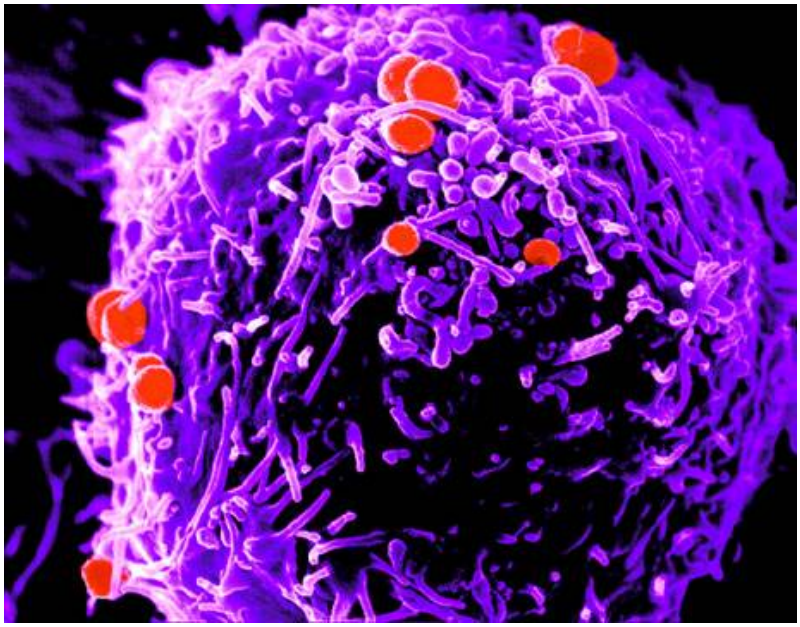
GRASP

The Gonococcal Resistance to Antimicrobials Surveillance Programme

Annual Report 2005



GRASP

The Gonococcal Resistance to Antimicrobials Surveillance Programme.
Annual Report, Year 2005 Collection.

GRASP monitors gonococcal antimicrobial resistance at a number of sentinel sites in England & Wales. The programme is coordinated by the Health Protection Agency Centre for Infections.

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Cover image courtesy of Dr. Ian Boulton *Nat Immunol* 2002; **3**: 229-236. Scanning electron micrograph image of gonococcal-lymphocyte interations.

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1. Key Points

1.1 Study Population

A total of 1948 isolates were collected by the 24 GRASP collaborating laboratories during the three month data collection period in 2005, and sent to the Sexually Transmitted Bacteria Reference Laboratory (STBRL) for antimicrobial susceptibility testing. After the exclusion of duplicates 1823 isolates remained, of which 1030 (56.5%) were recovered successfully and confirmed as *Neisseria gonorrhoeae*. This represented a decrease of 47% in the number of confirmed isolates observed between 2004 and 2005. To allow for the relatively low retrieval rate for some participating laboratories in 2005, the results shown are weighted. This is the first year of reporting weighted results. Results from previous years have also been weighted and may be different to those reported previously.

1.2 Antimicrobial Resistant *N. gonorrhoeae*

- Overall, 21.7% of GRASP isolates were resistant to ciprofloxacin (Minimum Inhibitory Concentration (MIC) ≥ 1mg/l) in 2005, a significant increase from the 14.0% observed in 2004 ($p<0.0005$). The prevalence reached greater than 10% in nearly all Government Health Regions of England and Wales in 2005. The prevalence of ciprofloxacin resistance remained stable in heterosexual men (11.8%) and women (6.3%) in 2005. However, the prevalence significantly increased in men who have sex with men (MSM), rising to 42.4% from 26.2% in 2004 ($p<0.0005$).

- Overall, 17.9% of isolates demonstrated penicillin resistance in 2005 (MIC ≥1mg/l or β-lactamase positive), compared with 11.4% in 2004 ($p=0.004$). Of this total 4.3% of isolates demonstrated plasmid-mediated penicillin resistance (PPNG or PP/TRNG), a decrease from the 5.9% in 2004 ($p=0.24$), whereas 11.1% of isolates demonstrated chromosomally-mediated penicillin resistance (CMRNG) in 2005, an increase from the 4.5% seen in 2004 ($p=0.001$).

- Azithromycin resistance (MIC ≥1mg/l), was identified in 2.2% of isolates in 2005, a small increase compared with the 1.8% observed in 2004 ($p=0.55$).

- Overall, 48% of isolates demonstrated tetracycline resistance (MIC ≥2mg/l) in 2005, a small increase on the 44.4% observed in 2004 ($p=0.12$). Plasmid-mediated tetracycline resistance (TRNG or PP/TRNG) was observed in 7.1% of isolates in 2005, a significant decrease from the 10.1% observed in 2004 ($p=0.02$).

- In 2005, no isolates demonstrated resistance to spectinomycin (MIC ≥128mg/l), or decreased susceptibility to ceftriaxone (MIC ≥ 0.125mg/l) or cefixime (MIC ≥ 0.25mg/l).

- Non-genitourinary medicine (non-GUM) isolates demonstrated lower prevalences of ciprofloxacin resistance (14.2%), penicillin resistance (11.5%) and tetracycline resistance (42%) compared with GUM isolates in 2005.

1.3 Patient Characteristics

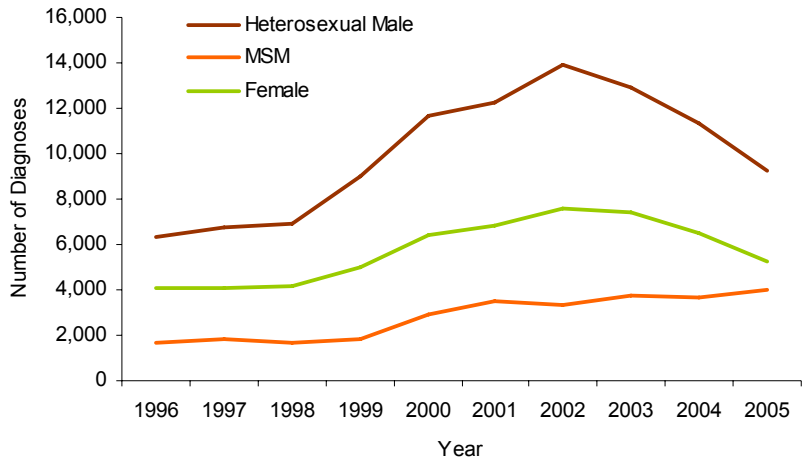
- The clinical and behavioural characteristics of GUM patients represented in the annual GRASP samples have remained relatively constant over time. However, compared with previous years there are fewer heterosexual men and women represented, and relatively more MSM.

2. Background

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

Neisseria gonorrhoeae is the second most common bacterial sexually transmitted infection (STI) in England and Wales, with a total of 18 483 infections diagnosed in GUM clinics in 2005. This represents a 14% decrease compared with the 21 473 diagnoses made in 2004[1], and follows the 11% decrease seen between 2003 and 2004[2]. However, diagnoses amongst MSM increased by 8% between 2004 and 2005. Young people remain the most commonly infected, with current rates highest in men aged 20-34 years and women aged 16-19 years. Gonococcal infection tends to be concentrated in core risk groups, in the UK these include MSM and black ethnic minority populations[2].

Figure 1. Diagnoses of uncomplicated gonorrhoea made in GUM clinics (B1B2) by gender and male sexual orientation, England and Wales: 1996 to 2005.



2.2 Global Gonococcal Antimicrobial Resistance

Penicillin and tetracycline resistant strains of *N. gonorrhoeae* are well documented throughout the world[3,4,5]. Fluoroquinolone resistance initially became widespread in the Far East[6] and has since spread throughout Asia[7,8], Australia[9], the Middle East[10] and Western Europe[3]. Resistance prevalences range from 8% in Greece[3] and 23% in Australia[9] to 99% in China and Hong Kong[8]. Endemic transmission has also been reported in North[11,12] and South America[13] as well as Africa[14]. In the USA, total fluoroquinolone resistance remained low at 8% in 2004, but an increase in the prevalence amongst MSM to 24% in 2004 (15% in 2003) was observed[12]. Furthermore, there have been reports of decreased susceptibility to ciprofloxacin in the Caribbean region[15,16].

