Determinants of penicillinase producing Neisseria gonorrhoeae infections in heterosexuals in Amsterdam

M Prins, P J E Bindels, R A Coutinho, C J M Henquet, G J J van Doornum, J A R van den Hoek

Abstract

Background and objectives—At the STD clinic of the Municipal Health Service in Amsterdam, the annual number of infections with penicillinase-producing Neisseria gonorrhoeae (PPNG) strains remained relatively stable from 1983 until 1990, while the number of non-PPNG infections declined dramatically. To investigate the PPNG and non-PPNG epidemic, a cross-sectional study was conducted in 1989 and 1990. The purpose of this study was to assess determinants of PPNG infections among heterosexuals diagnosed with gonorrhoea.

Methods—In addition to routinely collected data in new consultations for STDs, information on alcohol use, drug use and sexual behaviour was obtained from patients diagnosed with gonorrhoea. The diagnosis of gonorrhoea was based on a positive culture and isolates were screened for PPNG. Logistic regression analysis was used to assess independent predictors of PPNG infection.

Results—Additional information was available of 328 women and 995 heterosexual men diagnosed with gonorrhoea. PPNG was diagnosed in 36/328 (26%) women and in 329/995 (33%) men. Logistic regression analysis identified a Central/South American nationality (odds ratio (OR) = 2.46) and older age (OR = 1.04 per year) as positively associated with PPNG infection in female patients. An inverse relation was found with use of hard drugs (OR = 0.29). Among men diagnosed with gonorrhoea, sexual contacts with window prostitutes (mainly women from Central/South America) (OR = 1.98) and a foreign nationality (OR = 1.78) were positively associated with PPNG infection, and sexual contact with drug using prostitutes (OR = 0.47) inversely.

Conclusions—PPNG infections were especially common among Central and South American window prostitutes and their clients. Since window prostitutes originating from Central and South American countries are transient in Amsterdam, prevention activities targeted at these prostitutes and their clients should be continued to limit the spread of PPNG and other STDs within these groups.

Figure Non-PPNG and PPNG infections diagnosed among all STD clinic attenders in Amsterdam, the Netherlands, 1981–1990.
diagnosed among homosexual men attending the STD clinic in Amsterdam. This finding is consistent with the results of studies from other countries, implying that PPNG infections have mainly spread into heterosexual populations.

To investigate the PPNG epidemic and non-PPNG epidemic in heterosexuals, the present cross-sectional study was conducted in 1989 and 1990. In order to improve prevention measures, the purpose of the study was to identify populations at increased risk for PPNG infection among heterosexual men and women diagnosed with gonorrhoea.

Methods
Subjects and materials
All individuals attending the STD clinic in Amsterdam for a new consultation are physically examined for STDs and interviewed by specially trained nurses. Routinely cultures are taken for Neisseria gonorrhoeae. Specimens are obtained from the urethra in men and from the urethra, cervix and rectum in women. In case of receptive anal sexual contact in men, a rectal specimen is also collected. In case of orogenital sexual contact in men and women, a specimen is taken from the oropharynx as well. The specimens are inoculated directly onto the growth media at the STD clinic and transported in candle jars to the laboratory. All gonococcal isolates are screened for beta-lactamase production using the chromogenic cephalosporin, Nitrocefin (Oxoid).

In 1989 and 1990, additional information was obtained from patients who had a culture that was positive for gonorrhoea. After informed consent had been obtained, public health nurses interviewed the patients using a standardized questionnaire which included information on demographic characteristics, sexual preference, prostitution contacts and history of past STDs (routinely collected data), and current alcohol use, drug use, and sexual behaviour (additional information). “Current” behaviour was defined as behaviour in the three months preceding the consultation. Questions concerning sexual behaviour included type (regular, casual, commercial) and number of partners, number of traceable partners, condom use during sexual intercourse and setting of prostitution (window locations, street, clubs, escort agencies, etc.). Window locations are locations in the red light district where prostitutes sit behind the windows, facing the street, to attract clients.

If subjects had a diagnosis of gonorrhoea more than once in 1989–1990, data collected at the first visit in which gonorrhoea was diagnosed, were used for the present study. As PPNG infections were found to be rare in homosexual men, the male population studied was limited to men without homosexual contacts. All female participants were included in the present study.

Data analysis and statistics
To assess determinants of PPNG infections, patients infected with PPNG strains were compared with those infected with non-PPNG strains. Frequency scores for condom use ranged on a five-point scale from 1 (never) to 5 (always) and were given for regular partners as well as for casual partners. To calculate the percentage of traceable sexual partners, the number of sexual partners in the past three months that could be traced was divided by the total number of sexual partners in the preceding three months, and then, multiplied by 100. If participants reported no sexual contacts in the past three months (n = 11), the percentage of traceable sexual partners was set to 100%.

