Treatment of gonorrhoea and susceptibility to antimicrobials of PPNG and non-PPNG strains in Jamaica

S D King,* A R Brathwaite,† J R Dillon‡

From the *Department of Microbiology, University of the West Indies; the †Comprehensive Health Centre, Ministry of Health, Kingston, Jamaica, West Indies, and the ‡Antimicrobials and Molecular Biology Division, Laboratory Centre for Disease Control, Ottawa, Canada

SUMMARY Of 1400 patients in Jamaica screened for uncomplicated gonorrhoea, 54% (753 patients) were culture positive. Of the 459 patients who complied with the terms of the study, 97% (211/218) of those treated with aqueous procaine penicillin G were cured compared with 94% (227/241) of those treated with ampicillin. Penicillinase producing Neisseria gonorrhoeae (PPNG) strains were identified for the first time during the study, and 10 patients infected with PPNG strains (two treated with penicillin, eight with ampicillin) contributed to the 21 treatment failures. The in vitro susceptibility of eight antimicrobial agents for 629 non-PPNG and 20 PPNG strains was estimated. Of the non-PPNG isolates, 8% had an MIC of 1 mg/l or more of penicillin, 11% were resistant to this concentration of ampicillin, 32% to tetracycline, and under 1% to the same concentration of cefuroxime and erythromycin. Fewer than 2% of the isolates were resistant to 2 mg/l or more thiamphenicol, and all isolates were susceptible to spectinomycin and trimethoprim-sulphamethoxazole (at a ratio of 1:19). Significantly more strains from the 21 treatment failures were resistant to penicillin (52%) or ampicillin (62%) compared with 7% strains resistant to penicillin and 4% to ampicillin from the successfully treated group.

Gonorrhoea is the most commonly reported (80%) communicable disease in Jamaica, a Caribbean island with a predominantly black population of about 2.15 million.1 An average of 26240 cases of gonorrhoea was reported yearly in Jamaica during 1978–82, with a ratio of men to women of 3:1. The true incidence is estimated to be at least three times this figure. Adolescents and young adults are the primary targets, and 75% of infections occur in people aged 15 to 29. Those aged 20 to 24 are at greatest risk, having 33% of all reported infections and an incidence of 65 cases per thousand population.

Assessment of the susceptibility of strains of Neisseria gonorrhoeae to antimicrobial agents is essential if informed decisions are to be made about appropriate treatment. Treatment with an inappropriate antibiotic, or with an appropriate antibiotic in suboptimal doses, will not only fail to cure but will contribute to the selection of gonococcal mutants with decreased susceptibility to a given antimicrobial agent.2 The emergence in other parts of the world of strains with plasmid mediated resistance to penicillin and tetracycline, as well as strains with high levels of chromosomally mediated resistance to penicillin, tetracycline, and spectinomycin, has underlined the necessity of screening gonococci for their susceptibility to antimicrobial agents.2–9

Two factors contributing to the emergence of penicillinase producing N gonorrhoeae (PPNG) isolates include suboptimal antibiotic dosage (through self medication) and population movement.2,6 The former contributed to the emergence and maintenance of PPNG strains in areas such as the Phillipines and Singapore, the latter to the importation of strains into a variety of countries.10–12 Jamaica is vulnerable to both of these factors; self treatment of gonorrhoea
by buying antibiotics on the black market appears to be increasing in Jamaica in recent years (A Brathwaite, personal communication), and the national campaign to encourage tourism carries with it the possibility of importing PPNG strains which, up to 1983 when the present study was initiated, had not been isolated on the island.

The present study was undertaken to assess the prevalence of PPNG strains on the island, to compare the efficacy of aqueous procaine penicillin G with that of ampicillin in treating acute uncomplicated gonorrhoea, to estimate the minimum inhibitory concentrations (MICs) of eight antimicrobial agents for the *N gonorrhoeae* strains isolated during the study, and to correlate the susceptibility to antimicrobials with the efficacy of treatment.

