Public Health England

Protecting and improving the nation's health

GRASP 2013 Report

The Gonococcal Resistance to Antimicrobials Surveillance Programme (England and Wales)

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1. Key Points

- 86.5% of patients were prescribed the recommended dual therapy of ceftriaxone with azithromycin in 2013, similar to 86.8% in 2012
- Among patients not receiving the currently recommended dual therapy, prescribing of ceftriaxone with doxycycline increased from 27.1% to 29.7% between 2012 and 2013
- three isolates with decreased susceptibility to ceftriaxone were observed in 2013, all in heterosexual patients
- there was evidence of slight upwards drift in ceftriaxone minimum inhibitory concentrations (MICs) and emergence of bimodal MIC distributions in heterosexual men and women
- azithromycin resistance increased slightly in 2013, most notably in men who have sex with men (MSM)
- three gonoccocal isolates with high-level azithromycin resistance (MIC ≥256 mg/l) were observed in 2013
- decreased susceptibility to cefixime in MSM decreased from 6.8% in 2012 to 3.5% in 2013 but increased slightly in both heterosexual men and in women
- as in previous years, no spectinomycin resistance was observed in 2013
- high-level tetracycline resistance (TRNG) levels increased significantly from 9.5% in 2012 to 11.2% in 2013, highlighting the potential risk of using doxycycline as an alternative to azithromycin as part of the dual therapy to treat gonorrhoea, particularly in MSM

2. Introduction

The number of new cases of gonorrhoea has increased annually since 2008 in England, with 29,291 cases reported in 2013, representing a 15% increase from 2012.[1] With 106 million new cases estimated to occur globally in 2008,[2] it is clear that gonorrhoea continues to present a significant public health threat, highlighting the need to maintain effective management.

It has long been recognised that gonorrhoea is at risk of becoming an untreatable disease due to the ongoing threat of antimicrobial resistance (AMR). Strategies to address this threat are outlined in national, regional and global action plans,[3-5] all of which emphasise the importance of ongoing, high quality surveillance of AMR, prompt recognition and effective management of potential treatment failures and good communication of emerging problems to allow timely review of empirical treatment guidelines and public health policies.

Since it began in 2000, the Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP) has twice provided data which directly influenced changes in treatment guidelines in England and Wales.[6] GRASP is a national sentinel surveillance programme which collects isolates from consecutive patients attending a network of genitourinary medicine (GUM) clinics across England and Wales. These isolates undergo antimicrobial susceptibility testing in Public Health England's Sexually Transmitted Bacteria Reference Unit (STBRU) and are linked to demographic, clinical and behavioural data from the GUM clinics. The most recent strategy in the UK and in other countries or regions has been to adopt a more aggressive approach to therapy using a dual therapy of ceftriaxone (500mg dose recommended in the UK) and azithromycin (1g dose recommended in the UK). [6] There is a lack of clear evidence that these two agents work synergistically,[7,8] thus the main reason for this approach is to slow the development of resistance. Use of dual therapy should ensure that a strain developing resistance to one component would still be effectively treated by the other agent, preventing treatment failure and onward dissemination of any emerging resistance. Furthermore there is less likelihood of a strain simultaneously acquiring resistance mechanisms to both antimicrobials.

Since the implementation of new guidelines in 2011, GRASP data has provided evidence of increasing compliance in prescribing of the currently recommended dual therapy and shown falling rates of decreased susceptibility to cefixime, particularly in MSM where the burden of this resistance was observed previously. A key objective of GRASP is to remain vigilant to the possibility of emergence of any AMR which could pose a risk to the current first-line treatment. In the current report, susceptibility to the first line antimicrobial agents is examined for emerging trends and to explore the

epidemiology of this clinically relevant AMR. In addition, other potential threats to effective treatment of gonorrhoea are considered.

3. Antimicrobial susceptibility

In 2013, there were 3,737 gonorrhoea diagnoses made in the 25 GUM clinics that take part in GRASP. There were 2,295 samples sent to PHE's STBRU, of which 1,750 were successfully retrieved, tested for antimicrobial susceptibility and matched to clinical data. The characteristics of patients and percentage of gonorrhoea diagnoses from participating GUM clinics included in the GRASP 2013 sample by PHE centre is presented in Table 1 and Figure 1. The overall percentage of isolates exhibiting resistance/decreased susceptibility to specific antimicrobial agents in 2013 is summarised below, alongside annual data from 2009 to 2012 (Table 2). A description of variations in susceptibility seen among different patient groups is presented in Table 3. The overall characteristics of patients included in GRASP 2013 are also given (Table 3).

In 2013:

- three isolates showed decreased susceptibility to ceftriaxone all with a MIC of ≥0.125mg/L
- resistance to azithromycin increased to 1.6% from 0.8% in 2012 and three isolates had high level resistance with MICs ≥256 mg/L
- the prevalence of isolates exhibiting decreased susceptibility to cefixime at the lower MIC cut-off (≥0.125mg/L) was 5.2%; at the higher MIC cut-off (≥0.25mg/L), prevalence decreased to 1.3%
- there was a slight increase in the percentage of isolates resistant to ciprofloxacin to 29.3%; resistance to penicillin also increased to 18.4%
- tetracycline resistance remained high, accounting for 72.9% of isolates
- there were no isolates resistant to spectinomycin in 2013

Table 1 Characteristics of patients in GRASP sample 2013, by gender and male sexual orientation

GUM Clinic Location	Women (%)	Heterosexual Men (%)	MSM** (%)	Total* (%)
London	30.5	38.8	70.7	57.8
Outside London	69.5	61.2	29.3	42.2
Total N (%)*	246 (100)	376 (100)	1069 (100)	1691 (100)
Ethinicity				
White	59.8	48.2	81.3	70.9
Black Caribbean	14.9	19.1	4.0	8.9
Black African	4.4	9.3	2.0	3.9
Black Other	2.4	3.5	0.9	1.7
Asian (including Chinese)	3.2	6.3	4.1	4.5
Other Ethnic group	1.6	2.7	3.6	3.1
Mixed Ethnic group	13.7	10.9	4.0	7.0
Total N (%)*	249 (100)	367 (100)	1066 (100)	1682 (100)
Age Group (years)				
13-19	29.4	11.7	1.5	7.8
20-24	33.7	34.3	15.5	22.4
25-34	26.6	35.3	50.7	43.8
35-44	6.7	10.6	20.6	16.4
>=45	3.6	8.1	11.7	9.7
Total N (%)*	252 (100)	385 (100)	1090 (100)	1727 (100)
Symptoms				
Discharge and/or Dysuria	73.2	87.5	67.8	74.7
No Discharge and/or Dysuria	26.8	12.5	32.2	25.3
Total N (%)*	205 (100)	345 (100)	593 (100)	1143 (100)
Previously Diagnosed With Gonorrhoea				
Yes	12.0	11.8	38.0	25.6
No	88.0	88.2	62.0	74.4
Total N (%)*	274 (100)	397 (100)	742 (100)	1413 (100)
Concurrent STI	**Number tested for STI (% infected with STI)**			
Syphilis	227(0.0)	348(0.0)	645(0.7)	0.3
Chlamydia	88(38.6)	105(29.8)	136(20.9)	26.7
Herpes	129(4.7)	183(0.5)	386(2.1)	2.2
Warts	128 (3.9)	187(5.9)	380(2.1)	3.5
LGV	126(0.0)	182(0.0)	377(1.6)	0.9
Hepatitis B	126(0.0)	182(0.4)	377(0.0)	0.4
Hepatitis C	126(0.8)	182(0.5)	377(0.3)	0.4
New HIV diagnoses	227(0.0)	348(0.0)	646(2.3)	1.2
Site of Infection				
Genital†	95.1	97.3	56.0	75.0
Rectal†	12.2	5.2	56.3	33.6
Throat†	18.4	6.0	49.5	31.6
Total N (%)*	245 (100)	364 (100)	687 (100)	1296 (100)
Multiple Site Infection	23.7	6.6	52.1	33.9
Total N (%)	241 (100)	362 (100)	674 (100)	1277 (100)
HIV Status*				
Negative	99.4	96.8	52.3	771.6)
Positive	0.6	3.2	47.7	28.4)
Total N (%)*	176 (100)	282 (100)	623 (100)	1081 (100)
Total Partners (past 3 months)				
0-1	64.3	36.0	24.8	380(36.1)
2-5	31.4	57.5	58.8	557(52.9)
6-10	1.0	5.3	10.2	72(6.8)
11+	3.3	1.2	6.2	43(4.1)
Total N (%)*	210 (100)	322 (100)	520 (100)	1052 (100)
Sex Abroad				
Yes	5.2	12.7	14.4	127(12.1)
No	94.8	87.3	85.6	925(87.9)
Total N (%)*	210 (100)	322 (100)	520 (100)	1052 (100)

* N is less than the number presented in this report. Only data for which sexual orientation is recorded was included in this table.

