

COMMUNICABLE DISEASE SURVEILLANCE CENTRE

GRASP

*The Gonococcal Resistance to
Antimicrobials Surveillance Programme*

Annual Report, Year 2001 Collection



PHLS Communicable
Disease Surveillance and
The Genitourinary Infections
Reference Laboratory



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PUBLIC HEALTH LABORATORY SERVICE
PROTECTING THE POPULATION FROM INFECTION

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1.1 Results of the 2001 GRASP Collection

During the 3 month data collection period, 2666 isolates were collected by the 24 GRASP collaborating laboratories and sent to GUIRL or Imperial College for MIC testing. This represented a 7% decrease in the number of London isolates and a 21% increase in the number of Non-London isolates, collected from corresponding clinics compared to 2000. Ninety-five percent (2542) of all isolates were retrieved successfully and confirmed to be *Neisseria gonorrhoeae*. Of the confirmed isolates, 95% (2403) were from patients who had attended a GUM clinic. One percent of all GUM isolates were re-infections (i.e. where more than one isolate per individual was received, greater than 28 days apart, during the three-month collection).

1.2 Epidemiology of *N. gonorrhoeae* infection in GRASP collection

- Gonorrhoea remains highly concentrated within demographic and behavioral risk groups in England and Wales. 25% of infections were among homosexual and bisexual men. Black and ethnic minority groups were also disproportionately affected: among women, 31% of diagnoses were among Black Caribbeans, whilst in men 28% of diagnoses occurred in this ethnic group.
- High levels of re-infection among patients with gonorrhoea. Among patients diagnosed with gonorrhoea a third (33%) had been previously diagnosed with gonorrhoea.
- High levels of concurrent sexually transmitted infections (STI's). 31% of individuals diagnosed with gonorrhoea had at least one other concurrent STI. Females in particular had high levels of concurrent STI, with 36% presenting with concurrent chlamydial infection.
- High levels of asymptomatic infections among female GUM attenders. 42% of females were asymptomatic, compared with 13% of males. The high level of asymptomatic infection seen in females is particularly worrying as onward disease transmission can occur if the infection is untreated.

1.3 Antimicrobial resistance in *N. gonorrhoeae*

- Ciprofloxacin resistance (MIC \geq 1mg/l): Overall, 3.1% of isolates showed resistance to ciprofloxacin, 1.8% in London and 4.5% outside London. Relatively high prevalence levels of ciprofloxacin resistance were found in the North West (8.6%), South East (5.2%), Northern & Yorkshire (4.6%), Wales (4.0%) and Eastern (3.1%) regions. As with the 2000 collection a substantially lower prevalence (1.8%) was observed in London. Ciprofloxacin resistance is significantly higher in males than females (3.6% cf. 1.9%) and a significantly higher prevalence was found among heterosexual than homosexual males (4.5% cf. 2.2%).
- Ciprofloxacin intermediate resistance ((MIC \geq 0.125mg/l-<1mg/l): A further 2.6% of isolates showed intermediate resistance to ciprofloxacin 1.9% in London and 3.4% outside London. High prevalence levels of intermediate resistance to ciprofloxacin were found in Wales (10.0%) and the South East (6.0%), compared to low levels of 1.6% in the South West and 1.9% in London.
- Penicillin resistance: Overall 8.1% isolates showed penicillin resistance. Among these, plasmid-mediated resistance (PPNG or PP/TRNG) accounted for 3.0%. A slightly higher prevalence of PPNG or PP/TRNG was observed among heterosexual males than homosexual males (3.7%, cf. 2.2% respectively). Overall chromosomally-mediated penicillin resistance was seen in 5.1% of isolates (CMRNG - 4.64% and PenR - 0.42%), over half the total penicillin resistance. A significantly higher prevalence of CMRNG was found in males than females (5.8% cf. 1.7%) and a significantly higher prevalence of CMRNG was found among homosexual than heterosexual males (10.7% cf. 3.2%).
- Tetracycline and resistance to other antimicrobials: High levels of tetracycline resistance were observed throughout England and Wales, with 32.5% of isolates showing some resistance. Plasmid mediated resistance to tetracycline (TRNG or PP/TRNG) accounted for 4.6% of this total resistance. A significantly higher prevalence of TRNG or PP/TRNG was found among heterosexual than homosexual males (7.1% cf. 1.5%). Six isolates (0.3%) were found to be resistant to azithromycin (MIC \geq 1mg/l). All the isolates were susceptible to spectinomycin and ceftriaxone.

1.4 Comparison with GRASP 2000

- In 2001, a 21% increase was observed in the total number of isolates collected outside of London and a 7% decrease in the number of isolates collected in London (when matched and compared to participating clinics in 2000).
- The results of the 2001 study confirm the demographic and behavioural risk groups illustrated in 2000 with few changes observed between the 2000 and 2001 collections.

- A decrease in travel associated gonococcal infections was observed from 13% in 2000 to 9% in 2001. Of the regions in which the sexual contact occurred, Western Europe still had the highest percentage - 4% of all GRASP isolates in 2001, compared with 11% in 2000.
- Ciprofloxacin resistance has increased in 2001. In London it has doubled from 0.9% to 1.8%, whilst outside of London it has increased from 3.7% to 4.5%.
- Penicillin resistance (MIC \geq 1mg/l or β -lactamase positive) remained at levels similar to those found in 2000 in London (8.2% cf. 8.0%) and decreased outside of London (11.0% cf. 8.0%).
- Tetracycline (MIC \geq 2mg/l) remained high in London at 45.8% but decreased from the 50.4% found in 2000. Outside of London levels stabilized at 19.2% cf. 20.4% in 2000.

2.1 Epidemiology of *N. gonorrhoeae* in England and Wales

N. gonorrhoeae is the second most common bacterial sexually transmitted infection (STI) in England and Wales. Over 22,500 infections were diagnosed in genitourinary medicine (GUM) clinics in 2001 an increase of 7% from 2000¹. Rates of infection have increased substantially since 1995² and these rises have been greatest in the younger age groups. Current rates are highest in males aged 20-24 years (256/100 000) and females aged 16-19 years (198/100 000)¹.

2.2 Gonococcal antimicrobial resistance

N. gonorrhoeae infection can be easily treated with appropriate antimicrobials. Along with penicillin, UK guidelines now recommend the use of fluoroquinolones (ciprofloxacin or ofloxacin) as first line therapy³. Antimicrobial treatment should be expected to eradicate 95% of uncomplicated gonococcal infections within the community⁴. However, *N. gonorrhoeae* has developed resistance to several antimicrobials including both penicillin and ciprofloxacin. Decreased susceptibility to ciprofloxacin has been noted in the UK since the 1990s⁵ and, in GRASP 2000, antimicrobial resistance to penicillin and ciprofloxacin was found to be 9.3% and 1.8% respectively⁶. In the presence of decreased susceptibility or resistance to antimicrobials, the likelihood of onward transmission of the organism within the community and development of adverse clinical sequelae in the infected individual are substantially increased. In *N. gonorrhoeae*, antimicrobial resistance is acquired by two different mechanisms:

1. Plasmid-mediated transfer for penicillinase-producing strains (PPNG) and high-level tetracycline resistance (TRNG).
2. Chromosomal mutations for penicillin, tetracycline, fluoroquinolones and other antibiotics (See table 1 for definitions).

Table 1 Glossary of antibiotic resistance and classification types.