For the first time azithromycin resistance has been documented in Western Europe at a prevalence of 8%[3]. Resistance to azithromycin has also been reported in Cuba[5] and Brazil[17]. In addition, there have been reports of reduced susceptibility in a cluster of isolates from infected individuals in the USA[18]. While most isolates remain susceptible to cefixime, ceftriaxone and spectinomycin, there have been reports of low-level in vitro resistance to ceftriaxone in China[7], Australia[9] and Western Europe[3].

The influence of sex abroad was recently highlighted in a molecular epidemiology study in South Africa, which showed that the largest cluster of ciprofloxacin resistant isolates had the same sequence type as ciprofloxacin resistant isolates in Europe[19].

2.3 The Gonococcal Resistance to Antimicrobials Surveillance Programme

The Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP) was established in June 2000, as a collaboration between the Communicable Disease Surveillance Centre (CDSC), the Genitourinary Infections Reference Laboratory (GUIRL), Bristol and Imperial College, and was funded by the Department of Health[20]. In 2000 the pilot collection was carried out across 30 participating GUM clinics and laboratories. From 2001 the annual GRASP collection has consisted of 26 collaborating GUM clinics covered by 24 laboratories (see page 22).

In 2005, the GRASP annual collection was undertaken by the Health Protection Agency, Centre for Infections. GRASP has proven a successful collaboration with participating laboratories and GUM clinics collecting data on over 13 000 isolates since the first collection in 2000. GRASP has enabled us to calculate reliable prevalence estimates of gonococcal antimicrobial resistance in England and Wales[21,22]. It has also allowed epidemiological investigations of gonococcal antimicrobial resistance. Most importantly the prevalence estimates produced by GRASP have informed national antimicrobial prescribing policy[21,23].

This report presents the findings of the 6th year of isolate collection in this programme, highlighting the changes observed in antimicrobial susceptibility and gonococcal epidemiology from 2004 to 2005.

2.4 Antimicrobial Resistance Glossary

Table 1. Glossary of antimicrobial resistance and classification types.

Classification	Definition
Penicillin Resistant	Penicillin: MIC ≥ 1mg/l or β-lactamase +ve
Tetracycline Resistant	Tetracycline: MIC ≥ 2mg/l
PPNG	Penicillin: β-lactamase +ve AND tetracycline: MIC<16mg/l
TRNG	Tetracycline: MIC ≥ 16mg/l AND penicillin β-lactamase -ve
PP/TRNG	Penicillin: β-lactamase +ve AND tetracycline: MIC ≥ 16mg/l
CMRNG	Penicillin: MIC ≥ 1mg/l but β-lactamase -ve AND tetracycline: MIC between 2-8mg/l
PenR	Penicillin: MIC ≥ 1mg/l but β-lactamase –ve AND tetracycline: MIC<2mg/l
TetR	Tetracycline: MIC between 2-8mg/l AND penicillin: MIC <1mg/l
Ciprofloxacin Resistant	MIC ≥ 1mg/l
Ciprofloxacin Decreased Susceptibility	MIC ≥ 0.125mg/l to 0.5mg/l
Ciprofloxacin Decreased Susceptible or Resistant	MIC ≥ 0.125mg/l
Spectinomycin	MIC ≥ 128mg/l
Azithromycin	MIC ≥ 1mg/l
Ceftriaxone (Decreased susceptibility)	MIC ≥ 0.125mg/l
Cefixime (Decreased susceptibility)	MIC ≥ 0.25mg/l

3. Sample Description

3.1 Retrieval in 2005

In 2005, all participating laboratories were asked to freeze their culture samples in supplied glycerol broth with a monthly collection by courier to bring them frozen to STBRL. This method of sample collection, previously used successfully, was less labour intensive than previous methods and enabled storage of the isolates until laboratory staff were available to perform the testing. However, problems with the retrieval method coupled with a personnel shortage at STBRL resulted in variable retrieval rates among participating centres.

A total of 1948 isolates were collected by the 24 GRASP collaborating laboratories during the three month data collection period in 2005, and sent to STBRL for antimicrobial susceptibility testing. After the exclusion of duplicates 1823 isolates were retained, of these isolates 1030 (56.5%) were recovered successfully and confirmed as *N. gonorrhoeae*. This represents a decrease of 47% in the number of confirmed isolates observed in 2005 compared with 2004.

The retrieval rates by region are shown in detail in table 2. The overall retrieval rate in London was 65.1% compared with 49.3% of isolates outside of London, where retrieval ranged from 32.3% in the East of England to 79.3% in the North East. To correct for the retrieved sample being under or over representative of the total sample, the results presented in this report are weighted. Each result is a weighted average of the results from the participating sites and estimates what we expect to be the value of total confirmed and unconfirmed isolates.

Table 2. The proportion of GRASP isolates confirmed as *N.gonorrhoeae* by region in the 2005 collection.

Region	Submitted Isolates N (%)		Total
	Confirmed	Unconfirmed	
East Midlands	61 (51.3)	58 (48.7)	119
East of England	10 (32.3)	21 (67.7)	31
London	538 (65.1)	288 (34.9)	826
North East	46 (79.3)	12 (20.7)	58
North West	80 (41.9)	111 (58.1)	191
South East	37 (45.7)	44 (54.3)	81
South West	57 (53.3)	50 (46.7)	107
Wales	60 (53.1)	53 (46.9)	113
West Midlands	79 (49.4)	81 (50.6)	160
Yorkshire & Humberside	62 (45.3)	75 (54.7)	137
Total	**1030 (56.5)**	**793 (43.5)**	**1823**

3.2 Weighting of Data

The retrieved sample was found to be broadly representative of the total sample in respect of patient characteristics. This meant that the weighted and unweighted results were not very different. However, the preferred results are those weighted to reflect what would have been expected to be the value of total confirmed and unconfirmed isolates.

The same method of weighting has been applied to previous years although with less effect due to the generally higher retrieval rates. Furthermore, additional clinical data have also been added to the datasets as missing data have been received. Updated prevalences and data presented in this report may therefore differ from those previously published.

3.3 Sample Distribution in 2005

Of the total 1030 confirmed isolates in 2005, 965 were from patients who had attended a GUM clinic, whilst 65 attended another primary care setting such as general practice, hospital in- or out-patient departments (table 3). Where more than one isolate per individual was received during the data collection period, results for the second isolate were only included in the analyses if the date of isolation of the second isolate was ≥ 28 days after the first isolate. In 2005, as in previous years, such patients accounted for <1% of all isolates.

Table 3. Numbers of gonococcal isolates obtained in the GRASP collection: June-August 2005.

Region	Total number of confirmed isolates	Non-GUM isolates N (%)	GUM Clinic data	
			Number of Isolates	Number of Patients
East Midlands	61	2 (3.3)	59	58
East of England	10	0 (0.0)	10	10
London	538	20 (3.7)	518	514
North East	46	4 (8.7)	42	42
North West	80	0 (0.0)	80	79
South East	37	2 (5.4)	35	34
South West	57	13 (22.8)	44	43
Wales	60	14 (23.3)	46	46
West Midlands	79	9 (11.4)	70	68
Yorkshire & Humberside	62	1 (1.6)	61	61
Total	**1030 (100)**	**65 (6.3)**	**965 (93.7)**	**955**

In 2005, 52.3% of the confirmed isolates were from London and 49.2% were from outside of London. The proportion of GUM isolates contributed to the total by each region is shown in figure 2.

An increasing proportion of GRASP isolates in 2005 were from MSM, 34.1% compared with 30.2% in 2004, whilst the proportion of isolates from heterosexual men and women decreased to 65.9% (69.9% in 2004), which is in-line with the latest KC60 trends (figure 1).

