Is there an association between previous infection with *Neisseria gonorrhoeae* and gonococcal AMR? A cross-sectional analysis of national and sentinel surveillance data in England, 2015-2019.

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Key messages (4/4; ≤25 for each)

- Frequent screening for STIs could potentially increase antimicrobial resistance (AMR) in *Neisseria gonorrhoeae* by increasing asymptomatic STI detection and antibiotic usage in the population.
- We investigated the association between number of gonorrhoea diagnoses and reduced antimicrobial susceptibility using national and sentinel surveillance data from sexual health services in England.
- Gonococcal isolates from gay, bisexual and other men who have sex with men (MSM) more frequently treated for gonorrhoea had reduced ceftriaxone and cefixime susceptibility.
- As high-risk MSM are targeted for more frequent STI screening, further studies are needed on the role of intensive screening on AMR.

Abstract

Objectives

Quarterly STI screening is recommended for high-risk gay, bisexual and other men who have sex with men (MSM) in the UK, but frequent antibiotic exposure could potentially increase the risk of antimicrobial resistance (AMR) developing in *Neisseria gonorrhoeae*. We investigated whether repeat diagnosis of gonorrhoea in those attending sexual health services (SHSs) was associated with reduced antimicrobial susceptibility.

Methods

Antimicrobial susceptibility data relating to the most recent gonorrhoea diagnosis for each individual included in the Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP, 2015-2019) were matched to their historical records in the national GUMCAD STI surveillance dataset (2012-2019). The number of gonorrhoea diagnoses in the previous three years was calculated for each SHS attendee. Logistic regression was used to examine associations between the number of diagnoses and reduced susceptibility to ceftriaxone (minimum inhibitory concentration (MIC) >0.03 mg/L), cefixime (MIC >0.06 mg/L) and azithromycin (MIC >0.25 mg/L) at the time of the latest diagnosis.

Results

Of 6,161 individuals included in the analysis, 3,913 (63.5%) were MSM, 1,220 (19.8%) were heterosexual men and 814 (13.2%) were women. Among MSM, 2,476 (63.3%) had one past gonorrhoea diagnosis, 1,295 (33.1%) had 2-4, 140 (3.6%) 5-9 and 2 (0.1%) ≥10. Most women and heterosexual men (91.7%) had one past gonorrhoea diagnosis; none had >4. Reduced ceftriaxone and cefixime susceptibility was more common among MSM with 2-4 gonorrhoea diagnoses (3.8%, 5.8%, respectively) compared to those with one (2.2%, 3.9%, respectively). After adjusting for potential confounding, this association remained (adjusted OR: 1.59, 95% CI: 1.07-2.37, p=0.02; aOR: 1.54, 95% CI: 1.11-2.14, p=0.01). No evidence was found for any other associations.

Conclusions

Among MSM, repeat diagnosis of gonorrhoea may be associated with reduced ceftriaxone and cefixime susceptibility. As these are last-line therapies for gonorrhoea, further research is needed to assess the impact of intensive STI screening on AMR.

Introduction

Gonorrhoea is a major public health concern globally and the availability of effective treatment is threatened by the development of resistance to all antimicrobials used to treat the infection [1]. Antimicrobial resistance (AMR) in *Neisseria gonorrhoeae* (NG) has been classified as a high priority for research and surveillance by the World Health Organisation, who estimated that over 87 million new cases of gonorrhoea were reported globally in 2016 [2]. Additionally, reduced susceptibility and resistance to the extended-spectrum cephalosporin (ESC) ceftriaxone, the last existing option for empirical gonorrhoea monotherapy, has been reported worldwide [3].

Gonorrhoea is the second most commonly diagnosed STI in England (70,936 diagnoses in 2019), with almost half of diagnoses arising among gay, bisexual and other men who have sex with men (MSM) [4]. Reduced susceptibility to ceftriaxone, the current first-line therapy in the UK, and azithromycin, a second-line therapy, is more common in isolates from MSM compared to heterosexual men and women [1, 5]. Treatment success is further threatened by the global circulation of multidrug-resistant strains of NG. In 2018, three cases of extensively drug-resistant (XDR) NG, including resistance to both ceftriaxone (minimum inhibitory concentration (MIC)) 0.5 mg/L) and azithromycin (MIC >256 mg/L), were detected in England [6] and Australia [7], as well as two cases with both ceftriaxone resistance (MIC 1.0 mg/L) and reduced azithromycin susceptibility (MIC 0.5 mg/L) who had overlapping sexual networks [8]. Three further cases of ceftriaxone resistance were identified in England in 2019 (MICs 0.5 to 1 mg/L), all of which were associated with travel from the Asia Pacific region [1].

