

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

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Surveillance data suggest an intensification of the shigellosis epidemic associated with sexual transmission in men who have sex with men (MSM) in England with separate introductions into the population. In 2014, sexual transmission between MSM might have accounted for 97%, 89%, and 43% of non-travel associated *Shigella flexneri* 3a and *S. flexneri* 2a, and *S. sonnei* diagnoses. Clinicians should sensitively ascertain sexual history for men with enteric infections to facilitate prompt diagnosis and appropriate management.

Intensification of shigellosis transmission between men who have sex with men

Laboratory diagnoses of *Shigella flexneri* 2a in adult men without a reported travel history have increased markedly from 73 cases in 2013 to 220 cases in 2014 in England, while diagnoses in women have remained low (13 cases for each year). *S. sonnei* diagnoses in men have increased from 189 cases to 267 cases over the same period, again without increases in women. This pattern mirrors an earlier epidemic, from 2009, of *S. flexneri* 3a associated with sexual transmission between men. Here we report preliminary data suggesting an intensification of the shigellosis epidemic associated with sex between men in England continuing into 2015.

Background

There are four species of Gram-negative bacteria of the genus *Shigella* that cause severe bacillary dysentery in humans (*S. flexneri*, *S. sonnei*, *S. boydii*, and *S. dysenteriae*) with over 50 serotypes described. Although many cases in England are associated with travel to high-incidence regions such as the Indian subcontinent, North and East Africa and South America, outbreaks of *S. flexneri* and *S. sonnei* associated with sexual transmission between men who have sex with

men (MSM) have been reported in the United Kingdom (UK), Germany, Spain, Australia, Canada and the United States [1-9].

Shigella reporting in England

Faecal specimens from cases with symptoms of gastrointestinal infection are submitted to local hospital, private and regional laboratories in England for culture of Shiga toxin-producing *Escherichia coli*, *Salmonella*, *Campylobacter* and *Shigella* species. Local hospital laboratories are recommended to submit presumptive strains of *Shigella flexneri* and other *Shigella* spp. to the Public Health England (PHE) national reference laboratory in London, the Gastrointestinal Bacteria Reference Unit (GBRU), for confirmation and typing, using standard biochemistry and serological tests [10]. Neither sexual behaviour nor orientation are routinely collected in this dataset, but the number of cases associated with sexual transmission among men may be approximated by using the GBRU typing data to identify diagnoses for men and women aged 16 to 60 years and excluding cases where recent travel outside the UK was reported. Given an assumption that equal numbers of men and women would be affected if transmission between men were not a risk factor, excess male cases are deemed likely to be in MSM.

We have previously reported a national outbreak and investigation of *S. flexneri* 3a occurring in MSM between 2009 and 2011 [11]. Most of these were white, UK-born MSM, many were HIV-positive, and they reported being part of dense sexual networks involving high numbers of casual and regular partners. This outbreak was associated with (i) low awareness about the risk of enteric infections, (ii) chemsex (sexual activity while under the influence of [typically] stimulant drugs), and (iii) meeting sex partners and locating sex parties through social and sexual networking applications [12,13].

TABLE

Patients aged 16 to 60 years diagnosed with *Shigella* spp. infection with no reported history of travel outside the United Kingdom, by sex, and male to female sex ratios, England, 2004–2014 (n=4,909)

<i>Shigella</i> species	Serotype	Sex and sex ratio	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Total
<i>S. flexneri</i>	1b	Male	8	6	16	18	12	9	8	9	17	7	9	119
		Female	5	2	6	5	7	8	4	5	7	10	4	63
		Ratio	1.6	3.0	2.7	3.6	1.7	1.1	2.0	1.8	2.4	0.7	2.3	1.9
	2a	Male	9	21	27	18	22	23	50	30	42	73	220	535
		Female	8	16	28	21	18	17	14	21	12	13	13	181
		Ratio	1.1	1.3	1.0	0.9	1.2	1.4	3.6	1.4	3.5	5.6	16.9	3.0
	3a	Male	3	6	11	11	18	65	77	83	85	154	118	631
		Female	5	5	5	6	8	8	9	10	10	15	2	83
		Ratio	0.6	1.2	2.2	1.8	2.3	8.1	8.6	8.3	8.5	10.3	59.0	7.6
	6	Male	4	5	10	12	4	6	6	9	11	8	4	79
		Female	1	10	14	9	13	14	15	12	11	7	2	108
		Ratio	4.0	0.5	0.7	1.3	0.3	0.4	0.4	0.8	1.0	1.1	2.0	0.7
	Other	Male	11	6	9	21	15	14	33	31	45	37	36	258
		Female	7	4	13	9	6	15	15	13	11	14	12	119
		Ratio	1.6	1.5	0.7	2.3	2.5	0.9	2.2	2.4	4.1	2.6	3.0	2.2
<i>S. sonnei</i>	NA	Male	76	73	52	85	83	87	147	135	144	189	267	1,338
		Female	48	71	89	119	94	125	133	84	63	95	106	1,027
		Ratio	1.6	1.0	0.6	0.7	0.9	0.7	1.1	1.6	2.3	2.0	2.5	1.3
<i>S. boydii</i>	NA	Male	9	7	17	14	12	5	10	5	5	13	9	106
		Female	4	11	13	16	17	9	20	11	9	12	9	131
		Ratio	2.3	0.6	1.3	0.9	0.7	0.6	0.5	0.5	0.6	1.1	1.0	0.8
<i>S. dysenteriae</i>	NA	Male	2	2	2	3	12	2	7	2	4	1	2	39
		Female	2	6	4	10	4	4	9	7	9	2	5	62
		Ratio	1.0	0.3	0.5	0.3	3.0	0.5	0.8	0.3	0.4	0.5	0.4	0.6
Species unidentified	NA	Male	1	3	3	5	2	0	0	0	0	1	0	15
		Female	2	3	5	3	1	0	1	0	0	0	0	15
		Ratio	0.5	1.0	0.6	1.7	2.0	NA	0.0	NA	NA	NA	NA	1.0
Total	NA	NA	205	257	324	385	348	411	558	467	485	651	818	4,909

