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Laboratory surveillance of non-travel associated *Shigella* spp. infection in adult males, England: 2004 to 2017

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Laboratory surveillance of non-travel associated *Shigella* spp. infection in adult males, England: 2004 to 2017

Historically, diagnoses of shigellosis in England have been associated with travel to high prevalence countries. A number of *Shigella* species and serotypes are of public health interest, but most diagnoses in England are *S. flexneri* serotype 3a, *S. flexneri* 2a, or *S. sonnei* (Table 1). This report focuses on these organisms and uses methods described previously [1,2].

Key points

- in 2016, the majority of non-travel associated diagnoses of shigellosis were in men aged 16 to 60: *S. flexneri* 3a (93%), *S. flexneri* 2a (87%) and *S. sonnei* (62%)
- non-travel associated diagnoses of shigellosis in men aged 16 to 60 rose 502% (106 to 639) between 2004 and 2015, however fell 47% between 2015 and 2016 (from 765 to 416. Between January and August 2017, 239 non-travel associated diagnoses of shigellosis in men aged 16 to 60 were made
- diagnoses of *S. flexneri* 3a in men aged 16 to 60 peaked in 2013 whereas those of *S. flexneri* 2a and *S. sonnei* were highest in 2015
- shigellosis clusters in men identified by whole genome sequencing, account for the largest burden of cases and are predominantly associated with sexual transmission
- continued detection of activity in chronic adult male clusters (lasting six months or longer), even with the overall decline in cases, demonstrates the persistent nature of *Shigella* spp. transmission among men who have sex with men
- when managing men aged 16 to 60 diagnosed with shigellosis infection, clinicians should assess sexual history and promote appropriate testing, diagnosis, management, and referral to sexual health services where indicated.