Understanding the drivers and determinants of emerging resistance in NG is fundamental to mitigating its impact. It has been hypothesised that intensive STI screening may facilitate increased AMR in NG among MSM in the UK and USA [9, 10]. In the UK, MSM are screened for HIV and STIs more frequently than heterosexual men and women, with recommendations for annual [11] or quarterly screening according to risk [12]. Frequent STI screening increases the likelihood of diagnosing and treating asymptomatic infections, including gonorrhoea, among MSM [5]. Resultantly, intensive STI screening is thought to drive AMR by increasing antimicrobial exposure. Evidence shows that a major determinant for AMR in NG is exposure to broad-spectrum antibiotics, particularly at subtherapeutic doses, for example, if an individual has an undiagnosed NG infection but is receiving treatment for another infection [13, 14]. This may also occur if antimicrobial therapy clears genital infection but not (possibly undiagnosed) extra-genital infection, which then persists and is subject to the selective pressure of antimicrobial exposure. Another hypothesis is that gonococcal AMR is associated with widespread antibiotic consumption at the population-level and that AMR is associated with sustained transmission among densely connected sexual networks, leading to increased selection pressure and greater opportunities for NG to acquire resistance conferring genes from other gonococci or commensal *Neisseria* [15, 16], or via single point mutations [14, 17]. To test the hypothesis that previous antimicrobial exposure is a predictor of resistant infection, we investigated whether associations existed between the number of gonorrhoea diagnoses an individual had in the previous three years, as a proxy for STI treatment, with ceftriaxone, cefixime and/or azithromycin and reduced antimicrobial susceptibility.

Methods

Data were obtained from the Gonococcal Resistance to Antimicrobial Surveillance Programme (GRASP), a national sentinel surveillance programme monitoring AMR in NG in

England and Wales, and the GUMCAD STI surveillance system [18] (the national STI surveillance system in England). Detailed methodologies and protocols for both GRASP and GUMCAD have previously been published [19, 20].

Antimicrobial susceptibility data from the GRASP sentinel surveillance system were matched to data from the GUMCAD STI surveillance system from 2012-2019 to obtain information on history of gonorrhoea diagnoses for individuals resident in England who were recorded as being diagnosed with gonorrhoea in GRASP between 2015-2019. For individuals who were included in GRASP more than once over this time period, antimicrobial susceptibility data from their most recent gonorrhoea diagnosis were used for analyses. The presence of a prior gonorrhoea diagnosis was used as a proxy for previous antibiotic treatment for gonorrhoea, with the assumption that individuals coded with a gonorrhoea diagnosis were treated according to national guidelines [5].

Fisher's exact tests, univariate and multivariable logistic regression models were used to determine associations between the number of gonorrhoea diagnoses an individual had and reduced susceptibility to antibiotics at the time of their most recent diagnosis. Reduced antimicrobial susceptibility was defined as an elevated MIC, as follows: ceftriaxone MIC >0.03 mg/L, cefixime MIC >0.06 mg/L and azithromycin MIC >0.25 mg/L [21]. European Committee on Antimicrobial Susceptibility Testing (EUCAST) resistance breakpoints were not used due to the low number of isolates with ceftriaxone (MIC >0.125 mg/L) or cefixime (>0.125 MIC mg/L) resistance. Results were stratified by gender and sexual orientation (MSM, women and heterosexual men). Gay, bisexual and other women who have sex with women (WSW) were grouped with heterosexual women due to small sample size. Number of gonorrhoea diagnoses (including the diagnosis within GRASP) were categorised as: one diagnosis, indicating the individual had no gonorrhoea diagnoses recorded in GUMCAD in the three years prior to their diagnosis included in GRASP; 2-4 diagnoses; 5-9 diagnoses; ≥10 diagnoses.

Other variables examined were age group, ethnicity, sex abroad in the last three months, total number of sexual partners in the last three months, HIV status, presence of a concurrent STI diagnosis excluding HIV and year of gonorrhoea diagnosis, all of which related to information reported at the most recent diagnosis. Variables were considered potential confounders and included in multivariable analyses if they showed evidence of an association ($p \leq 0.05$) with reduced antimicrobial susceptibility in univariate analyses. All multivariable analyses were adjusted for year of diagnosis to account for secular trends in antimicrobial susceptibility. Those with missing antimicrobial susceptibility data were excluded from analyses.

All statistical analyses were carried out using STATA 15 v.1.0 (StataCorp LP, College Station, Texas, USA).

In its role providing infectious disease surveillance, the UK Health Security Agency (formerly Public Health England) has approval to handle data obtained by the GUMCAD STI surveillance system and GRASP under Regulation 3 of the Health Service (Control of Patient Information) Regulations 2002.

