What is the overlap between HIV and shigellosis epidemics in England: further evidence of MSM transmission?

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Abstract

Background

Evidence suggests that sexual transmission between men has replaced foreign travel as the predominant mode of *Shigella* transmission in England. However, sexuality and HIV status are not routinely recorded for laboratory-reported *Shigella,* and the role of HIV in the *Shigella* epidemic is not well understood.

Methods

The Modular Open Laboratory Information System (MOLIS) containing all *Shigella* cases reported to Public Health England (PHE) and the PHE HIV and AIDS Reporting System (HARS) holding all adults living with diagnosed HIV in England were matched using a combination of Soundex code, date of birth and gender.

Results

From 2004-2015, 88,664 patients were living with HIV, and 10,269 *Shigella* cases were reported in England; 9% (873/10,269) of *Shigella* cases were diagnosed with HIV of which 93% (815/873) were in men. *Shigella* cases without reported travel history were more likely to be living with HIV than those who had travelled (14% (751/5,427) vs. 3% (134/4,854); $p<0.01$). From 2004-2015, the incidence of *Shigella* in men with HIV rose from 47/100,000 to 226/100,000 ($p<0.01$) peaking in 2014 at 265/100,000, but remained low in women throughout the study period (0-24/100,000). Among *Shigella* cases without travel and with HIV, 91% (657/720) were men who have sex with men (MSM). HIV preceded *Shigella* diagnosis in 86% (610/720), and 65% (237/362) had an undetectable viral load (<50 copies/ml).

Discussion

We observed a sustained increase in the national rate of shigellosis in MSM with HIV, who may experience more serious clinical disease. Sexual history, HIV status, and sexually transmitted infection risk might require sensitive investigation in men presenting with gastroenteritis.

Keywords: *Shigella*, HIV, public health surveillance, epidemiology, male homosexuality, sexual behavior.

Introduction

The sexual transmission of *Shigella* was first described in a population with diagnosed HIV in the United States in the 1970s[1]. Since that time, international case-reports and epidemiological studies have provided further evidence of sexually transmitted *Shigella*, in particular for *Shigella flexneri* 3a, *S. flexneri* 2a, and *S. sonnei*, and this has been predominantly reported among men who have sex with men (MSM)[2-5]. Sexual behaviour is therefore now considered an important risk factor for *Shigella*[6] and, in some instances, this is also linked to travel. For example, an outbreak of *Shigella* among MSM in London in 2006 coincided with a similar outbreak in Berlin, and the epidemiology suggested that both travel and sexual behaviour linked these outbreaks[7].

In England, *Shigella* epidemiology has changed substantially over the past decade. Whereas travel associated cases previously predominated, by 2015, more than half of cases were not travel associated. There has been a large increase in the number of cases reported in men over these years and this is thought due to sexual transmission of *Shigella* between men[7,8]. Outbreak investigations and case reports have indicated that many of these men might be HIV positive[8-11].

There are around 35,000 MSM living with diagnosed HIV in England. New HIV diagnoses among MSM have risen steadily over the past decade, with 3320 diagnosed in 2015[12]. However, sexual identity and HIV status are not routinely recorded for laboratory-reported *Shigella* cases, and the extent to which patients with HIV are affected by *Shigella* is not well understood at a population level.

This study investigated the overlap between *Shigella* and HIV epidemics in England, by linking two public health surveillance datasets (the Modular Open Laboratory Information System (MOLIS) and the HIV and AIDS Reporting System (HARS)). Our aim was to understand the number of individuals diagnosed with both infections, and explore their characteristics and the timing of their infections to inform public health interventions and clinical management.

Methods

Shigella reporting in England

The reporting of *Shigella* cases in England has been described elsewhere and is summarised below[7]. Faecal specimens from cases with symptoms of gastrointestinal infection are submitted to local hospital, private and regional laboratories for culture of potential agents including *Shigella* species[8]. Local hospital laboratories are recommended to submit presumptive strains of *S. flexneri* and other *Shigella* species 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[8]. All results reported by laboratories at PHE are recorded in MOLIS, with regular updates and duplicate records removed. This study included *Shigella* cases reported in England from 2004-2015.

HIV and AIDS reporting in England

The HIV and AIDS reporting system (HARS) was developed by PHE in conjunction with Department of Health and the National Reference Group for HIV, replacing the previously used Survey of Prevalent HIV Infections Diagnosed (SOPHID) surveillance system in 2014 and

incorporating the HIV & AIDS New Diagnoses and Deaths (HANDD) surveillance system[13]. HARS collects comprehensive information covering demographic, service provider, clinic attendance, testing history and diagnosis, treatment, clinical information and death. Information has been used to understand HIV transmission, plan services, monitor the quality of care received by patients and their clinical outcomes[13]. This study included adults (aged >15 years) living with diagnosed HIV in England between 2004 and 2015.