In univariate analysis, associations between variables were examined using Pearson’s chi-square, Student’s t test, Mann-Whitney U test and Spearman’s correlation coefficient. Crude odds ratio’s (ORs) and their 95% confidence intervals (CIs) were calculated for statistically significant categorical variables.

Multivariate logistic regression analysis was used to construct a model predicting PPNG infections. Selection of variables was based on the likelihood ratio statistic. Univariately significant and potentially relevant, but non-significant variables were considered for entry into the model. Adjusted ORs and their 95% CIs were calculated for the variables included in the model.

All analyses were performed separately for both sexes. A p value of 0.05 or less was considered significant.

Results
Patient characteristics
Additional information was available of 328 women and 995 heterosexual men diagnosed with a gonococcal infection at the STD clinic in 1989 and 1990. PPNG infection was diagnosed in 86 of 328 (26%) women and 329 of 995 (33%) men. None of the participants was positive for both PPNG and non-PPNG infection at the same time.

Characteristics of the study population are listed in table 1a (women) and table 1b (men). Mean age of the female patients was 27 years, of the male patients 31 years. Nationality of the women was mainly Dutch or Central/South American, of the men Dutch or Turkish. Approximately one third of the women and half of the men reported to have had a gonococcal infection previously. The median number of sexual partners in the past three months was three partners among women as well as among men. Half of the women worked as a prostitute and half of the men had sex with prostitutes, mainly with those who sit behind the windows to attract clients. Of the drug using women, 84% worked as a prostitute in the past three months but none of these women worked behind the windows. Both men and women used condoms less consistent in sexual contacts with regular partners than in sexual contacts with casual partners and prostitutes/clients.

In addition, among male gonorrhoea
Table 1 (a) Characteristics of 328 female STD clinic attenders diagnosed with gonorrhoea in 1989–1990, Amsterdam, The Netherlands

<table>
<thead>
<tr>
<th>Age (year)</th>
<th>Total n=328</th>
<th>non-PPNG n=242</th>
<th>PPG n=86</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean (sd)</td>
<td>27 (7)</td>
<td>26 (7)</td>
<td>29 (7)</td>
<td>0.006</td>
</tr>
<tr>
<td>Number of sexual partners in past three months</td>
<td>3 (193)</td>
<td>3 (180)</td>
<td>3 (320)</td>
<td>0.39</td>
</tr>
<tr>
<td>Percentage of traceable sexual partners*</td>
<td>100 (46)</td>
<td>100 (46)</td>
<td>100 (48)</td>
<td>0.88</td>
</tr>
<tr>
<td>Nationality:</td>
<td>number (%)†</td>
<td>number (%)†</td>
<td>number (%)†</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Dutch</td>
<td>172 (53)</td>
<td>136 (56)</td>
<td>36 (42)</td>
<td></td>
</tr>
<tr>
<td>Central/South American</td>
<td>80 (26)</td>
<td>50 (21)</td>
<td>40 (47)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>66 (20)</td>
<td>56 (23)</td>
<td>10 (12)</td>
<td></td>
</tr>
<tr>
<td>History of gonorrhoea</td>
<td>92 (29)</td>
<td>68 (29)</td>
<td>24 (29)</td>
<td>0.97</td>
</tr>
<tr>
<td>Prostitute in past three months:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No prostitute</td>
<td>154 (50)</td>
<td>116 (51)</td>
<td>38 (46)</td>
<td></td>
</tr>
<tr>
<td>Behind the windows</td>
<td>50 (16)</td>
<td>29 (13)</td>
<td>21 (26)</td>
<td></td>
</tr>
<tr>
<td>Working elsewhere</td>
<td>107 (34)</td>
<td>84 (37)</td>
<td>23 (28)</td>
<td></td>
</tr>
<tr>
<td>Use of hard drugs in past three months</td>
<td>70 (23)</td>
<td>64 (28)</td>
<td>6 (7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Condom use in sexual contacts with regular partner(s) in past three months:</td>
<td></td>
<td></td>
<td></td>
<td>0.74**</td>
</tr>
<tr>
<td>Never</td>
<td>165 (56)</td>
<td>127 (57)</td>
<td>38 (54)</td>
<td></td>
</tr>
<tr>
<td>Sometimes</td>
<td>22 (8)</td>
<td>16 (7)</td>
<td>6 (9)</td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>9 (3)</td>
<td>7 (3)</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>No such partner</td>
<td>98 (33)</td>
<td>74 (33)</td>
<td>24 (34)</td>
<td></td>
</tr>
<tr>
<td>Condom use in sexual contacts with casual partners/clients in past three months:</td>
<td></td>
<td></td>
<td></td>
<td>0.17**</td>
</tr>
<tr>
<td>Never</td>
<td>32 (11)</td>
<td>10 (9)</td>
<td>9 (13)</td>
<td></td>
</tr>
<tr>
<td>Sometimes</td>
<td>98 (34)</td>
<td>70 (32)</td>
<td>28 (40)</td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>64 (22)</td>
<td>50 (23)</td>
<td>14 (20)</td>
<td></td>
</tr>
<tr>
<td>No such partner</td>
<td>97 (33)</td>
<td>78 (35)</td>
<td>19 (27)</td>
<td></td>
</tr>
</tbody>
</table>