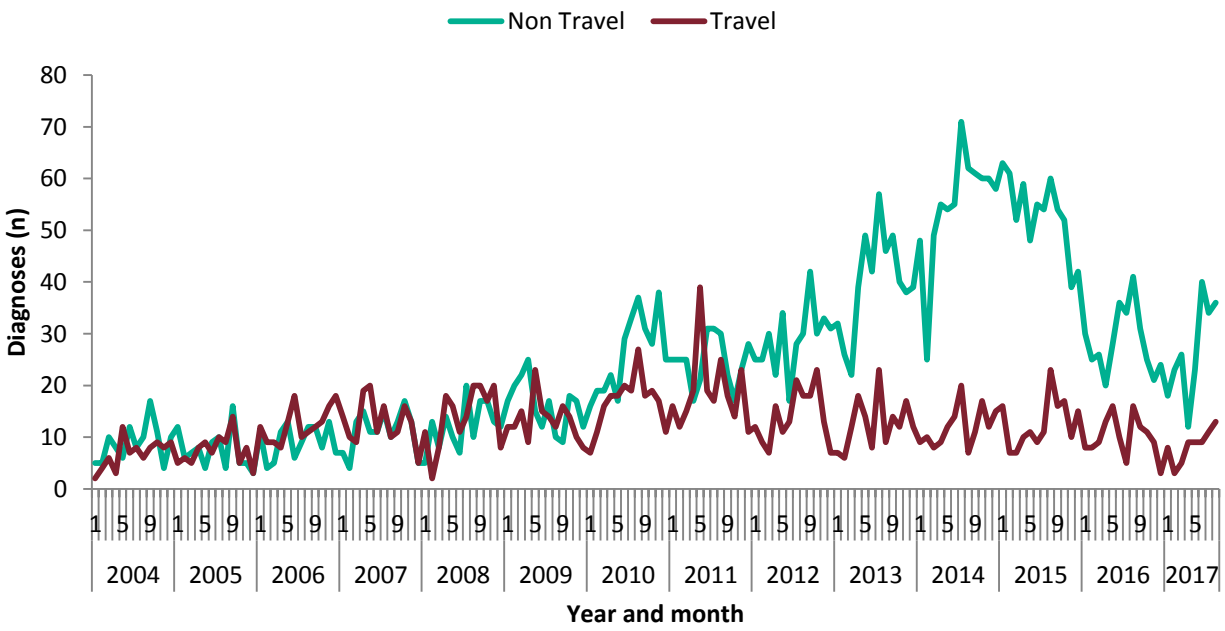
Overall trends

Non-travel associated diagnoses have increased since 2004 and exceeded those associated with travel since 2012. Diagnoses in men increased by 502% between 2004 and 2015, with substantial increases between 2013 and 2015 followed by a 47% fall between 2015 and 2016 (Figure 1a). In 2016, 74% (n=341) of shigellosis diagnoses among men aged 16 to 60 and 45% among women aged 16 to 60 were not known to be travel associated (Figure 1). Many of the diagnoses were associated with sexual transmission in men who have sex with men (MSM) [2]. After an initial increase in the late 2000's diagnoses in women have remained stable since 2004 (Figure 1b).