**Patients and methods**

**CLINICAL STUDIES**

The study population comprised 1400 patients (515 men, 885 women) aged over 14 who visited the Comprehensive Health Centre, Kingston, Jamaica, for suspected gonorrhoea in June 1983 to April 1984. People were excluded from the study if they were minors (aged 14 or under), pregnant, allergic to the proposed drug regimens, infected with coexisting syphilis, known prostitutes, or had been treated with antibiotics or other drugs (such as corticosteroids or immunosuppressives) within the preceding 14 days. Patients were requested to abstain from sexual intercourse and to avoid all other medication pending evaluation after treatment.

Before treatment, urethral or endocervical swabs were inoculated on to modified Thayer Martin medium, and were forwarded to the Microbiology Laboratory, University of the West Indies, where they were incubated for 48 hours at 35°C in a humid environment containing 5–10% carbon dioxide. Gram stained smears were immediately examined by direct microscopy at the Comprehensive Health Centre. Men were treated immediately on the basis of a positive smear. Women were asked to return within three days for the results of culture.

Men with positive Gram stained smears and women who had culture proved gonorrhoea on initial screening were allocated randomly to one of the following drug regimens: aqueous procaine penicillin G 4·8 MU given in two intramuscular injection sites, or ampicillin 3·5 g orally. Each antibiotic was given with 1 g of probenecid orally. Patients were asked to return to the clinic for reassessment within three to seven days. At follow up urethral, endocervical, or rectal swabs (from women who failed to respond to treatment) were taken for test of cure cultures. Patients with evidence of gonorrhoea at follow up, as diagnosed by Gram stain and culture, were treated with spectinomycin 2 g, followed by a further test of cure three to seven days later. These patients were regarded as treatment failures.

**IDENTIFICATION AND STORAGE OF ISOLATES**

Isolates of *N gonorrhoeae* were initially identified by Gram staining, oxidase testing, and colonial morphology after 48 hours growth on modified Thayer Martin medium. To purify the isolates, five to 10 typical colonies were subcultured on antibiotic free GC medium base (Difco Laboratories, Detroit, Michigan, USA) supplemented with 1% Kellogg’s defined supplement, and incubated for 18 to 24 hours in a humid environment supplemented with 5–10% carbon dioxide at 36°C. Isolates were also tested for the production of penicillinase using the chromogenic cephalosporin (Cefinase discs; BBL Microbiology Systems, Cockeysville, Maryland, USA) method. Suspensions of these cultures were prepared in tryptone soy broth (Difco) supplemented with 15% glycerol, and were frozen at −70°C.

Five hundred and five strains were forwarded to the Antimicrobials and Molecular Biology Division, Laboratory Centre for Disease Control, Ottawa, Canada, for confirmation of identity, reference antimicrobial susceptibility testing, and for biological, serological, and genetic characterisation (results of genetic and serological testing will be reported in a subsequent paper). Confirmation of the identity of the isolates was by carbohydrate utilisation, serology, and other standard tests.

**ANTIMICROBIAL SUSCEPTIBILITY TESTING**

The MICs of eight antimicrobial agents for the isolates was estimated either immediately after primary isolation or, in most cases, after storage at −70°C. The MICs of penicillin, ampicillin, erythromycin, tetracycline, trimethoprim-sulphamethoxazole (at a ratio of 1:19) (United States Pharmacopial, Maryland, USA), spectinomycin (Upjohn, Toronto, Ontario, Canada), cefuroxime (Glaxo, Toronto) and thiamphenicol (Inpharzam, Switzerland) were estimated using an agar dilution technique. Reference strains WHO III, WHO V, and WHO VIII and the PPNG strain GC1-182 (from JR Dillon) were included as controls. For testing MICs of sulphamethoxazole-trimethoprim diagnostic sensitivity test agar (DIST agar; OXoid, Basingstoke, England) supplemented with 5% lysed horse blood and 1% Kellogg’s defined supplement was used. GC medium base supplemented with 1% IsoVitalex (BBL Microbiology Systems, Becton Dickinson, Cockeysville MD 2130) was used when testing the other seven antibiotics. The inoculum was prepared by...
standardisation against a 0·5 McFarland opacity standard followed by a 1:100 dilution in 0·7% case-
mino acids 14 and subsequent inoculation with a Steers replicator on to medium containing antibi-
tic. 17 The plates were incubated as described pre-
viously for 18 to 24 hours. The MIC was considered to be the concentration of antibiotic either inhibiting all growth or allowing the growth of only one colony.