Dataset matching

A patient-level matching protocol was designed and applied to anonymously match records of individuals diagnosed with Shigella between 2004-2015 with records of individuals appearing in the HARS dataset between 2004-2015 using a combination of Soundex code, date of birth and gender. Cases missing any of these variables were excluded from the study. Soundex is a coding system for names based on phonetic spelling that generates an anonymous identifier[14]. The code consists of the first letter of the surname and three digits that represent the first three phonetic sounds in the name.

Statistical analyses

We estimated the proportion of patients diagnosed with *Shigella* in England between 2004 and 2015 who were known to be diagnosed with HIV, and stratified the analysis by reported travel association, age, gender, and *Shigella* strain/serotype. The chi-square test was used to compare differences between men and women in the proportion with diagnosed HIV

The national cohort of people attending for HIV care was used as the denominator to estimate annual rates of Shigellosis among HIV diagnosed persons, and the clinical characteristics and timing of diagnoses were described.

The 2015 mid-year population data for England calculated by year of age by the Office of National Statistics were used to estimate age-adjusted incidence rates and age adjusted incidence rate ratios for men and women.

All analyses were undertaken using STATA statistical software version 13.1.

Results

From 2004-2015, there were 88,664 adults (aged >15 years) living with diagnosed HIV in England. From 2004-2015, 16,244 *Shigella* cases were reported in England of which 10,269 had adequate completion of identifying variables to permit dataset-matching. The 5,975 cases not included in the analysis were similar in their gender profile (54% (3220/5975) were male), but were more likely to have a travel history associated with their Shigella diagnosis (70% (1813/5975).

Overall, 8% (873/10,269) of *Shigella* cases were identified as living with HIV, of whom 93% (715/873) were men, and 15% (815/5,533) of male *Shigella* cases were living with HIV (Table 1). *Shigella* cases without known travel history were more likely than those who had travelled to be diagnosed with HIV (14% (751/5,527) vs. 3% (134/4,854); $p<0.01$).

We focused on non-travel associated *Shigella* cases, and found that among *Shigella* cases not associated with travel in men, the proportion living with diagnosed HIV varied by *Shigella* species and phage-type, from 16% (242/1,488) for *S. sonnei* to 31% (190/616) for *S. flexneri* 3a. Among non-travel associated cases of *Shigella* in men, the proportion with diagnosed HIV was 21% (720/3,481), while in women, this proportion was low (2% ((31/1,946); p<0.01).

Most *Shigella* cases in individuals living with diagnosed HIV were reported to be MSM in the HARS dataset (91% (657/720)). The *Shigella* diagnosis was found to precede HIV diagnosis in 14% (100/720), and 65% (237/362) had an undetectable viral load (where available within 3 months of shigellosis)).

We observed year-on-year increases in *Shigella* incidence in men living with diagnosed HIV, with the rate rising nearly seven-fold from 47 per 100,000 HIV diagnosed population in 2004 to 226/100,000 in 2015 (p<0.01) peaking in 2014 at 265/100,000 (Table 2), and a similar but more pronounced trend among MSM with HIV. *Shigella* incidence in HIV-positive women remained low throughout the study period, and was 6.8/100,000 in 2005 and 19.5/100,000 in 2015. Overall, age-adjusted incidence rates in individuals diagnosed with HIV were estimated to be 4.9 (95% CI 4.5-5.2) per 100,000 in men, and 0.3 (95%CI 0.3-0.4) per 100,000 in women throughout the study period, with an age-adjusted incidence rate ratio between men and women of 14.4 (11.1-19.3).

Discussion

This study provides a unique insight at a national level into the overlap between *Shigella* and HIV epidemics. Over one fifth of men diagnosed with *Shigella* without reported travel were living with diagnosed HIV, and most were MSM. We observed a sharp year-on-year increase in *Shigella* incidence in men and MSM living with HIV. Around 14% of co-diagnosed men were diagnosed with HIV after *Shigella*, a finding that supports the 2008 UK national guidelines for HIV testing which cites *Shigella* diagnosis as an indicator for HIV testing[15].