The ratio of male to female cases reflects these trends, peaking in 2014 at 58:1 for *S. flexneri* 3a and 16:1 for *S. flexneri* 2a, then declining to 15:1 and 7:1 in 2016, respectively. For *S. sonnei*, the male to female ratio peaked in 2015 at 3:1 and fell to 2:1 in 2016 (Figure 2).

Figure 1 Diagnoses of shigellosis in patients aged 16 to 60 by recent travel history, month and year, England: 2004 to 2017 (August)

(i) Men



(ii) Women

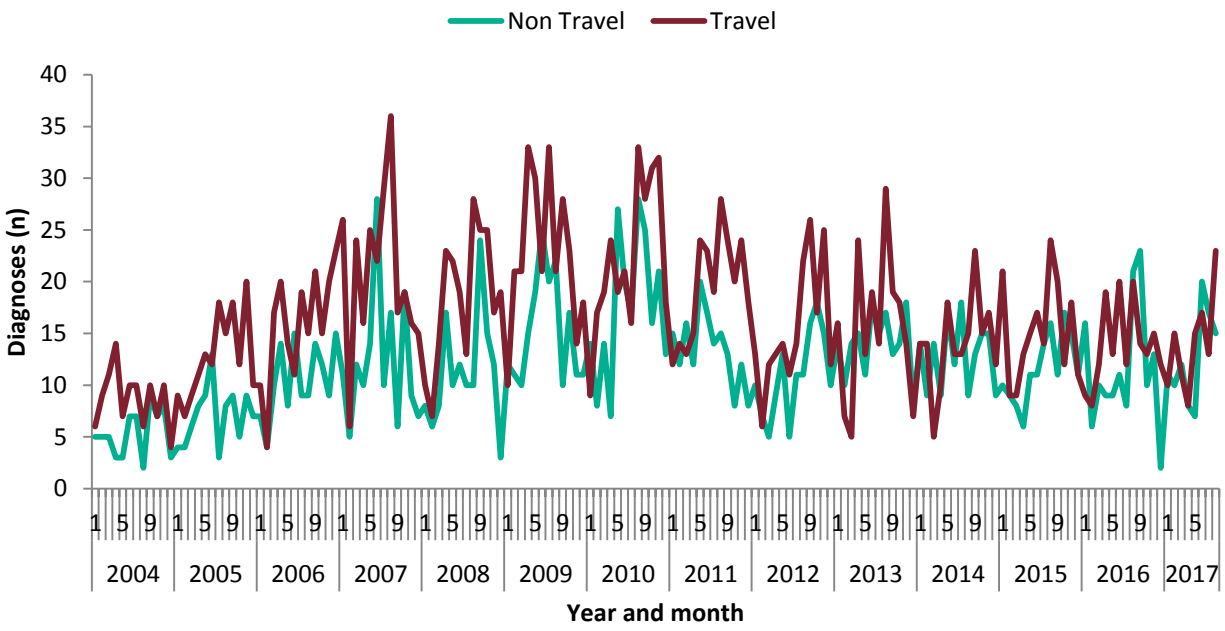


Figure 2 Male to female ratio of *S. flexneri 3*a, *S. flexneri* 2a and *S. sonnei* diagnoses in patients aged 16 to 60, England: 2004 to 2016