Classification	Definition
PPNG	Penicillin: β -lactamase positive But tetracycline <16mg/l
TRNG	Tetracycline: MIC \geq 16mg/l But penicillin β -lactamase negative
PP/TRNG	Penicillin: β -lactamase positive AND tetracycline: \geq 16mg/l
CMRNG	Penicillin: MIC \geq 1mg/l but β -lactamase negative AND tetracycline: MIC between 2-8mg/l
PenR	Penicillin: MIC \geq 1mg/l but β -lactamase negative AND tetracycline: MIC <2mg/l
TetR	Tetracycline: MIC between 2-8mg/l AND penicillin: MIC <1mg/l
Ciprofloxacin resistant	MIC \geq 1mg/l
Ciprofloxacin (Intermediate Resistance)	MIC \geq 0.125mg/l to <1mg/l
Spectinomycin	MIC \geq 128mg/l
Ceftriaxone (Decreased susceptibility)	MIC \geq 0.5mg/l
Azithromycin	MIC \geq 1mg/l

2.3 The Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP)

The PHLS Communicable Disease Surveillance Centre (CDSC), the Genitourinary Infections Reference Laboratory (GUIRL), Bristol and Imperial College, London launched the Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP) in June 2000. Key objectives of the programme are to determine the prevalence and geographic distribution of antimicrobial resistance in *N. gonorrhoeae*; to identify relevant clinical and epidemiological associations with gonococcal resistance; and to inform rational and cost-effective antimicrobial prescribing policies for *N. gonorrhoeae* infection.

This report presents the findings of the 2nd year of isolate collection in this programme. It describes the demographic, clinical and behavioural characteristics of individuals diagnosed with gonorrhoea from whom an isolate was taken and included in the 2001 collection. The report then describes the antimicrobial susceptibility profiles of the obtained isolates. This report does not present any clinic-level data, this will be published separately.

3.1 Study population

A total of 2666 isolates were collected by the 24 GRASP collaborating laboratories during the three-month data collection period and sent to GUIRL or Imperial College for antimicrobial susceptibility testing. This represented a 7% decrease in the number of London isolates and a 21% increase in the number of non-London isolates collected, from corresponding clinics compared to 2000. In 2001, the number of participating clinics in London decreased from 13 to 9 clinics and their corresponding 7 laboratories. All comparisons of London data contained throughout this report are made on matched data for these corresponding 9 clinics in 2000.

Ninety-five percent (2542) of all isolates were recovered successfully and confirmed to be *Neisseria gonorrhoeae*. Of the confirmed isolates, 94.5% (2403) were from patients who had attended a GUM clinic. The importance of primary care diagnoses can be seen in Table 2, with between 2.5% and 15.0% of isolates being diagnosed in settings such as general practice or hospital out-patient departments. Where more than one isolate per individual was received during the three month collection, results were only included in the analyses if the second date of isolation was greater than 28 days after the first isolate. In 2001, such patients accounted for 1% of all GUM isolates the same percentage as was seen in 2000. Repeat isolates within a 28-day period were considered to belong to a single patient episode.

Table 2: Numbers of gonococcal isolates obtained in the GRASP three-month collection period during 2001.

Region*	Total number of confirmed isolates	Non-GUM isolates	GUM Clinic data	
			Number of Isolates	Number of Patients
Eastern	75	10 (13.3%)	65	64
London	1219	34 (2.8%)	1185	1169
North West	242	6 (2.5%)	236	236
Northern & Yorkshire	146	9 (6.2%)	137	137
South East	127	9 (7.1%)	118	117
South West	167	25 (15.0%)	142	138
Trent	222	26 (11.7%)	196	195
West Midlands	286	14 (4.9%)	272	270
Wales	58	6 (10.3%)	52	51
Total	2542	139 (5.5%)	2403	2377

*For details of collaborating laboratories and GUM clinics see pages 30 and 31.

The majority of gonococcal infections were diagnosed among women aged 16-19 years and men aged 25 to 34 years. Gonococcal infection tends to be concentrated in 'core groups', i.e. population subgroups at increased risk. In England and Wales these include homosexual/bisexual men and black ethnic minority populations. The results in table 3 highlight the disproportionate disease burden in these groups. Twenty five percent (602/2363) of all gonococcal infections were diagnosed among gay and bisexual men. Despite black and ethnic minority groups accounting for only 5% of the total population of England and Wales (and proportionately less when London is excluded), they accounted for 49% of all infections diagnosed at GRASP clinics an increase from the 42% observed in 2000. Black ethnic groups, mainly Black Caribbean, are the most severely affected, and accounted for 48% and 39% of all infections in females and males respectively, an increase from the 41% and 35% observed in 2000.

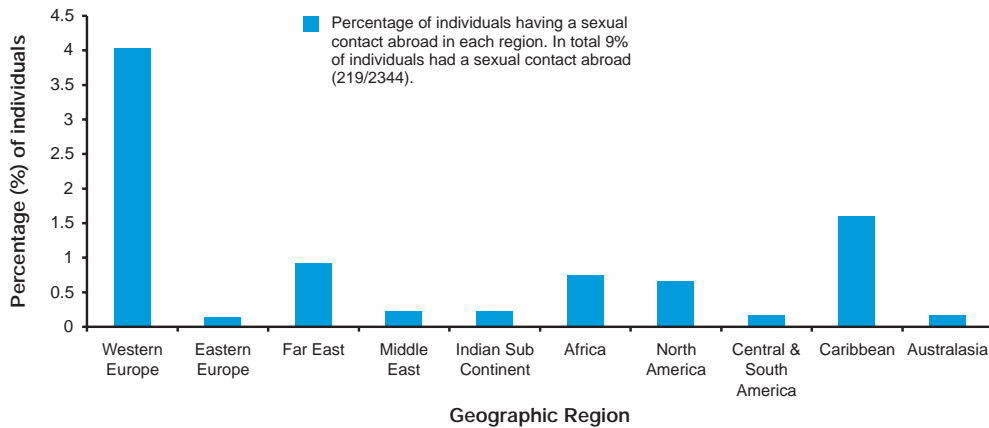
4.1 Clinical characteristics

Genital infections were the predominant site of infection among both males (89%) and females (98%), however in homosexual males 44% of gonococcal infection was isolated from the throat or rectum. Only 58% (383/656) of females diagnosed with gonorrhoea presented with a symptomatic infection (genital discharge and/or dysuria), however the majority of males 87% (1406/1617) were symptomatic. Thirty-three percent of patients were previously diagnosed with gonorrhoea (763/2295). Thirty one percent of individuals (719) presented with a concurrent STI. Thirty-six percent of females were concurrently infected with *Chlamydia trachomatis*, less than half this percentage (17%) was observed among males.

4.2 Sexual Behaviour

Table 3 highlights the importance of multiple sexual partnerships in the transmission of *N. gonorrhoeae* infection. Over 50% of individuals reported having more than one sexual partner in the previous three months, significantly higher than would be estimated for the general population. Nine percent (219/2344) of individuals reported having had a sexual contact abroad in the past 3 months, a decrease from the 13% observed in 2000. This decrease occurred amongst females and heterosexual males with the percentage of homosexual/bisexual men having a sexual contact abroad increasing marginally from 13% in 2000 to 14% in 2001. Figure 1 illustrates the geographic location where the last sexual contact abroad occurred. Of all those individuals infected with gonorrhoea 4% had a sexual contact in Western Europe a decrease from the 11% observed in 2000, and 2% had a sexual contact in the Caribbean an increase from the 0.4% observed in 2000.