The distribution of gonococcal infection in patients attending participating GRASP clinics in London in 2005 is shown in figure 3 by postcode of residence. The map highlights the large burden of gonococcal infection within London, particularly in South West London and to a lesser extent North and North East London.

A similar pattern of distribution to that seen in London is also seen in each participating GRASP centre outside of London, with the burden of gonococcal infection noticeably concentrated within the urban area served by each GUM clinic.

Figure 2. The distribution of confirmed gonococcal isolates from GUM patients: GRASP 2005 (N=965)

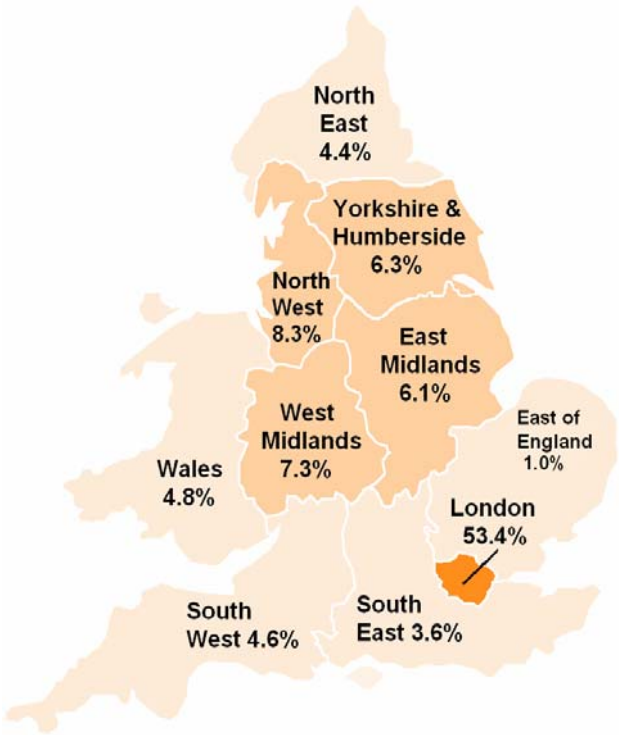
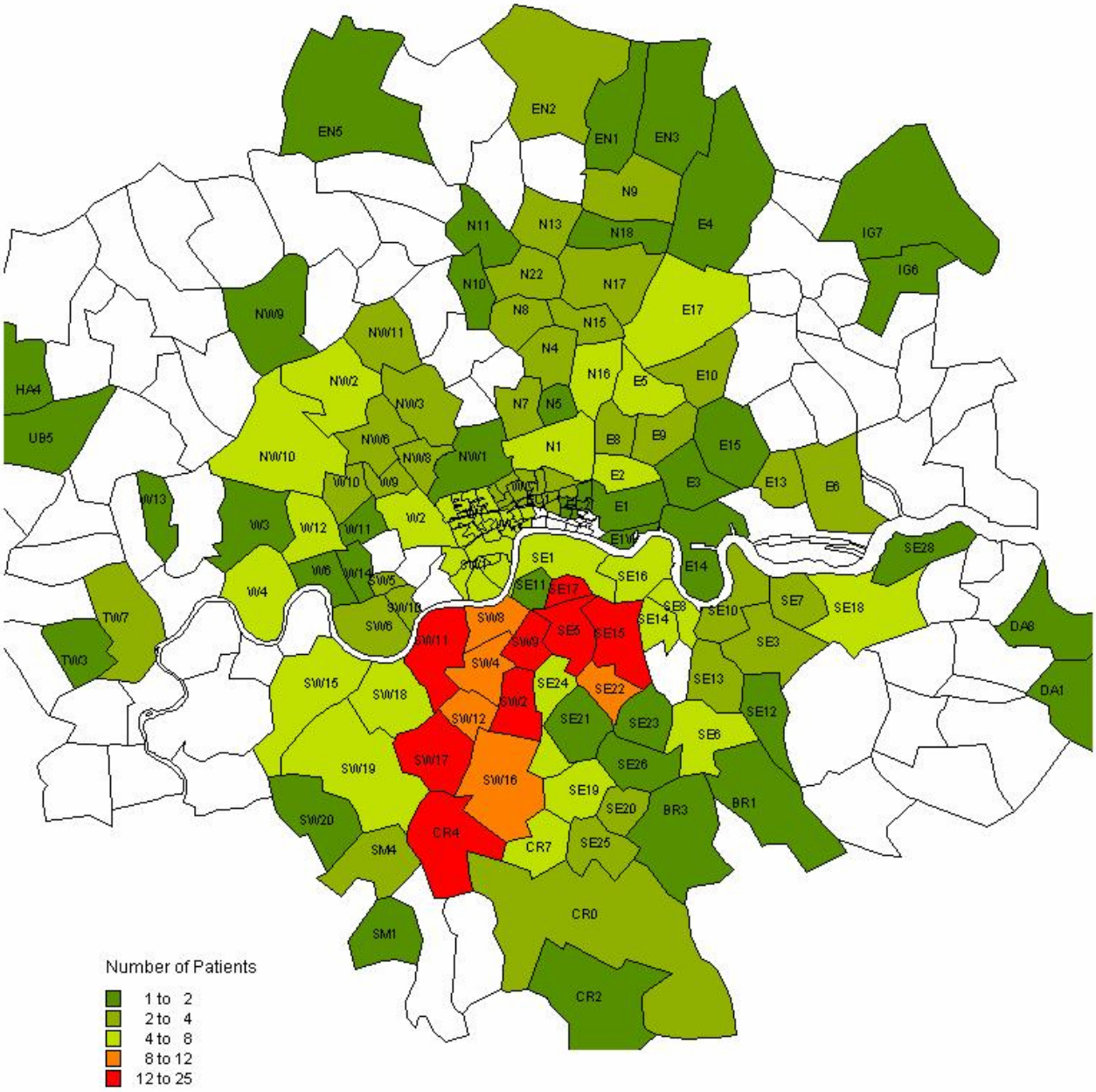


Figure 3. The geographic distribution of confirmed GUM patients within the London region by postcode of residence (n=440); GRASP 2005 collection.



4. Antimicrobial Susceptibility

In the 2005 GRASP collection, ciprofloxacin resistance was observed in 21.7% of isolates, with a further 1.3% showing decreased susceptibility. Penicillin resistance was observed in 17.9% of isolates, with plasmid-mediated resistance (PPNG or PP/TRNG) due to β-lactamase in 4.3% of isolates and chromosomally-mediated (CMRNG or PenR) resistance in 12.1% of isolates. Tetracycline resistance was observed in 48.0% of isolates, with high-level plasmid-mediated tetracycline resistance (TRNG or PP/TRNG) found in 7.1% of isolates and chromosomally-mediated tetracycline resistance (TetR) found in 26.7% of isolates. Azithromycin resistance was identified in 2.2% of isolates, whilst no isolates were resistant to spectinomycin in 2005. As observed in previous years, no isolates in 2005 showed decreased susceptibility to ceftriaxone or cefixime.

A significant difference was observed between the prevalence of CMRNG between London (16.0%) and non-London (6.7%) clinics ($p<0.05$) in 2005. No significant differences were observed between the London and non-London prevalences for ciprofloxacin, PPNG or PP/TRNG, TRNG or PP/TRNG, or azithromycin resistance in 2005.

Table 4 presents the percentage of isolates resistant to specific antimicrobials in London and non-London GRASP clinics in 2005, compared with 2004, and table 5 shows the percentage resistant to different types of penicillin and tetracycline resistance in London and non-London GRASP clinics in 2005 compared with 2004.

Table 4. Percentage of isolates resistant to specific antimicrobials 2004 to 2005 in London and Non-London.