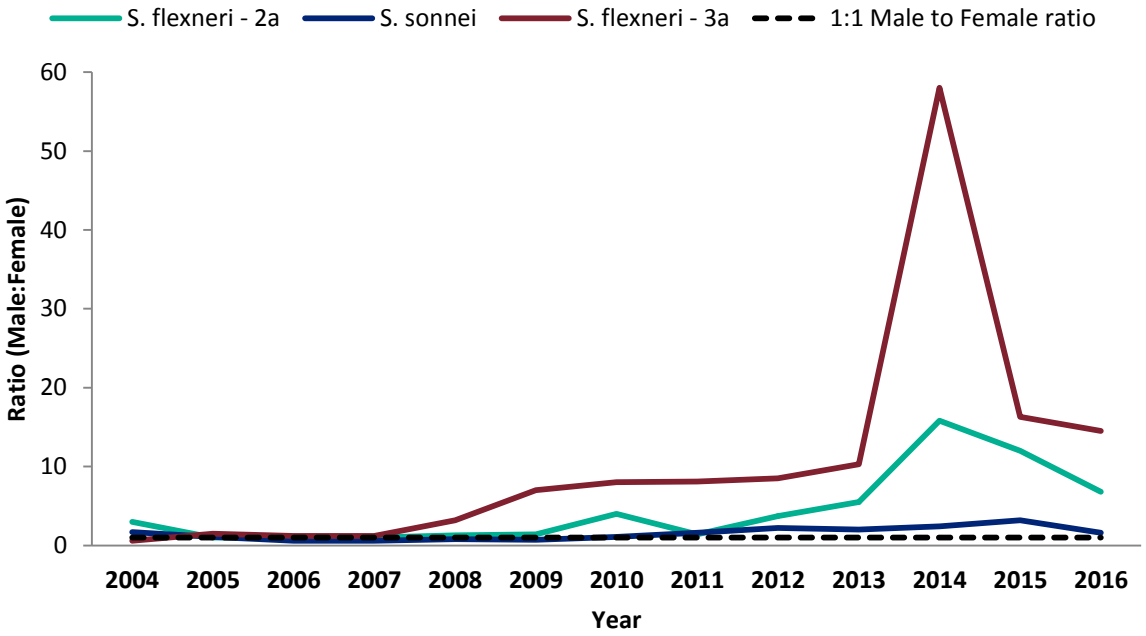
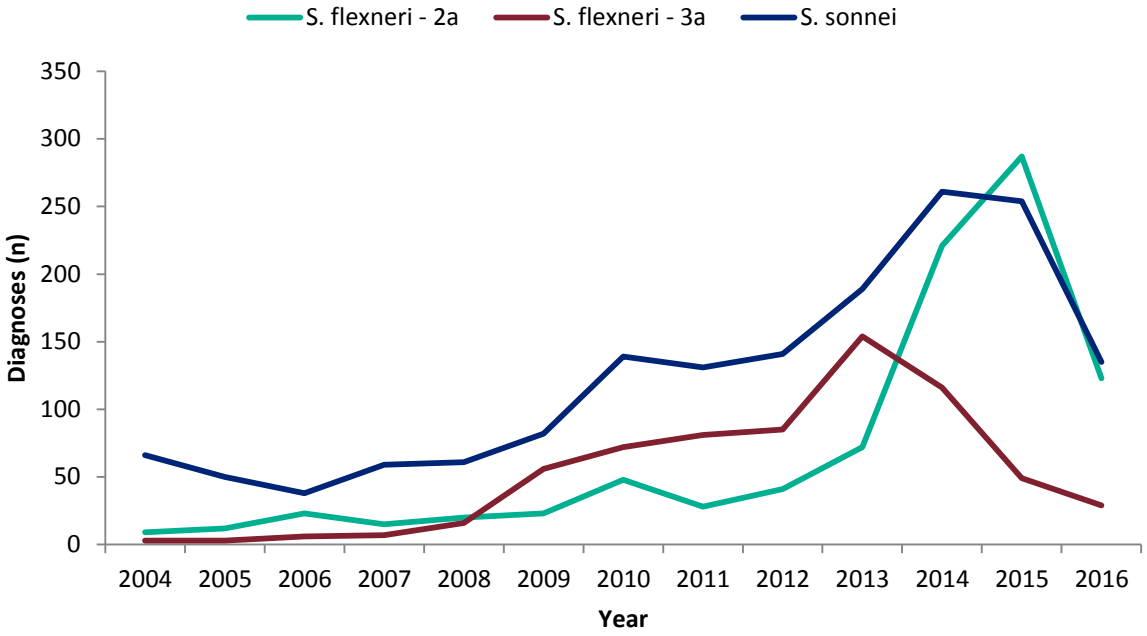