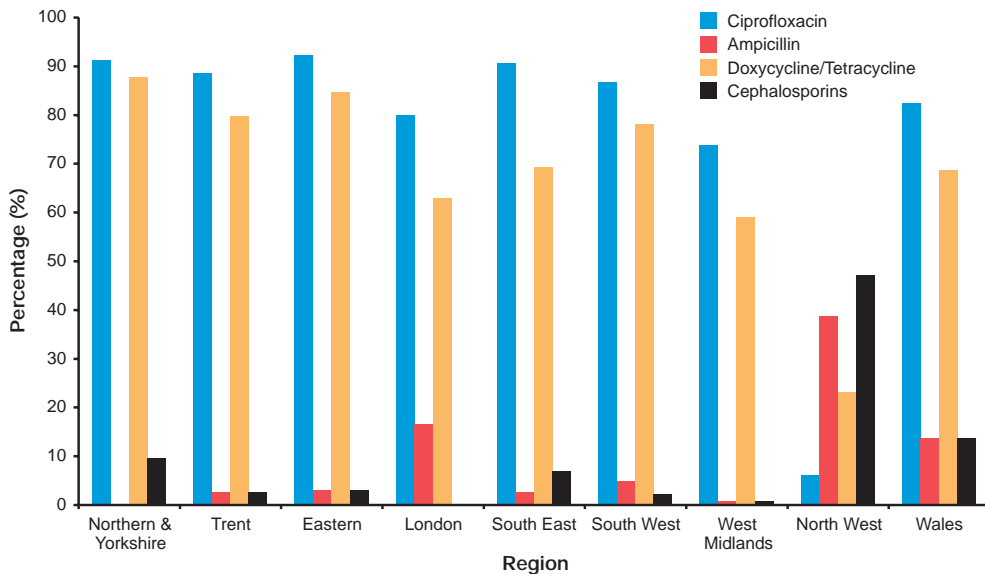
Figure 1: Distribution of geographic location of last sexual contact abroad for patients diagnosed with gonorrhoea at GRASP clinics, June-August 2001 (n = 2344).



4.3 Antimicrobial treatment

Along with penicillin, guidelines now recommend ciprofloxacin or ofloxacin as first line therapy for uncomplicated gonococcal infection in the UK³. Seventy-five percent of patients received ciprofloxacin (alone or in combination with other antibiotics) for each episode of gonorrhoea. Males were more likely than females to be prescribed ciprofloxacin (79% cf. 63%). Overall, 13% of patients received penicillin (alone or in combination with other antibiotics) during each episode of gonorrhoea. Penicillin was most likely to be prescribed in the North West (39%) region. Figure 2 outlines the prescribing practices by region for the four main antimicrobial groups to which gonococci are exposed. Ciprofloxacin, ampicillin and cephalosporins are used to treat for gonococcal infection whereas the tetracyclines are prescribed to treat chlamydial infection.

Figure 2: Percentage of prescribed antimicrobials by region, in patients diagnosed with gonorrhoea at GRASP clinics, June to August 2001 (n = 2323*).



*Patients may have received more than one antimicrobial per episode of gonococcal infection.

Table 3: Demographic characteristics among all GUM patients with confirmed gonorrhoea from participating GUM clinics during the GRASP 2001 collection (June, July & August 2001).

Characteristics	All females N (%)	All males N (%)	Homosexual males N (%)*	Total N (%)
<i>Geographic Distribution</i>				
London	339 (48.4)	845 (49.7)	370 (61.5)	1185 (49.3)
Outside London	361 (51.6)	857 (50.4)	232 (38.5)	1218 (50.7)
Total	700	1702	602	2403
<i>Ethnicity</i>				
White	282 (43.5)	871 (54.8)	510 (90.4)	1153 (51.5)
Asian or Asian British	13 (2.0)	47 (3.0)	10 (1.8)	60 (2.7)
Black Caribbean	204 (31.4)	452 (28.4)	8 (1.4)	656 (29.3)
Black African	32 (4.9)	71 (4.5)	7 (1.2)	103 (4.6)
Other Black	78 (12.0)	97 (6.1)	7 (1.2)	175 (7.8)
Other	40 (6.2)	52 (3.3)	22 (3.9)	92 (4.1)
Total	649	1590	564	2239
<i>Age Group</i>				
<16	22 (3.2)	8 (0.5)	0	30 (1.3)
16-19	284 (40.6)	196 (11.5)	20 (3.3)	480 (20.0)
20-24	221 (31.6)	419 (24.6)	88 (14.6)	640 (26.7)
25-34	119 (17.0)	675 (39.7)	297 (49.3)	794 (33.0)
35-44	43 (6.2)	300 (17.6)	153 (25.4)	343 (14.3)
45+	10 (1.4)	104 (6.1)	44 (7.3)	114 (4.8)
Total	699	1702	602	2401
Median age group	16-19	25-34	25-34	25-34
<i>Symptoms</i>				
Discharge and/or dysuria	383 (58.4)	1406 (87.0)	444 (76.3)	1789 (78.7)
No discharge or dysuria	273 (41.6)	211 (13.1)	138 (23.7)	484 (21.3)
Total	656	1617	582	2273
<i>Site of infection*</i>				
Genital	668 (98.1)	1468 (88.6)	422 (70.5)	2136 (91.4)
Rectal	36 (5.3)	172 (10.4)	167 (27.9)	208 (8.9)
Throat	23 (3.4)	120 (7.2)	95 (15.9)	143 (6.1)
Other	1 (0.2)	1 (0.1)	0	2 (0.1)
Total (Baseline)+	681	1657	599	2338
<i>Previously diagnosed with gonorrhoea</i>				
Yes	154 (23.1)	609 (37.4)	242 (41.6)	763 (33.3)
No	514 (77.0)	1018 (62.6)	340 (58.4)	1532 (66.8)
Total	668	1627	582	2295
<i>Concurrent STI*</i>				
Syphilis	0	14 (0.9)	6 (1.0)	14 (0.6)
Chlamydia	241 (35.7)	268 (16.7)	31 (5.3)	509 (21.9)
Herpes	12 (1.8)	13 (0.8)	4 (0.7)	25 (1.1)
Warts	23 (3.4)	39 (2.4)	19 (3.2)	62 (2.7)
Other	90 (13.3)	79 (4.8)	44 (7.5)	169 (7.3)
None	352 (52.1)	1252 (76.0)	491 (83.4)	1604 (69.0)
Total (Baseline)	676	1674	589	2323

Table 3: (continued)

Characteristics	All females N (%)	All males N (%)	Homosexual males N (%)*	Total N (%)
<i>UK Partners (past 3 months)</i>				
0-1	493 (73.4)	632 (38.4)	190 (32.3)	1125 (48.5)
2-5	177 (26.3)	890 (54.1)	310 (52.6)	1067 (46.0)
6-10	1 (0.2)	70 (4.3)	46 (7.8)	71 (3.1)
11+	1 (0.2)	54 (3.9)	43 (7.3)	55 (2.4)
Total (Baseline)	672	1646	589	2318
<i>Sex Abroad (Past 3 months)</i>				
	41 (6.0)	178 (10.7)	86 (14.4)	219 (9.3)
Total	680	1664	598	2344

* A patient may present with more than 1 site of infection and/or concurrent STI.

5.1 Summary of antimicrobial susceptibility data

Table 4 summarises the proportion of resistant isolates from all GRASP clinics in 2001 in comparison with the 2000 results and Table 5 summarises the types of resistance for penicillin and tetracycline for 2001 in comparison to 2000. 8.1% of all isolates from GRASP clinics were resistant to penicillin. Intermediate resistance or resistance to ciprofloxacin was found in 5.7% of all isolates. 32.5% of all isolates from GRASP clinics were resistant to tetracycline. All isolates were found to be susceptible to spectinomycin, and ceftriaxone. Six isolates (0.3%) were found to be resistant to azithromycin. 1.4% (32/2369) of all isolates were resistant to both penicillin and ciprofloxacin ($\geq 1\text{mg/l}$).

A significant difference in the prevalence of ciprofloxacin resistance was observed between London and non-London isolates ($p < 0.0005$) with a higher prevalence of ciprofloxacin resistance observed outside of London. Significant differences in the prevalence of ciprofloxacin and CMRNG resistant isolates were observed between regions ($p < 0.0005$, and $p < 0.05$ respectively).

Table 4: Number and percentage (%) of isolates resistant to specific antimicrobials from all GRASP laboratories, June to August 2001 (GUM patients only).