NA: not applicable.

The male to female sex ratios ≥ 2.0 are highlighted in bold.

Recent trends in shigellosis in England

We examined recent trends in national *Shigella* spp. diagnoses to explore whether there is evidence for (i) ongoing sexual transmission of *S. flexneri* 3a and (ii) transmission of other *Shigella* serotypes or species among men.

Between 1 January 2004 and 28 February 2015, the total number of *Shigella* spp. diagnoses in England among 16 to 60 year olds was 9,534 and of these, 5,051 (53%) were not known to be associated with travel outside the UK. Among those without recent travel history, diagnoses of *S. flexneri* 3a, *S. flexneri* 2a, and *S. sonnei* accounted for 77% (3,795/4,909) of all cases (Table). During the study period, 262 unique laboratories submitted isolates of *S. flexneri* and 254 laboratories submitted isolates of *S. sonnei*.

Diagnoses of *S. flexneri* 3a in men increased steadily from 2004 to 2013 (from 3 to 154 cases) and fell in 2014 (118 cases), with sharp increases noted in 2009 and 2013; diagnoses in women during this period remained low (Table; Figure 1A). Diagnoses of

S. flexneri 2a in men followed a similar pattern, although increases emerged later, rising from a baseline of nine cases in 2004 with peaks in 2010 (50 cases) and 2014 (220 cases); diagnoses in women during this period remained low (Table; Figure 1A). Diagnoses of *S. sonnei* in men began to exceed those in women (147 compared with 133 cases) in 2010, and have since risen steadily in men (267 cases in 2014) while remaining stable in women (Table; Figure 1B).

Male to female sex ratios also rose substantially during this period, and peaked in 2014 at 59.0:1, 16.9:1 and 2.5:1 for *S. flexneri* 3a, *S. flexneri* 2a, and *S. sonnei* (Table). The age distribution for cases of *S. flexneri* 3a, *S. flexneri* 2a, and *S. sonnei* was similar for men and women: 65% (1,629/2,504) of male cases and 61% (783/1,291) of female cases were in those aged 25 to 44 years. However, geographic distribution differed: 64% (1,574/2,504) of male cases of *S. flexneri* 2a, *S. flexneri* 3a and *S. sonnei* were reported by laboratories in London, Manchester, or Brighton, whereas only 38% (491/1,291) of female cases were from these areas.

In 2014, among those with no recent travel history and assuming all excess male cases were in MSM, we approximate that 116 cases of *S. flexneri* 3a (97% of all excess cases), 207 of *S. flexneri* 2a (89%), and 161 of *S. sonnei* (43%) might have been acquired through sex between MSM.

High levels of transmission of *S. flexneri* 3a, *S. flexneri* 2a, and *S. sonnei* in men have been sustained into 2015 (Figure 2). Monthly reporting data suggest that a switch in the predominant serotype of *S. flexneri* from type 3a to type 2a occurred from March 2014.