*For calculation of the percentage of traceable sexual partners, see Methods.
†Because of missing data some percentages are not based on the total number of women.
‡Central/South American nationality: from Colombia (n = 43) Dominican Republic (n = 30), Surinam (n=12) and three other countries (n = 5); other: 18 other nationalities.
§Club, escort agency, street or other prostitute working locations.
∥For the sake of simplicity of presentation the frequency of condom use is reduced to three categories (1 = "never"; 2,3,4 = "sometimes"; 5 = "always").* Tested with Mann-Whitney, on the complete 5-point scale ranging from 1 "never" to 5 "always". Women without such a partner were excluded from the analysis.

Determinants of PPNG infections in men
Univariate analysis identified being older, having Central or South American nationality and working as a prostitute behind the windows as positively and significantly associated with PPNG infection. Use of hard drugs was inversely associated. The mean age of the PPNG patients was 55% worked as a window prostitute, while of the women having other nationalities only 1% worked as a window prostitute in the three months preceding diagnosis of gonorrhoea (data not shown).

Determinants of PPNG infections in women
Univariate analysis identified being a client of window prostitutes (Spearman’s correlation coefficient r = 0.52; p < 0.001). Of the Turkish men, 79% reported having had sex with a window prostitute recently, while of the men with other nationalities 21% reported having had sex with a window prostitute. Among women, originating from a country in Central or South America and working as a prostitute behind the windows appeared to be highly correlated (Spearman’s correlation coefficient r = 0.65; p < 0.001). Of the Central and South American women 55% worked as a window prostitute, while of the women having other nationalities only 1% worked as a window prostitute in the three months preceding diagnosis of gonorrhoea (data not shown).

Determinants of PPNG infections in men
Univariate analysis, the variables concerning traceable sexual partners, nationality, prostitution contacts and use of hard drugs, alcohol and condoms distinguished men with PPNG infections from those with non-PPNG infections (table 1b). PPNG infection appeared to be inversely and significantly associated with the proportion of traceable partners: The median percentage of traceable partners was 50% for men infected with PPNG and 83% for those infected with non-PPNG. PPNG infections were more common among men who were not Dutch nationals than among the Dutch men: the crude OR for Turkish men was 2.84 (95% CI:2-043-96) and for those with other nationalities other than Dutch or Turkish 1.82 (95% CI:1-32-2.80). Compared with men who reported not having had sex with prostitutes in the past three months, the crude OR for clients of window prostitutes was 2.46 (95% CI:1-65-2.93) and 0.31–1.45), as compared with Dutch women.

Prostitution itself was not associated with PPNG infection (p = 0.59), but the setting of prostitution was (p < 0.001). In comparison with women not working as a prostitute, the crude OR for women working as a window prostitute was 2.21 (95% CI: 1.14–4.29) and for those engaged in prostitution settings other than window prostitution 0.84 (95% CI: 0.46–1.51). The crude OR for women who had used hard drugs in the previous three months was 0.21 (95% CI: 0.09–0.46) compared with those who had not.

In multivariate analysis age, Central or South American nationality and use of hard drugs were identified as independent and significant PPNG infection related risk factors according to the likelihood ratio statistic. Table 2 shows the final model. With the three variables in the model, female gonorrhoea patients having the nationality from a country in Central or South America were more likely to acquire PPNG infection than non-PPNG, as compared with women having other nationalities (adjusted OR = 2.46). The same was true for older women compared with younger women (adjusted OR = 1.04 per year). Conversely, women with gonorrhoea who used hard drugs recently were less likely to acquire PPNG than non-PPNG, as compared with female patients who did not (adjusted OR = 0.29). Potential confounders examined included condom use, the number of sexual partners and self-reported history of gonorrhoea. When forced separately into the model, the last three variables had only a very minor influence on the presented OR’s, implying confounding by these variables was not present. We did not find significant interactions between variables included in the model. To control for time trends, the year of the diagnosis was added to the model listed in table 2. It did not appear to be a confounder and no statistically significant interactions were present between the year of diagnosis and the variables independently associated with PPNG infection.
Table 1  (b) Characteristics of 995 heterosexual male STD clinic attenders diagnosed with gonorrhoea in 1989–1990, Amsterdam, The Netherlands