**STATISTICAL ANALYSIS**

Only patients with culture proved gonorrhoea who returned three to seven days after treatment were in-
cluded in the analysis of success or failure of the two treatment regimens. The χ² test was used to analyse the difference in failure rates between the two regi-
men.

**Results**

**TREATMENT**

Of 1400 patients screened initially, 753 (54%) had un-
complicated gonorrhoea proved by culture and 27 of 
these patients were excluded from treatment for rea-
sons cited in the Methods section. Of the 726 remain-
ing patients who were treated with one of the two 
treatment regimens, 459 (63%) returned for follow up 
within seven days. In patients returning within seven 
days, 97% (211/218) of those treated with penicillin 
were cured compared with 94% (227/241) of those 
treated with ampicillin (χ² 1·2; p > 0·1). More men 
treated with penicillin were cured (98%; 125/128) 
than those treated with ampicillin (91%; 126/139); χ² 
4·69; p < 0·05. Of women treated with penicillin, 
96% (86/90) were cured compared with 99% 
(101/102) of those treated with ampicillin (χ² 1·6; p > 
0·1). Of patients returning for follow up test of cure 
within seven days, 14 were infected with PPNG 
strains. All of these patients were men, and PPNG 
isolates were the cause of 10 treatment failures (two 
patients treated with penicillin, and eight patients 
treated with ampicillin). If patients with PPNG infec-
tions are excluded from the analysis, the cure rate for 
men was 99% of those treated with penicillin and 
96% of those treated with ampicillin, with no 
significant differences in results between drug regi-
mens or between sexes.

**ANTIMICROBIAL SUSCEPTIBILITY TESTING**

*N gonorrhoeae* was isolated from 753 of the 1400 pa-
tients screened, and 22 (3%) of these isolates pro-
duced β-lactamase. MICs of eight antimicrobial agents were estimated for 629 non-PPNG strains (table 1). If resistance to penicillin, ampicillin, ce-
furoxime, and erythromycin is arbitrarily defined as 
a MIC of 1 mg/l or more, then 7% of the non-PPNG 
isolates were resistant to penicillin, 11% were re-
sistant to ampicillin, and under 1% were resistant to 
cefuroxime and erythromycin. MICs of 2 mg/l or 
more of tetracycline were found in 12% of the strains. 
All isolates were inhibited by clinically achievable 
concentrations of spectinomycin and fewer than 2% 
of the isolates were resistant to thiamphenicol (MIC 
2 mg/l or more). 18 Each isolate was susceptible to 
sulphonamides. Brown et al. have reported that 
treatment with trimethoprim-sulphamethoxazole 
(TMPSMX) is more likely to fail with MICs of 
0·5 mg/l or more TMP and 9·5 mg/l or more SMX. 19 
In this study all isolates were inhibited by these 
concentrations. The median MICs of the antimicrobial agents were, in descending order: cefuroxime 0·032 mg/l, penicillin 0·056 mg/l, eryth-
romycin 0·05 mg/l, ampicillin 0·157 mg/l, thiamphen-
icol 0·206 mg/l, tetracycline 0·708 mg/l, sulphameth-
oxazole-trimethoprim (19:1) 1·10·06 mg/l, and 
spectinomycin 10·8 mg/l.