To date, the role of sexual transmission between men in the *Shigella* epidemic has been largely inferred from gender ratio studies, case series and small epidemiological studies[8, 9,11]. Our study adds to this evidence base and suggests that the national increase in *Shigella* incidence in England might be due, at least in part, to *Shigella* infections in MSM with HIV. The observed increase in *Shigella* incidence in men living with diagnosed HIV is consistent with previously noted increases in high-risk sexual behaviours leading to faecal-oral transmission among networks of HIV-positive MSM[16]. During the period under observation, there were simultaneous large increases in diagnoses of gonorrhoea, lymphogranuloma venereum and other sexually transmitted infections (STI) within the MSM population, particularly those living with diagnosed HIV[17]. Similarities in the characteristics of men affected may indicate sexual networking among HIV-diagnosed MSM engaging in HIV seroadaptive behaviours, possibly facilitated by geo-spatial apps[8]. Three social phenomema, highlighted in the literature, might be important in driving *Shigella* transmission and deserve further research. These are; (1) sex parties and the use of chemsex, which might influence decision-making about risky sexual behaviour[19,20,20] , (2) use of social media apps to meet previously unknown partners, which might facilitate serosorting practices[9], and (3) acceptability of sexual practices leading to faecal-oral contact[7,9].

There are also plausible biological explanations for the overlap between *Shigella* and HIV epidemics, including increased shedding of *Shigella* species, a prolonged infectious period, and increased susceptibility to *Shigella* in people living with HIV[16]. While our data suggest that most MSM with HIV and *Shigella* were not clinically immunosuppressed, HIV might still affect immunological responses to *Shigella*, increasing the severity of clinical disease and duration of infectiousness[21].

We observed a small number of *Shigella* diagnoses in women living with diagnosed HIV. However, the extent to which heterosexual sex, including heterosexual sex between MSM and women, has a role in *Shigella* transmission remains an area for further research.

The key strength of this study is the linking of two national datasets to estimate the proportion of individuals diagnosed with *Shigella* and living with HIV, allowing year on year comparisons to be made. However, patients with mild gastrointestinal symptoms might not seek attention from health services, leading to incomplete *Shigella* case ascertainment and underestimation of *Shigella* incidence. There might also be bias introduced by under-reporting of same sex behaviour in HIV databases, such that *Shigella* incidence in MSM may be under-estimated. The matching protocol used key variables to enable individual-level matching, which might generate false positive and false negative matches, and our study might underestimate the true number of *Shigella* diagnoses in people living with HIV due to cases excluded from the study with incomplete identifying variables, and because an estimated 17% of people living with HIV are unaware of their infection[22]. We also recognise that neither the health consequences of *Shigella* infection nor the antimicrobial susceptibility of *Shigella* isolates are reported here, which might assist in understanding the

impact on health services and the implications for people living with HIV. Nevertheless, overall, our study is likely to have under- rather than overestimated the extent to which HIV and *Shigella* epidemics have overlapped.

This study has important and immediate clinical and public health implications, highlighting the need for clinicians to consider and test for enteric pathogens such as *Shigella* in men presenting with gastrointestinal symptoms, who might not disclose male partners, and for increased awareness about *Shigella* amongst MSM, particularly those living with HIV infection. Sexual history, HIV status, and sexually transmitted infection risk might require sensitive investigation in men presenting with gastrointestinal symptoms and/or *Shigella*.

Key messages

- We used national surveillance datasets for HIV and Shigella to investigate the role of HIV in the recent *Shigella* epidemic in England.
- *Shigella* cases without reported travel history were most likely to be living with HIV (14%)
- Among cases of *Shigella* without travel history and diagnosed with HIV, 91% were reported to be men who have sex with men (MSM).
- In most cases, HIV preceded the *Shigella* diagnosis and for most patients with HIV, the most recent viral load was undetectable.

- These data emphasise the importance of sensitively asking about sexual history, HIV status, and sexually transmitted infections in men presenting with gastrointestinal symptoms and/or *Shigella*.

Author contributions

KM, VD, ZY, GH and NF conceived this article. KM wrote the first draft with further contributions from MH, VD, GH, IS, CJ, PK and NF. KM did the literature review. MH, TC, PK and ZY managed data and undertook data cleaning and linkage. KM undertook the statistical analysis with support from MH, GR, MC, TC, PK and NF . All authors interpreted data, reviewed successive drafts and approved the final version of the article.

