genes were defined as present if they represented 100% of the reference sequence with greater than 90% nucleotide identity [17]. The reference database for AMR determinants can also be found in the GeneFinder github repository (https://github.com/phe-bioinformatics/gene_finder/tree/master/refs). The prevalence of resistance to streptomycin, tetracycline, sulphonamides, and trimethoprim in *Shigella* species is high, and the trends have been consistent for many years [20–22]. We, therefore, focused our AMR analysis on the presence of genomic makers of resistance to azithromycin, ciprofloxacin, and the third generation cephalosporins as the trends in resistance to these clinically relevant classes of antimicrobials fluctuated during the study period.

Results

Overview of local and regional diagnostic laboratory data from SGSS

Between Q1 2016 and Q1 2020, notifications of shigellosis showed an increasing trend (Figure 1). However, following the implementation of the first lockdown restrictions in Q2 2020 in response to the COVID-19 pandemic, reported diagnoses more than halved (Figure 1). From Q1 2016 to Q1 2020, on average there were 581 diagnoses of shigellosis reported to SGSS each quarter, whereas from Q2 2020 to Q3 2021, there was an average of 208 diagnoses of shigellosis recorded in SGSS each quarter (Figure 1). Following the

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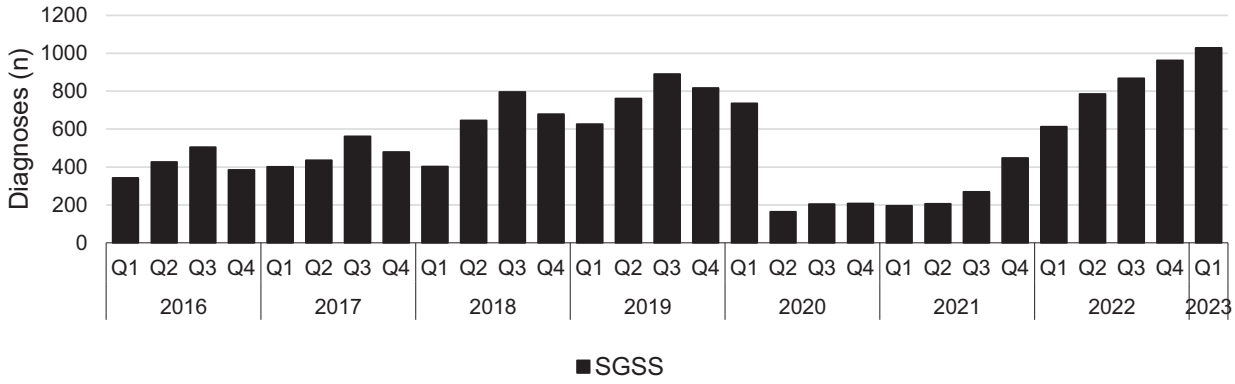

Figure 1. Total number of *Shigella* spp. diagnoses, England, Q1 2016 to Q1 2023 (data source: SGSS).

Table 1. Average quarterly number of reported *Shigella* spp. diagnoses pre COVID-19, during COVID-19 restrictions, and post COVID-19 in SGSS, England

	Pre COVID-19 (Q1 2016 to Q1 2020)	COVID-19 restrictions (Q2 2020 to Q3 2021)	Post COVID-19 restrictions (Q4 2021 to Q1 2023)	% change from pre COVID-19 to post COVID-19
All persons	581	208	785	37.2% increase
Adults	465	175	644	38.5% increase
Children	105	32	138	31.4% increase
Males	322	151	458	42.2% increase
Females	246	55	324	31.7% increase
Travel	111	8	80	27.9% decrease
Non-travel/unknown	461	200	705	52.9% increase

relaxation of the lockdown restrictions in Q3 2021, the number of notifications among all persons returned to, and then exceeded, pre-pandemic levels, with an average of 785 reported diagnoses per quarter (Figure 1 and Table 1). The increase in diagnoses following the final removal of lockdown restrictions occurred among both adults and children and in both males and females (Table 1 and Figure 2). The largest proportional increases were among adult males who did not travel or where travel history was not reported (Figure 2).

Analyses of data on GDW from isolates referred to the reference laboratory

Shigella speciation data for isolates referred to GBRU between Q1 2016 and Q1 2023 showed the majority were *S. sonnei* or *S. flexneri* (94%, n = 7 339/7 782). From Q1 2016 to Q3 2019, the highest number of diagnoses were *S. sonnei* (Figure 3). However, notifications of *S. flexneri* had been increasing since 2018 and just prior to the pandemic lockdown, *S. flexneri* became the dominant species in Q4 2019 (Figure 3). In Q2 2020, notifications of both *S. sonnei* and *S. flexneri* declined steeply, but the decrease was more striking for *S. sonnei* (from 128 in Q1 2020 to 17 in Q2 2020, 87% decrease). Following the removal of lockdown restrictions in Q3 2021, case numbers increased for both *S. sonnei* and *S. flexneri*, with *S. sonnei* exhibiting the largest increase, peaking at 262 cases in Q4 2022 before decreasing in Q1 2023 (Figure 3). There was an increase in notifications of *S. flexneri* during the latter half of 2022, and *S. flexneri* was the most frequently reported species in Q1 2023.