| Age (year) | Total n=995 | non-PPNG n=666 | PPNG n=329 | p-value
|------------|-------------|----------------|-------------|----------------
| mean (sd)  | 31 (9)      | 31 (10)        | 31 (9)      | 0.52
| Number of sexual partners in past three months | 3 (8) | 3 (9) | 3 (6) | 0.69
| Percentage of traceable sexual partners* | 67 (40) | 83 (39) | 50 (42) | < 0.001
| Nationality: | | | | < 0.001
| Dutch      | 422 (43)    | 524 (49)      | 98 (30)    | |
| Turkish    | 253 (26)    | 136 (21)      | 117 (36)   | |
| Other†     | 316 (32)    | 204 (31)      | 112 (34)   | |
| History of gonorrhoea | 440 (46) | 312 (48) | 128 (41) | 0.052
| Client of prostitutes in past three months: | | | | < 0.001
| No client | 446 (47)    | 336 (52)      | 110 (36)   | |
| Mainly of window prostitutes | 343 (36) | 190 (29) | 153 (50) | |
| Mainly of prostitutes working elsewhere§ | 169 (18) | 124 (19) | 45 (15) | |
| Number of prostitution settings visited in the past three months: | | | | < 0.001
| No client | 446 (47)    | 336 (52)      | 110 (36)   | |
| One setting | 411 (43)    | 239 (37)      | 172 (56)   | |
| Two or three settings | 101 (11) | 75 (12) | 26 (8) | |
| Client of drug-using prostitutes in past three months | 79 (8) | 65 (10) | 14 (4) | 0.004
| Use of hard drugs in past three months | 102 (10) | 80 (12) | 22 (7) | 0.01
| Use of alcohol in past three months | 679 (72) | 479 (74) | 200 (67) | 0.03
| Condom use in sexual contacts with regular private partner(s) in past three months: | | | | 0.55**
| Never | 355 (38)    | 239 (40)      | 96 (32)    | |
| Sometimes | 43 (5)      | 35 (5)        | 8 (3)      | |
| Always | 22 (2)      | 15 (2)        | 7 (2)      | |
| No such partner | 526 (56) | 341 (53) | 185 (63) | |
| Condom use in sexual contacts with prostitutes in past three months: | | | | 0.04**
| Never | 246 (26)    | 143 (22)      | 103 (34)   | |
| Sometimes | 198 (21)    | 129 (20)      | 69 (23)    | |
| Always | 60 (6)      | 42 (7)        | 18 (6)     | |
| No such partner | 446 (47) | 336 (52) | 110 (36) | |
| Condom use in sexual contacts with casual private partner(s) in past three months: | | | | 0.25**
| Never | 244 (26)    | 172 (27)      | 72 (24)    | |
| Sometimes | 184 (20)    | 142 (22)      | 42 (14)    | |
| Always | 70 (7)      | 50 (8)        | 20 (7)     | |
| No such partner | 448 (47) | 283 (44) | 165 (57) | |

*For calculation of the percentage of traceable sexual partners, see Methods.
†Because of missing data some percentages are not based upon the total number of men.
§562 nationalities.
¶For the sake of simplicity presentation the frequency of condom use is reduced to three categories (1 = "never"; 2,3,A = "sometimes"; S = "always").
**Tested with Mann-Whitney, on the complete 5-point scale ranging from 1 "never" to 5 "always". Men without such a partner were excluded from the analysis.

Discussion

The present study shows that PPNG infections were common among the Central and South American women diagnosed with gonorrhoea at the STD clinic. Since window prostitutes have mainly the nationality from a Central or South American country, this result corresponds completely with the finding that having had sex with window prostitutes distinguished heterosexual men with PPNG infections from those with non-PPNG infections. Conversely, PPNG infections were not common among drug using women who often work as a prostitute elsewhere and among the clients of the drug using prostitutes. Other risk factors for PPNG infections appeared to be a foreign nationality for men and older age for women.