** Men who have sex with men

† The percentages are for patients who were infected at this site

Figure 1 Isolates as a percentage of gonorrhoea diagnoses in participating GUM clinics, by patient residence

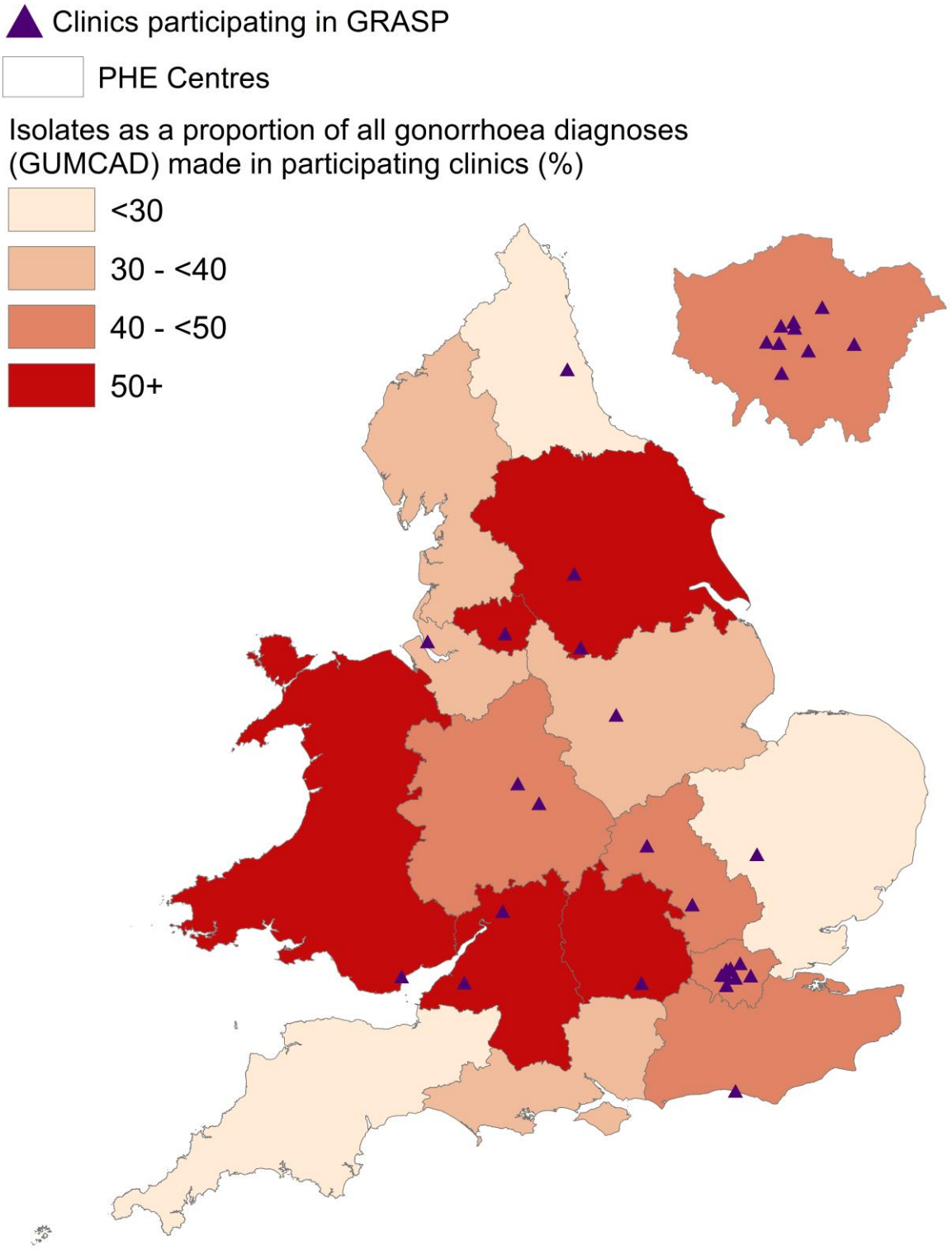


Table 2 Percentage of gonococcal isolates resistant or showing decreased susceptibility to selected antimicrobials. GRASP clinics: 2009 to 2013

Antimicrobial (Resistance/Decreased susceptibility cut-off)	Resistant or decreased susceptible isolates, % (95% Confidence Interval)				
	2009	2010	2011	2012	2013
Ceftriaxone (≥0.125mg/L)	**0.3** (0.1,0.7)	**0.0** (-,-)	**0.0** (-,-)	**0.2** (0.1,0.7)	**0.1** (0.1,0.6)
Azithromycin (≥1mg/L)	**1.2** (0.8,1.8)	**0.5** (0.2,1.2)	**0.5** (0.3-1.0)	**0.8** (0.4,1.7)	**1.6** (1.2,1.8)
Cefixime (≥0.125mg/L)	**10.6** (7.3,15.1)	**17.1** (12.5,22.9)	**10.8** (8.2,14.1)	**5.7** (4.4,7.3)	**5.2** (3.7,7.2)
Cefixime (≥0.25mg/L)	**1.2** (0.5,2.8)	**6.3** (4.5,8.6)	**1.3** (0.8,2.2)	**2.2** (1.6,2.9)	**1.3** (0.7,2.1)
Ciprofloxacin (≥1mg/L)	**35.3** (28.1,43.3)	**35.2** (28.5,42.5)	**34.0** (28.4,40.1)	**25.2** (21.0,29.9)	**29.3** (24.5,34.7)
Spectinomycin	**0.0** (-,-)	**0.0** (-,-)	**0.0** (-,-)	**0.0** (-,-)	**0.0** (-,-)
Penicillin (≥2mg/L)	**21.5** (15.9,28.4)	**19.7** (14.6,26.0)	**11.4** (9.1,14.3)	**14.5** (12.5,16.7)	**18.4** (15.8,21.3)
Tetracycline (≥2mg/L)	**67.2** (59.2,66.7)	**67.5** (59.6,74.5)	**67.6** (58.5,75.5)	**75.0** (66.8,81.8)	**72.9** (64.4,80.0)

Table 3 Percentage of gonococcal isolates resistant or showing decreased susceptibility to selected antimicrobials by patient characteristic. GRASP clinics: 2013

		Azithromycin ≥1mg/L	Cefixime ≥0.125mg/L	Ciprofloxacin ≥1mg/L	Penicillin ≥2mg/L	Tetracycline ≥2mg/L	MDR**
Total N (%)	1750 (100)	28 (1.6)	90 (5.1)	513 (29.3)	321 (18.3)	1360 (77.7)	232 (13.1)
Age group (years)	Total N*	Row %					
13-19	136	0.0	2.2	10.3	5.1	39.0	3.6
20-24	390	1.8	6.4	24.1	14.4	66.7	12.0
25-34	764	2.1	4.7	33.6	20.0	83.2	14.3
35-44	291	1.4	7.9	35.1	26.5	90.4	16.9
>=45	169	0.6	1.8	27.2	16.6	87.6	11.7
Gender/Male Sexual Orientation							
Women	252	1.2	6.3	17.9	15.1	41.3	13.4
Heterosexual Men	385	0.3	8.8	26.5	19.2	59.5	16.6
MSM	1090	2.1	3.5	32.9	18.5	92.5	11.7
Ethinicity							
White	1203	1.8	4.9	30.1	16.7	81.5	11.8
Black Caribbean	151	1.3	4.0	19.2	18.5	59.6	11.3
Black African	69	0.0	5.8	33.3	27.5	75.4	17.4
Black Other	32	0.0	9.4	34.4	31.3	65.6	28.1
Asian (including Chinese)	76	2.6	11.8	43.4	34.2	81.6	31.2
Other Ethnic group	53	0.0	3.8	22.6	17.0	88.7	7.4
Mixed Ethnic group	119	0.8	3.4	22.7	16.8	58.8	13.4
Total Partners (past 3 months)							
0-1	386	0.8	6.5	26.2	18.1	63.2	13.4
2-5	561	1.6	6.6	27.1	21.0	76.3	15.0
6+	116	2.6	6.9	26.7	15.5	85.3	13.6
Sex Abroad							
No	936	1.4	6.5	25.3	18.3	69.8	13.5
Yes	127	1.6	7.1	37.0	27.6	92.9	20.3
Symptoms							
No	289	1.7	4.8	32.9	18.0	74.0	14.4
Yes	865	1.4	6.4	26.1	18.2	72.4	12.6
Previously Diagnosed With Gonorrhoea							
No	954	1.7	6.8	26.7	18.0	69.8	14.5
Yes	339	0.9	2.7	27.7	16.8	80.2	8.8
Concurrent STI							
No	428	2.6	6.1	27.3	20.8	81.8	13.7
Yes	367	0.8	3.0	18.8	11.2	55.9	7.9
HIV Status							
Negative	782	1.4	7.0	25.3	19,1	67.5	14.6
Positive	309	0.6	1.9	33.3	17.8	92.2	9.9
Multiple Site Infection							
No	853	1.2	5.7	25.2	17.5	66.4	12.9
Yes	436	2.1	5.7	30.3	18.6	84.9	13.2
GUM Clinic Location							
Outside London	720	1.4	6.5	24.0	16.4	64.6	13.2
London	993	1.8	4.1	33.4	19.8	87.3	13.2

*N is the number of patients for which information was reported for that particular characteristic

**Multidrug resistance/decreased susceptibility is defined as resistance or reduced susceptibility to any three or more antimicrobials

3.1 Ceftriaxone

Three isolates from two women and one man with decreased susceptibility to ceftriaxone (MIC=0.125mg/l in all three isolates) were detected. All were from patients who self-identified as heterosexual and were from different ethnic backgrounds (Asian, White and other Black ethnicity). The average age was 26 years. Two of the patients were symptomatic and one had previously been infected with gonorrhoea. Two patients reported having two or more sex partners in the previous three months but none reported sexual contact abroad. Isolates from two patients also had decreased susceptibility to cefixime and were resistant to ciprofloxacin, penicillin and tetracycline.

The ceftriaxone MIC distribution appeared to be drifting towards higher MICs, compared with the preceding two years, and the percentage of highly sensitive isolates (MIC≤0.002mg/l) continued to decline (Figure 2). The bi-modal distribution of ceftriaxone MICs observed in MSM in 2011 and 2012 was less marked in 2013 but the distribution of MICs in heterosexual men and women appeared bimodal for the first time (Figure 3).