Figure 3 Diagnoses of non-travel related *S. flexneri* 3a, *S. flexneri* 2a and *S. sonnei* in men aged 16-60: 2004 and 2016



Recent trends in non-travel associated *S. flexneri* 3a, 2a and *S. sonnei*

Non-travel associated diagnoses of *S. flexneri* 3a, *S. flexneri* 2a, and *S. sonnei* in men aged 16 to 60 accounted for 84% (287/341) of all shigellosis diagnoses in 2016, an 8% decrease from 92% (590/639) in 2015 (Table 1). Combined diagnoses of non-travel related *S. flexneri* 3a, *S. flexneri* 2a and *S. sonnei* in men increased between 2004 and 2014, but then decreased 51% between 2015 and 2016.

Table 1 Diagnoses of non-travel associated shigellosis in patients aged 16 to 60 by species, serotype, and year, England: 2013 to 2016

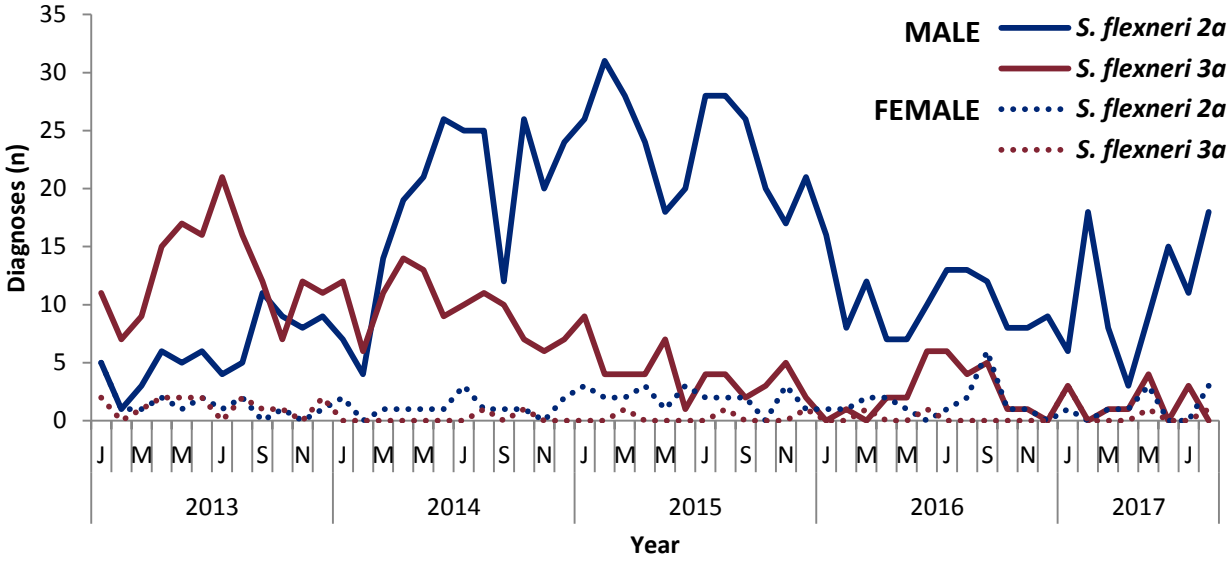
Shigella species and serotype	Gender	2013	2014	2015	2016	Total
***S. flexneri* 1b**	**Male**	8	9	2	7	26
	Female	8	4	4	5	21
	Male excess	0	5	-2	2	5
	ratio	1	2.3	0.5	1.4	5.2
***S. flexneri* 2a**	**Male**	72	221	287	123	703
	Female	13	14	24	18	69
	Male excess	59	207	263	105	634
	ratio	5.5	15.8	12	6.8	40.1
***S. flexneri* 3a**	**Male**	154	116	49	29	348
	Female	15	2	3	2	22
	Male excess	139	114	46	27	326
	ratio	10.3	58	16.3	14.5	99.1
***S. flexneri* 6**	**Male**	8	4	4	3	19
	Female	7	2	2	10	21
	Male excess	1	2	2	-7	-2
	ratio	1.1	2	2	0.3	5.4
***S. flexneri* other**	**Male**	34	36	39	39	148
	Female	15	11	16	10	52
	Male excess	19	25	23	29	96
	ratio	2.3	3.3	2.4	3.9	11.9
S. sonnei	**Male**	189	261	254	135	839
	Female	95	107	79	83	364
	Male excess	94	154	175	52	475
	ratio	2	2.4	3.2	1.6	9.2
S. boydii	**Male**	13	9	4	4	30
	Female	12	9	6	8	35
	Male excess	1	0	-2	-4	-5
	ratio	1.1	1	0.7	0.5	3.3
S. dysenteriae	**Male**	1	2	0	1	4
	Female	2	5	5	2	14
	Male excess	-1	-3	-5	-1	-10
	ratio	0.5	0.4	0	0.5	1.4
Shigella spp.	**Male**	**415**	**598**	**590**	**287**	**1890**
	Female	**123**	**123**	**106**	**103**	**455**
	Male excess	**292**	**475**	**484**	**184**	**1435**
	ratio	**3.4**	**4.9**	**5.6**	**2.8**	**16.7**