Antimicrobial*	London % (95% CI)		Non-London % (95% CI)		Total % (95% CI)	
	2004	2005	2004	2005	2004	2005
Penicillin (≥ 1mg/l or β-lactamase +)	14.4 [9.8,20.8]	25.4 [16.4,37.1]	8.8 [5.7,13.3]	11.2 [7.5,16.5]	11.4 [8.6,14.8]	17.9 [12.8,24.5]
Tetracycline (≥ 2mg/l)	52.2 [39.6,64.6]	56.4 [38.6,72.8]	37.8 [31.3,44.7]	40.3 [32.1,49.2]	44.4 [37.8,51.3]	48.0 [38.8,57.2]
Ciprofloxacin (≥ 1mg/l)	16.7 [8.7,29.5]	24.7 [13.0,41.9]	11.8 [7.8,17.4]	19.0 [12.9,27.2]	14.0 [0.0,19.4]	21.7 [15.5,29.5]
Ciprofloxacin (≥0.125mg/l)	18.1 [9.9,30.8]	25.9 [13.4,44.3]	13.4 [9.6,18.5]	20.4 [14.1,28.6]	15.6 [11.5,20.8]	23.0 [16.5,31.3]
Azithromycin (≥ 1mg/l)	1.6 [1.1,2.3]	2.2 [0.8,6.1]	2.0 [1.2,3.3]	2.2 [1.1,4.5]	1.8 [1.3,2.5]	2.2 [1.3,3.8]
Spectinomycin (≥128mg/l)	0.4 [0.2,0.8]	0.0 [-,-]	0.0 [-,-]	0.0 [-,-]	0.2 [0.1,0.5]	0.0 [-,-]
Ceftriaxone (≥ 0.125mg/l)	0.0 [-,-]	0.0 [-,-]	0.0 [-,-]	0.0 [-,-]	0.0 [-,-]	0.0 [-,-]
Cefixime (≥ 0.25mg/l)	0.0 [-,-]	0.0 [-,-]	0.0 [-,-]	0.0 [-,-]	0.0 [-,-]	0.0 [-,-]

Table 5. Percentage of isolates resistant to penicillin and tetracycline 2004 to 2005, in London and Non-London.

Resistance Classification*	London % (95% CI)		Non-London % (95% CI)		Total % (95% CI)	
	2004	2005	2004	2005	2004	2005
PPNG	2.6 [1.8,3.8]	5.1 [2.7,9.3]	3.5 [1.5,7.9]	1.5 [0.6,3.7]	3.1 [1.8,5.1]	3.2 [1.8,5.6]
TRNG	9.3 [6.4,13.4]	8.2 [5.2,12.8]	5.5 [3.7,8.1]	4.0 [2.2,7.3]	7.3 [5.5,9.6]	6.0 [4.2,8.5]
PP/TRNG	3.1 [2.3,4.1]	0.7 [0.2,2.6]	2.6 [1.5,4.6]	1.5 [0.5,4.6]	2.8 [2.1,3.8]	1.1 [0.5,2.6]
CMRNG	7.1 [3.9,12.7]	16.0 [7.2,32.0]	2.2 [1.3,3.9]	6.7 [4.8,9.4]	4.5 [2.9,6.9]	11.1 [6.8,17.7]
PenR	0.4 [0.1,1.2]	1.5 [0.6,4.1]	0.2 [0.1,1.0]	0.5 [0.1,4.5]	0.3 [0.1,0.7]	1.0 [0.4,2.4]
TetR	30.7 [23.7,38.8]	26.6 [17.5,38.2]	24.4 [20.0,29.3]	26.8 [20.9,33.7]	27.3 [23.5,31.4]	26.7 [21.7,32.4]
PPNG or PP/TRNG	5.7 [4.4,7.4]	5.8 [2.9,11.2]	6.1 [3.3,10.7]	3.0 [1.3,6.8]	5.9 [4.2,8.2]	4.3 [2.6,7.2]
TRNG or PP/TRNG	12.4 [9.6,15.9]	8.9 [6.2,12.7]	8.1 [5.8,11.2]	5.5 [2.9,10.1]	10.1 [8.1,12.5]	7.1 [5.1,9.8]

*Resistance category definitions are listed on page 6.

5. Ciprofloxacin

In 2005, 21.7% of isolates were resistant to ciprofloxacin, an increase from the 14.0% observed in 2004 (p<0.0005). A further 1.3% of isolates demonstrated decreased susceptibility to ciprofloxacin, compared with the 1.6% observed in 2004. Consequently, 23.0% of isolates demonstrated decreased susceptibility or resistance to ciprofloxacin in 2005, compared with 15.6% in 2004.

The prevalence of ciprofloxacin resistance varied significantly by region (p=0.03) in 2005, ranging from 8.9% in the East of England to 41.6% in the South East. In nearly all regions the prevalence remained greater than 10% in 2005 (figure 4).

The prevalence of resistance remained stable in isolates from women at 6.3% (cf. 5.2% in 2004) and heterosexual men 11.8% (cf. 10.3% in 2004). However, the prevalence significantly increased in MSM from 26.2% in 2004 to 42.4% in 2005 (p<0.0005), figure 5.

The prevalence of ciprofloxacin resistance by ethnic group is shown in figure 6. In 2005, 40.9% of isolates from Asian and 23.9% of isolates from white individuals were ciprofloxacin resistant. The high prevalence of resistance amongst isolates from Asian individuals is largely due to the high prevalence amongst heterosexual men, who have had sexual contact in Asia. Whilst the high prevalence of resistance amongst isolates from white individuals is due to the high proportion of white MSM with high prevalences of resistance in both endemic (41.0%) and imported strains (47.7%) in 2005.

Despite the high burden of gonorrhoea in black ethnic groups, the prevalence of ciprofloxacin resistance remains much lower in the black Caribbean (4.1%), and black African (13.5%) populations than other ethnic groups because the majority of transmission within these groups remains heterosexual and within the UK.

Figure 4. The prevalence of ciprofloxacin resistance by region 2001 to 2005.

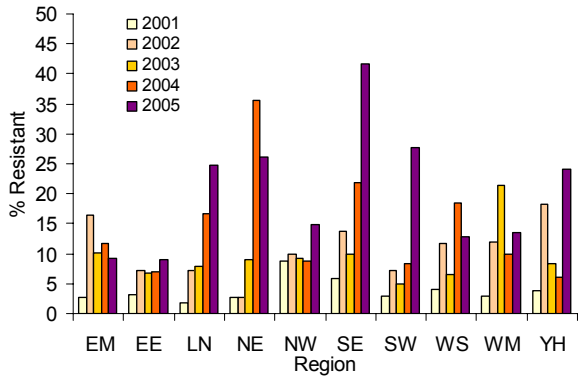


Figure 5. The prevalence of ciprofloxacin resistance by gender and male sexual orientation:2001 to 2005.

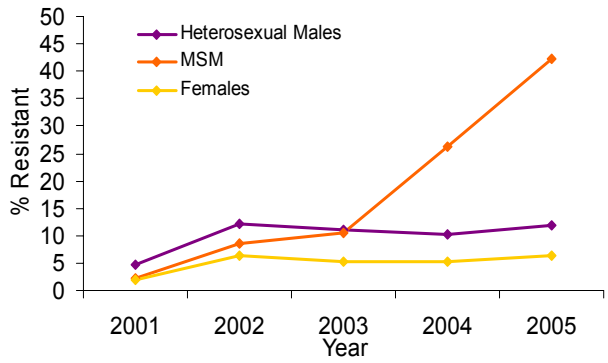
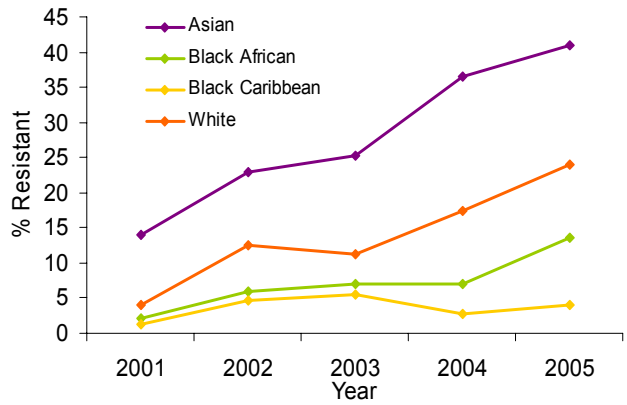


Figure 6. The prevalence of ciprofloxacin resistance by ethnic group: 2001 to 2005.