Figure 2 Percentage of gonococcal isolates by ceftriaxone MIC (mg/l). GRASP clinics: 2007 to 2013

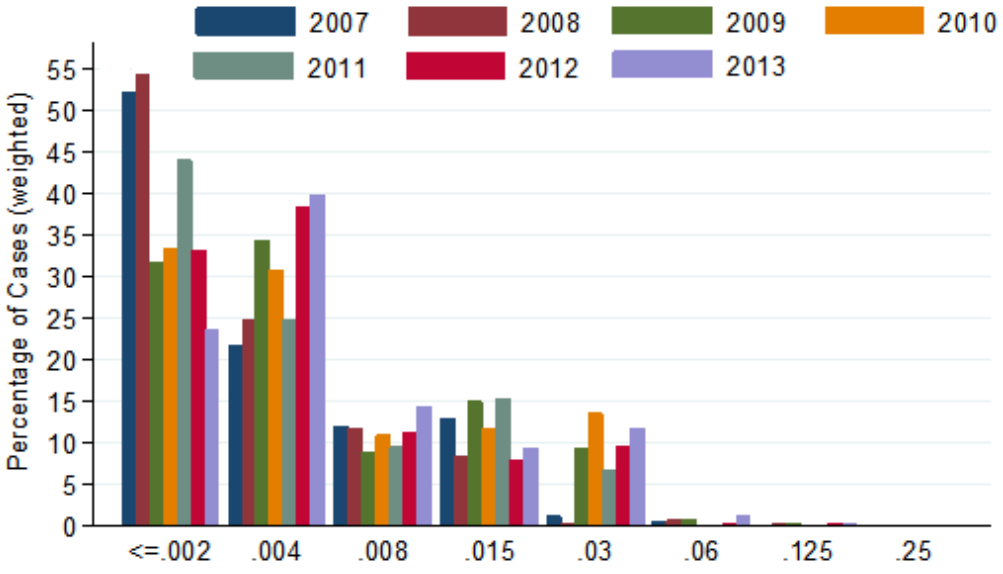
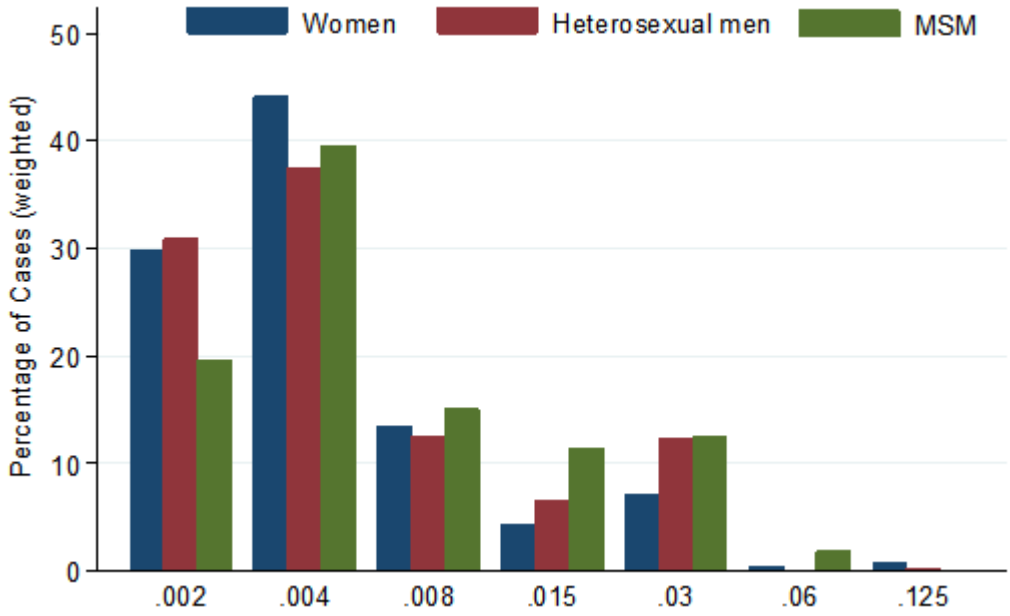


Figure 3 Percentage of gonococcal isolates by ceftriaxone MIC (mg/l) and by gender and male sexual orientation. GRASP clinics: 2013



3.2 Azithromycin

Between 2012 and 2013, the prevalence of azithromycin resistant isolates significantly increased to 1.6% from 0.8% in 2012 ($p<0.05$). An increase in azithromycin resistance had been observed in MSM in the last two years, rising from 0.7% in 2011 to 2% in 2013 (Figure 4). As in previous years, the MIC distribution in MSM showed a less susceptible gonococcal population (Figure 5). Similarly to 2012, there were three isolates showing high-level azithromycin resistance (MIC≥256mg/l). Two isolates were from women aged 20-24 years and the third was from an older man (30-35 years) of unknown sexual orientation. One isolate showed raised MICs (0.03mg/l) to ceftriaxone and cefixime as well as ciprofloxacin resistance, while another was ciprofloxacin resistant and exhibited PPNG/TRNG.

Figure 4 Percentage of gonococcal isolates resistant to azithromycin (≥1mg/l) by gender and male sexual orientation. GRASP clinics: 2004 to 2013

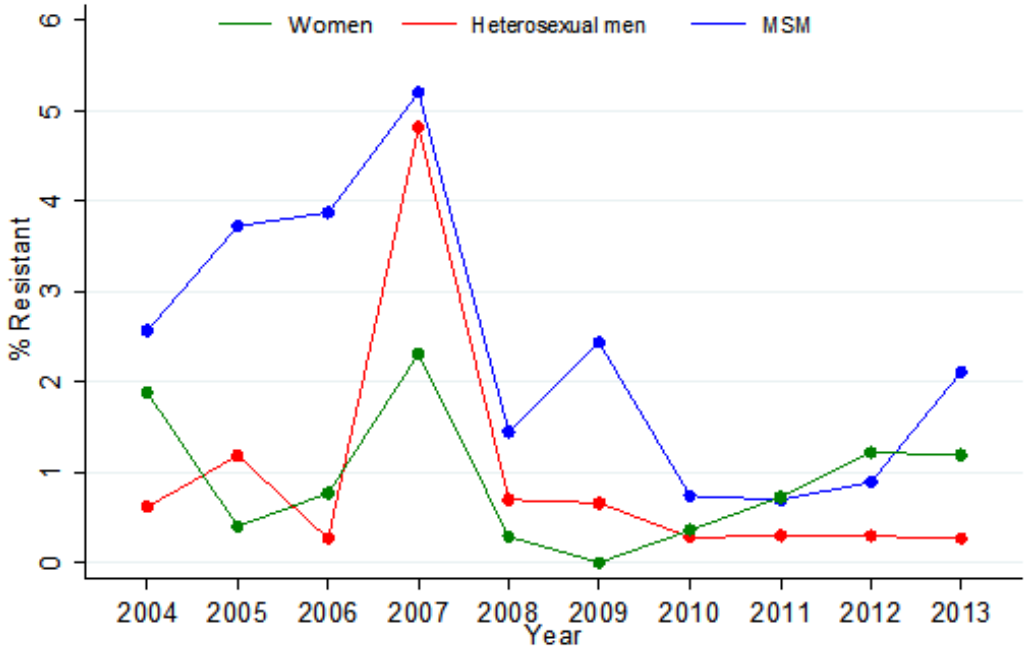
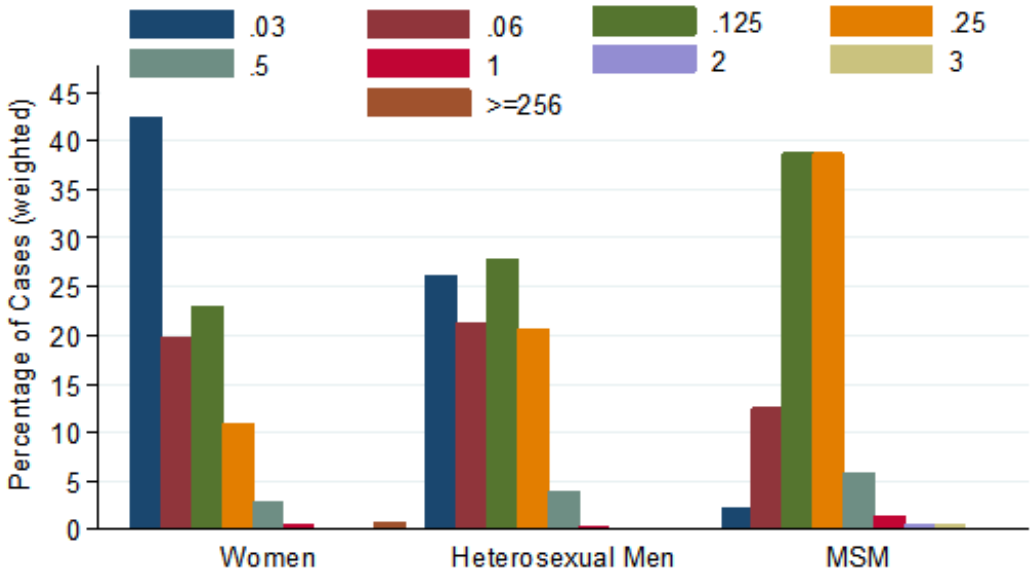


Figure 5 Percentage of gonococcal isolates by azithromycin MIC (mg/l) by gender and male sexual orientation. GRASP clinics: 2013



3.3 Cefixime

The percentage of isolates exhibiting decreased susceptibility to cefixime (MIC≥0.125mg/l) in 2013 is similar to that in 2012 (5.2% and 5.7% respectively) (p=0.637). The modal cefixime MIC continues to be 0.008mg/l and the MICs appear to be normally distributed (Figure 6).