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Table 1. *Shigella* diagnoses by HIV status in England between 2004 and 2015, stratified by sex and travel association

All Shigella diagnoses	Male (%)	Female (%)	Total (%)	P value
HIV positive	815 (15)	58 (1)	873 (8)	<0.01
HIV negative/status unknown	4718 (85)	4678 (99)	9396 (92)	
Total	5533 (100)	4736 (100)	10269 (100)	
Non-travel associated Shigella diagnoses				
HIV positive	720 (21)	31 (2)	751 (14)	<0.01
HIV negative/status unknown	2761 (79)	1915 (98)	4676 (86)	
Total	3481 (100)	1946 (100)	5427 (100)	
Travel associated Shigella diagnoses				
HIV positive	95 (5)	27 (1)	134 (3)	<0.01
HIV negative/status unknown	1957 (95)	2763 (99)	4720 (97)	
Total	2052 (100)	2790 (100)	4854 (100)	
Non travel associated Shigella diagnoses				
S.flexneri 2a				
HIV positive	192 (26)	8(4)	200 (21)	<0.01
HIV negative/status unknown	543 (74)	195 (96)	738 (79)	
Total	735 (100)	203 (100)	938 (100)	
S.flexneri 3a				
HIV positive	190 (31)	6 (7)	196 (28)	<0.01
HIV negative/status unknown	426 (69)	80 (93)	506 (72)	
Total	616 (100)	86 (100)	702 (100)	
S.Sonnei				
HIV positive	242 (16)	6 (1)	244 (10)	<0.01
HIV negative/status unknown	1246 (84)	1113 (99)	2359 (90)	
Total	1488 (100)	1119 (100)	2537 (100)	
Other Shigella				
HIV positive	96 (15)	11 (2)	107 (7)	<0.01
HIV negative/status unknown	546 (85)	927 (98)	1473 (93)	
Total	642 (100)	1473 (100)	1580 (100)	
Non travel associated Shigella diagnoses				
Age 16-20				
HIV positive	6 (5)	0 (0)	6 (2)	0.01
HIV negative/status unknown	115 (95)	121 (100)	236 (98)	
Total	121 (100)	121 (100)	242 (100)	
Age 21-40				
HIV positive	399 (19)	21 (2)	420 (13)	<0.01
HIV negative/status unknown	1655 (81)	1161 (98)	2816(87)	
Total	2054 (100)	1182 (100)	3236(100)	
Age 41-60				
HIV positive	311 (24)	15 (2)	326 (20)	<0.01
HIV negative/status unknown	996 (76)	628 (98)	1624 (80)	
Total	1307 (100)	643 (100)	1950 (100)	

Table 2. Shigella diagnoses and rates in HIV positive individuals with no travel association between 2004 and 2015

a) Shigella diagnoses and rates in HIV positive men with no travel association

Year of Shigella Diagnosis	Shigella cases in HIV positive men	Adults seen for HIV care in England	Shigella rate per 100000 HIV diagnosed population	Shigella incidence rate ratio*
2004	12	25,384	47.3	1
2005	12	28,051	42.8	0.90
2006	16	30,951	51.7	1.09
2007	25	33,856	73.8	1.56
2008	26	36,650	70.9	1.50
2009	38	39,391	96.5	2.04
2010	57	41,933	135.9	2.87
2011	61	44,668	136.6	2.89
2012	84	47,436	177.1	3.74
2013	124	49,959	248.2	5.25
2014	140	52,913	264.6	5.59
2015	125	55,391	225.7	4.77

* Shigella incidence in 2004 used as baseline

b) Shigella diagnoses and rates in HIV positive adult MSM with no travel association

Year of Shigella Diagnosis	Shigella cases in HIV positive MSM	MSM seen for HIV care in England	Shigella rate per 100000 HIV diagnosed population	Shigella incidence rate ratio*
2004	10	16741	59.7	1
2005	9	18407	48.9	0.82
2006	14	20219	69.2	1.16
2007	22	22103	99.5	1.67
2008	21	23797	88.2	1.48

2009	35	25540	137.0	2.30
2010	52	27414	189.7	3.18
2011	56	29278	191.3	3.20
2012	79	31321	252.2	4.22
2013	112	33109	338.3	5.67
2014	130	35407	367.2	6.15
2015	117	37215	314.4	5.27

* Shigella incidence in 2004 used as baseline

c) Shigella diagnoses and rates in HIV positive women with no travel association

Year of Shigella Diagnosis	Shigella cases in HIV positive women	Adults seen for HIV care in England	Shigella rate per 100000 HIV diagnosed population	Shigella incidence rate ratio*
2004	0	12,639	0.0	0.00
2005	1	14,779	6.8	1.00
2006	6	16,521	36.3	5.34
2007	3	17,923	16.7	2.46
2008	3	19,516	15.4	2.26
2009	2	20,633	9.7	1.43
2010	2	21,708	9.2	1.35
2011	0	22,854	0.0	0.00
2012	1	23,749	4.2	0.62
2013	6	24,335	24.7	3.63
2014	2	25,326	7.9	1.16
2015	5	25,671	19.5	2.87

* Shigella incidence in 2005 used as baseline