The trends of *S. flexneri* and *S. sonnei* among adults and children, males and females, individuals reporting travel, and those with no or unknown travel history, revealed that *S. sonnei* diagnoses declined universally during the COVID-19 pandemic (Table 2). Conversely, *S. flexneri* diagnoses continued to be reported among adult males and those reporting no or unknown travel status, yet declined among children, females and people reporting travel (Table 2). A more detailed analysis of the serotypes influencing the trends in *S. flexneri* notifications showed that prior to the implementation of lockdown restrictions, serotype 2a was dominant in England. However, the increase in *S. flexneri* in Q3 2019 was driven by a combination of serotypes 1b, 2a, and 3a, and all three serotypes continued to circulate during the pandemic (Figure 4), mainly amongst adult males. After lockdown restrictions were lifted, diagnoses of *S. flexneri* serotypes 1b and 2a were most common, with reports of *S. flexneri* 2a rising sharply in the first quarter of 2023.

Analysis of antimicrobial resistance data

Overall, the number and proportion of extensively drug resistant (XDR) isolates increased over the period between Q1 2016 and Q1 2023. The proportion of XDR isolates was higher for *S. sonnei* compared to *S. flexneri*, such that in 2022, 34% (219/636) of *S. sonnei* isolates and 6% (34/537) *S. flexneri* isolates were defined as XDR (Figure 5a,b).

Analyses of the presence of AMR across different demographic groups revealed that among individuals reporting travel, adult females, and children, the proportions of cases infected with *S. flexneri* isolates that had *ermB* and/or *mphA* (travellers, 8.7%; adult female non-travellers, 8.7%; children, 5.7%), *gyrA*, *parC* and/or *qnr* (travellers, 61.7%; adult female non-travellers, 53.8%; children, 66.9%), and $bla_{\text{CTX-M-27}}$ (travellers, 1.2%; adult female non-travellers, 0.3%; children, 0.2%), were similar (Table 3). In comparison, adult

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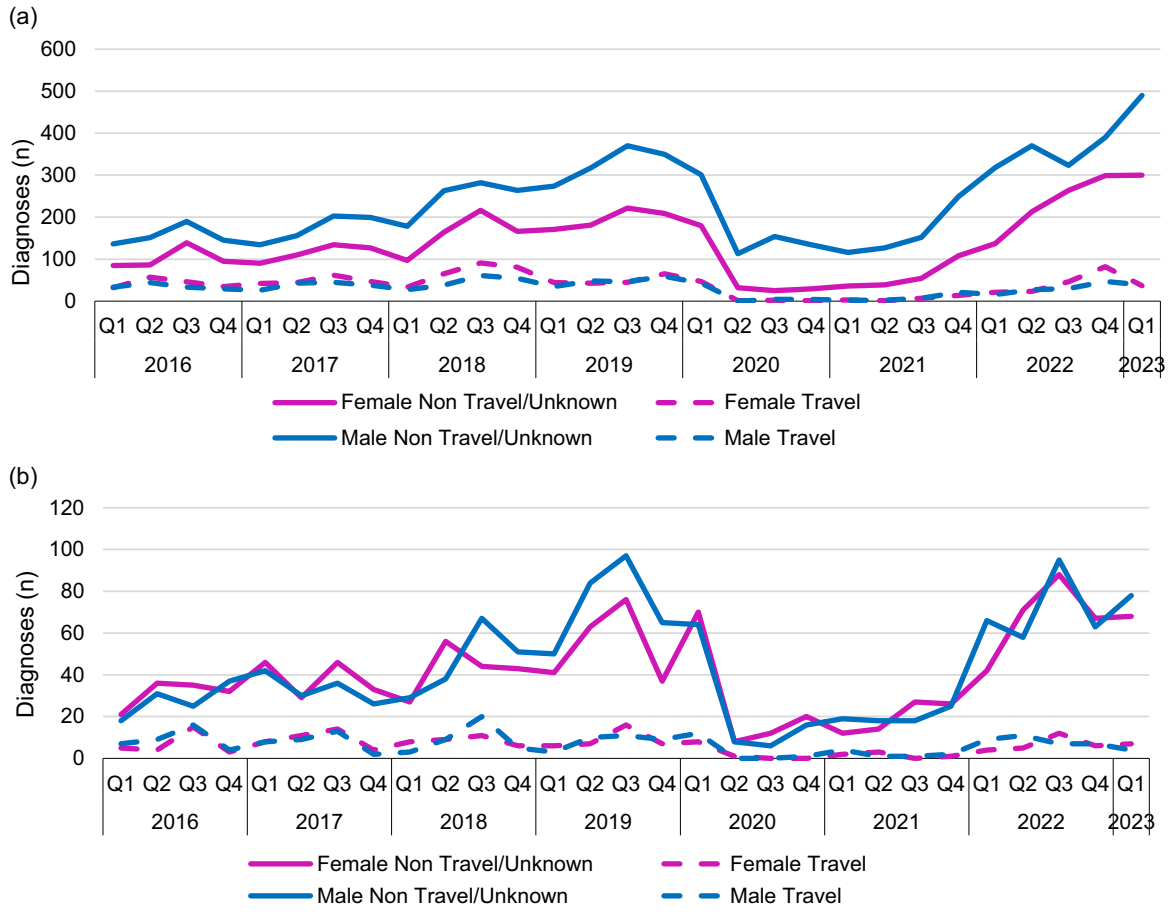

Figure 2. Number of *Shigella* spp. diagnoses associated with sex and travel, England, Q1 2016 to Q1 2023 in adults (a) and children (b) (data source: SGSS).