The prevalence of decreased susceptibility to cefixime continued to decline in MSM from 6.8% in 2012 to 3.5% in 2013 (Figure 7). In contrast cefixime decreased susceptibility increased slightly in both women and heterosexual men, reaching above 5% for the first time in women.

In 2013, all isolates exhibiting decreased susceptibility to cefixime were also resistant to ciprofloxacin and had MICs to azithromycin ranging from 0.125-1.0mg/l. These isolates were more likely to exhibit higher ceftriaxone MICs (Figure 8).

Figure 6 Percentage of gonococcal isolates by cefixime MIC (mg/l). GRASP clinics: 2007 to 2013

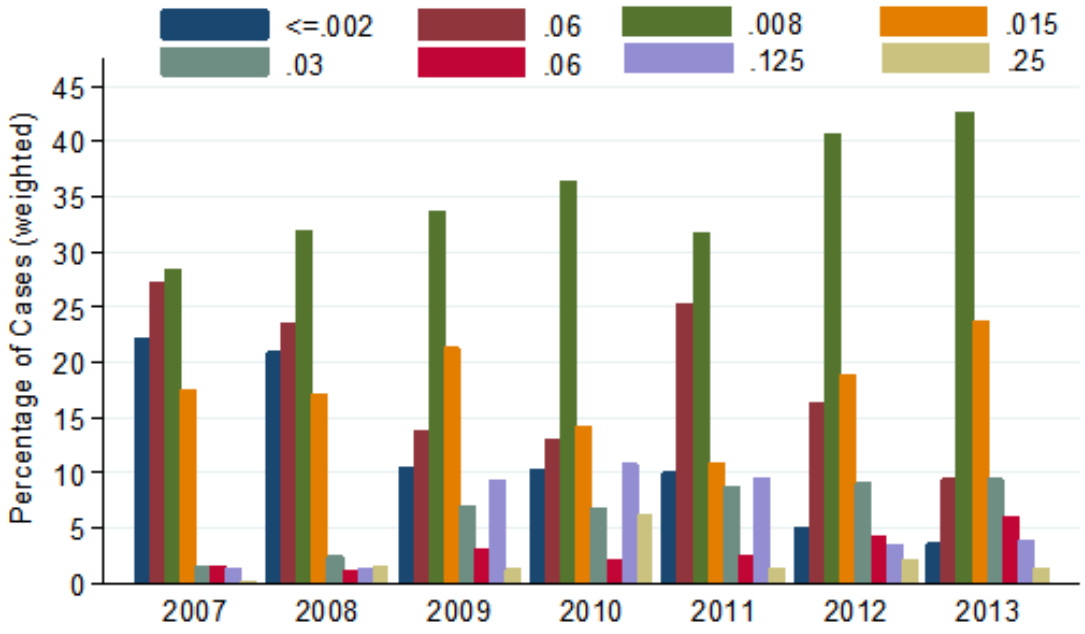


Figure 7 Percentage of gonococcal isolates exhibiting decreased susceptibility to cefixime (MIC ≥0.125mg/l) by gender and male sexual orientation. GRASP clinics 2007 to 2013

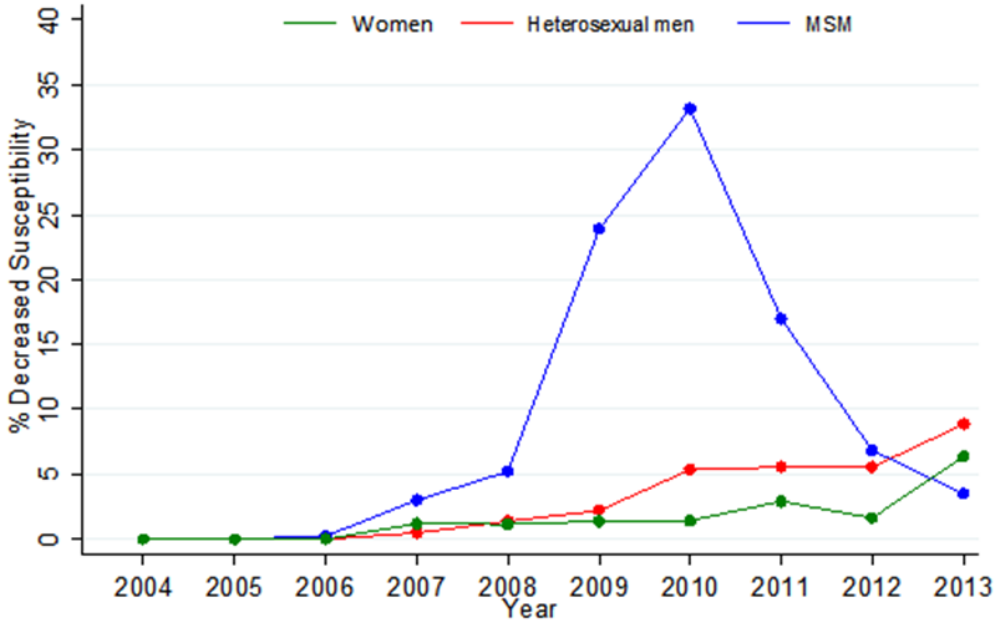
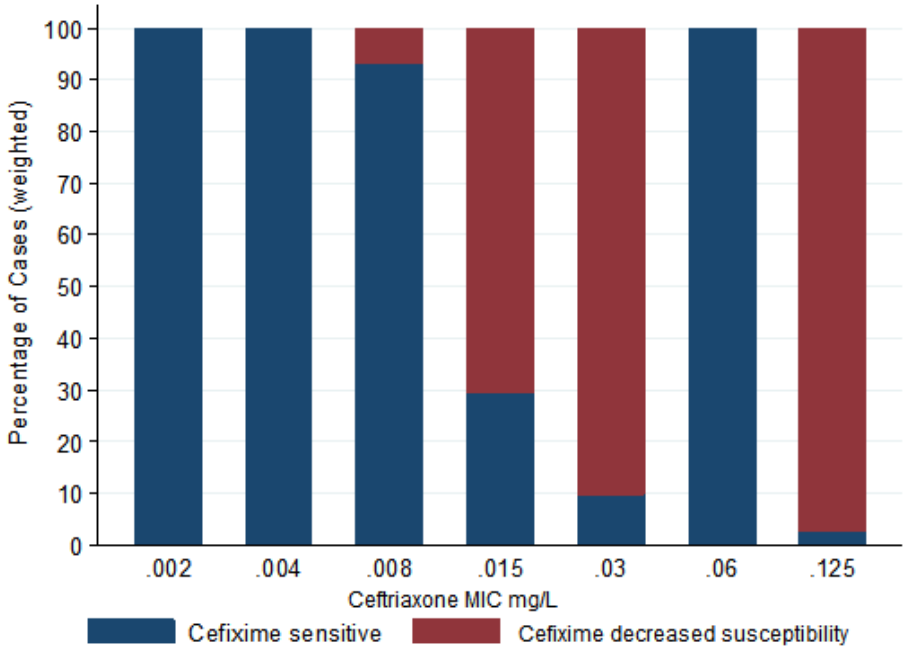


Figure 8 Percentage of gonococcal isolates showing decreased susceptibility to cefixime MIC≥0.125mg/L by ceftriaxone MICs (mg/l). GRASP clinics: 2013



3.4 Ciprofloxacin

In 2013, 29.3% of isolates from patients diagnosed with gonorrhoea were resistant to ciprofloxacin compared to 25.2% in 2012. This increase was seen in all risk groups (Figure 9). Isolates resistant to ciprofloxacin tended to show higher cefixime MICs (mg/l) although ciprofloxacin resistance was also evident in the cefixime sensitive population (Figure 10).

Figure 9 Percentage of gonococcal isolates resistant to ciprofloxacin by gender and male sexual orientation. GRASP clinics: 2004 to 2013