Antimicrobial	London*		Non-London		Total	
	2001	2000	2001**	2000	2001	2000
Penicillin $\geq 1\text{mg/l}$ or β -lactamase positive	97/1185 (8.2)	108/1352 (8.0)	95/1187 (8.0)	110/999 (11.0)	192/2372 (8.1)	218/2351 (9.2)
Tetracycline $\geq 2\text{mg/l}$	543/1185 (45.8)	681/1352 (50.4)	228/1185 (19.2)	204/999 (20.4)	771/2370 (32.5)	885/2351 (37.6)
Ciprofloxacin $\geq 1\text{mg/l}$	21/1185 (1.8)	12/1352 (0.9)	53/1184 (4.5)	37/999 (3.7)	74/2369 (3.1)	49/2351 (2.1)
Ciprofloxacin -Intermediate resistance $\geq 0.125\text{mg/l}$ - $< 1\text{mg/l}$	22/1185 (1.9)	35/1352 (2.6)	40/1184 (3.4)	24/999 (2.4)	62/2369 (2.6)	59/2351 (2.5)
Azithromycin $\geq 1\text{mg/l}$	0/1180 (0.0)	N/A	6/1170 (0.5)	N/A	6/2350 (0.3)	N/A
Ceftriaxone $\geq 0.5\text{mg/l}$	0/1185 (0.0)	0/1352 (0.0)	0/1186 (0.0)	0/999 (0.0)	0/2371 (0.0)	0/2351 (0.0)
Spectinomycin $\geq 128\text{mg/l}$	0/1185 (0.0)	1/1352 (0.1)	0/1187 (0.0)	1/999 (0.1)	0/2372 (0.0)	2/2351 (0.1)

*The London data presented above for 2000 is data which has been adjusted to match the participating clinics in 2001.

**Baseline figures for non-London isolates vary as not all isolates were successfully susceptibility tested for each antimicrobial.

Table 5: Number and percentage (% , 95 % confidence intervals) of isolates resistant to penicillin and tetracycline, by resistance classification type from all GRASP laboratories, June to August 2001 (GUM patients only).

Classification*	London		Non-London		Total	
	2001	2000	2001	2000	2001	2000
Base	N = 1185**	N = 1352	N = 1185**	N = 999	N = 2370	N = 2351
PPNG	22 (1.9)	44 (3.3)	27 (2.3)	19 (1.9)	49 (2.1, 1.5-2.7)	63 (2.7, 2.1-3.4)
TRNG	39 (3.3)	59 (4.4)	50 (4.2)	39 (3.9)	89 (3.8, 3.0-4.6)	98 (4.2, 3.4-5.1)
PP/TRNG	8 (0.7)	31 (2.3)	13 (1.1)	15 (1.5)	21 (0.9, 0.5-1.4)	46 (2.0, 1.4-2.6)
CMRNG	63 (5.3)	29 (2.1)	47 (4.0)	62 (6.2)	110 (4.6, 3.8-5.6)	91 (3.9, 3.1-4.7)
PenR	3 (0.3)	2 (0.2)	7 (0.6)	12 (1.2)	10 (0.4, 0.2-0.8)	14 (0.6, 0.3-1.0)
TetR	416 (35.0)	520 (38.0)	102 (8.6)	75 (7.5)	518 (22.0, 20.0-24.0)	595 (25.0, 23.6-27.1)

* See glossary on page 7 for definitions

** 1185/1185 of London isolates and 1185/1224 isolates for non-London clinics were successfully susceptibility tested for penicillin and tetracycline resistance types.

Table 6: Percentage change in the prevalence of gonococcal antimicrobial resistance, from GRASP laboratories by region, June-August 2000-2001.

Region	Ciprofloxacin ($\geq 1\text{mg/l}$)			Penicillin PPNG or PP/TRNG			Penicillin CMRNG			Tetracycline TRNG or PP/TRNG		
	2001	2000	% change	2001	2000	% change	2001	2000	% change	2001	2000	% change
Eastern	3.1	0.0	n.a.	6.2	8.2	-24	4.6	0.0	n.a.	6.2	12.2	-49
London	1.8	0.9	100	2.5	5.5	-55	5.3	2.1	152	4.0	6.7	-40
North West	8.6	4.4	96	1.7	1.0	70	4.3	4.9	-12	0.9	4.9	-82
Northern and Yorkshire	4.6	6.5	-29	2.2	5.6	-61	3.0	17.7	-83	6.8	4.0	70
South East	5.2	1.0	420	4.3	2.9	48	9.5	10.8	-12	0.9	2.9	-69
South West	3.0	4.2	-29	2.2	4.2	-48	3.0	1.0	200	13.3	17.7	-25
Trent	2.7	3.8	-29	3.2	3.3	-3	1.0	2.2	-55	3.2	1.6	100
West Midlands	3.0	3.4	-12	5.2	4.6	13	3.3	6.9	-52	8.2	2.9	183
Wales	4.0	3.0	33	2.0	0.0	n.a.	8.0	3.0	167	2.0	7.6	-74

Table 6 illustrates the percentage change in antimicrobial resistance between 2000 and 2001 by region. The South East experienced the greatest increase in ciprofloxacin resistance, the prevalence increasing five-fold since 2000 (1.0% cf. 5.2%). Large increases in ciprofloxacin resistance were also seen in London and the North West with increases in prevalence of 100% (0.9% cf. 1.8%, 4.4% cf. 8.6% respectively).

The largest increase, although still a relatively low value, of plasmid mediated penicillin resistance occurred in the North West region (1.0% cf. 1.7%) a 70% increase, with the prevalence in other regions generally stabilizing or slightly decreasing. Several regions experienced large increases in chromosomally mediated penicillin resistance, the South West (1.0% cf. 3.0%), Wales (3.0% cf. 8.0%) and London (2.1% cf. 5.3%). A notable decrease in the prevalence of CMRNG was observed in the Northern & Yorkshire region from 17.7% in 2000 to 3.0% in 2001. A 200% increase in the prevalence of high level tetracycline resistance occurred in the West Midlands (2.9% cf. 8.2%), and a 100% increase was also seen in Trent (1.6% cf. 3.2%). These changes illustrate the increasing heterogeneity of antimicrobial resistance between regions and demonstrates the rapid changes in resistance prevalence which can occur over a relatively short period of time.

6.1 Ciprofloxacin resistance (MIC ≥ 1 mg/l)

In 2001, 3.1% of isolates showed resistance (≥ 1 mg/l) to ciprofloxacin. High prevalence of resistant isolates were observed in the North West (8.6%), South East (5.2%), Northern & Yorkshire (4.6%), Wales (4.0%) and Eastern (3.1%) regions. This compares with a lower prevalence level of 1.8% in London. Table 7, shows the distribution of ciprofloxacin resistant isolates by gender and age. Ciprofloxacin resistance prevalence is significantly higher in males than females ($p < 0.05$). A significantly higher prevalence was found among heterosexual than homosexual males ($p < 0.05$).

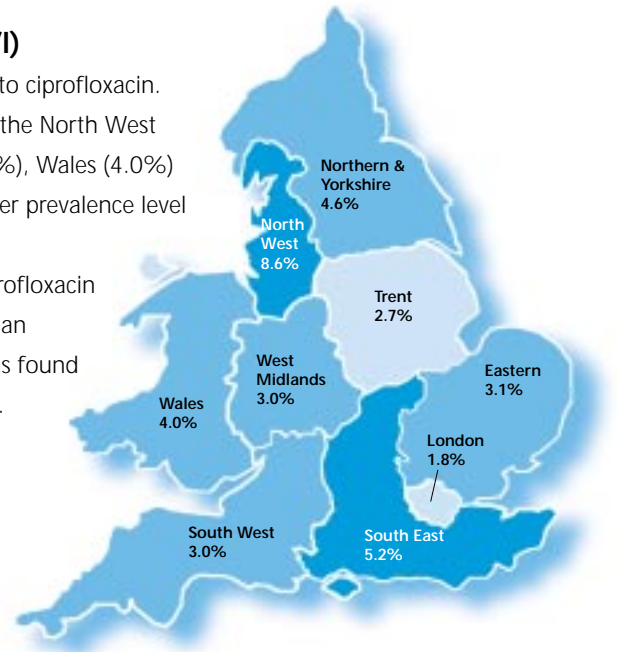


Figure 3: Percentage distribution of ciprofloxacin MICs ≥ 0.125 mg/l among GRASP isolates, June to August 2001 (n = 2369).

