# Prevalence and characteristics of gastrointestinal infections in men who have sex with men diagnosed with rectal chlamydia infection in the UK: an 'unlinked anonymous' cross-sectional study

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**ABSTRACT (word count 212)**

**Introduction**

Gastrointestinal infections (GII) can cause serious ill-health and morbidity. Although primarily transmitted through faecal contamination of food or water, transmission through sexual activity is well-described, especially among men who have sex with men (MSM).

**Methods**

We investigated the prevalence of GIIs among a convenience sample of MSM who were consecutively diagnosed with rectal *Chlamydia trachomatis* (CT) at 12 UK genitourinary medicine clinics during 10 weeks in 2012. Residual rectal swabs were coded, anonymised and tested for *Shigella*, *Campylobacter*, *Salmonella*, shiga toxin-producing *Escherichia coli* (STEC) and enteroaggregative *E. coli* (EAEC) using a real-time PCR. Results were linked to respective coded and anonymised clinical and demographic data. Associations were investigated using Fisher's Exact tests.

**Results**

Of 444 specimens tested, overall GII prevalence was 8.6%[95% CI 6.3%-11.6%]: 1.8% [0.9%-3.6%] tested positive for *Shigella*, 1.8%[0.9%-3.6%] for *Campylobacter* and 5.2%[3.5%-7.7%] for EAEC. No specimens tested positive for *Salmonella* or other diarrhoeagenic *E. coli* pathotypes. Among those with any GII, 14/30 were asymptomatic (2/7 with *Shigella,* 3/6 with *Campylobacter,* and 9/17 with EAEC). *Shigella* prevalence was higher in MSM who were HIV-positive (4.7%[2.1%-10.2%] versus 0.5%[0.1%-3.2%] in HIV-negative MSM; p=0.01).

**Conclusions**

In this small feasibility study, MSM with rectal CT appeared to be at appreciable risk of GII. Asymptomatic carriage may play a role in sexual transmission of GII.

## KEY MESSAGES

- About 9% of men who have sex with men with rectal chlamydia were co-infected with a gastrointestinal infection (GII); 13% if they were HIV-positive
- Among those with GII, 14 of 30 were asymptomatic suggesting asymptomatic carriage may play a role in sexual transmission of GII
- Testing rectal swabs may be a feasible and acceptable method for detecting GIIs

## INTRODUCTION

Gastrointestinal infections (GII) can cause serious ill-health and morbidity, including diarrhoea, dehydration, bacteraemia, Reiter's syndrome and haemolytic uraemic syndrome (HUS). Transmission occurs through the faecal-oral route and is primarily associated with contaminated food or water. Sexual transmission is well-described, especially among men who have sex with men (MSM) among whom it is usually associated with exposure through direct or indirect oro-anal contact.[1-5]

In the last decade there have been remarkable changes in the epidemiology of some GII in England.[4,6,7] Diagnoses of non-travel associated *Shigella flexneri,* usually associated with travel to endemic areas, have risen sharply; non-travel associated cases now out-number travel-associated cases.[6] Control measures have focussed on raising awareness amongst clinicians and patients to reduce spread in those with symptoms. However, these have made little impact on the *Shigella* spp. epidemics.[6] It is unclear whether asymptomatic infection, which is an important characteristic for many sexually transmitted infections (STIs), plays a role in sexual transmission of GII.

The prevalence, incidence and transmission dynamics of GII in MSM is poorly understood because (i) surveillance data reflect the subset with acute infection presenting to clinical services, (ii) sexual exposure is not routinely recorded for GII, and (iii) there is no simple method for routinely screening MSM for GII. We used a convenience sample of MSM diagnosed with rectal *Chlamydia trachomatis* (CT) at selected UK sexual health clinics to investigate whether rectal swabs from routine

STI screens would make suitable specimens for GII testing and to provide crude estimates of GII prevalence in these men. Infection with rectal chlamydia suggests a history of receptive condomless anal intercourse and identifies a group potentially at higher risk of GII from indirect oro-anal contact. As such, MSM with rectal CT are an appropriate population for a feasibility study on GII.

## METHODS

### Study population and study period

We used a convenience sample of MSM from a Lymphogranuloma venereum (LGV) case-finding study.[8] The LGV study included only MSM who had been consecutively diagnosed with rectal CT at 12 clinics in the UK (in Brighton, Glasgow, London and Manchester) between 24th September and 7th December 2012 except those who had taken any antibiotics during the previous 6 weeks.[8] The recruiting clinics serve large MSM populations; they undertake routine testing of MSM for rectal CT (using clinician or self-taken rectal swabs) regardless of symptoms and follow up some cases according to UK guidelines.[9] Specimens were submitted to the PHE Reference Laboratory for CT confirmation and LGV typing.[8] Residual CT-positive specimens were included in the GII study.