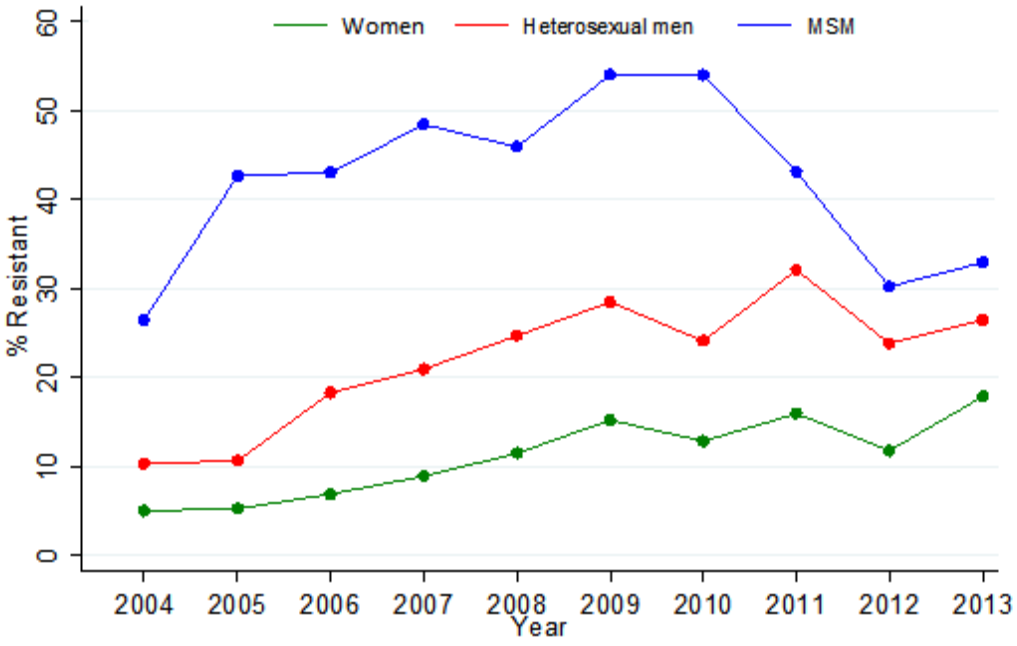
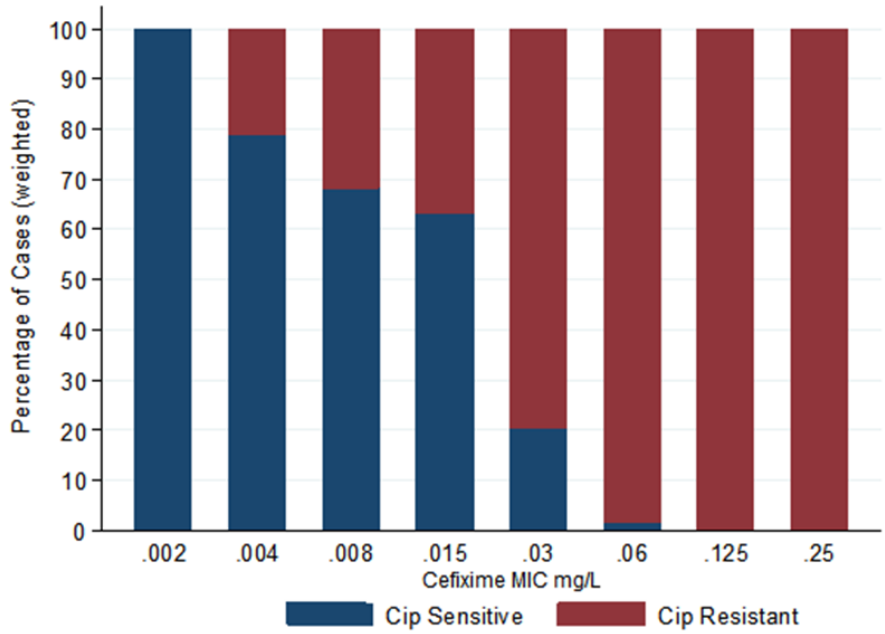


Figure 10 Percentage of gonococcal isolates resistant to ciprofloxacin by cefixime MICs (mg/l). GRASP clinics: 2013



3.5 Penicillin

The percentage of isolates resistant to penicillin continued to increase significantly, rising from 14.5% in 2012 to 18.4% in 2013 (p=0.004). The largest increase was seen in women, from 8.5% in 2012 to 15.1% in 2013 (Figure 11). Between 2012 and 2013, prevalence rose from 5.8% to 18.5% among patients of black Caribbean ethnicity.

Among isolates resistant to penicillin, 60.7% were also resistant to ciprofloxacin and 21.5% exhibited decreased susceptibility to cefixime. There was a slight increase in plasmid-mediated resistance (PPNG or PP/TRNG) from 4.6% in 2012 to 6.7% in 2013 and in chromosomally-mediated-resistance (CMRNG) from 8.1% in 2012 to 10.5% in 2013, which was statistically significant (p<0.001) (Figure 12).

Figure 11 Percentage of gonococcal isolates resistant to penicillin, by gender and male sexual orientation. GRASP clinics: 2004 to 2013

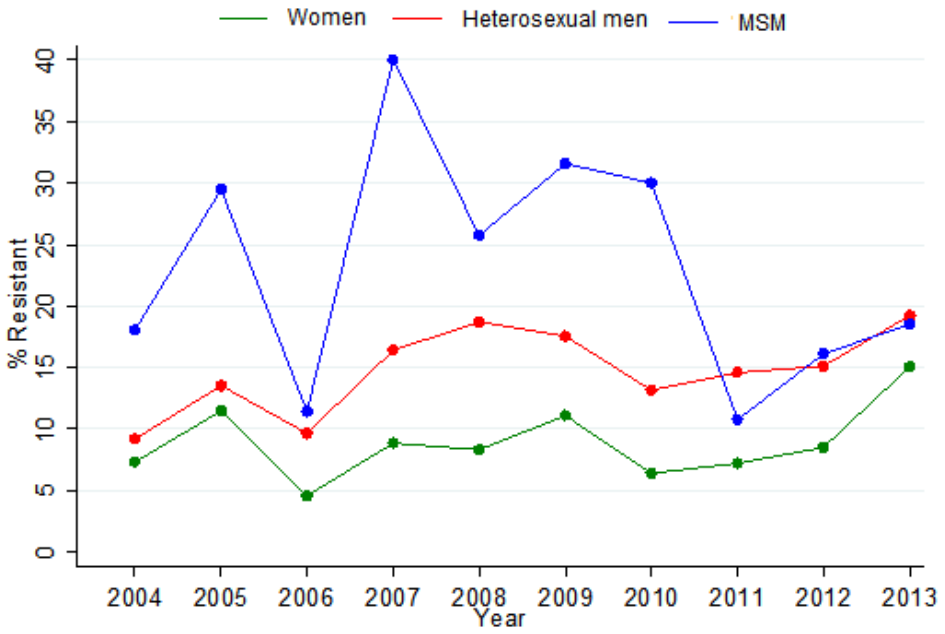
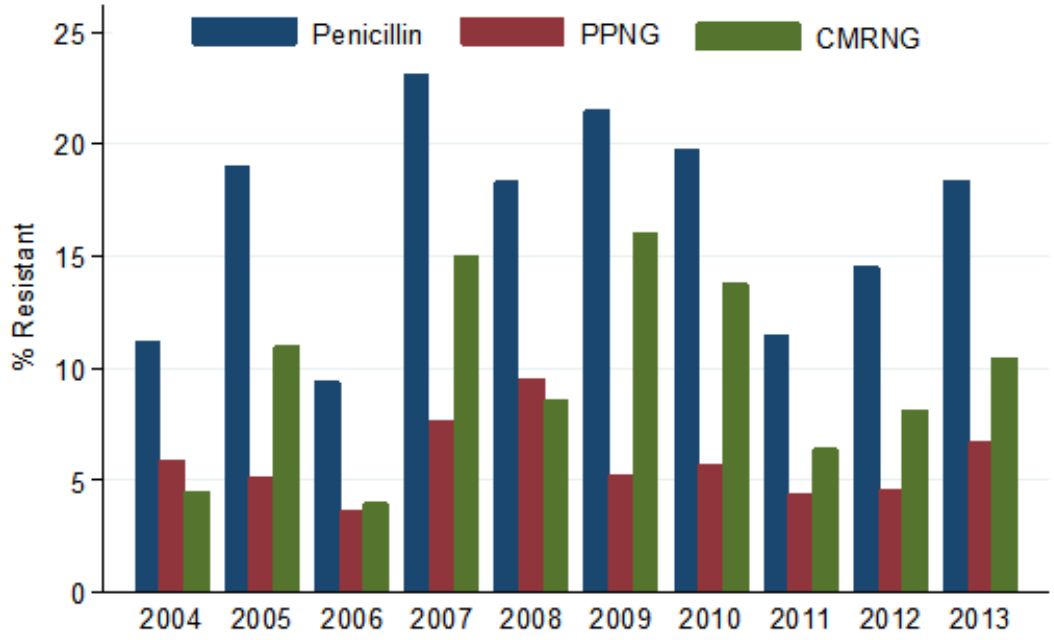


Figure 12 Percentage of gonococcal isolates resistant to penicillin and split into PPNG (including PP/TRNG) and CMRNG*. GRASP clinics: 2004 to 2013

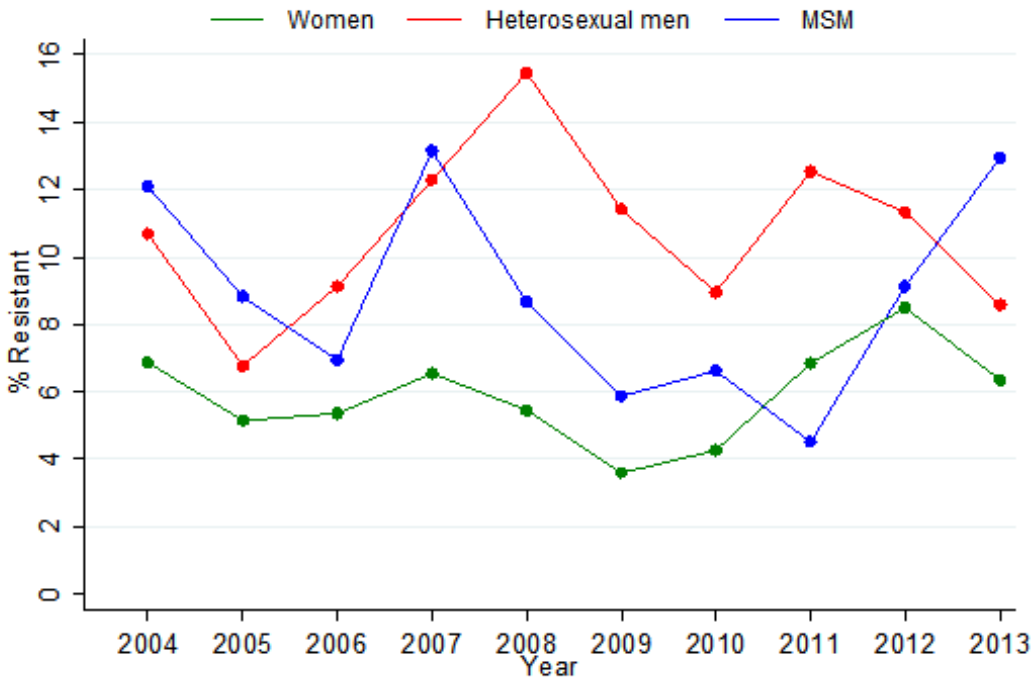


* Pencillin = PPNG plus CMRNG, PPNG = Penicillininase producing *Neisseria gonorrhoeae,* CMRNG = Chromosomally mediated resistant *Neisseria gonorrhoeae*

3.6 Tetracycline

Compared to 2012, the prevalence of tetracycline resistance (≥2mg/l) in 2013 remained constant (76.9% in 2012 compared to 77.8% in 2013). MSM remains the group with the highest percentage of isolates resistant to tetracycline (92.5%) compared to heterosexual men (59.5%) and women (41.3%). Chromsomally-mediated tetracycline resistance was observed in 52.6% of isolates compared to 57.1% in 2012. High-level tetracycline resistance (TRNG or PP/TRNG) increased significantly from 9.5% in 2012 to 11.2% in 2013 (p=0.01), and this increase was evident in MSM only (Figure 13).