Results

Of the 6,161 individuals included in GRASP between 2015-2019 with available antimicrobial susceptibility data, 3,913 (63.5%) were MSM, 1,220 (19.8%) were heterosexual men and 814 (13.2%) were women (Table 1).

Among 3,913 MSM, most (46.9%) were 24-34 years old (median age: 31, range: 16-75 years) and 73.7% were of White ethnicity. Sex abroad in the last three months was reported by 4.9% of individuals and 23.0% reported having 2-5 sexual partners in the last three months. Twenty-one percent were known to be living with HIV and 22.0% were diagnosed with a concurrent STI (excluding HIV) at the time of their most recent gonorrhoea diagnosis. Most (63.3%) had been diagnosed with gonorrhoea once and had no gonorrhoea diagnoses in the three years prior to the one included in GRASP, while 33.1% had a total of 2-4 diagnoses, 3.6% had 5-9 diagnoses and 0.1% had 10 or more diagnoses. A higher proportion of isolates from those with 2-4 gonorrhoea diagnoses had elevated ceftriaxone (3.8%) and cefixime (5.8%) MICs compared to those with one diagnosis (2.2%, 3.9%, respectively) (Table 2). The proportion of isolates with an elevated azithromycin MIC, however, decreased with the number of diagnoses; one (25.2%), 2-4 (24.6%), 5-9 (17.9%) diagnoses. The median ceftriaxone MIC was 0.015 mg/L (MIC90: 0.03 mg/L, interquartile range (IQR): 0.008-0.015 mg/L), 0.03 mg/L for cefixime (MIC90: 0.06 mg/L, IQR: 0.015-0.03 mg/L) and 0.25 mg/L for azithromycin (MIC90: 0.5 mg/L, IQR: 0.125-0.25 mg/L). Using EUCAST breakpoints, no isolates were resistant to ceftriaxone (MIC>0.125 mg/L), 0.6% of isolates were resistant to cefixime (MIC>0.125 mg/L) and 3.5% (MIC>1.0 mg/L) to azithromycin.

Among 2,034 heterosexual men and women, 1,220 (60.0%) were heterosexual men and 814 (40.0%) were women. Most (35.0%) individuals were aged 25-34 years old, followed by those aged 20-24 years old (29.9%) (median age: 25, range: 13-76 years). Individuals were commonly of White (46.5%) ethnicity, followed by those of Black Caribbean (13.5%) and Mixed ethnicity (10.5%). Sex abroad in the last three months was reported by 8.2%, and 31.2% reported 2-5 sexual partners in the last three months. Few (1.7%) individuals were living with HIV and 31.4% had a concurrent STI diagnosis. The vast majority (91.7%) had been diagnosed with gonorrhoea once and 8.3% had 2-4 diagnoses in the three-year period . The proportion of isolates with reduced susceptibility to ceftriaxone decreased marginally with the number of gonorrhoea diagnoses: one (3.2%), 2-4 (3.0%) diagnoses, as well as for cefixime; one (5.9%), 2-4 (4.2%) diagnoses, and azithromycin; one (12.3%), 2-4 (10.1%) diagnoses (Table 3). The median ceftriaxone MIC was 0.008 mg/L (MIC90: 0.03 mg/L, IQR: 0.008-0.015 mg/L), 0.015 mg/L for cefixime (MIC90: 0.06 mg/L, IQR: 0.015-0.03 mg/L) and 0.125 mg/L for azithromycin (MIC90: 0.5 mg/L, IQR: 0.06-0.25 mg/L). Using EUCAST breakpoints, no isolates were resistant to ceftriaxone (MIC>0.125 mg/L), 2.7% of isolates were resistant to cefixime (MIC>0.125 mg/L) and 3.0% (MIC>1.0 mg/L) to azithromycin.

Table 1: Demographic characteristics of individuals diagnosed with *Neisseria gonorrhoeae* (NG) in the Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP), stratified by gay, bisexual and other men who have sex with men (MSM), heterosexual men and women, England, 2015-2019 (n=6,161). (Created by the authors)