Shigella flexneri 2a and 3a

Diagnoses of *S. flexneri* 3a in men fell from 154 diagnoses in 2013 to 29 in 2016 and have been stable since 2015. The predominant serotype of *S. flexneri* reported in men switched from 3a to 2a after February 2014. Diagnoses of *S. flexneri* 2a peaked at 287 in 2015 and subsequently fell to 123 in 2016. Since 2016, diagnoses of *S. flexneri* 2a in men have started to increase but not to the same extent previously seen. Diagnoses in women remained below 20 throughout this period (Table1, Figure 2).

Between January and August 2017 S.*flexneri 2a* and S.*flexneri 3a* have fluctuated with consistently higher numbers of S.*flexneri 3a* diagnoses.

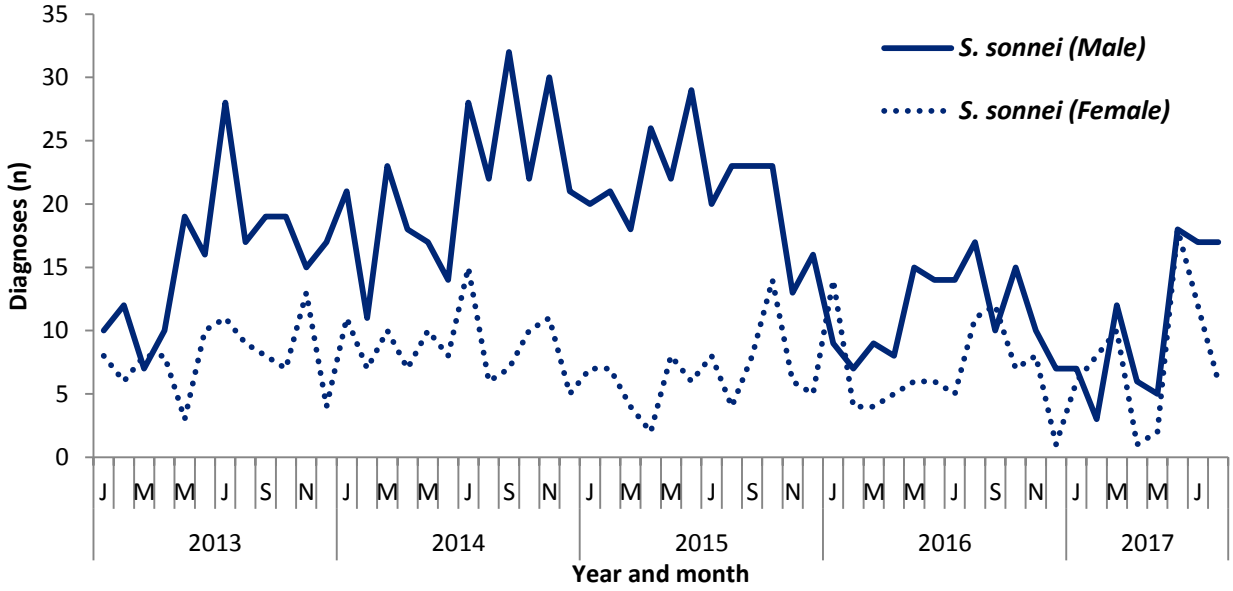
Figure 4 Diagnoses of *S. flexneri* serotypes 3a and 2a in men and women aged 16 to 60 by year and month, England: 2013 to 2017 (August)



Shigella sonnei

In 2010, diagnoses of *S. sonnei* in men (139) exceeded those in women (128) a trend which has continued until 2016 (Figure 5). In 2014, diagnoses in men peaked at 261 while those in women remained stable. Diagnoses in men have declined since October 2015 and in 2017 non-travel diagnoses in men increased from January to June (15 to 23) and then remained stable in July and August (Figure 5).

Figure 5 Diagnoses of *S. sonnei* in men and women aged 16-60 by year and month, England: January 2013 to 2017 (August)



Age and geographic distribution

Between 2004 and 2016, the age distribution for cases of *S. flexneri* 3a, *S. flexneri* 2a, and *S. sonnei* was similar for men and women: 65% (2072/3205) of male cases and 59% (795/1340) of female cases were in those aged 25 to 44 years. However, geographic distribution differed: 53% (1685/3205) of male cases of *S. flexneri* 3a, *S. flexneri* 2a and *S. sonnei* were reported by laboratories in London, whereas only 33% (440/1340) of female cases were reported from London laboratories.

Whole genome sequencing, cluster detection and outbreak investigation

Whole genome sequencing (WGS) provides a level of genetic discrimination beyond serotyping and speciation, which can be used to identify cases associated with probable sexual transmission. WGS is undertaken routinely by PHE on a range of gastrointestinal (GI) infections, including *Shigella* spp. The surveillance team in the national GI Infections Department have implemented an automated system – the SNP (single nucleotide polymorphism) Cluster Tool – to detect and characterise WGS clusters with new cases in the preceding week. A cluster is defined as two or more cases where the WGS of the isolates are within a defined SNP distance from each other. Clusters are then characterised in terms of time (cluster size, duration and growth rate), geography (location of cases, travel history outside the UK) and case demographics (age and sex). These details are used to categorise clusters according to the most likely transmission setting as household, travel associated, community or adult male (probable sexual transmission among MSM).

Adult male clusters are defined as those where >90% of the cases are men aged 16 years or older. Cluster detection thresholds are currently set at the 10-SNP level for *S. flexneri* and *S. sonnei*. Approximately two thirds of *Shigella* spp. isolates detected at hospital laboratories are sent to the Gastrointestinal Bacteria Reference Unit (GBRU, the national reference laboratory for shigella) for further typing and characterisation.

In the 27 month period from the start of the routine WGS service for shigella to date, 1705 cases have been identified that cluster with at least one other isolate. At the 10-SNP level, 283 clusters were detected, of which 168 were *S. sonnei*, 103 were *S. flexneri*, six were *S. dysenteriae* and six were *S. boydii*. Clusters vary in size (median: two cases; range: 2 to 262 cases) and duration (median: three months; range: one day to 40 months). Clusters designated as adult male account for the majority of the case burden (44%, *n* = 751 cases) followed by community clusters (41%, *n* = 704 cases), travel associated clusters (13%, *n* = 225 cases) and household transmission (1.5%, *n* = 25 cases)*****.