Figure 13 Percentage of gonococcal isolates with high-level tetracycline resistance, by gender and male sexual orientation. GRASP clinics: 2004 to 2013



3.7 Spectinomycin

There were no isolates showing resistance to spectinomycin at MIC≥128mg/l in 2013.

4. Factors associated with antimicrobial resistance

An analysis of all isolates with linked clinical and susceptibility data was carried out to determine risk factors associated with resistance or decreased susceptibility to specific antimicrobial agents (Table 4).

4.1 Azithromycin

MSM were more likely to be infected with an azithromycin resistant isolate compared to heterosexual men (Crude Odds Ratio (OR) 8.28; 95% Confidence Interval (95% CI): 1.11-61.5). This was the only patient characteristic strongly associated with azithromycin resistance.

4.2 Cefixime

Patients aged 35-44 years were the group most at risk for infection with a cefixime decreased susceptible isolate, compared to the 13-19 year age group (OR 6.63; 95% CI: 2.97-14.81). In contrast to 2012, MSM were significantly less likely to be infected with a cefixime decreased susceptibility isolate than heterosexual men (OR 0.37; 95% CI: 0.23-0.60). Isolates from patients of Asian ethnicity were significantly more likely to exhibit decreased susceptibility to cefixime compared to isolates from patients of white ethnicity (OR 2.60; 95% CI: 1.24-5.48). Patients with concurrent STIs were significantly less likely to be infected with cefixime decreased susceptible isolates (OR 0.48; 95% CI: 0.23-0.98).

4.3 Ciprofloxacin

There was a strong association between the age of the patient and infection with isolates exhibiting resistance to ciprofloxacin; in particular isolates from patients of the younger age group (13 to 19 years) were significantly less likely to be resistant to ciprofloxacin compared to those from older patients. The group most at risk were the 35-44 years age range (OR 4.70; 95% CI: 2.57-8.60). Compared to heterosexual men, MSM were more likely to be infected with a ciprofloxacin resistant isolate (OR 1.36; 95% CI: 1.05-1.77), while isolates from women were significantly less likely to exhibit resistance to ciprofloxacin (OR 0.60; 95% CI: 0.41-0.89). Compared to the patients of white ethnicity, patients of Asian ethnicity were significantly more likely to be infected with a ciprofloxacin resistant isolate (OR 1.78; 95% CI: 1.11-2.85). Reporting sexual contact abroad was strongly associated with isolates resistant to

ciprofloxacin (OR 1.73; 95% CI: 1.17-2.56). Patients with concurrent STIs were significantly less likely to acquire isolates resistant to ciprofloxacin (OR 0.62; 95% CI: 0.44-0.86).

4.4 Penicillin

Isolates from the patients aged 13-19 years were significantly less likely to be resistant to penicillin compared to those from older patients. Similarly to ciprofloxacin, patients aged 35-44 years are the group most at risk of infection with penicillin resistant isolates (OR 6.63; 95% CI: 2.97-14.81). Compared to patients of white background, isolates infecting patients of Asian ethnicity were significantly more likely to be resistant to penicillin (OR 2.59; 95% CI: 1.58-4.26) while there was also increased risk in patients of black African ethnicity (OR 1.89; 95% CI: 1.09-3.28) and black 'other' ethnic background (OR 2.27; 95% CI: 1.06-4.86). There was a strong association between the patients reporting sexual contact abroad and resistance to penicillin (OR 1.70; 95% CI: 1.11-2.60). Similarly to cefixime and ciprofloxacin, patients with concurrent STIs were significantly less likely to be infected with a penicillin resistant isolate (OR 0.48; 95% CI: 0.32-0.71).

Table 4 Risk factors associated with antimicrobial resistance or decreased susceptibility to specific antimicrobial agents. GRASP clinics: 2013

	Crude Odds Ratio (95% Confidence Interval)			
	Azithromycin≥1mg/L	Cefixime MIC≥0.125mg/L	Ciprofloxacin≥1mg/L	Penicillin ≥2mg/L
Age Group				
13-19	1	1	1	1
20-24	3.07 (0.37-25.15)	3.04 (0.90-10.22)	**2.77 (1.52-5.04)**	**3.09 (1.37-6.96)**
25-34	3.6 0(0.47-27.26)	2.19 (0.67-7.22)	**4.41 (2.50-7.83)**	**4.61 (2.11-10.08)**
35-44	2.34 (0.26-21.12)	**3.08 (1.12-12.90)**	**4.70 (2.57-8.60)**	**6.63 (2.97-14.81)**
>=45	-	0.80 (0.16-4.03)	**3.26 (1.70-6.23)**	**3.66 (1.55-8.67)**
Sexual Orientation				
Heterosexual Men	1	1	1	1
MSM	**8.28 (1.11-61.5)**	**0.37 (0.23-0.60)**	**1.36 (1.05-1.77)**	0.96 (0.71-1.29)
Women	4.63 (0.48-44.73)	0.70 (0.37-1.30)	**0.60 (0.41-0.89)**	0.75 (0.49-1.15)
Ethinicity				
White	1	1	1	1
Black Caribbean	0.72 (0.17-1.31)	0.80 (0.34-1.89)	**0.55 (0.36-0.84)**	1.13 (0.73-1.76)
Black African	-	1.19 (0.42-3.39)	1.16 (0.69-1.94)	**1.89 (1.09-3.28)**
Black Other	-	2.01 (0.59-6.77)	1.22 (0.58-2.55)	**2.27 (1.06-4.86)**
Asian (including Chinese)	1.45 (0.33-6.29)	**2.60 (1.24-5.48)**	**1.78 (1.11-2.85)**	**2.59 (1.58-4.26)**
Other Ethnic group	-	0.76 (0.18-3.20)	0.68 (0.35-1.31)	1.02 (0.49-2.12)
Mixed Ethnic group	0.45 (0.06-3.41)	0.67 (0.24-1.89)	0.68 (0.44-1.07)	1.01 (0.61-1.67)
Total Partners (past 3 months)				
0-1	1	1	1	1
2-5	2.08 (0.56-7.74)	1.02 (0.60-1.72)	1.05 (0.78-1.41)	1.20 (0.87-1.67)
6+	3.39 (0.67-17.02)	1.07 (0.47-2.44)	1.02 (0.64-1.65)	0.83 (0.47-1.46)
Sex Abroad				
No	1	1	1	1
Yes	1.14 (0.25-5.09)	1.09 (0.53-2.26)	**1.73 (1.17-2.56)**	**1.70 (1.11-2.60)**
Symptoms				
No	1	1	1	1
Yes	0.80 (0.28-2.29)	1.33 (0.73-2.40)	**0.72 (0.54-0.96)**	1.01 (0.71-1.43)
Previously diagnosed with gonorrhoea				
No	1	1	1	1
Yes	0.52 (0.15-1.81)	**0.37 (0.18-0.76)**	1.05 (0.80-1.39)	0.91 (0.65-1.26)
Concurrent STI (Excluding HIV)				
No	1	1	1	1
Yes	0.31 (0.09-1.13)	**0.48 (0.23-0.98)**	**0.62 (0.44-0.86)**	**0.48 (0.32-0.71)**
HIV Status				
Negative	1	1	1	1
Positive	0.45 (0.10-2.07)	**0.26 (0.11-0.61)**	**1.48 (1.12-1.96)**	0.92 (0.65-1.29)
Red bold text indicates p<0.005				

5. Prescribing practice

Antimicrobial prescription data were available for 65.7% of patients in the GRASP sample (1,150/1,750). Of these 86.5% received the recommended treatment with ceftriaxone at 500mg combined with azithromycin at 1g compared to 86.8% of patients in 2012 (Figure 14). More heterosexual men received the recommended treatment (93.7%) than women (84.3%) and MSM (82.4%) ($p<0.001$). Women may have received doxycycline instead of azithromycin for pelvic inflammatory disease treatment.

Among patients not prescribed the recommended treatment for their gonococcal infection, 29.7% were given ceftriaxone with doxycycline while 7.0% were given cefixime with azithromycin. A small percentage of patients (5.7%) was prescribed ciprofloxacin only, of whom 22.0% were infected with a ciprofloxacin resistant isolate. The remaining patients received various other combinations of antimicrobials. There was a slight increase in the percentage of MSM and women prescribed ceftriaxone with doxycycline in combination therapy in 2013 (Figure 15), however this was not significantly higher than in 2012 and remained significantly lower than in 2011.