	MSM	%	Heterosexual men	%	Women	%	Unknown	%
Age group (years)								
13-15	3	0.1	2	0.2	13	1.6	0	0.0
16-19	93	2.4	120	9.8	200	24.6	16	7.5
20-24	631	16.1	316	25.9	292	35.9	33	15.4
25-34	1,834	46.9	484	39.7	227	27.9	93	43.5
35-44	891	22.8	178	14.6	54	6.6	43	20.1
≥45	461	11.8	120	9.8	28	3.4	29	13.6
Ethnicity								
White	2,882	73.7	496	40.7	450	55.3	78	36.4
Black Caribbean	105	2.7	193	15.8	81	10.0	19	8.9
Black African	80	2.0	132	10.8	29	3.6	6	2.8
Black Other	34	0.9	36	3.0	21	2.6	3	1.4
Asian (including Chinese)	190	4.9	80	6.6	29	3.6	8	3.7
Other Ethnic Group	140	3.6	40	3.3	21	2.6	4	1.9
Mixed Ethnic Group	241	6.2	123	10.1	89	10.9	14	6.5
Unknown	241	6.2	120	9.8	94	11.5	82	38.3
HIV								
Positive	821	21.0	22	1.8	12	1.5	29	13.6
Negative	2,250	57.5	1,000	82.0	659	81.0	84	39.3
Unknown	842	21.5	198	16.2	143	17.6	101	47.2
Total number of UK sexual partners (previous 3 months)								
0-1	474	12.1	344	28.2	315	38.7	26	12.1
2-5	898	22.9	452	37.0	183	22.5	22	10.3
6+	365	9.3	50	4.1	17	2.1	7	3.3
Unknown	2,176	55.6	374	30.7	299	36.7	159	74.3
Concurrent STI								
Yes	859	22.0	351	28.8	287	35.3	30	14.0
No	3,054	78.0	869	71.2	527	64.7	184	86.0

Total number of sexual partners abroad (previous 3 months)								
Yes	190	4.9	128	10.5	38	4.7	2	0.9
No	1,547	39.5	718	58.9	477	58.6	53	24.8
Unknown	2,176	55.6	374	30.7	299	36.7	159	74.3
Gonorrhoea								
1 diagnosis	2,476	63.3	1,110	91.0	756	92.9	172	80.4
2-4 diagnoses	1,295	33.1	110	9.0	58	7.1	40	18.7
5-9 diagnoses	140	3.6	0	0.0	0	0.0	2	0.9
10-15 diagnoses	2	0.1	0	0.0	0	0.0	0	0.0
Total	**3,913**		**1,220**		**814**		**214**	

MSM

Among MSM, univariate analysis showed evidence of elevated ceftriaxone (OR: 1.58, 95% CI: 1.08-2.32, p=0.02) and cefixime (OR: 1.51, 95% CI: 1.11-2.05, p=0.01) MICs among those with 2-4 gonorrhoea diagnoses compared to those with one diagnosis (Table 2). Conversely, there was weak evidence of an association between reduced odds of an elevated azithromycin MIC with 5-9 gonorrhoea diagnoses (odds ratio (OR: 0.65, 95% confidence interval (CI): 0.41-1.00, p=0.05) compared to those with one diagnosis.

Among isolates from MSM, elevated ceftriaxone MICs were associated with having had sex abroad in the last three months (OR: 2.15, 95% CI: 1.02-4.54, p=0.05), being HIV-negative (OR: 1.81, 95% CI: 1.07-3.07, p=0.03) and later year of gonorrhoea diagnosis (2019 vs. 2015: OR: 2.99, 95% CI: 1.37-6.53, p=0.006). After adjusting for confounders, the association between an increased number of gonorrhoea diagnoses and an elevated ceftriaxone MIC for isolates from MSM remained. There was evidence of increased odds of an elevated ceftriaxone MIC for isolates from MSM with 2-4 gonorrhoea diagnoses compared to those with one (adjusted odds ratio (aOR): 1.59, 95% CI: 1.07-2.37, p=0.02). While no evidence of an association was found between having 5-9 gonorrhoea diagnoses and an elevated ceftriaxone MIC, the trend of reduced antimicrobial susceptibility with an increasing number of diagnoses remained (aOR: 1.85, 95% CI: 0.71-4.82, p=0.21).

For cefixime, recent sex abroad (OR: 2.43, 95% CI: 1.32-4.49, p=0.01), being HIV-negative (OR: 2.00, 95% CI: 1.29-3.09, p=0.002) and later year of gonorrhoea diagnosis (2019 vs. 2015: OR: 2.30, 95% CI: 1.02-5.18, p=0.05) were also associated with elevated MICs for isolates from MSM. After adjusting for confounders, the association between an increased number of gonorrhoea diagnoses and an elevated cefixime MIC for isolates from MSM remained. Among those with 2-4 gonorrhoea diagnoses, there was evidence of an association with elevated cefixime MICs (aOR: 1.54, 95% CI: 1.11-2.14, p=0.01) compared to those with one diagnosis. As was observed for elevated ceftriaxone MICs, there was no evidence of an association between having 5-9 gonorrhoea diagnoses and an elevated cefixime MIC, although a similar trend towards reduced susceptibility with increasing diagnoses was seen (aOR: 1.53, 95% CI: 0.63-3.74, p=0.35).