We recovered 22 primary PPNG isolates during the 
study. Not all the patients infected with PPNG strains 
could be included in the final analysis of treatment 
success, as eight of the 22 did not return to the clinic 
for test of cure. One of these patients was a woman. 
MICs were estimated for 20 strains (table 2). As might 
be expected, all PPNG strains were resistant to peni-

---

**Table 1** _Minimum inhibitory concentrations of eight antimicrobial agents for 629 non-PPNG isolates_

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Cumulative % of strains inhibited by concentration (mg/l) of:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0·032</td>
</tr>
<tr>
<td>Penicillin</td>
<td>29</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>12</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>57</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>32</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>4</td>
</tr>
<tr>
<td>Spectinomycin*</td>
<td></td>
</tr>
<tr>
<td>TMP-SMX* (19:1)</td>
<td>33</td>
</tr>
</tbody>
</table>

*626 strains tested with spectinomycin.
†TMPSMX, trimethoprim-sulphamethoxazole (19:1). Only trimethoprim concentration indicated (concentration of 0·032 implies trimethoprim 0·032 mg/l, sulphamethoxazole 0·64 mg/l).
cillin and ampicillin and over half had MICs of 32 mg/l or more. PPNG strains were generally more resistant than non-PPNG strains to antimicrobial agents, as indicated by the MIC50 (MIC inhibiting 50% of the isolates).

Of the 459 patients who returned for test of cure within seven days, 427 (including 21 treatment failures) yielded strains that were available for MIC testing. Of the 21 strains from treatment failures, 11 (52%) had MICs of penicillin of 1 mg/l or more compared with only 29 (7%) of the 406 strains from the successfully treated patients, a significant difference ($\chi^2 = 48.13; p < 0.01$). Of the 21 strains from the treatment failures, 13 (62%) were shown to have MICs of ampicillin of 1 mg/l or more compared with 4% (46/406) of successfully treated patients ($\chi^2 = 42.89; p < 0.01$). Ten (48%) of the N gonorrhoeae strains from patients who failed to respond to either treatment regimen were also penicillinase positive.

**Discussion**

Few studies have been undertaken to estimate the antimicrobial susceptibility patterns of gonococci isolated in the Caribbean area and no evaluations have been published about the outcome of treatment in the area. Statistical data on the incidence of gonorrhoea including cases caused by PPNG strains may be reported to the Pan American Health Organisation (PAHO), but the true magnitude of the problem is difficult to assess. Two previous studies have estimated the susceptibility of strains of N gonorrhoeae isolated in Jamaica to antimicrobial agents. Table 3 compares the results of these previous studies (undertaken in 1971 and 1978) with those of the present study (undertaken in 1983–4); significant differences in levels of resistance were observed between each test period. Strains with MICs of 0.25 mg/l or more penicillin were observed in 38% of the 1971 isolates and in only 9% of the 1978 isolates ($\chi^2 = 15.34; p < 0.001$). In the present 1983–4 study the proportion of strains with MICs of 0.25 mg/l or more increased to 16% compared with the 1978 results, but decreased in comparison with the 1971 results. These differences were not significant. The percentage of isolates resistant to this concentration of ampicillin showed an even greater increase, from 2% in 1978 to 26% in 1983–4 ($\chi^2 = 31.72; p < 0.01$). Similarly, MICs of tetracycline in the present study resembled the distribution observed in 1971, as opposed to observations in 1978.

Interestingly, in the present study the MIC50 of erythromycin (0.5 mg/l) and tetracycline (4 mg/l) compared with resistance levels reported by Rodriguez et al in Puerto Rico. The median MICs observed in the present study, however, were lower than those observed in the Puerto Rican study. It would be interesting to ascertain whether tetracycline resistant gonococci were generally distributed throughout the Caribbean area. Several studies have established that treatment failure rates of at least 20% can be expected in strains with MICs of tetracycline of 1 mg/l or more. The in vitro susceptibility estimates in the present study, in which 12% of the non-PPNG strains had an MIC of 2 mg/l or more, indicated that tetracycline alone would not be an optimum treatment regimen for gonococcal infections in Jamaica.