Figure 14 Antimicrobial prescribing practice. GRASP clinics: 2004 to 2013

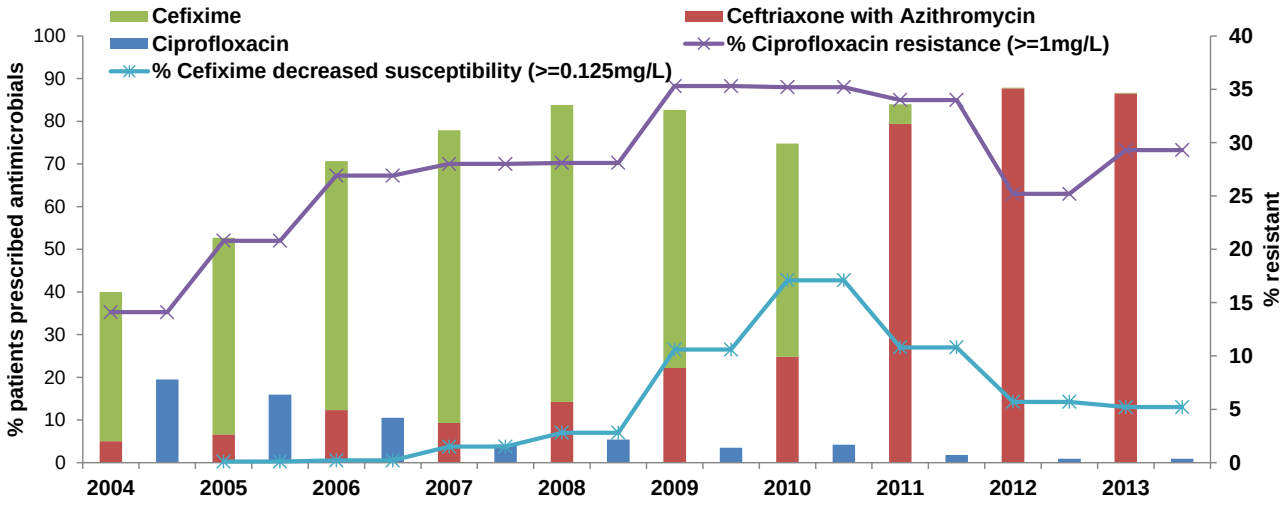
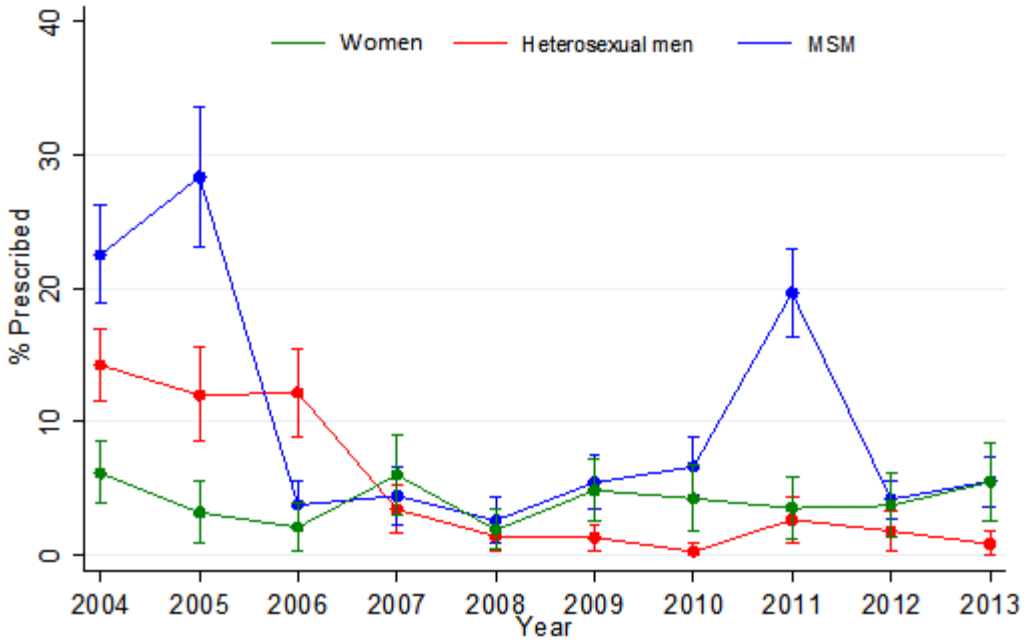


Figure 15 Percentage of patients prescribed ceftriaxone with doxycycline by gender and male sexual orientation. GRASP clinics: 2013



6. Discussion

Neisseria gonorrhoeae is highly adept at developing AMR, so it is encouraging to note that examples of decreased susceptibility to ceftriaxone remained stable in 2013, accounting for just 0.1% of the population sampled. Furthermore cefixime decreased susceptibility peaked at just over 17% in 2010 and has since declined and stabilised at 5-6%. While this may largely be attributable to the implementation of a more aggressive dual therapy treatment strategy, the central role of gonococcal nucleic acid amplification tests recommended in recent guidelines[9] in improving effective detection and treatment at extra-genital sites and in asymptomatic patients, thereby preventing onward transmission of resistant strains, may have played a role.

The data in the current report demonstrate, however, that there is no room for complacency. The three isolates showing ceftriaxone decreased susceptibility had MICs of ≥0.125mg/l. Treatment failure at this level for pharyngeal infection has been documented.[10, 11] Indeed failure of treatment using 500mg ceftriaxone has been documented for pharyngeal infection with strains showing MICs as low as 0.03mg/l.[12,13] The emergence of bimodal ceftriaxone MIC distributions and increases in cefixime decreased susceptibility in women and heterosexual men suggest ongoing dissemination of decreased susceptibility to third generation cephalosporins within this population. This may have emerged as a result of bridging of resistant strains between MSM and heterosexual networks within the UK. Certainly NG-MAST ST1407, which has previously been reported to account for most examples of cefixime decreased susceptibility observed in MSM in earlier GRASP years[14,15] was observed in the heterosexual population in 2013 (data not shown). However evidence suggests decreased susceptibility to cefixime and ST1407 may have been prevalent in heterosexual networks in Europe for some time,[16] so alternatively acquisition of infection abroad may have introduced this resistant strain into the heterosexual population in the UK.

The emergence of decreased cephalosporin susceptibility in the heterosexual population is concerning given that most cases of high-level azithromycin resistance have been observed in this patient group. High-level azithromycin resistance presents a significant threat to the current dual therapy. Fortunately cases of these remained low in 2013, but the circulation of strains showing high level azithromycin resistance and strains showing decreased cefixime susceptibility in the same patient population increases the risk of strains emerging showing resistance to both antimicrobials. It is concerning that there was one example of an isolate showing high-level resistance to azithromycin and raised MICs of 0.03m/l to both cefixime and ceftriaxone in 2013. While lower level azithromycin resistance is increasing in MSM, the clinical

significance of this remains unclear. However a recent report of failure of a 2g dose of azithromycin to treat a pharyngeal infection with a ST1407 strain showing an azithromycin MIC of 4mg/l[17] demonstrates the need to monitor all levels of azithromycin resistance carefully.

In other bacterial species, Extended-Spectrum β-lactamases (ESBLs) have severely compromised the efficacy of third generation cephalosporins. ESBLs have never been reported in N. gonorrhoeae, but a recent survey demonstrated the widespread global distribution of an ESBL precursor, *bla* $_{\text{TEM-135}}$, among PPNG[18]. While it is reassuring that the single point mutation required to allow the ESBL gene (*bla* $_{\text{TEM-20}}$) to evolve from *bla* $_{\text{TEM-135}}$ has not emerged in spite of the extensive selection pressure created by use of cefixime, it is nevertheless prudent to monitor the prevalence and epidemiology of PPNG within GRASP as a potential reservoir for emergence of ESBLs.

The current report presents evidence of continued adherence to the recommended dual therapy. Where this was not prescribed, a subset of patients continued to receive the alternative combination therapy of ceftriaxone and doxycycline. While this may be effective in treating Chlamydia co-infection, it should be noted that high level tetracycline resistance (TRNG) increased to 11.2% in 2013, and rose most notably in MSM. Therefore as the doxycycline component of the dual therapy is likely to be ineffective in these patients, the gonococcal infection is effectively being treated with a monotherapy, thereby creating a potential pressure for selection of ceftriaxone resistance. Given these concerns, it is encouraging that the percentage of patients receiving this combination therapy has decreased markedly since 2011, although a slight increase was observed between 2012 and 2013.

Since GRASP began in 2000, it has been the aim to continue to develop and improve the programme for maximum public health benefit. A key objective in the coming years will be to supplement GRASP with next generation sequencing (NGS) to provide a resource to understand the relationship between phenotype and genotypic markers of resistance, and to facilitate characterisation of mechanisms of emerging resistance identified by phenotypic testing. This information could be key in supporting development and validation of point of care tests for AMR.

As is the case for most sentinel surveillance programmes, the representativeness of GRASP is an ongoing consideration. The change in 2012 to link GRASP with GUMCAD has been invaluable in identifying a population group where AMR susceptibility data is unavailable due to lack of culture, and has demonstrated that certain sub-groups such as symptomatic patients are over-represented in GRASP[19]. Future research within GRASP will focus on exploring ways to determine AMR susceptibility in these patients, by

developing and applying molecular methods to detect markers of antimicrobial resistance – an approach which would be validated by the programme of NGS work proposed as part of core GRASP activity. These proposed developments will be critical in delivering an improved programme of surveillance to facilitate preservation of treatment options for gonorrhoea for the future.