Elevated azithromycin MICs were less common among those with a concurrent STI (OR: 0.73, 95% CI: 0.61-0.88, p=0.001) and in later years (2019 vs. 2015: OR: 0.47, 95% CI: 0.38-0.58, p<0.001). After adjusting for potential confounding, there was no longer evidence of reduced odds of elevated azithromycin MICs for isolates from MSM with 5-9 gonorrhoea diagnoses compared to those with one (aOR: 0.73, 95% CI: 0.46-1.14, p=0.17). Similarly, no association was found between having 2-4 gonorrhoea diagnoses and elevated azithromycin MICs (aOR: 1.02, 95% CI: 0.87-1.19, p=0.17).

Table 2: Univariate and multivariable results showing the odds and adjusted odds ratios among *Neisseria gonorrhoeae* (NG) isolates from gay, bisexual and other men who have sex with men of elevated ceftriaxone (>0.03 mg/L), cefixime (>0.06 mg/L) and azithromycin (>0.25 mg/L) minimum inhibitory concentrations (MIC) by number of gonorrhoea diagnoses in the previous three years, England, 2015-2019 (n=3,913). (Created by the authors)

	Diagnoses	Elevated MIC	(%)	Total	Odds ratio	Lower 95% CI	Upper 95% CI	*p* value	Adjusted odds ratio	Lower 95% CI	Upper 95% CI	*p* value
Ceftriaxone												
	1	60	2.2	2,476	1.00	-	-	-	1.00*	-	-	-
	2-4	49	3.8	1,295	1.58	1.08	2.32	0.02	1.59	1.07	2.37	0.02
	5-9	5	3.6	140	1.49	0.59	3.78	0.40	1.85	0.71	4.82	0.21
	≥10	0	0.0	2	-	-	-	-	-	-	-	-
Cefixime												
	1	97	3.9	2,476	1.00	-	-	-	1.00*	-	-	-
	2-4	75	5.8	1,295	1.51	1.11	2.05	0.01	1.54	1.11	2.14	0.01
	5-9	6	4.3	140	1.10	0.47	2.55	0.83	1.53	0.63	3.74	0.35
	≥10	0	0.0	2	-	-	-	-	-	-	-	-
Azithromycin												
	1	624	25.2	2,476	1.00	-	-	-	1.00†	-	-	-
	2-4	319	24.6	1,295	0.97	0.83	1.13	0.70	1.02	0.87	1.19	0.83
	5-9	25	17.9	140	0.65	0.41	1.00	0.05	0.73	0.46	1.14	0.17
	≥10	0	0.0	2	-	-	-	-	-	-	-	-

* Adjusted for HIV status, sex abroad in the past three months and year of NG diagnosis
† Adjusted for concurrent STI diagnosis and year of NG diagnosis

Heterosexual men and women

On univariate analyses among heterosexual men and women, there was no evidence of an association between increasing gonorrhoea diagnoses and elevated ceftriaxone (2-4 vs. 1 diagnosis: OR: 0.94, 95% CI: 0.37-2.37, p=0.90), cefixime (2-4 vs. 1 diagnosis: OR: 0.69, 95% CI: 0.31-1.50, p=0.35) or azithromycin (2-4 vs. 1 diagnosis: OR: 0.80, 0.48-1.35, p=0.41) MICs (Table 3), as corroborated by sensitivity analyses with Fisher's exact test (results not shown here).

Table 3: Univariate results showing the odds ratios among *Neisseria gonorrhoeae* (NG) isolates from heterosexual men and all women of elevated ceftriaxone (>0.03 mg/L), cefixime (>0.06 mg/L) and azithromycin (>0.25 mg/L) minimum inhibitory concentrations (MIC) by the number of gonorrhoea diagnoses in the previous three years, England, 2015-2019 (n=2,034). (Created by the authors)

	Diagnoses	Elevated MIC	(%)	Total	Odds ratio	Lower 95% CI	Upper 95% CI	*p* value	Fisher's exact
Ceftriaxone									
	1	59	3.2	1,866	1.00	-	-	-	0.41
	2-4	5	3.0	168	0.94	0.37	2.37	0.90	
Cefixime									
	1	111	5.9	1,866	1.00	-	-	-	0.99
	2-4	7	4.2	168	0.69	0.31	1.50	0.35	
Azithromycin									
	1	229	12.3	1,866	1.00	-	-	-	0.51
	2-4	17	10.1	168	0.80	0.48	1.35	0.41	

Discussion

Our findings provide some evidence to support the hypothesis that among MSM with 2-4 gonorrhoea diagnoses in the past 3 years, a proxy for more frequent treatment for STIs, were more likely to be infected with strains of NG with reduced susceptibility to ceftriaxone and cefixime. The likelihood of elevated ceftriaxone and cefixime MICs were 59% and 54% greater, respectively, for isolates from MSM with 2-4 gonorrhoea diagnoses within the preceding 3 years, compared to those with one diagnosis. Similar trends were observed among MSM with 5-9 gonorrhoea diagnoses, although there were too few individuals in this category to assess whether the observed odds differed statistically.