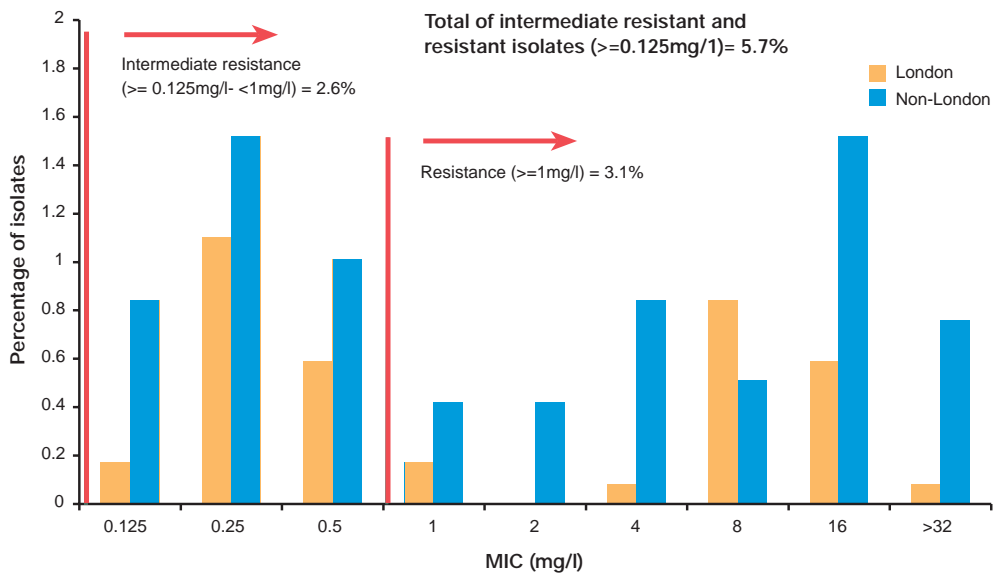


Table 7: Number and percentage (%) of ciprofloxacin resistant isolates ($\geq 1\text{mg/l}$) among all isolates from GRASP clinic patients by age group, sex and sexual orientation, June to August 2001.

Age Group	All females N (%)	All males N (%)	Homosexual males N (%)*	Total N (%)
≤ 19	2/301 (0.7)	3/201 (1.5)	0/20 (0.0)	5/502 (1.0)
20-24	6/215 (2.8)	11/411 (2.7)	3/86 (3.5)	17/626 (2.7)
25-34	4/119 (3.4)	26/667 (3.9)	6/296 (2.0)	30/786 (3.8)
35-44	1/43 (2.3)	11/296 (3.7)	2/153 (1.3)	12/339 (3.5)
45+	0/10 (0.0)	10/104 (9.6)	2/44 (4.6)	10/114 (8.8)
Total	13/688 (1.9)	61/1679 (3.6)	13/599 (2.2)	74/2367 (3.1)

6.2 Intermediate resistance to ciprofloxacin (MIC $\geq 0.125\text{mg/l}$ < 1mg/l)

Intermediate resistance to ciprofloxacin occurs at MIC $\geq 0.125\text{mg/l}$ < 1mg/l .

At these lower MIC levels treatment failure may occur, so it is therefore important to monitor any changes in intermediate resistance levels.

As shown in Figure 3, in 2001 a total of 2.6% of isolates showed intermediate resistance to ciprofloxacin. High prevalence of intermediate resistant isolates was seen in Wales (10.0%) and the South East (6.0%). This compares to a low prevalence levels of 1.6% in the South West and 1.9% in London.

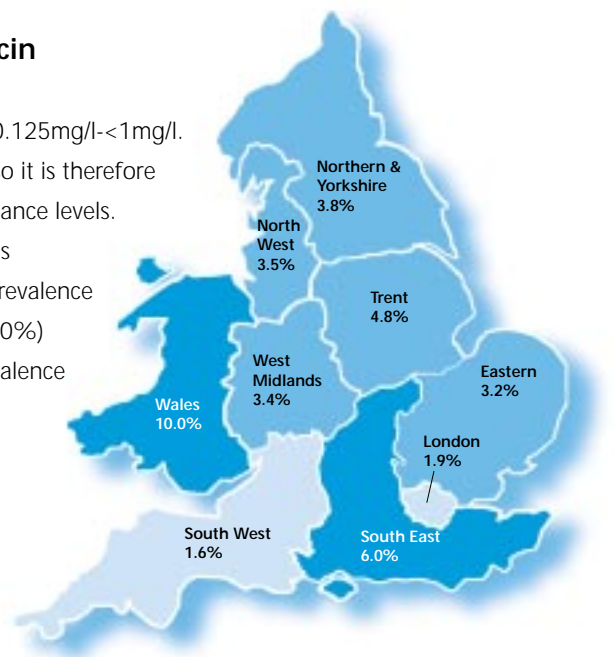


Table 8: Number and percentage (%) of intermediate resistance ciprofloxacin isolates ($\geq 0.125\text{mg/l}$ < 1mg/l) among all isolates from GRASP clinic patients by age group, sex and sexual orientation, June to August 2001.

Age Group	All Females N (%)	All Males N (%)	Homosexual Males N (%)	Total N (%)
≤ 19	2/301 (0.7)	2/201 (1.0)	1/20 (5.0)	4/502 (0.8)
20-24	0/215 (0.0)	16/411 (3.9)	10/86 (11.6)	16/626 (2.6)
25-34	3/119 (2.5)	23/667 (3.4)	14/296 (4.7)	26/786 (3.3)
35-44	0/43 (0.0)	10/296 (3.4)	8/153 (5.2)	10/339 (2.9)
45+	0/10 (0.0)	6/104 (5.8)	2/44 (4.5)	6/114 (5.3)
Total	5/688 (0.7)	57/1679 (3.4)	35/599 (5.8)	62/2367 (2.6)

Figure 4: The percentage distribution of ciprofloxacin resistance and intermediate resistance by region among GRASP isolates, June to August 2001.