Discussion and conclusion

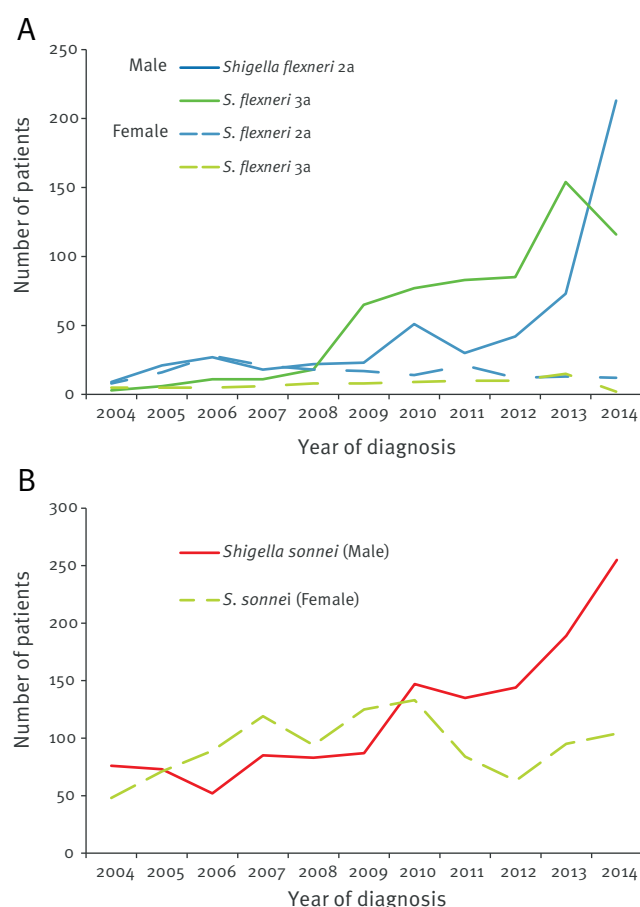
Laboratory data over an 11-year period show ongoing endemic transmission of *S. flexneri* 3a among men since 2009, and emerging epidemics of *S. flexneri* 2a and *S. sonnei* among men since 2011. Diagnoses in women during the same period have remained stable or declined. These data strongly suggest an intensification of the previously reported shigellosis epidemic in England associated with sexual transmission between MSM. The actual numbers are probably underestimated due to individuals in the community not seeking healthcare or not providing diagnostic stool specimens.

Early investigations into the *S. flexneri* 3a outbreak in 2011 failed to identify a point source and found most cases occurred in MSM [11-13]. The present analysis lacks sexual behaviour data, but the concentration of shigellosis diagnoses in urban settings, where we know rates of HIV, gonorrhoea and syphilis in MSM are high, and the increase in specific strains and serotypes found in adult men and not women is consistent with most likely continued sexual transmission of *Shigella* spp. among MSM. Nevertheless, there are other possible explanations for the excess in men. While reporting guidelines have not changed during the study period, some reporting practices may have changed leading to more samples obtained from men than from women being referred by laboratories. However, it seems unlikely that this would fully explain the extent of increases seen. Proactive campaigns have been undertaken by Public Health England (PHE) and the Terrence Higgins Trust (www.tht.org.uk/shigella) to alert general practitioners (GPs) and other health professionals to sexually transmissible enteric infections (STEI) in MSM and to raise awareness among MSM through social media, the gay press, and leaflets in health clinics. These campaigns may have increased healthcare seeking and diagnostic testing among men. However, the campaigns did not start until 2013, after increases in *Shigella* spp. diagnoses were first observed.

The emergence of these STEIs has coincided with increased diagnoses of gonorrhoea, lymphogranuloma venereum, infectious syphilis and a recent cluster of verocytotoxin-producing *Escherichia coli* O117:H7 among MSM, particularly those co-infected with HIV [14-17]. The characteristics of men affected by these overlapping epidemics are very similar and

FIGURE 1

Patients aged 16 to 60 years diagnosed with (A) *Shigella flexneri* serotypes 2a and 3a (n=1,430) and (B) *S. sonnei* (n=2,365), with no reported history of travel outside the United Kingdom, by sex, England, 2004–2014