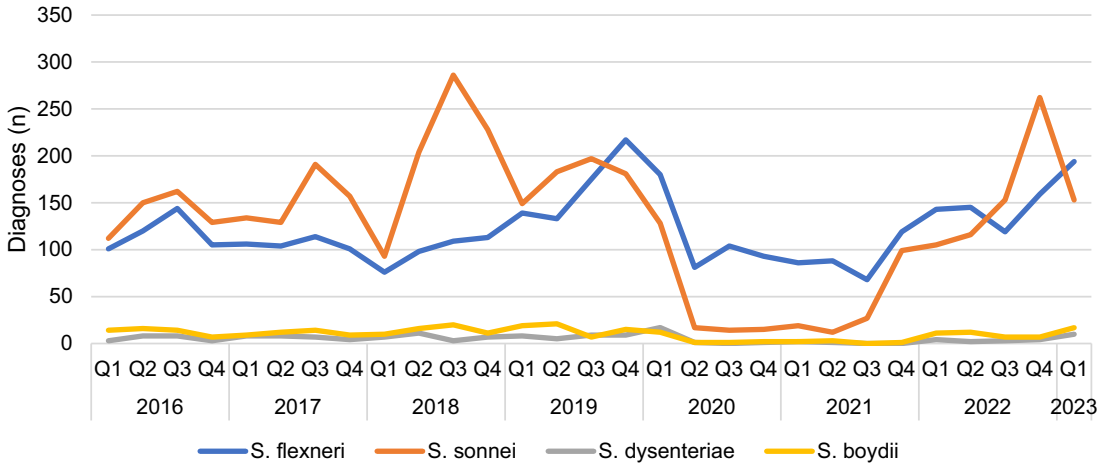

Figure 3. Number of all *Shigella* spp. diagnoses by species, England, Q1 2016 to Q1 2023 (all persons) (data source: GDW).

male non-travellers were associated with a higher proportion of isolates that had *ermB* and/or *mphA* (adult male non-travellers, 45.6%) or $bla_{\text{CTX-M-27}}$ (adult male non-travellers, 2.9%), but a lower proportion of isolates that had *gyrA*, *parC* and/or *qnr* (adult male non-travellers, 45.6%) and $bla_{\text{CTX-M-15}}$ than the other demographic groups (travellers, 7.5%; adult female non-travellers, 9.5%, adult male non-travellers, 1.9%; children, 16.1%) (Table 3).

For *S. sonnei*, the proportions of AMR isolates were generally higher than for *S. flexneri*, although a similar pattern among the different population groups was observed (Table 4). With the

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Table 2. Quarterly number of *Shigella* diagnoses by species and population group, England, Q1 2016 to Q1 2023

	2016				2017				2018				2019				2020				2021				2022				2023
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1
S. flexneri	**101**	**120**	**144**	**105**	**106**	**104**	**114**	**101**	**76**	**98**	**109**	**113**	**139**	**133**	**175**	**217**	**180**	**81**	**104**	**93**	**86**	**88**	**68**	**119**	**143**	**145**	**119**	**159**	**194**
Adults	88	93	118	84	85	89	98	84	57	80	88	90	119	122	148	189	150	75	101	83	79	80	65	114	131	127	105	143	167
Children	13	27	25	21	21	15	16	16	19	18	21	23	20	10	27	28	30	6	2	9	7	8	3	5	12	18	14	16	27
Males	74	80	91	63	74	64	77	71	47	60	70	64	96	108	124	157	128	71	95	82	73	78	61	96	115	124	88	116	151
Females	25	39	52	42	32	39	36	29	24	38	37	46	42	25	50	60	48	8	8	11	12	9	6	22	24	21	30	43	39
Travel	31	32	43	38	34	37	40	22	30	29	38	43	39	37	33	64	58	4	2	6	3	6	19	25	31	22	31	38	39
Non-travel/Unknown	70	88	101	67	72	67	74	79	46	69	71	70	100	96	142	153	122	81	100	91	80	85	62	100	118	114	97	128	156
S. sonnei	**112**	**150**	**162**	**129**	**134**	**129**	**191**	**157**	**93**	**204**	**286**	**228**	**149**	**183**	**197**	**181**	**128**	**17**	**14**	**15**	**19**	**12**	**27**	**99**	**105**	**116**	**153**	**262**	**153**
Adults	91	126	126	108	87	100	147	132	83	177	249	204	130	142	154	153	113	14	12	11	13	9	22	94	91	101	128	222	139
Children	21	23	36	21	47	28	44	25	10	27	37	23	19	41	43	28	15	3	2	4	6	3	5	5	14	15	25	40	14
Males	55	74	78	67	55	69	93	86	62	124	146	130	84	105	115	107	76	9	7	8	8	6	17	57	76	72	74	124	96
Females	55	76	84	60	77	59	95	71	31	80	138	96	61	78	82	72	52	8	7	7	11	6	10	41	28	42	78	136	56
Travel	41	78	62	47	40	52	74	49	27	67	125	83	39	61	69	64	39	1	2	3	3	2	10	20	17	28	65	105	42
Non-travel/Unknown	71	72	100	82	94	77	117	108	66	137	161	145	110	122	128	117	89	16	12	12	16	10	17	79	88	88	88	157	111
S. boydii	**14**	**16**	**14**	**7**	**9**	**12**	**14**	**9**	**10**	**16**	**20**	**11**	**19**	**21**	**7**	**15**	**12**	**1**	**1**	**2**	**2**	**3**	**1**	**11**	**12**	**7**	**7**	**17**	**18**
Adults	14	13	10	7	7	10	13	9	8	15	13	7	17	18	6	14	8	1	1	1	2	2	1	6	8	6	3	13	13
Children	0	3	4	0	2	2	1	0	2	1	7	4	2	3	1	1	4	0	0	1	0	1	0	5	4	1	4	4	5
Males	7	5	5	3	6	4	4	3	5	6	11	5	8	12	3	7	5	1	1	6	6	2	3	7	6	6	2	3	8
Females	7	11	9	3	3	8	9	6	5	10	9	5	11	9	4	8	7	1	1	2	3	1	5	6	5	3	10	3	10
Travel	8	11	7	6	4	7	9	7	6	10	12	5	10	8	6	9	8	0	0	0	1	1	0	0	5	4	6	4	9
Non-travel/Unknown	6	5	7	1	5	5	5	2	4	6	8	6	9	13	1	6	4	1	1	2	1	2	0	1	6	8	1	3	8
S. dysenteriae	**3**	**8**	**8**	**3**	**8**	**8**	**7**	**4**	**7**	**11**	**3**	**7**	**8**	**5**	**9**	**9**	**17**	**1**	**0**	**1**	**2**	**1**	**0**	**0**	**4**	**2**	**3**	**4**	**10**
Adults	1	6	8	3	6	7	5	4	5	7	2	7	6	4	5	7	11	1	0	0	1	1	0	0	2	1	2	2	9
Children	2	2	0	0	2	1	2	0	2	4	1	0	2	1	4	2	6	0	0	1	1	0	0	0	2	1	1	2	1
Males	0	2	4	2	2	3	4	1	5	2	2	3	4	2	5	3	7	0	0	1	1	0	0	0	2	1	0	3	4
Females	3	6	4	0	6	5	3	3	2	9	1	4	4	3	4	6	10	1	0	0	1	1	0	0	2	1	3	1	6
Travel	3	5	6	2	4	4	4	3	5	6	2	2	3	3	5	8	14	0	0	1	0	0	0	0	3	2	2	2	8
Non-travel/Unknown	0	3	2	1	4	4	3	1	2	5	1	5	5	2	4	1	3	1	0	0	2	1	0	0	1	0	1	2	2