The susceptibility of non-PPNG strains to penicillin varies widely according to geographical source. Sng et al reported that countries in South East Asia generally had the highest percentage of strains with reduced susceptibility to penicillin (MIC 0.5 mg/l or more), whereas developed countries, except Japan and Canada, generally had a larger number (more than 80%) of susceptible strains. It should be pointed out that the report of Sng et al did not exclude PPNG strains, and the high incidence of penicillin resistant isolates observed in South East

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Year</th>
<th>Isolated*</th>
<th>MICs (mg/l)</th>
<th>No (%) of strains with MICs of</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>1971</td>
<td>4(15)</td>
<td>0-016-20</td>
<td>0-25</td>
<td>0-64</td>
</tr>
<tr>
<td></td>
<td>1978</td>
<td>10(9)</td>
<td>0-012-20</td>
<td>0-016-20</td>
<td>0-64</td>
</tr>
<tr>
<td></td>
<td>1983-4</td>
<td>2(2)</td>
<td>0-012-20</td>
<td>0-012-20</td>
<td>0-64</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>1971</td>
<td>2(8)</td>
<td>0-012-20</td>
<td>0-012-20</td>
<td>0-64</td>
</tr>
<tr>
<td></td>
<td>1978</td>
<td>2(2)</td>
<td>0-012-20</td>
<td>0-012-20</td>
<td>0-64</td>
</tr>
<tr>
<td></td>
<td>1983-4</td>
<td>68(11)</td>
<td>0-012-20</td>
<td>0-012-20</td>
<td>0-64</td>
</tr>
</tbody>
</table>

*17 strains tested with spectinomycin.
†See footnote of table 1.

---

**Table 2** Minimum inhibitory concentrations (MICs) of eight antimicrobial agents for 20 PPNG isolates

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>50% strains</th>
<th>90% strains</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>32-0</td>
<td>64-0</td>
<td>2-0-64-0</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>0-125</td>
<td>2-0</td>
<td>0-016-2-0</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>0-25</td>
<td>1-0</td>
<td>0-032-2-0</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>1-0</td>
<td>2-0</td>
<td>0-25-40</td>
</tr>
<tr>
<td>Spectinomycin*</td>
<td>8-0</td>
<td>8-0</td>
<td>8-0-160</td>
</tr>
<tr>
<td>Thiamphenicol</td>
<td>0-5</td>
<td>2-0</td>
<td>0-125-4-0</td>
</tr>
<tr>
<td>TMP:SMX (1:19)†</td>
<td>16-0</td>
<td>32-0</td>
<td>0-5-32-0</td>
</tr>
</tbody>
</table>

---

**Table 3** Comparative susceptibility to penicillin and ampicillin of gonococcal strains from Jamaica (1971–84)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Year</th>
<th>Isolated*</th>
<th>MICs (mg/l)</th>
<th>No (%) of strains with MICs of</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>1971</td>
<td>4(15)</td>
<td>0-016-20</td>
<td>0-25</td>
<td>0-64</td>
</tr>
<tr>
<td></td>
<td>1978</td>
<td>10(9)</td>
<td>0-012-20</td>
<td>0-016-20</td>
<td>0-64</td>
</tr>
<tr>
<td></td>
<td>1983-4</td>
<td>68(11)</td>
<td>0-012-20</td>
<td>0-012-20</td>
<td>0-64</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>1971</td>
<td>2(8)</td>
<td>0-012-20</td>
<td>0-012-20</td>
<td>0-64</td>
</tr>
<tr>
<td></td>
<td>1978</td>
<td>2(2)</td>
<td>0-012-20</td>
<td>0-012-20</td>
<td>0-64</td>
</tr>
<tr>
<td></td>
<td>1983-4</td>
<td>68(11)</td>
<td>0-012-20</td>
<td>0-012-20</td>
<td>0-64</td>
</tr>
</tbody>
</table>

†These MICs are comparative and do not denote levels of resistance.

n/a, not applicable.
Asia reflected the high incidence of PPNG strains in those areas. In the present study, 9% of non-PPNG strains isolated in Jamaica had MICs of penicillin of 0.5 mg/l or more. This means that the susceptibility to penicillin of the Jamaican non-PPNG strains is similar to that of countries with a less than 5% incidence of PPNG strains. Most Jamaican gonococcal strains tested in this study were therefore susceptible to penicillin and ampicillin, a general characteristic of gonococcal isolates in Canada, most areas of the United States of America, and other countries where PPNG strains do not predominate. The overall sensitivity of the isolates to penicillin was reflected in treatment results showing that 97% of patients treated with penicillin were cured. Regimens with less than 95% cure rates are associated with an increased prevalence of resistant organisms.