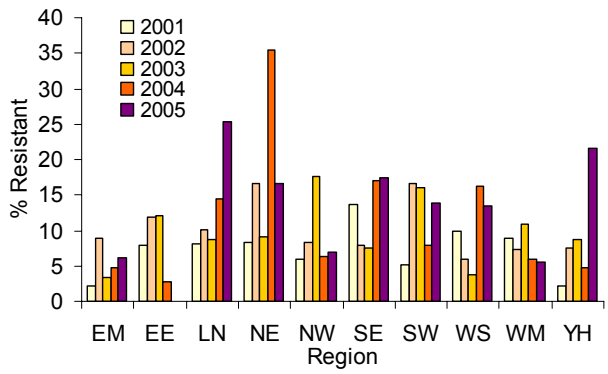


Region Key: East Midlands EM, East of England EE, London LN, North East NE, North West NW, South East SE, South West SW, Wales WS, West Midlands, WM, Yorkshire & Humberside YH.

6. Penicillin

Overall, 17.9% of isolates demonstrated penicillin resistance in 2005, compared with 11.4% in 2004 (p<0.005). The prevalence of penicillin resistance varied significantly by region in 2005 (p<0.005), ranging from 0% in the East of England to 25.4% in London in 2005.

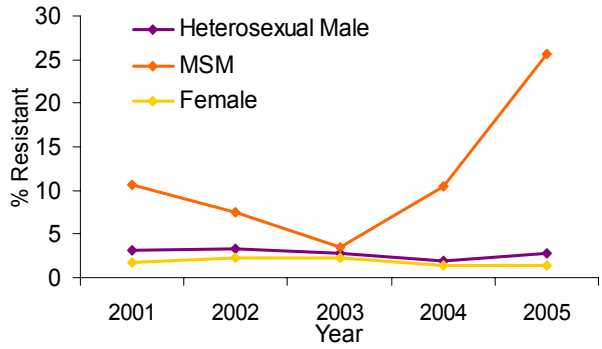
Figure 7. The prevalence of penicillin resistance by region over time: 2001 to 2005.



6.1 Chromosomally-mediated resistance (CMRNG)

In 2005, 11.1% of isolates demonstrated chromosomally-mediated penicillin resistance (CMRNG), compared with 4.5% in 2004 (p<0.005). No significant differences were observed in the prevalence of CMRNG amongst heterosexual men (2.8% cf. 2.0%) and women (1.4% cf. 1.4%) in 2005 compared with 2004. However, a significant increase in the prevalence of CMRNG amongst MSM was observed, rising from 10.5% in 2004 to 25.6% in 2005 (p<0.0005), figure 8.

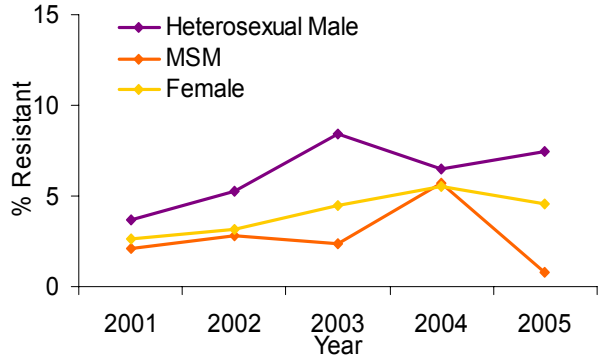
Figure 8. The prevalence of CMRNG by gender and male sexual orientation: 2001 to 2005.



6.2 Plasmid-mediated resistance (PPNG or PP/TRNG)

In 2005, 4.3% of isolates demonstrated plasmid-mediated penicillin resistance (PPNG or PP/TRNG), compared with 5.9% in 2004 (p=0.24). A small increase was observed in the prevalence of PPNG or PP/TRNG amongst isolates from heterosexual men (7.5% cf. 6.5%) and a small decrease amongst women (4.6% cf. 5.5%) in 2005 compared with 2004, although these were not significant. However, a significant decrease in the prevalence amongst MSM was observed, falling from 5.7% in 2004 to 0.8% in 2005 (p<0.005), figure 9.

Figure 9. The prevalence of PPNG or PP/TRNG by gender & male sexual orientation: 2001 to 2005.



Region Key: East Midlands EM, East of England EE, London LN, North East NE, North West NW, South East SE, South West SW, Wales WS, West Midlands WM, Yorkshire & Humberside YH.

7. Other Antimicrobials

7.1 Tetracycline

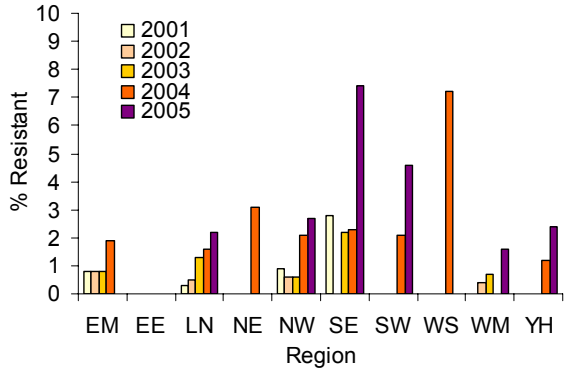
In 2005, 48% of isolates demonstrated tetracycline resistance, compared with 44.4% in 2004 (p=0.12). Chromosomally-mediated tetracycline resistance (TetR) was observed in 26.7% of isolates in 2005 compared with 27.3% in 2004 (p=0.81). Plasmid-mediated tetracycline resistance (TRNG or PP/TRNG) was observed in 7.1% of isolates in 2005, a significant decrease on the 10.1% observed in 2004 ($p<0.05$). The prevalence of TRNG or PP/TRNG significantly decreased in heterosexual men from 10.6% in 2004 to 6.5% in 2005 ($p<0.05$), it also decreased in women (5.4% cf. 7.1%) and MSM (8.8% cf. 12.3%) but these decreases were not significant. Tetracycline is prescribed to patients with gonorrhoea to treat concurrent *Chlamydia trachomatis* infection; 43% of patients were prescribed tetracycline (doxycycline) in 2005, the same proportion as seen in 2004.

7.2 Azithromycin

In 2005, 2.2% of isolates demonstrated resistance to azithromycin, a slight increase on the 1.8% prevalence observed in 2004, although this was not significant. The prevalence of resistance remained low in most regions in 2005 ranging from 0% in the East Midlands, North East, Wales and the East of England, to 7.4% in the South East (figure 10).

In 2005 the prevalence of azithromycin resistance increased amongst isolates from heterosexual men (1.9% cf. 0.7%) and MSM (3.7% cf. 2.8%) and decreased in those from women (0.5% cf. 2.2%), although these changes were not significant.

Figure 10. The prevalence of azithromycin resistance by region: 2001 to 2005.



7.3 Ceftriaxone and Cefixime

As observed in previous years, no isolates demonstrated decreased susceptibility to ceftriaxone or cefixime in 2005.

7.4 Spectinomycin

In 2005 no isolates were resistant to spectinomycin, a decrease from the three isolates (0.2%) observed in 2004.

Region Key: East Midlands EM, East of England EE, London LN, North East NE, North West NW, South East SE, South West SW, Wales WS, West Midlands WM, Yorkshire & Humberside YH.

8. Prescribing Practice

Fluoroquinolones are no longer a recommended first-line therapy for gonococcal infection owing to the increases in ciprofloxacin resistance prevalence in England and Wales, identified during the 2002 GRASP collection[21]. Current treatment guidelines now recommend cephalosporins as first-line treatment for gonococcal infection[23]. The impact of these recommendations can be seen in table 6, which compares the prescribing pattern observed across the regions in the 2002 and 2005 GRASP collections.