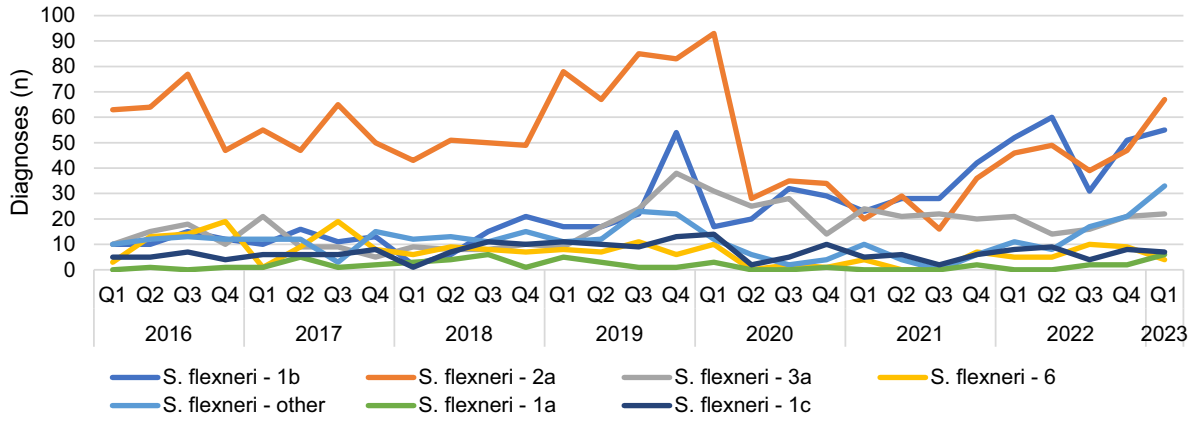

Figure 4. Number of all *S. flexneri* diagnoses by serotype, England, Q1 2016 to Q1 2023 (all persons) (data source: GDW).

exception of those in the adult male non-travellers group, the proportions of cases with *S. flexneri* isolates that had *ermB* and/or *mphA* (travellers, 15.5%; adult female non-travellers, 14.6%; children, 17.8%), *gyrA*, *parC* and/or *qnr* (travellers, 61.7%; adult female non-travellers, 57.5%; children, 56.3%), and $bla_{\text{CTX-M-27}}$ (travellers, 1.9%; adult female non-travellers, 2.4%; children, 0.5%), were similar (Table 4). In comparison, adult male non-travellers were associated with a higher proportion of isolates that had *ermB* and/or *mphA* (adult male non-travellers, 59.5%), *gyrA*, *parC* and/or *qnr* (adult male non-travellers, 79.4%), or $bla_{\text{CTX-M-27}}$ (adult male non-travellers, 15.7%), but a lower proportion of isolates that had $bla_{\text{CTX-M-15}}$ than the other three groups (travellers, 23.8%; adult female non-travellers, 23.0%, adult male non-travellers, 9.8%; children, 33.8%) (Table 4).