We found no evidence of an association between the number of gonorrhoea diagnoses among MSM and reduced azithromycin susceptibility, as is consistent with previous studies in England and the US. A cross-sectional study of 4,660 individuals found no evidence of a relationship between recent (≤6 months) treatment for chlamydia, non-gonococcal urethritis or gonorrhoea (a proxy for azithromycin exposure) with azithromycin resistant NG [13]. Similarly, a study of 1,845 individuals diagnosed with gonorrhoea, most of whom were MSM, found no evidence of an association between azithromycin exposure in the previous year and resistance [22]. While further research is needed, decreasing azithromycin susceptibility in these settings might be more attributable to population-wide macrolide use or the importation of resistant strains [15, 23, 24], rather than azithromycin use selecting for resistance within an individual. On the former, azithromycin is a broad-spectrum antibiotic used for the management of several STIs, whereas ceftriaxone and cefixime and are only used for gonorrhoea. Consequently, any association between azithromycin susceptibility and number of gonorrhoea diagnoses may be obscured by increased use, whereas, the impact of cephalosporin use may be more easily observed given its more limited applications.

There was no evidence that, among heterosexual men and women, increased exposure to antimicrobials was associated with reduced antimicrobial susceptibility. However, unlike among MSM none of the heterosexual men and women in our dataset had more than four previous gonorrhoea diagnoses. This is a reflection of gonorrhoea being less common among heterosexual men and women compared to MSM, as well as less frequent STI screening among the former [4]. As antimicrobial susceptibility did not differ with increasing gonorrhoea diagnoses among heterosexual men and women, but did among MSM, these data offer some support to the hypothesis that AMR is more prevalent among populations targeted for intensive STI screening. Increased AMR among MSM compared to heterosexual groups is associated with several factors. Firstly, diagnosis rates of gonorrhoea and other bacterial STIs are higher among MSM than heterosexuals; therefore, this results in increased antimicrobial exposure at sexual health services among MSM. Additionally, there are higher rates of multiple partnerships and high risk sexual behaviour such as chemsex among MSM compared to heterosexuals. The high prevalence of bacterial STIs among concentrated networks of MSM may therefore also have a higher prevalence of AMR [9]. In an analysis of sentinel surveillance data in England and Wales in 2019, 7.4% of 971 MSM diagnosed with gonorrhoea reported ≥6 sexual partners in the three months prior to their diagnosis, compared to 3.0% of 400 heterosexual men and 1.3% of 287 women [1]. Long or repeated periods of infectiousness, in turn, may result in increased exposure to broad-spectrum antibiotics which could facilitate the development of AMR in NG, particularly at subtherapeutic doses [13].

However, number of recent (≤3 months) sexual partners, a measure of sexual connectedness, and recent sex abroad, a measure of possible travel-associated infection, were not associated with reduced antimicrobial susceptibility in any of our adjusted models. The former finding counters the proposition that it is densely connected sexual networks in conjunction with high antibiotic consumption at the population-level that may be driving gonococcal AMR among MSM [15, 16]. The latter suggests that although cases of ceftriaxone resistance in the UK have been associated with heterosexuals and international travel in recent years [1, 6, 8, 25], the acquisition of and importation of ESC resistant infections from abroad has not resulted in widespread reduced antimicrobial susceptibility beyond the level of individual infections.