8.1 Cephalosporins

Overall 71.2% of patients were prescribed a cephalosporin to treat gonococcal infection in 2005 compared with only 14.6% in 2002. Prescribing differences were observed across the regions, with the proportion of individuals prescribed a cephalosporin ranging from 49.4% in the North West region to 95.1% in the North East. Prescribing also differed significantly by gender and male sexual orientation; with 67.4% of heterosexual men, 82.6% of MSM and 59.3% of women prescribed cephalosporins in 2005 ($p<0.0005$). Of those prescribed, the most commonly administered were cefixime (62.6%) and ceftriaxone (36.5%).

8.2 Fluoroquinolones

In 2005, 18.6% of GRASP patients were prescribed fluoroquinolones, compared with the 69.2% observed in 2002. However, 47.6% of individuals in the East of England and 44.1% in the North West were prescribed fluoroquinolones in 2005. Prescribing varied significantly by gender and male sexual orientation, with 24.9% of women, 22.9% of heterosexual men and 16.8% of MSM receiving fluoroquinolones in 2005 ($p<0.05$).

8.3 Penicillin

Penicillin (ampicillin) was prescribed to 5.7% of individuals in 2005 compared with 11.7% in 2002. Only clinics in Wales (20.4%) and London (10.5%) prescribed penicillin to GRASP patients in 2005. Prescribing varied significantly by gender and male sexual orientation, with 6.4% of women, 4.3% of heterosexual men and 1% of MSM being prescribed penicillin in 2005 ($p<0.005$).

8.4 Azithromycin

Azithromycin is used to treat patients with concurrent chlamydial infection and, in 2005, was prescribed to 28.2% of individuals, compared with 22.4% in 2002. The proportion of individuals prescribed azithromycin in 2005 was highest in the South East (54.9%), East Midlands (38.5%) and London (38%).

Table 6. The proportion of patients (%) receiving selected antimicrobials to treat gonorrhoea and/or chlamydial infection in 2005 compared with 2002.

Region	Fluoroquinolones		Cephalosporins		Penicillin		Azithromycin	
	2002	2005	2002	2005	2002	2005	2002	2005
East Midlands	18.4	18.4	77.0	76.9	0.8	0.0	13.9	38.5
East of England	83.3	47.6	14.3	52.4	0.0	0.0	4.8	7.9
London	78.2	18.2	1.7	66.5	17.2	10.5	34.1	38.0
North East	86.1	2.4	16.7	95.1	0.0	0.0	0.0	0.0
North West	14.4	44.1	45.6	49.4	33.7	0.0	2.2	1.6
South East	93.9	11.3	12.3	88.7	0.0	0.0	6.2	54.9
South West	88.9	12.1	2.2	87.9	2.0	0.0	8.1	35.4
Wales	54.9	8.7	9.8	65.9	35.3	20.4	3.9	7.9
West Midlands	68.9	3.1	2.8	84.6	0.5	0.0	26.5	15.6
Yorkshire & Humberside	66.0	12.7	40.7	89.9	0.5	0.0	10.3	27.3
Overall Percentage	**69.2**	**18.6**	**14.6**	**71.2**	**11.7**	**5.7**	**22.4**	**28.2**

9. Patient Characteristics

9.1 Demographic characteristics

In recent years, there has been a decline in the number of heterosexual men and women represented in the GRASP collections and an increase in the number of MSM. As in previous years, the 2005 data highlights the burden of gonococcal infection in core groups including MSM, young people and ethnic minorities (table 7). A slight increase in the proportion of infection diagnosed in MSM was observed rising from 30.7% in 2004 to 32.9% in 2005. The majority of gonococcal infections were diagnosed in young women aged 16-19yrs (43.1%) and in heterosexual men aged 20-24yrs (41.7%). Ethnic minorities accounted for 41% of the total diagnoses in 2005, compared with 42.3% in 2004.

9.2 Clinical Characteristics

The clinical characteristics of the patients in GRASP have remained relatively constant over time; thus in 2005, 29.4% of individuals diagnosed with gonorrhoea had a previous history of gonococcal infection, rising to 43.6% in MSM. Whilst 35.9% of individuals diagnosed with gonorrhoea presented with one or more concurrent STI. Forty-one percent of women, and 30.6% of heterosexual men presented with concurrent chlamydial infection in 2005. The majority of women (98.0%) and heterosexual men (96.2%) presented with genital infection, whilst 49.8% of MSM presented with rectal and/or pharyngeal gonorrhoea. As observed in 2004, 13.9% of patients diagnosed with gonorrhoea with a known HIV status were HIV positive in 2005. This varied by gender and sexual orientation with 32.6% of MSM, 2.3% of heterosexual men and 0.4% of women diagnosed as HIV positive.

9.3 Behavioural Characteristics

In 2005, 72.7% of women reported 0-1 partners in the past three months, compared with 42.1% of heterosexual men and 28.8% of MSM. Overall, 54.6% of individuals reported multiple sexual partners in the last 3 months, significantly higher than is estimated for the general population[24]. This varied by gender and sexual orientation with 27.2% of women, 57.8% of heterosexual men and 71.3% of MSM reporting multiple partners in the past three months. As seen in 2004, 11% of individuals reported a sexual partner abroad in 2005. Sexual contact abroad in the past 3 months varied by gender and male sexual orientation and was reported in 10.9% of heterosexual men, 14.5% of MSM and 10.2% of women in 2005. Of the individuals reporting sexual partners abroad in 2005 for whom region of sexual contact was known (n=102), 33.3% reported a sexual contact in Western Europe, 21.6% in the Caribbean, 8.8% in the Far East and 8.8% in Eastern Europe.

9.3.1 Antimicrobial Resistance due to Sex Abroad

Of the individuals who had sexual contact abroad in the past three months, 39.4% yielded ciprofloxacin resistant isolates compared with a prevalence of 17.9% in those who only had partners in the UK. The prevalence of ciprofloxacin resistance amongst isolates from heterosexual men who had sexual contact abroad was 49.6%, compared with a prevalence of 6.2% in those who did not. Heterosexual men who had sexual contact abroad also had a higher prevalence of PPNG or PP/TRNG isolates; 32% compared with 4.6% in those who only had partners in the UK. Of the MSM who had sexual contact abroad in the past three months, 41.5% had CMRNG resistant isolates compared with 22.4% of MSM who only had partners in the UK.

Table 7. Demographic, clinical and behavioural characteristics among all GUM patients with confirmed gonorrhoea from participating GUM clinics by gender and sexual orientation: GRASP 2005.

Characteristics	Females %	Heterosexual males %	MSM %	Total %
GUM Clinic Locality				
London	46.6	35.1	56.7	45.6
Outside London	53.4	64.9	43.3	54.4
Total (Baseline‡)	259	346	300	905
Ethnicity				
White	52.7	36.3	88.9	59.0
Asian or Asian British	3.6	7.0	1.4	4.1
Black Caribbean	19.1	29.1	4.0	17.7
Black African	5.3	10.9	0.9	6.0
Other Black	8.8	9.0	2.0	6.5
Other	9.8	7.5	2.3	6.2
Total (Baseline‡)	217	332	288	837
Age Group				
≤15	4.4	0.5	0.0	1.4
16-19	43.1	13.2	4.3	18.4
20-24	28.2	41.7	16.4	29.4
25-34	16.7	28.2	42.2	29.8
35-44	5.3	9.8	28.7	15.0
45+	2.2	6.6	8.4	6.0
Total (Baseline‡)	259	346	300	905
Symptoms				
Discharge and or dysuria	58.7	86.9	78.8	76.9
No discharge or dysuria	41.3	13.1	21.2	23.1
Total Baseline‡)	223	339	287	849
Previously diagnosed with gonorrhoea				
Yes	16.2	25.8	43.6	29.4
No	83.8	74.2	56.4	70.6
Total (Baseline‡)	223	336	281	840
Concurrent STI†				
Syphilis	0.5	2.6	2.8	2.1
Chlamydia	41.3	30.6	13.2	27.3
Herpes	0.7	0.7	1.7	1.0
Warts	4.1	0.7	0.8	1.6
Other	12.4	2.1	6.3	6.2
Total (Baseline) ‡	224	337	290	851
Site of Infection†				
Genital	98.0	96.2	67.3	86.6
Rectal	5.2	2.4	36.8	15.0
Throat	4.0	1.9	13.0	6.3
Other	0.0	0.0	0.0	0.0
Total (Baseline) ‡	224	341	290	855
HIV Status				
Negative	99.6	97.7	67.4	86.1
Positive	0.4	2.3	32.6	13.9
Total (Baseline) ‡	156	216	233	605
UK Partners (past 3 months)				
0-1	72.7	42.1	28.8	45.4
2-5	25.8	54.4	49.0	45.2
6-10	0.8	2.6	12.3	5.5
11+	0.6	0.8	10.0	3.9
Total (Baseline) ‡	224	338	284	846
Sex Abroad (past 3 months)				
Yes	10.2	10.9	14.5	11.9
Total (Baseline) ‡	24	38	41	103