Discussion

Overall, we observed a steady increase in notifications of shigellosis from 2016 to 2023 in children and in adults of both sexes not reporting travel abroad. Although we cannot accurately determine the proportion of the cases that had travelled abroad due to the low completion of travel history information, the numbers of cases reporting travel abroad remained constant during this time. This suggests that domestic transmission was increasing both within GBMSM sexual transmission networks and amongst men, women and children in the wider community. It also suggests that sexual transmission may not be the only factor driving the reproductive rate of shigellosis.

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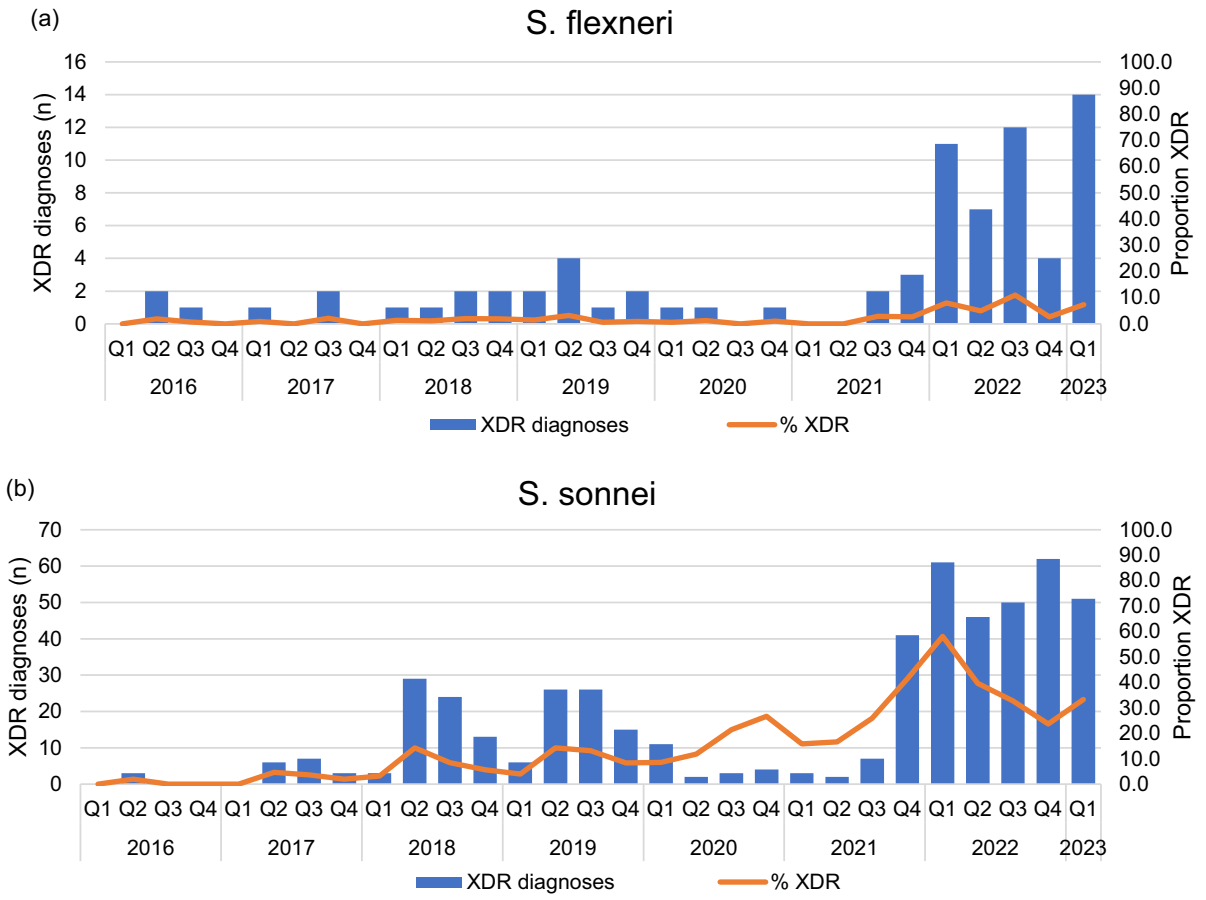

Figure 5. Number and proportion of extensively drug resistant isolates, England, Q1 2016 to Q1 2023 (all persons) (a) *S. flexneri* and (b) *S.sonnei.*

Table 3. Presence of AMR determinants encoding resistance to azithromycin, ciprofloxacin and third-generation cephalosporins among *S. flexneri* isolates, England, Q1 2016 to Q1 2023

AMR determinants	*n* (%)			
	All travellers	Adult female non-travellers	Adult male non-travellers	Children
Azithromycin (ermB and/or mphA)	73 (8.7)	31 (8.7)	906 (45.6)	27 (5.7)
Ciprofloxacin (gyrA, parC and/or qnr)	515 (61.7)	192 (53.8)	906 (45.6)	319 (66.9)
Third generation cephalosporins				
$bla_{CTX\text{-}M\text{-}15}$	63 (7.5)	34 (9.5)	37 (1.9)	77 (16.1)
$bla_{CTX\text{-}M\text{-}27}$	10 (1.2)	1 (0.3)	58 (2.9)	1 (0.2)