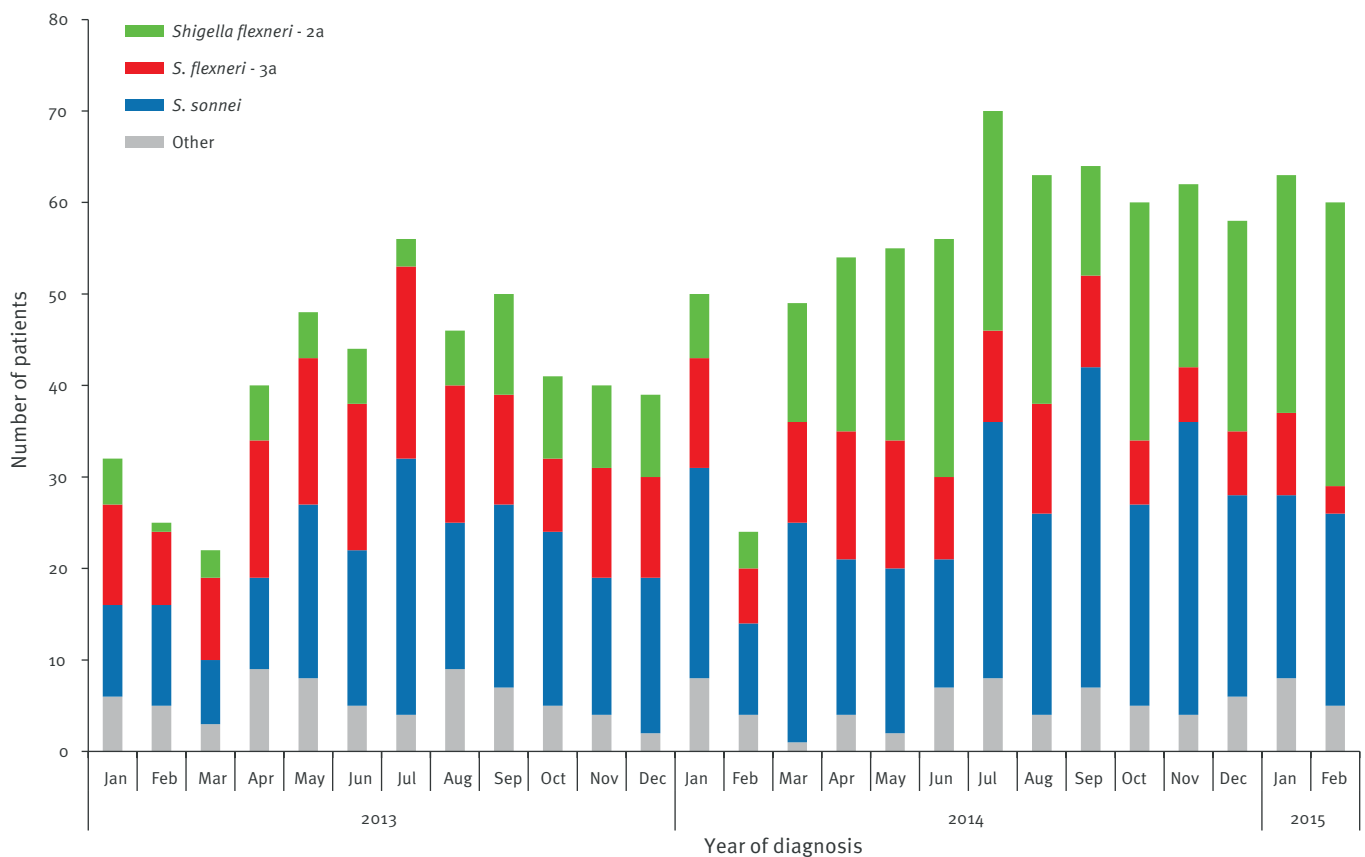


this suggests an intensification of sexual networking among HIV-diagnosed MSM engaging in HIV seroadaptive behaviours, possibly facilitated by geo-spatial apps [14-18]. Indeed, the different timing and heterogeneity in species and types indicate separate introductions of *Shigella* spp. into this population, and is consistent with this hypothesis.

Rapid intercontinental dissemination through sexual transmission in MSM of a *S. flexneri* 3a lineage with an azithromycin-resistance conferring plasmid has recently been demonstrated [19], and outbreaks of other STIs in MSM can spread quickly across Europe [20]. There is evidence that MSM may be more likely to engage in sexual risk behaviours while travelling abroad [21], raising the possibility of shigellosis outbreaks occurring elsewhere in Europe. We are currently reviewing laboratory reports of other enteric pathogens to explore whether sex between men might be an important route of transmission. MSM with symptoms of enteric pathogens may present to a range of healthcare settings including primary care, emergency departments, and specialist sexual health and gastroenterology services. To limit missed diagnostic opportunities, facilitate prompt diagnosis and appropriate

FIGURE 2

Men aged 16 to 60 years diagnosed with *Shigella flexneri* 2a, *S. flexneri* 3a, and *S. sonnei* with no reported history of travel outside the United Kingdom, by month, England, January 2013–February 2015 (n=1,271)



management, including partner notification and appropriate antibiotic stewardship, healthcare professionals need to recognise the potential for STEIs in MSM and sensitively ascertain sexual history. Public health actions for shigellosis cases are described [22], but for MSM they should additionally include advice about when to resume sexual activity, partner notification, preventative advice about risky sexual behaviours, and screening for co-infection with STIs.

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Conflict of interest

None declared.

Authors' contributions

IS, NF, and GH drafted the manuscript. TC undertook data analysis assisted by CJ and TJD. VLG, PM and PDC contributed to data interpretation and revised the manuscript.

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