While this analysis included five-years of antimicrobial susceptibility data with complete episode-level information comprising over 6,000 gonococcal isolates, it is worth noting that the GRASP sentinel surveillance system over-represents MSM, those living in London and those with symptomatic infection when compared to the population attending sexual health clinics nationally [26]. Information on sex abroad is also often incomplete in GRASP, with 58% of individuals lacking these data in 2019 [1]. The inclusion of mostly symptomatic individuals in GRASP is unsurprising as culture is more likely to be successful from symptomatic patients [5]. However, the hypothesis that intensive STI screening might be driving AMR in NG is partly predicated on the assumption that individuals with asymptomatic NG infection, who would otherwise remain undiagnosed, are being detected and treated [9]. The under-representation of individuals with asymptomatic NG infection in GRASP therefore introduces a selection bias and limits our ability to ascertain how the management of those without symptoms might impact antimicrobial susceptibility at the individual-level. Ascertainment bias may also explain the relationship between previous diagnoses and AMR, with reduced antimicrobial susceptibility most likely to be detected among intensively screened populations simply because of increased testing frequency. The lack of information on sex abroad also likely impacted our ability to detect an association between reduced antimicrobial susceptibility and imported NG infections. Additionally, as individuals' data cannot be linked across sexual health clinics in England, previous gonorrhoea diagnoses for some individuals were likely underestimated in our dataset if they attended different services, thereby reducing the power of the analysis. Furthermore, without including information on antibiotic treatment for diseases other than STIs, a wider spectrum of factors including AMR cannot be explored using these data. Finally, antimicrobial susceptibility data were taken from the most recent diagnosis. Previous infections may have shown different susceptibility profiles to those observed at the latest episode, however any effect of this was likely minimal given that the majority (70.0%) of individuals in our dataset only had one reported diagnosis.

We found evidence from sentinel and national surveillance data that reduced ceftriaxone and cefixime susceptibility is associated with repeat diagnosis of gonorrhoea in MSM in England. Although the proportion of gonococcal isolates with reduced susceptibility to these last-line cephalosporins was low, the emergence of NG strains with ESC resistance, particularly ceftriaxone, would significantly endanger our ability to control gonorrhoea given the lack of alternative treatments. Therefore, despite the limitations described above, findings presented here suggest further research is required to explore the potential harms, as well as benefits, of frequent STI screening. Future analyses of the determinants of resistant NG infection should compare populations with and without frequent STI screening programmes to assess if it is the management of asymptomatic and otherwise undiagnosed individuals, and therefore increased antimicrobial exposure at a population level, that is driving AMR.. More broadly, further research including modelling, exploring behavioural, biological mechanisms

and other factors underpinning the genesis of AMR in NG is needed to identify potential areas for intervention [27].

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Contributorship statement

HA and RM carried out the analysis and write up of this project. ZI carried out the susceptibility testing of samples. HM, KS, GH, RP, HF and MJC provided statistical and interpretive guidance and assisted in the write up of the project.

Ethics approval

Ethics approval: All data were collected within statutory approvals granted to UK Health Security Agency (formerly Public Health England) for infectious disease surveillance and control. Information was held securely and in accordance with the Data Protection Act 2018 and Caldicott guidelines.

Competing interest statement

None declared.

References

1. Merrick R, A.H., Ivanov Z, Pitt R, , M.H. Day M, Sinka K, Mohammed H, Fifer H, Livermore D,, and C.M. Hughes G, *Antimicrobial resistance in Neisseria gonorrhoeae in England and Wales. Key findings from the Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP 2019)*. 2020, Public Health England
2. Rowley, J., et al., *Chlamydia, gonorrhoea, trichomoniasis and syphilis: global prevalence and incidence estimates, 2016.* Bull World Health Organ, 2019. **97**(8): p. 548-562P.
3. Unemo, M., et al., *World Health Organization Global Gonococcal Antimicrobial Surveillance Program (WHO GASP): review of new data and evidence to inform international collaborative actions and research efforts.* Sex Health, 2019. **16**(5): p. 412-425.
4. Mitchell H, A.H., Sonubi T, Kuyumdzhieva G, Harb A, Shah A, Glancy M, Checchi M, and F.K. Milbourn H, Mohammed H and contributors, *Sexually transmitted infections and screening for chlamydia in England, 2019.* 2020, Public Health England London
5. Fifer, H., et al., *2018 UK national guideline for the management of infection with Neisseria gonorrhoeae.* Int J STD AIDS, 2020. **31**(1): p. 4-15.
6. Eyre, D.W., et al., *Gonorrhoea treatment failure caused by a Neisseria gonorrhoeae strain with combined ceftriaxone and high-level azithromycin resistance, England, February 2018.* Euro Surveill, 2018. **23**(27).
7. Jennison, A.V., et al., *Genetic relatedness of ceftriaxone-resistant and high-level azithromycin resistant Neisseria gonorrhoeae cases, United Kingdom and Australia, February to April 2018.* Euro Surveill, 2019. **24**(8).
8. Eyre, D.W., et al., *Detection in the United Kingdom of the Neisseria gonorrhoeae FC428 clone, with ceftriaxone resistance and intermediate resistance to azithromycin, October to December 2018.* Euro Surveill, 2019. **24**(10).