Table 4. Presence of AMR determinants encoding resistance to azithromycin, ciprofloxacin and third-generation cephalosporins among *S. sonnei* isolates, England, Q1 2016 to Q1 2023

AMR determinants	*n* (%)			
	All travellers	Adult female non-travellers	Adult male non-travellers	Children
Azithromycin (ermB and/or mphA)	204 (15.5)	102 (14.6)	792 (59.5)	111 (17.8)
Ciprofloxacin (gyrA, parC and/or qnr)	811 (61.7)	403 (57.5)	1 057 (79.4)	351 (56.3)
Third generation cephalosporins				
$bla_{CTX\text{-}M\text{-}15}$	313 (23.8)	161 (23.0)	131 (9.8)	211 (33.8)
$bla_{CTX\text{-}M\text{-}27}$	25 (1.9)	17 (2.4)	206 (15.5)	3 (0.5)

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Despite the perceived increase in domestic transmission, previous studies have shown that shigellosis is travel-related [6, 7, 16, 17]. The COVID-19 pandemic and associated lockdown restrictions highlighted the impact of travel and social distancing restrictions on the transmission of shigellosis, as notifications dramatically declined and then gradually increased as restrictions were relaxed [23]. *S. sonnei* diagnoses were more affected by lockdown restrictions than *S. flexneri*, indicating that imported, travel-associated infection may be a contributing factor to *S. sonnei* notifications and that returning travellers may be a source of subsequent ongoing domestic transmission of *S. sonnei* in England.

Species-specific pathogen characteristics and host attributes that may enhance person to person transmission, and specifically sexual transmission, of *S. flexneri* over *S. sonnei*, were considered. Historically, *S. flexneri* has been associated with more severe clinical outcomes than *S. sonnei* [24], and it is possible that only the most severe cases were captured by UKHSA surveillance systems, due to the difficulties in accessing health care during the pandemic [25]. We also considered the possibility that chronic infection and long-term carriage may be more prevalent following infection with *S. flexneri* than with *S. sonnei* [4]. Another consideration was that *S. flexneri* and *S. sonnei* were associated with different host transmission networks: *S. flexneri* continued to interact and/or travel during the lockdown restrictions, whereas *S. sonnei* did not.

Genomic epidemiology of these species outside of the COVID-19 pandemic in both South Africa and globally suggests that *S. flexneri* may have a different ecology that supports local geographical persistence relative to *S. sonnei*, possibly through greater stability of the *S. flexneri* virulence plasmid [26–30]. Furthermore, we noted that notifications of *S. flexneri* were on the rise prior to lock-down whereas *S. sonnei* notifications were in decline, and this may have facilitated persistence the in community despite the reduced person to person contact [32]. Although AMR is known to drive transmission among GBMSM, it is unlikely that AMR is a factor in this context as the *S. sonnei* and *S. flexneri* GBMSM clades exhibit similar AMR profiles [3, 32]. Moreover, we noted that the *S. sonnei* isolates that persisted during 2020 and 2021 were XDR, although the *S. flexneri* isolates circulating during the pandemic period, were not [13, 14].

We have previously shown that AMR is a potential driver of epidemic and endemic transmission of shigellosis and here we reviewed the AMR profiles of the isolates in the UKHSA archive, specifically resistance to azithromycin, fluroquinolones, and third-generation cephalosporins [3, 11, 20]. As expected, the proportion of isolates of *S. flexneri* and *S. sonnei* that had genes known to confer resistance to azithromycin was higher in the adult males not reporting travel group compared to other population groups. Azithromycin resistance has been driving epidemics of sexually transmissible S. *flexneri* and *S. sonnei* for the last decade, and this study indicates that this continues to be a feature [3, 11, 20]. For *S. sonnei*, we also continue to detect resistance to fluroquinolones in isolates from adult male cases not reporting travel at a higher frequency than those from travel-associated cases but this was not the case for *S. flexneri.* This is despite the evidence of increasing fluroquinolone resistance worldwide, and particularly in southeast Asia [31].

There was a difference in the distribution of the $bla_{\text{CTX-M}}$ variant genes conferring resistance to third-generation cephalosporins across the different population groups, with adult male non-travellers being the only group to exhibit a higher proportion of isolates harbouring $bla_{\text{CTX-M-27}}$ compared to $bla_{\text{CTX-M-15}}$. A high proportion of individuals in the adult male non-travel group identified as GBMSM and during this study period, XDR *Shigella* species associated with sexual transmission among men almost exclusively had $bla_{\text{CTX-M-27}}$ [13, 15, 33]. In contrast, during this study period, the majority of XDR *Shigella* species from travellers had $bla_{\text{CTX-M-15}}$. The similar proportion of cases with $bla_{\text{CTX-M-15}}$ in (i) travellers, (ii) females not reporting travel, and (iii) children, may be confounded by the inclusion of travel-associated cases that have been misclassified due to missing travel histories in the latter two groups. Alternatively, this may be evidence of ongoing domestic transmission of imported strains across the wider community, seeded by returning travellers.