### Data collection

Data on symptom presentation in study participants were systematically recorded by clinicians during the consultation and submitted to Public Health England (PHE) through a secure web-portal. The proforma covered CT- or LGV-related symptoms and included a free-text field to record non-specific symptoms (e.g. diarrhoea, loose stools).[8] Patients presenting with symptoms at any attendance associated with a single STI care episode (typically 2-4 weeks duration) were defined as symptomatic. (In the original study only three patients were initially asymptomatic but subsequently symptomatic during the same care episode). Data on HIV status were available for patients in England (97%) from the national electronic STI surveillance system.[8,10]

## Unlinked anonymous testing protocol

As the GII testing protocol was not part of patients' clinical care, to comply with the Data Protection Act, all residual specimens were irreversibly unlinked and anonymised prior to GII testing, a technique originally developed to monitor HIV prevalence.[11] A unique GII study number was assigned to each specimen and associated clinical data and a 'GII study dataset' created. Patient ID numbers in the GII study dataset were irreversibly deleted as were GII study numbers in all source datasets. Clinical data in the GII study dataset were restricted and summarised to prevent deductive disclosure of patients, into the following groups: (1) Region of residence (London/non-London), (2) Symptom status (symptomatic/asymptomatic), (3) HIV status (positive/negative), (4) LGV status (positive/negative). As only one patient presented with symptoms consistent with GII, GII symptoms were grouped with CT and LGV-related symptoms.

## DNA extraction and GII testing

Residual rectal swabs which had been tested for CT/LGV as part of the LGV case-finding study which had been stored at -20ºC were used for GII testing. DNA was extracted using the QIAsymphony DSP DNA mini kit (Qiagen) according to manufacturer's instructions. Specimens were tested for *Shigella* sp., *Campylobacter* sp., *Salmonella* sp., shiga toxin-producing *Escherichia coli* (STEC) and enteroaggregative *E. coli* (EAEC) using a real-time PCR on a Rotorgene (Qiagen). The amplification parameters were 95ºC for 5 minutes, followed by 95ºC for 15 seconds and 60ºC for 60 seconds. The cycle threshold was set at 0.05 for all targets. Details of the primers, probes and gene targets are listed in the Web Table.

## Data analysis

Summary clinical data were linked to the GII PCR test result using the GII study number. We estimated GII prevalence with 95% confidence intervals (CI) and used Fisher's exact tests to compare test results by patient characteristics, for each GII, and for all GII combined.

## Ethical statement

No individual patient consent was required or sought as PHE has authority to handle patient data for public health monitoring and infection control under section 251 of the UK National Health Service Act of 2006 (previously section 60 of the Health and Social Care Act of 2001).

## RESULTS

Of 489 stored rectal specimens, 444 (91%) had DNA successfully extracted for PCR testing. Of these, 38 (8.5%) tested positive for any GII: 8 (1.8%) tested positive for *Shigella* sp., 8 (1.8%) for *Campylobacter* sp. and 23 (5.2%) for EAEC (Table). No specimens tested positive for *Salmonella* sp. or the other diarrhoeagenic *E. coli* pathotypes. One patient was co-infected with *Shigella* sp. and EAEC.

Among those with GII, 30/38 were in London residents (8/8 with *Shigella* sp., 7/8 *Campylobacter* sp. and 16/23 EAEC infections), 14/30 were asymptomatic (2/7 with *Shigella* sp., 3/6 with *Campylobacter* sp. and 9/17 with EAEC infections) and 16/30 were HIV-positive (6/7 with *Shigella* sp., 4/6 with *Campylobacter* sp. and 6/17 with EAEC infections).

GII prevalence was weakly associated with symptom presentation (13.1% in symptomatic versus 6.4% in asymptomatic; p=0.05) and in those who were HIV-positive (12.6% in HIV-positive versus 6.3% in HIV-negative; p=0.05)(Table). The prevalence of *Shigella* sp. was significantly higher in MSM who were HIV-positive (4.7% versus 0.5% in HIV-negative MSM, p=0.01; Table).

## DISCUSSION

To our knowledge, this is the first study to estimate GII prevalence in MSM with rectal CT attending STI clinics, much of which is likely to have been sexually transmitted. We show that 9% of MSM infected with rectal CT were co-infected with a GII; 13% if they were HIV-positive. Although not directly comparable, in a cohort of over 700 people attending UK general practice who developed GII symptoms, *Shigella* sp. was not detected and the detection rate of EAEC was lower, suggesting the burden of GII experienced by some MSM may be appreciable.[12] We have also

demonstrated the feasibility of using rectal swabs for GII testing. Rectal swabs are routinely taken for STI screening in sexual health clinics and might provide a practicable and acceptable method for investigating prevalence, clinical presentation and risk factors of GII in MSM to inform the public health response. Aside from bacterial GII, MSM have historically been at risk of various protozoan and viral GII, including *Giardia* spp., *Entamoeba* spp. and Hepatitis A.[13,14] We are exploring whether our approach can be used to identify a broader range of pathogens. Whether rectal swabs might replace faecal specimens for clinical diagnosis requires further investigation to validate test performance and determine whether swabs would facilitate organism culture for typing and antimicrobial resistance profiling. Even if feasible and acceptable, further research on the clinical and public health benefit is needed before introducing routine testing of asymptomatic MSM for GII in STI clinics.