9. Kenyon, C.R. and I.S. Schwartz, *Effects of Sexual Network Connectivity and Antimicrobial Drug Use on Antimicrobial Resistance in Neisseria gonorrhoeae.* Emerg Infect Dis, 2018. **24**(7): p. 1195-1203.
10. Kenyon, C.R., I. De Baetselier, and T. Crucitti, *Does gonorrhoea screening intensity play a role in the early selection of antimicrobial resistance in men who have sex with men (MSM)? A comparative study of Belgium and the United Kingdom.* F1000Research, 2018. **7**: p. 569-569.
11. British HIV Association, *Recommendations for Testing for Sexually Transmitted infections in Men who have Sex with Men*. 2014, British HIV Association
12. Clutterbuck D, A.D., Barber T, Emerson C, Field N, Gibson S, Hughes G, and M.M. Jones R, Nori AV, Rayment R, Ann Sullivan A, *2016 United Kingdom national guideline on the sexual health care of men who have sex with men.* International Journal of STD & AIDS, 2018. **0(0)**: p. 1-46.
13. Clifton, S., et al., *Is previous azithromycin treatment associated with azithromycin resistance in Neisseria gonorrhoeae? A cross-sectional study using national surveillance data in England.* Sex Transm Infect, 2018. **94**(6): p. 421-426.
14. Chisholm, S.A., J. Dave, and C.A. Ison, *High-level azithromycin resistance occurs in Neisseria gonorrhoeae as a result of a single point mutation in the 23S rRNA genes.* Antimicrob Agents Chemother, 2010. **54**(9): p. 3812-6.
15. Olesen, S.W., et al., *Azithromycin Susceptibility Among Neisseria gonorrhoeae Isolates and Seasonal Macrolide Use.* J Infect Dis, 2019. **219**(4): p. 619-623.
16. Kenyon, C., S.S. Manoharan-Basil, and C. Van Dijck, *Gonococcal resistance can be viewed productively as part of a syndemic of antimicrobial resistance: an ecological analysis of 30 European countries.* Antimicrobial resistance and infection control, 2020. **9**(1): p. 97-97.
17. Ng, L.K., et al., *Mutation in 23S rRNA associated with macrolide resistance in Neisseria gonorrhoeae.* Antimicrob Agents Chemother, 2002. **46**(9): p. 3020-5.
18. Public Health England. *GUMCAD STI Surveillance System*. 2020; Available from: https://www.gov.uk/guidance/gumcad-sti-surveillance-system.
19. Public Health England. *GRASP protocol*. 2020; Available from: https://www.gov.uk/government/publications/gonococcal-resistance-to-antimicrobials-surveillance-programme-grasp-protocol/gonococcal-resistance-to-antimicrobials-surveillance-programme-grasp-protocol.
20. Public Health England, *GUMCAD STI Surveillance System: Data Specification and Technical Guidance*. 2020.
21. Jacobsson, S., et al., *Associations between antimicrobial susceptibility/resistance of Neisseria gonorrhoeae isolates in European Union/European Economic Area and patients' gender, sexual orientation and anatomical site of infection, 2009-2016.* BMC Infect Dis, 2021. **21**(1): p. 273.
22. Rowlinson E, S.O., Berzkalns A, Thibault C, Kerani R, Golden M, Barbee L, *O09.2 Lack of association between azithromycin-resistant Neisseria gonorrhoeae infection and prior exposure to azithromycin among persons attendig a Sexual Health Clinic.* STI, 2021. **97**: p. A35.
23. Kenyon, C., J. Buyze, and T. Wi, *Antimicrobial Consumption and Susceptibility of Neisseria gonorrhoeae: A Global Ecological Analysis.* Front Med (Lausanne), 2018. **5**: p. 329.
24. Kirkcaldy, R.D., et al., *Antimicrobial Drug Prescription and Neisseria gonorrhoeae Susceptibility, United States, 2005-2013.* Emerg Infect Dis, 2017. **23**(10): p. 1657-1663.
25. Fifer, H., et al., *Failure of Dual Antimicrobial Therapy in Treatment of Gonorrhea.* N Engl J Med, 2016. **374**(25): p. 2504-6.
26. Mohammed, H., et al., *Frequency and correlates of culture-positive infection with Neisseria gonorrhoeae in England: a review of sentinel surveillance data.* Sex Transm Infect, 2015. **91**(4): p. 287-93.

27. Sena, A.C., et al., *Optimising treatments for sexually transmitted infections: surveillance, pharmacokinetics and pharmacodynamics, therapeutic strategies, and molecular resistance prediction.* Lancet Infect Dis, 2020. **20**(8): p. e181-e191.