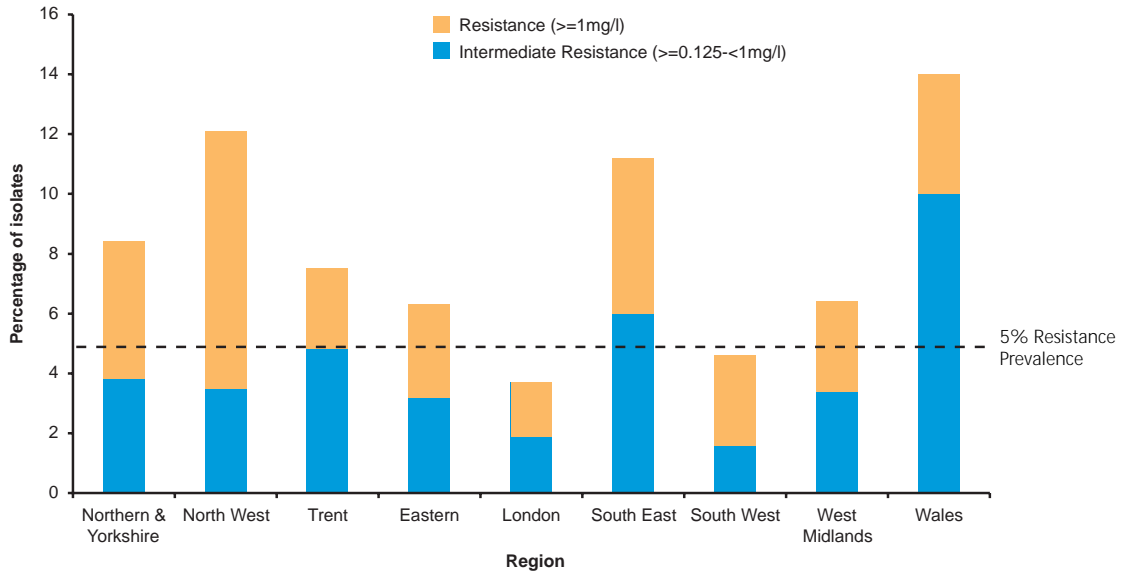
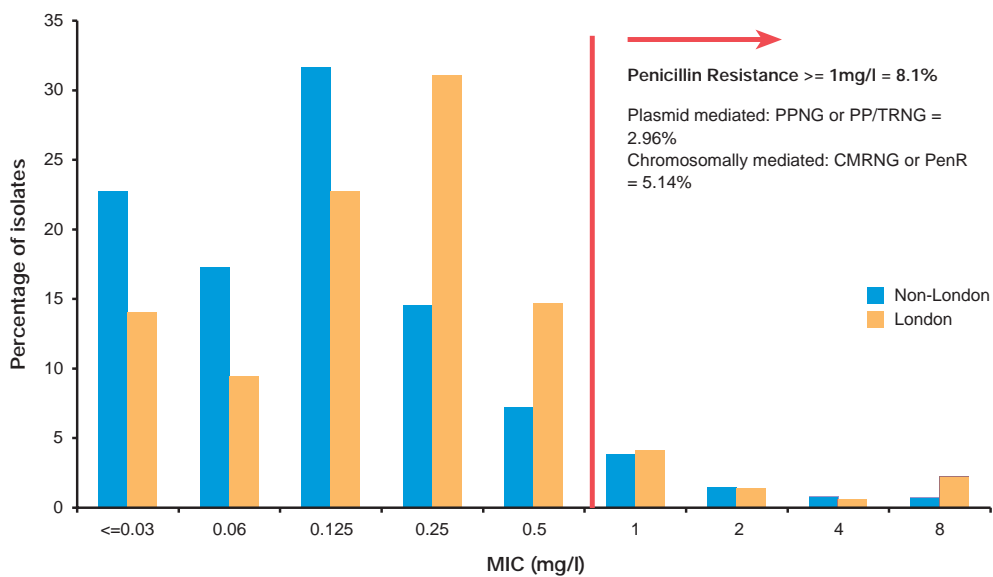


Figure 4 shows the prevalence of ciprofloxacin resistance and intermediate resistance by region with the dotted line indicating a 5% resistance prevalence. As a first-line antimicrobial treatment is recommended to be effective at eradicating 95% of uncomplicated gonococcal infection within the community⁴, levels of ciprofloxacin resistance (≥ 1 mg/l) above 5% are a serious cause for concern and may indicate the need for changes in prescribing policy. This has occurred in the North West region where cephalosporins are now most commonly prescribed as the first-line treatment for uncomplicated gonococcal infection (Figure 2, page 12).

In England and Wales 8.1% of isolates collected through GRASP from GUM patients demonstrated penicillin resistance. The MIC distribution for penicillin is shown in Figure 5.

Figure 5: Percentage distribution of penicillin MICs among GRASP isolates, June to August 2001 (n= 2355).



7.1 Plasmid mediated resistance (PPNG or PP/TRNG)

A total of 3.0% of isolates showed plasmid mediated resistance to penicillin (PPNG or PP/TRNG). A high prevalence of plasmid mediated penicillin resistance was observed in the Eastern (6.2%) and West Midlands (5.2%) regions, although no significant difference between regions was found.

A slightly higher prevalence of PPNG or PP/TRNG was observed among both females and heterosexual males than homosexual males (2.6%, 3.7%, cf. 2.2% respectively), however this was not significant in the multivariate analysis, (Table 9).

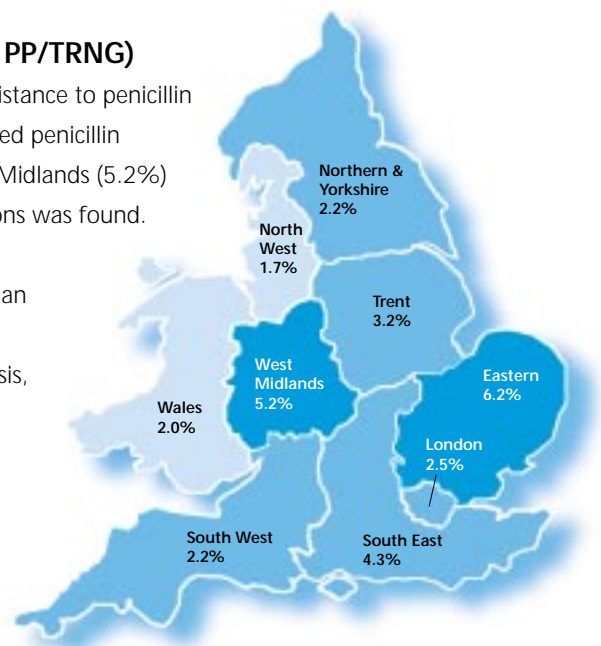


Table 9: Number and percentage (%) of penicillinase producing (PPNG or PP/TRNG) resistant isolates among all isolates from GRASP clinic patients by age group, sex and sexual orientation, June to August 2001.

Age Group	All Females N (%)	All Males N (%)	Homosexual Males N (%)	Total N (%)
≤19	3/301 (1.0)	4/202 (2.0)	1/20 (5.0)	7/503 (1.4)
20-24	9/216 (4.2)	7/412 (1.7)	1/86 (1.2)	16/628 (2.6)
25-34	1/119 (0.8)	27/666 (4.1)	6/295 (2.0)	28/785 (3.6)
35-44	4/43 (9.3)	9/296 (3.0)	3/153 (2.0)	13/339 (3.8)
45+	1/10 (10.0)	5/103 (4.9)	2/44 (4.6)	6/113 (5.3)
Total	18/689 (2.6)	52/1679 (3.1)	13/598 (2.2)	70/2368 (3.0)

7.2 Chromosomally mediated resistance (CMRNG)

Overall chromosomally mediated resistance (CMRNG) accounted for 4.6% (over half the total of penicillin resistance). High prevalences of CMRNG were observed in the South East (9.5%), Wales (8%) and London (5.3%) regions. There was a significant heterogeneity of CMRNG between regions ($p < 0.05$). CMRNG was significantly higher in males compared to females ($p < 0.0005$) and a significantly higher prevalence of CMRNG resistance was found in homosexual men compared to heterosexual men ($p < 0.0005$), (Table 10).

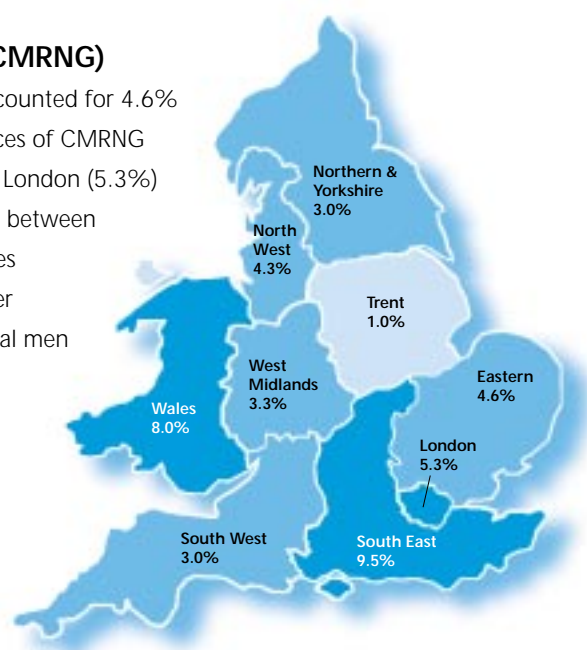


Table 10: Number and percentage (%) of CMRNG resistant isolates among all isolates from GRASP clinic patients by age group, sex and sexual orientation, June to August 2001.