*Sexual orientation was reported for 92% (646/706) of males at participating GRASP clinics.
† A patient may present with more than 1 site of infection and/or concurrent STI.
‡ Baseline figure is the number of patients for whom that variable is known.

10. Data from non-GUM settings

In 2005, as in previous years, the GRASP collection received non-GUM isolates as well as GUM isolates. Non-GUM isolates accounted for 6% of the total sample in 2005, which is similar to the proportion seen in previous years (7% in 2004). These isolates come from a range of settings such as General Practice, and in-patient or out-patient hospital services such as family planning. The GRASP analyses presented in each annual report consists of GUM data only, as limited clinical information is available on non-GUM patients. Here, for the first time, we present the available data on the non-GUM sample collected annually as part of GRASP.

10.1 Demographic characteristics

Table 8 presents the demographic data available for the non-GUM isolates collected as part of GRASP from 2001 to 2005. The proportion of non-GUM isolates from London and clinics outside of London has remained relatively constant over time, in 2005, 23.1% of isolates were from London and 76.9% from clinics outside London. This is in contrast to the pattern seen in the 2005 GUM sample where the London and outside London sample is more evenly split (45.6% cf. 54.4%). In 2005, the regions outside of London with the largest proportions of non-GUM isolates were Wales (23.9%), the South West (22.4%) and the West Midlands (16.4%). In contrast the East of England and North West had no non-GUM isolates in 2005.

A difference in the gender breakdown of the non-GUM isolates occurred over time, with an increasing proportion of isolates from male patients, 41.4% in 2005 compared with 25.5% 2001, whilst the female proportion decreased from 74.5% in 2001 to 58.6% in 2005. This is dissimilar to the gender breakdown of the GUM sample which had a majority of male patients in 2005 (74%). In 2005, the majority of the non-GUM isolates were from individuals aged 20-24 years (30.1%) and 25-34 years (26.0%), which is in-line with the age breakdown of GUM isolates collected in 2005.

10.2 Antimicrobial Susceptibility

The percentages of non-GUM isolates resistant to specific antimicrobials during the 2001 to 2005 GRASP collections are shown in table 9. In 2005 ciprofloxacin resistance was observed in 14.2% of non-GUM isolates, an increase from the 8.4% observed in 2004. Penicillin resistance was observed in 11.5% of isolates in 2005, compared with the 8.4% observed in 2004. Tetracycline resistance was observed in 42% of isolates in 2005, an increase from the 33.4% observed in 2004. Azithromycin resistance was identified in 1.7% of non-GUM isolates in 2005 compared with the 0% seen in 2004. No non-GUM isolates demonstrated resistance to spectinomycin or decreased susceptibility to ceftriaxone or cefixime between 2001 and 2005.

In each year's GRASP collection the GUM isolates demonstrated higher prevalences of resistance to each antimicrobial than the corresponding year's non-GUM isolates. In 2005, 21.7% of GUM isolates demonstrated ciprofloxacin resistance compared with 14.2% of non-GUM isolates. Likewise, 17.9% of GUM isolates were penicillin resistant compared with 11.5% of non-GUM isolates, 48% compared with 42% were tetracycline resistant and 2.2% compared with 1.7% were azithromycin resistant.

Table 8. Demographic characteristics among non-GUM patients with confirmed gonorrhoea from participating GRASP centres over time 2001 to 2005.

Characteristics	Year %					Total
	2001	2002	2003	2004	2005	
Location						
London	25.5	22.5	10.5	25.2	23.1	21.2
Outside London	74.5	77.5	89.5	74.8	76.9	78.8
Region						
East Midlands	19.1	2.5	1.3	4.4	5.2	6.5
East of England	7.8	7.5	7.2	3.8	0.0	5.2
London	25.5	22.5	10.5	25.2	23.1	21.2
North East	0.7	4.2	1.3	0.6	3.0	1.8
North West	4.3	5.8	10.5	3.1	0.0	4.8
South East	5.0	1.7	7.2	3.1	3.7	4.2
South West	17.7	28.3	38.8	28.3	22.4	27.3
Wales	4.3	13.3	13.8	11.9	23.9	13.3
West Midlands	9.2	5.0	5.9	6.3	16.4	8.5
Yorkshire & Humberside	6.4	9.2	3.3	13.2	2.2	6.9
Gender						
Male	25.5	29.1	33.7	35.1	41.4	33.1
Female	74.5	70.9	66.3	64.9	58.6	66.9
Age Group						
≤15	3.9	9.3	5.3	0.8	3.7	4.4
16-19	28.7	28.6	32.3	29.9	16.8	27.4
20-24	32.9	20.7	25.0	25.5	30.1	26.9
25-34	21.6	23.5	24.8	29.4	26.0	25.2
35-44	9.7	12.3	10.2	10.9	14.6	11.5
45+	3.2	5.6	2.4	3.5	8.7	4.6

Table 9. Percentage and number of isolates resistant to specific antimicrobials among non-GUM patients with confirmed gonorrhoea from participating GRASP centres over time 2001 to 2005

Antimicrobial	Year % (95% CI)				
	2001	2002	2003	2004	2005
Penicillin (≥ 1mg/l or β lactamase +ve)	6.5 [3.1, 13.4]	10.6 [5.7, 18.7]	8.5 [4.7, 14.9]	8.4 [4.6, 14.8]	11.5 [5.0, 24.3]
Tetracycline (≥ 2mg/l)	22.8 [13.5, 35.9]	33.8 [20.6, 50.0]	22.9 [16.7, 30.4]	33.4 [25.2, 42.7]	42.0 [30.4, 54.6]
Ciprofloxacin (≥ 1mg/l)	4.4 [2.1, 9.0]	7.1 [3.7, 13.0]	4.7 [1.7, 12.1]	8.4 [3.4, 19.3]	14.2 [7.6, 25.1]
Ciprofloxacin (≥ 0.125mg/l)	6.8 [3.6,12.7]	8.8 [5.2,14.7]	5.6 [2.2,13.6]	9.0 [4.1,18.7]	14.2 [7.6,25.1]
Spectinomycin (≥ 128mg/l)	0.0 [-,-]	0.0 [-,-]	0.0 -,-]	0.0 [-,-]	0.0 [-,-]
Azithromycin (≥ 1mg/l)	1.4 [0.2, 11.1]	0.0 [-,-]	0.7 [0.1, 5.8]	0.0 [-,-]	1.7 [0.3, 9.2]
Ceftriaxone (≥ 0.125mg/l)	0.0 [-,-]	0.0 [-,-]	0.0 [-,-]	0.0 [-,-]	0.0 [-,-]
Cefixime (≥ 0.25mg/l)	N/A	N/A	N/A	0.0 [-,-]	0.0 [-,-]

11. Discussion

GRASP has proven to be a successful collaboration, with *N. gonorrhoeae* isolates obtained from 24 laboratories and 26 GUM clinics collecting data on over 13 000 isolates over six years. The data have allowed us to determine annual antimicrobial susceptibility patterns of *N. gonorrhoeae* in England and Wales over time[20,21,22]. In addition, they have enabled us to characterize the demographic and behavioural characteristics of patients with infections caused by antibiotic resistant gonococci and have informed the national treatment guidelines[23].