Between 2009 and 2019, we recorded a series of epidemics of azithromycin resistance *S. flexneri* 3a, *S. flexneri* 2a and *S. sonnei* in England [3, 12, 34]. Despite fluctuations in notifications, *S. sonnei* clade 5 carrying resistance to azithromycin and ciprofloxacin, remained the dominant strain until 2019 when we observed a resurgence of *S. flexneri*, partially but not entirely reduced by the COVID-19 pandemic [3, 32]. Post-pandemic, *S. sonnei* rapidly re-emerged having acquired a plasmid encoding $bla_{\text{CTX-M-27}}$ conferring the XDR profile [13]. In the first quarter of 2023, we observed the landscape changed once more, with a sharp rise in *S. flexneri* 2a, a proportion of these carrying $bla_{\text{CTX-M-27}}$, and a corresponding decrease in *S. sonnei* [14]. Although the drivers of the rise and fall of the different clades of *Shigella* are likely to be multifactorial, there is accumulating evidence that AMR has a role, and modelling and seroepidemiological work are needed to study this, and other factors, further.

The pandemic presented a unique opportunity to study the microbiological and epidemiological drivers of persistence of shigellosis within GBMSM sexual networks and the wider population. However, it is unclear whether the sustained transmission of *S. flexneri* during the pandemic was due to a fitness advantage of the strain, differences in access to care or care-seeking behaviour, or clinical manifestation or severity. It could be that travel is a more significant driver of sexual transmission of *S. sonnei* than previously thought. Travel restrictions during the COVID-19 lockdown were the most likely cause of reduced notifications of both *S. flexneri* and *S. sonnei* among children and adult females.

Over the last decade, we have focused on the transmission of MDR and XDR shigellosis within sexual networks. Previous studies have highlighted the global transmission of MDR and XDR *Shigella* species driven by travel, and this study provides further evidence with nearly a quarter of travel-associated *S. sonnei* isolates harboured $bla_{\text{CTX-M-15}}$ [6, 7, 16, 17, 26–30]. Currently, in England, it is not mandatory for isolates of *S. sonnei* to be referred to UKHSA for further characterization by genome sequencing. Given the high incidence of XDR *S. sonnei*, we recommend that enhanced surveillance is carried out on all isolates of this clinically significant pathogen. We also recommend that accurate and more complete case travel histories should be sought to better understand the impact of travel, and the epidemiological exposures associated with travel, on the acquisition of AMR and domestic transmission.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/S0950268824001006.

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References

[1] **Charles H**, et al. (2023) Spotlight on drug-resistant *Shigella*: Raising awareness within general practice. *British Journal General Practice* **73**, 187–188. http://doi.org/10.3399/bjgp23X732537.

[2] **Terry LM**, et al. (2018) Antimicrobial resistance profiles of Shigella dysenteriae isolated from travellers returning to the UK, 2004–2017. *Journal Medical Microbiology* **67**, 1022–1030. http://doi.org/10.1099/jmm.0.000779.

[3] **Bardsley M**, et al. (2020) Persistent transmission of shigellosis in England is associated with a recently emerged multidrug-resistant strain of *Shigella sonnei*. *Journal Clinical Microbiology* **58**, e01692–e01619. http://doi.org/10.1128/JCM.01692-19.

[4] **Allen H**, et al. (2021) Evidence for re-infection and persistent carriage of Shigella species in adult males reporting domestically acquired infection in England. *Clinical Microbiology Infection* **27**, e7, e13–e126. http://doi.org/10.1016/j.cmi.2020.03.

[5] **Bentley CA**, et al. (1996) Phage typing and drug resistance of *Shigella sonnei* isolated in England and Wales. *Epidemiology & Infection* **116**, 295–302. http://doi.org/10.1017/s0950268800052602.

[6] **Dallman TJ**, et al. (2016) Use of whole-genome sequencing for the public health surveillance of Shigella sonnei in England and Wales, 2015. *Journal Clinical Microbiology* **65**, 882–884. http://doi.org/10.1099/jmm.0.000296.

[7] **Chattaway MA**, et al. (2017) Whole-genome sequencing for National Surveillance of *Shigella flexneri*. *Frontiers in Microbiology* **8**, 1700. http://doi.org/10.3389/fmicb.2017.01700.

[8] **McDonnell J**, et al. (2013) Retrospective analysis of whole genome sequencing compared to prospective typing data in further informing the epidemiological investigation of an outbreak of Shigella sonnei in the UK. *Epidemiology & Infection* **141**, 2568–2575. http://doi.org/10.1017/S0950268813000137.

[9] **Maguire HC**, et al. (1998) Shigella outbreak in a school associated with eating canteen food and person to person spread. *Communicable Disease Public Health* **1**, 279–280.

[10] **Jenkins C**, et al. (2023) Foodborne outbreak of extended Spectrum Beta-lactamase producing Shigella sonnei associated with contaminated spring onions in the United Kingdom. *Journal Food Protection* **86**, 100074. http://doi.org/10.1016/j.jfp.2023.100074.

[11] **Baker KS**, et al. (2015) Intercontinental dissemination of azithromycin-resistant shigellosis through sexual transmission: A cross-sectional study. *Lancet Infectious Disease* **15**, 913–921. http://doi.org/10.1016/S1473-3099(15)00002-X.

[12] **Simms I**, et al. (2015) Intensified shigellosis epidemic associated with sexual transmission in men who have sex with men - Shigella flexneri and S. sonnei in England, 2004 to end of February 2015. *EuroSurveillance* **20**, 21097. http://doi.org/10.2807/1560-7917.es2015.20.15.21097.

[13] **Charles H**, et al. (2022) Outbreak of sexually transmitted, extensively drug-resistant Shigella sonnei in the UK, 2021-22: A descriptive epidemiological study. *Lancet Infectious Disease* **22**, 1503–1510. http://doi.org/10.1016/S1473-3099(22)00370-X.