7. Appendix: metadata and methodology

7.1 GRASP methodology

Isolates from consecutive patients attending 25 GUM clinics between July and September 2013 were submitted by local laboratories to PHE's STBRU for antimicrobial susceptibility testing. Demographic, clinical and behavioural data for each patient was extracted from the national genitourinary medicine clinic dataset (GUMCADv2).[20] Additional behavioural and antibiotic prescribing data were submitted by GUM clinics electronically. Data for patients from the clinic in Wales were collected using paper-based forms. The antimicrobial susceptibility and clinical data were linked using the patient's unique identifier number, the unique clinic code and the patient's date of attendance. Of the 2,295 isolates sent to PHE's STBRU, 1,750 were retrieved, tested for antimicrobial susceptibility data and matched to clinical data.

Since 2005, the percentage of isolates that are resistant to a particular antibiotic has been estimated using a weighted analysis. This is because a simple percentage would underweight isolates from sites that have a lower retrieval rate. The weight for a particular clinic in a particular year is inversely proportional to its retrieval rate and each estimate of the percentage resistant to a particular antibiotic in a particular year is a weighted average of the percentages from the participating sites in that year.

The χ^2 test was used to compare percentages of isolates resistant or exhibiting decreased susceptibility to specific antimicrobials over time. Univariate logistic regression models were used to identify the risk factors associated with isolates exhibiting decreased susceptibility or resistance to specific antimicrobial agents.

Data for 2012 has been updated to include only isolates that have antimicrobial susceptibility data and clinical data.

7.2 GRASP sample characteristics

Patients in the GRASP sample have similar demographic, clinical and behavioural characteristics to all the patients diagnosed with gonorrhoea in the 25 GUM clinics sampled (Table 5). Almost two thirds of patients were MSM, most were aged between 20 and 34 years and were of white ethnicity. In the three months prior to diagnosis, over half of patients had more than two sexual partners but the majority had not had sex abroad. More patients had symptoms in the GRASP sample than in the overall GUM clinic sample. Patients from Wales were similar to those from England overall.

Table 5 Characteristics of patients in the 2013 GRASP sample compared to all patients diagnosed with gonorrhoea in the same GUM clinics sampled in 2013

Characteristics	Gonorrhoea diagnoses in English GUM clinics sampled	Gonorrhoea diagnoses in GRASP sample	Gonorrhoea diagnoses in Welsh GUM clinic sampled
Total (N)	**3737**	**1682**	**68**
Gender/Male Sexual Orientation			
Heterosexual Men	17.8	22.5	17.6
MSM	62.8	63.2	61.8
Females	19.4	14.3	20.6
Total (Baseline‡)	**3697**	**1659**	**68**
Ethinicity			
White	72.1	69.6	97.0
Black Caribbean	7.7	9.2	0.0
Black African	3.5	4.2	0.0
Black Other	2.2	2	0.0
Asian (including Chinese)	4.6	4.6	0.0
Other Ethnic group	3.1	3.1	3.0
Mixed Ethnic group	6.8	7.3	0.0
Total (Baseline‡)	**3639**	**1637**	**70**
Age Group (years)			
13-19	9.0	7.6	11.8
20-24	21.9	22.1	27.9
25-34	41.8	43.7	42.6
35-44	18.3	16.9	8.8
>=45	9.1	9.7	8.8
Total (Baseline‡)	**3736**	**1682**	**68**
Symptoms			
Discharge and/or Dysuria	54.2	75.0	0.0
No Discharge and/or Dysuria	45.8	25.0	0.0
Total (Baseline‡)	**2613**	**1154**	**0**
Previously Diagnosed With Gonorrhoea			
Yes	24.3	26.7	17.9
No	75.7	73.3	82.1
Total (Baseline‡)	**2957**	**1226**	**67**
Concurrent STI†	**Total tested for concurrent STI (% with STI)**		
Syphilis	2672(0.7)	1162(0.3)	67(0.0)
Chlamydia	2726(25.0)	1173(26.9)	67(23.9)
Herpes	1515(2.0)	633(2.4)	67(0.0)
Warts	1526(3.5)	634(3.8)	67(0.0)
LGV	1507(1.3)	624(1.0)	67(0.0)
Hepatitis B	1505(0.3)	624(0.5)	67(0.0)
Hepatitis C	1504(0.3)	624(0.5)	67(0.0)
New HIV diagnoses	2674(0.9)	1163(1.2)	67(1.5)
HIV Status			
Negative	66.7	71.0	83.9
Positive	25.1	29.0	16.1
Total (Baseline‡)	**2543**	**1035**	**56**
Multiple Site Infection	25.1	33.6	38.2
Total (Baseline‡)	**2816**	**1221**	**68**
Total Partners (past 3 months)			
0-1	38.6	36.1	38.8
2-5	49.8	53.1	47.8
6+	11.6	10.7	13.4
Total (Baseline‡)	**2302**	**996**	**67**
Sex Abroad			
Yes	11.9	12.4	4.5
No	88.1	87.6	95.5
Total (Baseline‡)	**2302**	**996**	**67**
Geographical Location			
London	58.6	60.4	-
Outside London	41.4	39.6	-
Total (Baseline‡)	**3643**	**1645**	**-**

Total (N) is the number of patients or isolates included in the data for analysis

‡ the total for which the data was available for each variable

8. References

1. Public Health England. Sexually transmitted infections and chlamydia screening in England, 2013. 2014 Health Protection Report 8.24. http://webarchive.nationalarchives.gov.uk/20140714084352/http://www.hpa.org.uk/hpr/archives/2014/hpr2414_AA_stis.pdf (Last accessed 14.10.14)
2. World Health Organisation. Global incidence and prevalence of selected curable sexually transmitted infections - 2008. 2012 ISBN 978 92 4 150383 9. http://apps.who.int/iris/bitstream/10665/75181/1/9789241503839_eng.pdf (Last accessed 14.10.14)
3. Health Protection Agency. Gonoccocal Resistance to Antimicrobials Surveillance Programme (GRASP) Action Plan for England and Wales:Informing the Public Health Response. 2013. http://webarchive.nationalarchives.gov.uk/20140714084352/http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317138215954 (Last accessed 14.10.14)
4. European Centre for Disease Prevention and Control. Response plan to control and manage the threat of multidrugresistant gonorrhoea in Europe. European Centre for Disease Prevention and Control. 2012. http://www.ecdc.europa.eu/en/publications/Publications/1206-ECDC-MDR-gonorrhoea-response-plan.pdf (Last accessed 14.10.14)
5. World Health Organisation. Global action plan to control the spread and impact of antimicrobial resistance in *Neisseria gonorrhoeae*. 2012 World Health Organisation ISBN 978 92 4 150350 1. http://whqlibdoc.who.int/publications/2012/9789241503501_eng.pdf (Last accessed 14.10.14)
6. Bignell C and Fitzgerald M. UK national guideline for the management of gonorrhoea in adults, 2011. *Int J STD AIDS* 2011;22(10):541-7.
7. Pereira R. *et al*. Combination therapy for gonorrhoea: in vitro synergy testing. *J Antimicrob Chemother*. 2013;68(3):640-3.
8. Barbee LA. *et al*. In vitro synergy testing of novel antimicrobial combination therapies against Neisseria gonorrhoeae. *J Antimicrob Chemother.* 2014;69(6):1572-8.
9. Public Health England. Guidance for the detection of gonorrhoea in England. 2014. https://www.gov.uk/government/publications/guidance-for-the-detection-of-gonorrhoea-in-england (Last accessed 17.10.14)
10. Unemo, M. *et al.* Ceftriaxone treatment failure of pharyngeal gonorrhoea verified by international recommendations, Sweden, July 2010. *Euro.Surveill.* 2011;16.6: 19792.
11. Unemo, M. *et al*. Treatment failure of pharyngeal gonorrhoea with internationally recommended first-line ceftriaxone verified in Slovenia, September 2011. *Euro.Surveill.* 2012;17.25: 20200.
12. Chen, M. *et al*. Failure of 500 mg of ceftriaxone to eradicate pharyngeal gonorrhoea, Australia. *J.Antimicrob.Chemother.* 2013;68.6: 1445-47.
13. Read, P., et al. One confirmed and one suspected case of pharyngeal gonorrhoea treatment failure following 500mg ceftriaxone in Sydney, Australia. *Sexual Health* 2013;10.5: 460-62.

14. Chisholm, S. A. *et al*. Emergence of a Neisseria gonorrhoeae clone showing decreased susceptibility to cefixime in England and Wales. *J.Antimicrob.Chemother.* 2011;66.11: 2509-12.
15. Ison, C. A. *et al*. Decreased susceptibility to cephalosporins among gonococci: data from the Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP) in England and Wales, 2007-2011. *Lancet Infect.Dis.* 2013; 13.9: 762-68.
16. Chisholm, S. A. *et al*. Molecular epidemiological typing within the European Gonococcal Antimicrobial Resistance Surveillance Programme reveals predominance of a multidrug-resistant clone. *Euro.Surveill.* 2013;18.3: 20358.
17. Morita-Ishihara T. *et al*. Treatment failure with 2 g of azithromycin (extended-release formulation) in gonorrhoea in Japan caused by the international multidrug-resistant ST1407 strain of Neisseria gonorrhoeae. *J Antimicrob Chemother*. 2014;69(8):2086-90.
18. Muhammad I. *et al*. Characterisation of bla TEM genes and types of β-lactamase plasmids in Neisseria gonorrhoeae - the prevalent and conserved bla TEM-135 has not recently evolved and existed in the Toronto plasmid from the origin. *BMC Infect Dus* 2014; 14:454
19. Mohammed H *et al.* Frequency and correlates of culture-positive infection with *Neisseria gonorrhoeae* in England: a review of sentinel surveillance data. *In Press, Sex Transm Infect, 2014.*
20. Public Health England. Genitourinary medicine clinic dataset (GUMCADv2). https://www.gov.uk/genitourinary-medicine-clinic-activity-dataset-gumcadv2 (last accessed 20/10/2014).

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