The present study is the first to report the detection of PPNG strains in Jamaica. Although the prevalence was only 3% of the total number of gonococcal strains isolated, this was undoubtedly an underestimate. Statistics on the incidence of PPNG strains in other Caribbean countries are sparse, although PPNG strains have been reported from Trinidad and Tobago to PAHO officials (F Zacarias, personal communication) and strains have been imported into Canada from Antigua, Barbados, the Bahamas, the Dominican Republic, the Virgin Islands, Martinique, and Grenada. Sng et al attributed the high prevalence of resistant strains in Singapore to the dominant role of prostitutes in the transmission of disease and to the improper use and inadequate control of sales of antibiotics to prostitutes and their clients. These factors may play a part in the spread of PPNG strains in Jamaica. It is also probable that tourism plays a more important part by importing PPNG and other gonococcal strains.

In the present study 21 patients infected with PPNG strains were men and only one was a woman. The presence of PPNG strains in men in 21 of 22 patients is somewhat anomalous, despite the fact that many underdeveloped countries report high ratios of men to women infected. There may be several reasons for the skewed ratio of men to women in this study; women who were prostitutes and therefore at highest risk for infection with PPNG strains were screened out of the study. As women were screened before men (before January 1984), PPNG strains were possibly not introduced to the island before December 1983 or January 1984, a period coincident with the onset of the annual tourist season.

Monitoring both the prevalence of PPNG strains and the susceptibility of gonococcal isolates to antibiotics is essential to Jamaican public health practice. The appearance of PPNG strains at a 3% level in Jamaica in 1984, coupled with the increasing resistance to penicillin compared with the results of studies undertaken in 1978, indicates an urgent need for careful monitoring of the incidence of antibiotic resistant strains throughout the island. In addition, the susceptibility to antibiotics of all gonococcal isolates should continue to be monitored to ascertain whether antibiotic treatment for gonorrhoea on this island continues to be effective.

This study was supported by a grant (No 3-P-81-0240) from the International Development Research Centre, Ottawa, Canada.

We thank Dr Macfarlane, Department of Microbiology, University of the West Indies for his help in the initial stages of the study. We thank K Moodie, L Rainford, and E de Gouville of the Department of Microbiology, University of the West Indies; A Hinds, M Burke, and P Gordon of the Comprehensive Health Centre, Kingston, Jamaica; and M Carballo of the Laboratory Centre for Disease Control, Ottawa, for their technical help. We also thank Drs R St John and F Zacarias of PAHO, Washington, for their advice.

References

of Neisseria gonorrhoeae. Applied Microbiology 1974;27:802-5.


18 Lind I. In-vitro susceptibility of Neisseria gonorrhoeae to thiamphenicol: results for selected groups of strains from different geographic areas and from different times. Sex Transm Dis 1984;11:360-3.


Treatment of gonorrhoea and susceptibility to antimicrobials of PPNG and non-PPNG strains in Jamaica.
S D King, A R Brathwaite and J R Dillon

doi: 10.1136/sti.63.6.365

Updated information and services can be found at:
[http://sti.bmj.com/content/63/6/365](http://sti.bmj.com/content/63/6/365)

These include:
**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
[http://group.bmj.com/group/rights-licensing/permissions](http://group.bmj.com/group/rights-licensing/permissions)

To order reprints go to:
[http://journals.bmj.com/cgi/reprintform](http://journals.bmj.com/cgi/reprintform)

To subscribe to BMJ go to:
[http://group.bmj.com/subscribe/](http://group.bmj.com/subscribe/)