[14] **Thorley K**, 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 Disease* **23**, 732–739. http://doi.org/10.1016/S1473-3099(22)00807-6.

[15] **Mook P**, et al. (2016) ESBL-producing and macrolide-resistant Shigella sonnei infections among men who have sex with men, England, 2015. *Emerging Infectious Disease* **22**, 1948–1952. http://doi.org/10.3201/eid2211.160653.

[16] **Kotloff KL**, et al. 20180 shigellosis. *Lancet* **391**, 801–812. http://doi.org/10.1016/S0140-6736(17)33296-8.

[17] **Sadouki Z**, et al. (2017) Comparison of phenotypic and WGS-derived antimicrobial resistance profiles of Shigella sonnei isolated from cases of diarrhoeal disease in England and Wales, 2015. *Journal Antimicrobial Chemotherapy* **72**, 2496–2502. http://doi.org/10.1093/jac/dkx170.

[18] **Mitchell HD**, et al. (2019) Use of whole-genome sequencing to identify clusters of *Shigella flexneri* associated with sexual transmission in men who have sex with men in England: A validation study using linked behavioural data. *Microbial Genomics* **5**, e000311. http://doi.org/10.1099/mgen.0.000311.

[19] **Chattaway MA**, et al. (2017) Identification of Escherichia coli and Shigella species from whole-genome sequences. *Journal Clinical Microbiology* **55**, 616–623. http://doi.org/10.1128/JCM.01790-16.

[20] **Baker KS**, et al. (2016) Travel- and community-based transmission of multidrug-resistant Shigella sonnei lineage among international orthodox Jewish communities. *Emerging Infectious Diseases* **22**, 1545–1553. http://doi.org/10.3201/eid2209.151953.

[21] **Baker KS**, et al. (2018) Genomic epidemiology of Shigella in the United Kingdom shows transmission of pathogen sublineages and determinants of antimicrobial resistance. *Scientific Reports* **8**, 7389. http://doi.org/10.1038/s41598-018-25764-3.

[22] **Baker KS**, et al. (2018) Horizontal antimicrobial resistance transfer drives epidemics of multiple Shigella species. *Nature Communications* **9**, 1462. http://doi.org/10.1038/s41467-018-03949-8.

[23] **Love NK**, et al. (2023) Understanding the impact of the COVID-19 pandemic response on GI infection surveillance trends in England, January 2020–April 2022. *Epidemiology & Infection* **151**, e147. http://doi.org/10.1017/S095026882300136X.

[24] **Hale TL**, **Keusch GT**. (1996) Chapter 22: Shigella. In: Baron S (ed.), *Medical Microbiology*, 4th Edn. Galveston, TX: University of Texas Medical Branch at Galveston. Available at https://www.ncbi.nlm.nih.gov/books/NBK8038/.

[25] **Goyal DK**, et al. (2021) Restricted access to the NHS during the COVID-19 pandemic: Is it time to move away from the rationed clinical response? *Lancet Regional Health - Europe* **8**, 100201. https://doi.org/10.1016/j.lanepe.2021.100201.

[26] **Holt KE**, et al. (2012) Shigella sonnei genome sequencing and phylogenetic analysis indicate recent global dissemination from Europe. *Nature Genetics* **44**, 1056–1059. http://doi.org/10.1038/ng.2369.

[27] **Connor TR**, et al. (2015) Species-wide whole genome sequencing reveals historical global spread and recent local persistence in Shigella flexneri. *eLife* **4**, e07335. http://doi.org/10.7554/eLife.07335.

[28] **McVicker G and Tang CM** (2016) Deletion of toxin-antitoxin systems in the evolution of Shigella sonnei as a host-adapted pathogen. *Nature Microbiology* **2**, 16204. http://doi.org/10.1038/nmicrobiol.2016.204.

[29] **McVicker G**, et al. (2019) Maintenance of the virulence plasmid in Shigella flexneri is influenced by Lon and two functional partitioning systems. *Molecular Microbiology* **111**, 1355–1366. http://doi.org/10.1111/mmi.14225.

[30] **Stenhouse GE**, et al. (2023) The genomic epidemiology of shigellosis in South Africa. *Nature Communications* **14**, 7715. http://doi.org/10.1038/s41467-023-43345-5.

[31] **Dallman TJ**, et al. (2021) Emergence of novel strains of *Shigella flexneri* associated with sexual transmission in adult men in England, 2019–2020. *Journal Medical Microbiology* **70**, 001437. http://doi.org/10.1099/jmm.0.001437.

[32] **Chung The H and Baker S** (2018) Out of Asia: The independent rise and global spread of fluoroquinolone-resistant Shigella. *Microbial Genomics* **4**, e000171. http://doi.org/10.1099/mgen.0.000171.

[33] **Mason LCE**, et al. (2023) The evolution and international spread of extensively drug resistant Shigella sonnei. *Nature Communications* **14**, 1983. http://doi.org/10.1038/s41467-023-37672-w.

[34] **Borg ML**, et al. (2012) Ongoing outbreak of Shigella flexneri serotype 3a in men who have sex with men in England and Wales, data from 2009–2011. *EuroSurveillance* **17**, 20137.

https://doi.org/10.1017/S0950268824001006 Published online by Cambridge University Press