Age Group	All Females N (%)	All Males N (%)	Homosexual Males N (%)	Total N (%)
≤19	7/301 (2.3)	11/202 (5.5)	2/20 (10.0)	18/503 (3.6)
20-24	2/216 (0.9)	23/412 (5.6)	16/86 (18.6)	25/628 (4.0)
25-34	2/119 (1.7)	35/666 (5.3)	24/295 (8.1)	37/785 (4.7)
35-44	0/43 (0.0)	21/296 (7.1)	16/153 (10.5)	21/339 (6.2)
45+	1/10 (10.0)	8/103 (7.8)	6/44 (13.6)	9/113 (8.0)
Total	12/689 (1.7)	98/1679 (5.8)	64/598 (10.7)	110/2368 (4.6)

8.1 Tetracycline

Tetracycline is no longer recommended for treating *N. gonorrhoeae* infections. Continuing high levels of tetracycline resistance were observed throughout England and Wales with 32.5% of isolates showing either chromosomal (27.9%) or plasmid mediated (4.6%) resistance. High prevalences of TRNG or PP/TRNG were observed in the South West (13.3%), West Midlands (8.2%), Northern & Yorkshire (6.8%) and Eastern (6.2%) regions. The prevalence of TRNG & PP/TRNG is significantly higher among heterosexual males and females than homosexual males (P<0.0005), (Table 11).

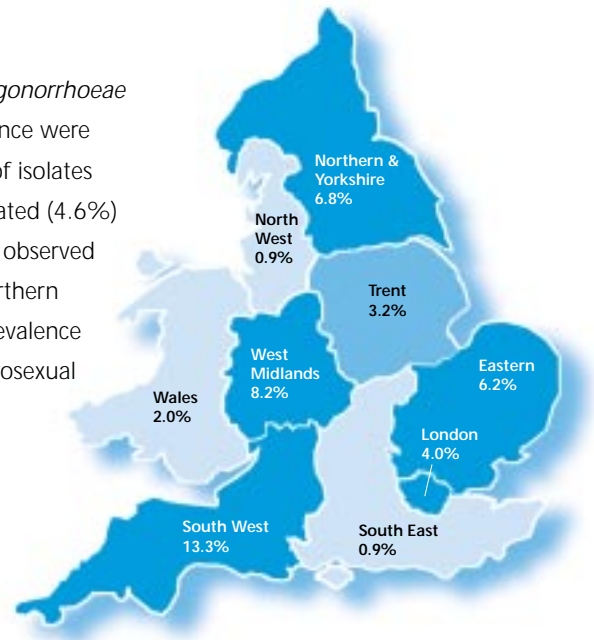


Figure 6: Percentage distribution of tetracycline MICs among GRASP isolates, June to August 2001 (n = 2370).

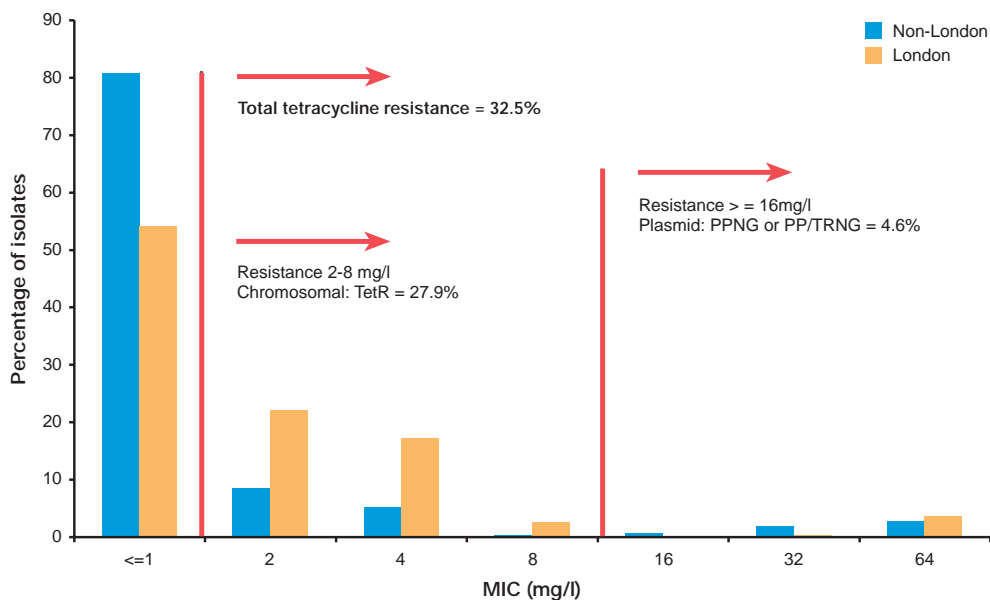


Table 11: Number and percentage (%) of TRNG or PP/TRNG resistant isolates among all isolates from GRASP clinic patients by age group, sex and sexual orientation, June to August 2001.

Age Group	All Females N (%)	All Males N (%)	Homosexual Males N (%)	Total N (%)
≤19	7/301 (2.3)	10/202 (5.0)	0/20 (0.0)	17/503 (3.4)
20-24	10/216 (4.6)	15/412 (3.6)	2/86 (2.3)	25/628 (4.0)
25-34	5/119 (4.2)	39/666 (5.9)	4/295 (1.4)	44/785 (5.6)
35-44	3/43 (7.0)	17/296 (5.7)	3/153 (19.6)	20/339 (5.9)
45+	1/10 (10.0)	3/103 (2.9)	0/44 (0.0)	4/113 (3.5)
Total	26/689 (3.8)	84/1679 (5.0)	9/598 (1.5)	110/2368 (4.6)

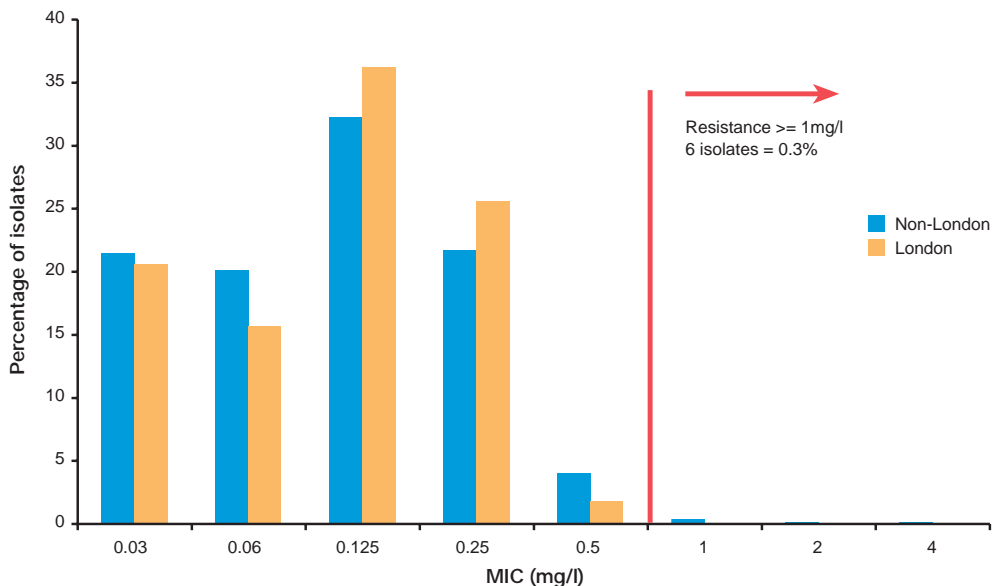
8.2 Other antimicrobial agents

In 2001 all isolates were found to be susceptible to spectinomycin whereas two resistant isolates (0.1%) were seen in the 2000 collection. In both the 2000 and 2001 collections, all isolates were susceptible to ceftriaxone ($\leq 0.5\text{mg/l}$).

8.2.1 Azithromycin resistance

Six isolates outside of London were resistant to azithromycin, four from the South East (3.5%), and two from the North West (0.9%) regions. The MIC distribution of azithromycin is shown in figure 7. Isolates in 2000 were not tested with azithromycin.

Figure 7: Percentage distribution of azithromycin MICs among GRASP isolates, June to August 2001 (n = 2350).