***** The low proportion of cases attributed to a household transmission setting is likely an artefact of under ascertainment of secondary cases, which may not be reported or may not have a laboratory test result.

The majority of individual 10-SNP clusters are travel associated (*n* = 141)** followed by adult male clusters (*n* = 72), community clusters (*n* = 62) and household clusters (*n* = 12).

The largest cluster is a cluster of *S. flexneri* 2a in adult males which has persisted for three years and four months to date. As of November 2017, 262 cases have been reported within this cluster; an average of 4.8 cases are detected per week. Transmission in this cluster is likely predominantly due to sexual contact among MSM, most of whom are resident in London (98%)[3].

The persistence of this strain among MSM may be due in part to the presence of a plasmid encoding for multiple drug resistance mechanisms resulting in longer periods of infection, particularly among immunocompromised patients [3]. The plasmid has also been identified in the larger adult male *S. sonnei* clusters. Among non-travel associated *S. sonnei* cases, adult male clusters also account for the highest burden (maximum cluster size: 66 cases) and have the longest duration (39 months). The length of existence of these clusters demonstrates the persisting nature of *Shigella* spp. transmission in MSM populations.

Discussion

This surveillance data shows that three overlapping epidemics of shigellosishave occurred in MSM since 2009 [1,2,4,5]. Routine surveillance of WGS data allows us to identify long term persistence of the same strain that are exclusively or predominantly seen in adult males. This enables in-depth monitoring and characterisation of strains circulating among adult males and provides the opportunity to better understand determinants of incidence and transmission routes. The first epidemic, seen in *S. flexneri* 3a between 2009 and 2013, was replaced by *S. flexneri* 2a and *S. sonnei* in 2014. The emergence of shigellosis epidemics among MSM coincided with increased diagnoses of gonorrhoea, lymphogranuloma venereum, syphilis and sexually transmissible enteric pathogens [6,7].

** Based on travel history reported on the GBRU laboratory request form, where at least 40% of cluster cases report travel to the same destination, or at least two cases report travel to the same destination and there is evidence of similar travel history for the remaining cases from other sources.

This syndemic is linked to low awareness of infection risk, use of chemsex drugs, and involvement in dense sexual networks including high numbers of casual and regular partners [5].

The decline in diagnoses that started in 2016 could have been due to a number of factors. The pool of susceptible individuals within the population may have fallen and transient immunity or asymptomatic carriage could have reduced the number of clinical presentations in people who were re-infected. Insights from the SNP Cluster Tool shows that although the number of diagnoses associated with *Shigella* clusters varied over time, clusters can persist for several years. These observations suggest that awareness of *Shigella* spp. transmission mechanisms needs to be improved. In 2016, PHE conducted a campaign in collaboration with Do It London, Terrence Higgins Trust and LGBT Foundation [4]. Evaluation at three London sexual health clinics found that awareness of *Shigella* among MSM in London was low. Only 29% of MSM attending the services had heard of *Shigella*, suggesting it is unlikely that control initiatives aimed at *Shigella* contributed to a reduction in risky sexual behaviour among MSM. The findings also indicated that MSM generally learn about shigella from sexual health services through posters, leaflets or staff, and from friends rather than social media sources.

MSM with shigella infection may present to a range of healthcare settings. A sexual history should be sensitively obtained if shigellosis is diagnosed among men and is not associated with travel to an endemic area. Patients reporting same sex partners are likely to be at risk of other STIs and HIV co-infection, and clinicians should consider referral to sexual health services for appropriate screening, partner notification and prevention advice. In addition to advice about handwashing, personal hygiene, and returning to work [8], patients should be advised about the risk of sexual transmission and to avoid sexual activity for at least one week after symptoms cease

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