Use of a convenience sample to estimate GII prevalence introduces obvious limitations to our study. All men in the study had been diagnosed with rectal CT and do not represent MSM attending STI clinics overall, only those with a history of condomless receptive anal intercourse. Testing MSM with specific sexual risk behaviours has likely led to higher GII prevalence. Conversely, repeating DNA extraction from stored swabs for the GII study is likely to have reduced DNA quantity and quality and therefore test sensitivity, leading to under-estimation of GII prevalence. Furthermore, we had no information on specific practices associated with GII acquisition and the small sample size limited statistical power.

Despite these limitations, the study provides important insights into GII epidemiology in MSM. Although numbers were small, 14 of 30 MSM with GII were asymptomatic, suggesting asymptomatic carriage may play a role in infection transmission. Our findings further strengthen the association between *Shigella* sp. transmission and HIV-positive MSM, and suggest that a similar association may exist for *Campylobacter* sp.[5,7] The factors underlying this relationship may be associated with HIV-sero-adaptive behaviours (choosing to have condomless sex with partners according to their perceived HIV status) as has been observed in other STIs epidemics among MSM, and the effect of HIV infection on biological susceptibility and shedding of *Shigella* sp..[15,16]

The clinical and public health response to sexual transmission of *Shigella* spp. and other GII has been inadequate, partly because the role of asymptomatic and persistent infections in maintaining transmission remains unclear. This study contributes to our understanding of GII in MSM and demonstrates the potential value of using rectal swabs to detect GII in studies addressing these questions.

**Table. Gastrointestinal infection (GII) PCR test results on rectal swabs taken from MSM diagnosed with rectal *Chlamydia trachomatis* at selected STI clinics in the UK: Prevalence with 95 confidence intervals (CI) and association with selected patient characteristics (N=444).**

| | *Shigella* sp. | | | | *Campylobacter* sp. | | | | EAEC | | | | Any GII | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Variable**** | **PCR-+ve/ total tested (n/N)** | **Prevalence (%) ± 95% CI** | | **P value *** | **PCR-+ve/ total tested (n/N)** | **Prevalence (%) ± 95% CI** | | **P value *** | **PCR-+ve/ total tested (n/N)** | **Prevalence (%) ± 95 CI** | | **P value *** | **PCR-+ve/ total tested (n/N)** | **Prevalence (%) ± 95 CI** | | **P value *** |
| **Total** | 8/444 | 1.8 | (0.9-3.6) | | 8/444 | 1.8 | (0.9-3.6) | | 23/444 | 5.2 | (3.5-7.7) | | 38/444 | 8.6 | (6.3-11.6) | |
| **Region of UK residence** | | | | | | | | | | | | | | | | |
| London | 8/349 | 2.3 | (1.2-4.5) | 0.21 | 7/349 | 2.0 | (1.0-4.2) | 1.00 | 16/349 | 4.6 | (2.9-7.4) | 0.30 | 30/349 | 8.6 | (6.1-12.1) | 1.00 |
| Outside London | 0/95 | 0.0 | (0.0-0.0) | | 1/95 | 1.1 | (0.1-7.3) | | 7/95 | 7.4 | (3.5-14.8) | | 8/95 | 8.4 | (4.2-16.1) | |
| **Presence of symptoms** | | | | | | | | | | | | | | | | |
| Yes | 5/122 | 4.1 | (1.7-9.6) | 0.10 | 3/122 | 2.5 | (0.8-7.5) | 0.67 | 8/122 | 6.6 | (3.3-12.7) | 0.31 | 16/122 | 13.1 | (8.1-20.5) | **0.05** |
| No | 2/220 | 0.9 | (0.2-3.6) | | 3/220 | 1.4 | (0.4-4.2) | | 9/220 | 4.1 | (2.1-7.7) | | 14/220 | 6.4 | (3.8-10.4) | |
| **HIV status** | | | | | | | | | | | | | | | | |
| Positive | 6/127 | 4.7 | (2.1-10.2) | **0.01** | 4/127 | 3.2 | (1.2-8.2) | 0.20 | 6/127 | 4.7 | (2.1-10.2) | 1.00 | 16/127 | 12.6 | (7.8-19.7) | **0.05** |
| Negative | 1/222 | 0.5 | (0.1-3.2) | | 2/222 | 0.9 | (0.2-3.6) | | 11/222 | 5.0 | (2.8-8.8) | | 14/222 | 6.3 | (3.8-10.4) | |
| **LGV status** | | | | | | | | | | | | | | | | |
| Positive | 1/51 | 2.0 | (0.3-13.4) | 0.58 | 1/51 | 2.0 | (0.3-13.4) | 1.00 | 3/51 | 5.9 | (1.8-17.3) | 0.72 | 4/51 | 7.8 | (2.9-19.7) | 1.00 |
| Negative | 5/332 | 1.5 | (0.6-3.6) | | 7/332 | 2.1 | (1.0-4.4) | | 15/332 | 4.5 | (2.7-7.4) | | 27/332 | 8.1 | (5.6-11.6) | |

*Fisher's Exact test.

**Includes specimens with known variable information only.

PCR-+ve = PCR test positive result

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## COMPETING INTERESTS

None.

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