This report represents the findings from the second year of isolate collection in the GRASP sentinel surveillance programme. In this section we highlight some of the key methodological developments during the 2001 collection and review some of the key findings.

9.1 New developments

During 2001, the number of participating GUM clinics in London was reduced from 13 to 7. The seven clinics were purposively selected to obtain and reflect broadly similar geographic and risk group distribution as had been obtained for the 13 centres in the 2000 collection. This adjustment in clinic numbers was undertaken in order to streamline isolate collection in preparation for national roll-out of the surveillance programme. All analyses presented in this report comparing the prevalences for London for the two years are adjusted for the change in participating clinics. In 2001 azithromycin was added to the list of antimicrobials to which all isolates are susceptibility tested.

9.2 Key findings from 2001 collection

The year 2001 GRASP collection showed relatively few changes in the clinical presentations and risk factors of gonococcal disease since 2000. In so doing, they serve to confirm the results obtained previously. Gonorrhoea remains highly concentrated within demographic and behavioral risk groups in England and Wales. Twenty five percent of infections were among homosexual and bisexual men. Among patients diagnosed with gonorrhoea, one third (33%) had been previously diagnosed with gonorrhoea. Thirty one percent of individuals diagnosed with gonorrhoea had at least one concurrent STI infection. Females in particular had high levels of concurrent STI infection, with 36% presenting with a concurrent chlamydial infection. Few changes in the demographic and behavioural characteristics of patients diagnosed with gonorrhoea were observed between the two years.

During 2001 we observed substantial changes in the patterns of antimicrobial resistance across England and Wales. Compared with 2000, a substantial increase (21.2%) in the number of patients diagnosed with gonorrhoea was observed in GUM clinics outside of London during 2001. Some of the most marked increases were observed in the West Midlands (58.3%), South West (47.9%), and Eastern Regions (32.7%). The increases are consistent with preliminary reports from KC60 data comparing the first two quarters of 2000 and 2001. Compared with the previous year, gonorrhoea infections in patients attending the 7 participating London clinics decreased by 7%.

In contrast, marked changes in antimicrobial susceptibility were observed within the GRASP participating centres.

- In London, ciprofloxacin resistance (MIC \geq 1mg/l) doubled from 0.9% to 1.8% whilst intermediate resistance levels decreased slightly from 2.6% to 1.9%. Penicillin resistance (MIC \geq 1mg/l or β -lactamase positive) also remained relatively similar (8.2% cf. 8.0% in 2000) whilst slight declines in tetracycline resistance (MIC \geq 2mg/l) were observed during this period (45.8% cf. 50.4% in 2000).
- Outside of London, a broadly similar pattern was observed between 2000 and 2001. Ciprofloxacin resistance increased from 3.7% to 4.5%, whilst intermediate resistance increased slightly from 2.4% to 3.4%. Overall declines in the proportion of isolates resistant to penicillin were also observed, from 11.0% to 8.0% in 2001.

The increases in ciprofloxacin resistance raise cause for concern, particularly as this remains the first line therapeutic choice in many clinics. The marked increase in resistance observed in the North West (8.6% cf. 4.4% in 2000) and South East (5.2% cf. 1.0%) were in part driven by ongoing outbreaks of ciprofloxacin resistant gonorrhoea in these areas. The doubling of the prevalence of ciprofloxacin resistance in London and the marked increases in Eastern region (from 0.0% to 3.1%) between 2000 and 2001 attest to the rapid changes in the prevalence of resistance which can occur and the need for ongoing systematic monitoring of this nature.

9.3 Conclusions:

Recently released KC60 data for 2001 confirm that diagnoses of uncomplicated gonorrhoea in England, Wales and Northern Ireland rose by 8% in males (14 721 to 15 900) and 6% in females (6404 to 6785) between 2000 and 2001. Amongst MSM, diagnoses rose by 20% (2935 to 3532). In 2001, 43% of all gonorrhoea diagnoses made were seen in London, although compared to 2000, the increase in diagnoses was relatively small (4%). The highest increase was seen in the West Midlands region, where diagnoses rose by 24% (1472 to 1820) and 22% (742 to 903) in males and females respectively. Given these increases, the high proportion of asymptomatic infections, and the substantial geographic clustering of disease, strategies for reducing new diagnoses of gonorrhoea may benefit from the introduction of targeted screening of those at greatest risk in hyper-endemic areas (both within and outside the GUM clinic setting). Such community based screening could be best achieved by using non-invasive specimens and nucleic acid amplification tests. Consideration should be given to piloting these alongside chlamydia screening in target sites, as well as to examining the acceptability and cost-effectiveness of such targeted strategies.

Gonorrhoea remains an STI of major public health concern. Continued surveillance of the patterns and distribution of antimicrobial resistance is required to ensure that prevention and treatment strategies remain responsive to its changing epidemiology.

GRASP Methodology

GRASP Structure

The GRASP collection combines laboratory and clinical data on gonococcal isolates diagnosed in sentinel laboratories. GRASP covers two distinct geographical regions: London, which includes 7 laboratories and 9 GUM clinics part of an established collaboration with Imperial College in the London Gonococcal Working Group Surveillance Project and outside of London where 17 GUM clinics and laboratories were purposely selected to provide good geographic coverage (with representation of all NHS regions) and to maximise the number of isolates collected. Further details on the structure and process of GRASP are contained in the GRASP protocol⁷ available from CDSC, Colindale.

Laboratory methods

All consecutive gonococcal isolates (one from each patient episode) identified in participating laboratories during the months of June, July and August were sent to either the GUIRL (outside London) or Imperial College (London) for susceptibility testing. At each local laboratory, primary isolates of *N. gonorrhoeae* were sub-cultured to obtain a pure growth and then either sub-cultured onto chocolate agar slopes or stored in 15% glycerol broth at -70°C for transportation to GUIRL or Imperial College. At the reference laboratories, MICs were determined for the following antimicrobial agents (the range of concentrations tested is shown in parentheses): penicillin (0.03-4.0mg/l), ciprofloxacin (0.002-0.125mg/l) extended range 0.125 - 32mg/l tested as necessary, spectinomycin (2-64mg/l), tetracycline (1-32mg/l), ceftriaxone (0.12mg/l, single concentration), and azithromycin (0.03 - 2mg/l).

As a quality control, a panel of isolates was exchanged between the two GRASP reference laboratories and the Scottish *Neisseria gonorrhoeae* Reference Laboratory (SNGRL) during the isolate collection period in July 2001. Isolates were tested, blinded to the originator's results, using the agar dilution method for susceptibility to penicillin G, ceftriaxone, ciprofloxacin, spectinomycin and tetracycline. The results for each isolate/antibiotic combination were compared at CDSC and an error was recorded if a laboratory result was more than two doubling dilutions from the other. One error was recorded in the MIC determinations of the 5 WHO antimicrobial control strains (1.3%). The three laboratories made 900 MIC determinations on the exchanged isolates and 9 (1.0%) errors were detected.

Clinical data collection

GUM clinics provided demographic and behavioural data for each GUM patient included in the GRASP collection. Routinely collected clinical data were utilised. These included: gender, age, ethnic background, sexual orientation, postal area, previous infections, symptom presence,

concurrent STIs, number of partners, sexual partnerships abroad, test of cure and therapy received. CDSC collected, collated and linked the behavioural data from patients (from GUM clinics) and susceptibility data (from reference laboratories) of their isolates.

Statistical analysis

The percentage of resistant isolates was calculated and comparisons made between the categories of each variable. "Fisher's Exact Test" was most often used to test for significant associations although, for comparisons between the nine geographic regions Chi-squared tests were used instead. Tests of whether the log odds of being resistant linearly increases or linearly decreases with age group and the number of sexual partners were also carried out. Confidence intervals were calculated for the more interesting results.

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- 7 *The Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP).* Protocol of operational aspects and data management of GRASP. HIV & STI Division PHLS Communicable Disease Surveillance Centre.

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