In 2005, we observed a further increase in the prevalence of ciprofloxacin resistance to 21.7% in England and Wales, which is comparable to the prevalence in Scotland[25] (25%) and several countries in Europe[3]. The prevalence of ciprofloxacin resistance in isolates from MSM (42.4%) rose significantly to over four times that of heterosexual males (11.8%) in 2005, and the prevalence amongst certain ethnic groups continues to rise. The high prevalence amongst white ethnic groups is largely driven by MSM, but the high prevalence amongst Asian ethnic groups appears to be driven by sexual contact abroad. The prevalence of ciprofloxacin resistance amongst isolates from heterosexual men who had sexual partners abroad was 49.6%, compared with a prevalence of 6.2% in those who did not. The locales for sex abroad vary by population group, with MSM having partners in Western Europe and North America, whilst for heterosexual Asian men, the region of exposure correlates with the individual's country of origin[26]. With several countries in Asia having a prevalence of ciprofloxacin resistance greater than 90% and parts of Europe reaching greater than 50% the importation of new resistant strains into these sexual networks is inevitable[3,8,26]. A continued increase in the prevalence of ciprofloxacin resistance despite decreased usage of fluoroquinolones in England and Wales suggests that the use of ciprofloxacin in the treatment of gonorrhoea is not the only factor driving resistance. It is in marked contrast that despite the high burden of gonorrhoea amongst black Caribbean and black African populations the prevalence of ciprofloxacin resistance remains stable and low as the transmission in these populations appears to be largely heterosexual and within the UK.

A significant increase in the prevalence of CMRNG among isolates from MSM was also seen, rising from 10% in 2004 to 26% in 2005. CMRNG is strongly associated with MSM because strains carrying the *mtr* mutation confer resistance to hydrophobic environments such as the rectum[27]. CMRNG resistance is also strongly correlated with sexual contact abroad: of the MSM who had a sexual partner abroad, 41.5% had CMRNG compared with 22.4% of MSM who did not.

Ceftriaxone (intramuscular) or cefixime (oral) are the recommended first-line treatments for gonorrhoea in the UK[22]. In 2005, fluoroquinolones were prescribed to 19% of cases, whilst the majority were prescribed cephalosporins (71%). Seventeen percent of MSM were prescribed a fluoroquinolone in 2005 which is particularly worrying given their high prevalence of ciprofloxacin resistance. Of the cephalosporins prescribed 99% were given cefixime or ceftriaxone as recommended, which is important as not all cephalosporins are equally efficacious in treating gonococcal infection[28].

For the first time in 2005, we also studied the non-GUM sample in more detail, finding differences in both the demographics and antimicrobial susceptibilities of these isolates compared with those from the GUM setting, suggesting further analyses of these isolates is needed to better understand the epidemiology of infection in this population.

The findings discussed in this report continue to highlight the changes in prevalence of antimicrobial resistance observed in England and Wales, alongside the continued constancy in the epidemiology of gonococcal infection in 2005. Moreover, the continued heterogeneity of antimicrobial resistance prevalence seen across the regions highlights the continued need for local and national monitoring of antimicrobial resistance so treatment strategies can remain responsive to its changing epidemiology.

12. Future Challenges for GRASP

12.1 Timely production of results

The timely production of results and the clinical and annual reports have always been a high priority for GRASP. However, in 2005 we experienced considerable problems with the retrieval rate, which were exacerbated by the lack of resources to employ sufficient personnel dedicated to GRASP. This has highlighted that, for GRASP to be successful, continuing resources are needed together with a considerable time commitment from the collaborators. In 2006 and 2007 we have obtained extra funding from the Department of Health to support our core team. We also held a collaborators meeting in May 2005 to provide information, address poor retrieval rates, and initiate more rapid feedback to improve the 2006 collection. We plan that the collaborators meeting should be an annual event.

12.2 Maintenance of a representative sample

GRASP is a sentinel surveillance study and has maintained a consistent sample over the last 6 years. The number and distribution of sites and collection strategy was chosen in 2000. We are currently comparing the GRASP sample to KC60 reports and it may be that the strategy needs to be re-evaluated in the coming years. The analysis produced focuses on patients attending GUM clinics and there is currently no systematic collection of community diagnosed gonorrhoea. Gonococcal isolates are collected and tested from patients attending General Practice, but there is insufficient demographic data available for full analysis. Screening of asymptomatic individuals for gonorrhoea, such as those participating in the National Chlamydia Screening Programme (NCSP), will necessitate the inclusion of a representative sample from non-GUM services in the future. Any change in protocol will require ethical approval which will need renewing in 2008.

12.3 Molecular detection of gonorrhoea

There is increasing usage of nucleic acid amplification tests (NAAT) for the detection of *N. gonorrhoeae*, primarily because the available commercial kits can provide a result for *C. trachomatis* and *N. gonorrhoeae* either simultaneously or in the same sample at little or no extra cost[29,30]. While it is ideal to use NAATs for screening and then confirm using culture there are many instances, particularly in community services, where this is not achievable. Hence the isolates available for susceptibility testing may not be representative of the total gonococcal population and it may be necessary to consider collection of specimens at sentinel sites. This will require additional ethical approval for an extra specimen to be taken, resources to maintain high quality culture methods and personnel to process the specimens which would then be additional clinical samples.

GRASP has been a very successful project and all of these issues should be seen as challenges rather than problems. It is essential that effective therapy for gonorrhoea is sustained, and viable cultures will be necessary to detect emerging resistance for the foreseeable future.

13. GRASP Methodology

The GRASP collection combines laboratory and clinical data from sentinel laboratories. GRASP covers two distinct geographical regions: London, which includes seven laboratories and nine GUM clinics 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 policies and procedures of GRASP can be found in the GRASP protocol[31].

All gonococcal isolates from consecutive patients (one from each patient episode, according to a hierarchy of preferred swab sites) identified in participating laboratories during the months of June, July and August were sent to STBRL for susceptibility testing. At each local laboratory, primary isolates of *N. gonorrhoeae* were sub-cultured to obtain a pure growth and frozen in glycerol broth for transportation. At the reference laboratory, MICs were determined for the following antimicrobial agents (the range of concentrations tested is shown in parentheses): penicillin (0.03-4.0mg/l), ciprofloxacin (0.002-32mg/l) spectinomycin (2-64mg/l), tetracycline (1-32mg/l), ceftriaxone (0.002 to 0.125mg/l), azithromycin (0.03–2mg/l) and cefixime (0.002-0.25mg/l).

As a quality control, a two-way panel of isolates was exchanged twice between the GRASP reference laboratory and the Scottish *Neisseria gonorrhoeae* Reference Laboratory (SNGRL) during the isolate collection period. Isolates were tested, blinded to the originator's results, using the agar dilution method for susceptibility to azithromycin, ceftriaxone, ciprofloxacin, penicillin, spectinomycin and tetracycline. The results for each isolate/antimicrobial combination were compared and an error was recorded if a laboratory result was more than one or two doubling dilutions from the other. These results showed that the MICs obtained by the two laboratories were within one dilution of each other in 89% of cases and within two dilutions of each other in 98% of cases.

GUM clinics provided demographic, behavioural and clinical 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, HIV Status, number of partners in the UK and abroad, test of cure and therapy received. The behavioural data from patients (from GUM clinics) and susceptibility data (from the reference laboratory) of their isolates was then linked.

Results are based on confirmed isolates only (and unless otherwise stated on those taken from GUM patients only). To allow for the low retrieval rate for some participating laboratories in 2005, the results shown are weighted. Most significance tests are based on logistic regression models, but the time trend analysis uses models with a log link function to estimate the percentage change between years.

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