Several studies have described outbreaks of PPNG infections spread by core groups such as prostitutes, ethnic minority groups, drug users and their heterosexual partners. One study in which risk factors were determined for the continuing epidemic in Miami did not find any association between PPNG infections and race, age, sexual preference, drug use or prostitution activities among STD clinic attenders diagnosed with gonorrhoea. It is suggested that travel to PPNG endemic areas and prostitution activities may play an important role in the spread of PPNG infections within communities previously free of PPNG infections, but, once the disease becomes endemic, those risk factors become epidemiologically unimportant. The results of our study do not support this hypothesis.
Determinants of penicillinase producing Neisseria gonorrhoeae infections in heterosexuals in Amsterdam

While PPNG infections had been present in Amsterdam for more than a decade, we found one setting of prostitution to be associated with this STD, namely window locations. A national study found that of the Turkish men diagnosed with PPNG infections in 1989, 85% reported that they had become infected through sexual contacts with prostitutes. As Turkish men enrolled into our study predominantly visit window prostitutes, this finding also suggests that subjects engaging in window prostitution are at high risk for infection with PPNG. Probably PPNG infections continue to be introduced by women originating from Central or South America who work as window prostitutes in Amsterdam and who appear to be highly mobile, as has been shown recently. Another explanation is that the men having sex with window prostitutes are responsible for the spread of PPNG infections into this setting of prostitution. However, since no information was obtained on the presumed locality of acquisition of infection, it is not known which of the two explanations is the most likely. Characterisation of the isolate by the plasmid content, serotype and auxotype of the isolates may have helped to elucidate the spread of PPNG in more detail.

Drug addicted prostitutes and their clients were found to be at increased risk for PPNG infections among our STD clinic visitors in the early 1980s, just after the introduction of PPNG in Amsterdam. In response to the identification of prostitution as risk factor for PPNG infection, it was decided to use antibiotics that were active against PPNG as routine therapy for all suspected cases of gonorrhoea in prostitutes and their clients. From then on, treatment was based on physical examination and microscopy and regimens were given before laboratory testing determined whether the infection was caused by PPNG or non-PPNG strains. In contrast to the previous finding, in 1989 and 1990 PPNG infections turned out to be inversely associated with drug use in patients with gonorrhoea. It is likely that the change of treatment of gonorrhoea diagnosed in prostitutes and their clients, because of the emergence of PPNG infections in this group in the early eighties, has contributed to a decrease of PPNG infections in the prostitutes and their clients thereafter. The inverse association between drug use and PPNG infection may be the result of an increasing STD control and counselling in drug addicted prostitutes due to the start of specific outreach programs for these prostitutes in the past decade.

Although it is suggested that patients with a history of gonorrhoea may contribute to the introduction of antibiotic-resistant gonococci, we were unable to demonstrate an association between prior episodes of gonorrhoea and acquisition of PPNG.

A number of studies have determined the impact of prophylactic use or self-medication of antibiotics on the epidemic of gonorrhoea caused by PPNG strains. Albeit prophylactic use reduces the risk of acquiring gonorrhoea and self-medication reduces the probability of diagnosing, the data of these studies indicate that when gonorrhoea was acquired and diagnosed, subjects who had taken prophylactic antibiotics or who had self-medicated were more likely to be diagnosed with PPNG than with non-PPNG infection, as compared with those who had not. An explanation may be that the antibiotics they used as prophylaxis or self-medicated therapy did not prevent or cure an infection caused by PPNG strains. Our interview did not include questions on self-administration of antibiotics. Nonetheless, it is known that prostitutes originating from Latin America often take antibiotics as STD prevention. The antibiotics, which can only be purchased with a prescription in The Netherlands, are bought at the black market or sent from their native country. Since a Central/South American nationality was related to PPNG infections in women, it could be argued that self-administered antibiotics may play a role in the PPNG epidemic in Amsterdam.

Previous studies have shown that in the Netherlands some migrant groups, including prostitutess from Latin America, have played an important role in the spread of STDs. In response to these observations, specific prevention activities had already been started in the prostitution areas in Amsterdam before we knew the results of the present study which confirmed the results of the previous studies. This means that since 1990 window prostitutes have been informed about the risks for STDs including HIV and the importance of safe sex in their own language.

The STD clinic data of 1991 and 1992 demonstrate that PPNG infections have also started to decline among the heterosexual population. The number of PPNG infections diagnosed in this group fell from approximately 200 infections per year between 1983 and 1990 to 112 infections in 1991 and 71 infections in 1992. Especially among foreign prostitutes and clients the number of PPNG infections declined, while the number of visits at the STD clinic did not decrease among these subjects (unpublished data). This fall may be the result of the above mentioned risk reduction activities. The fact that in 1991 the Municipal Health Service recommended medical practitioners to use cefalosporins or quinolones that are active against PPNG as routine therapy for all gonorrhoea cases may also have contributed to the decrease of PPNG cases.

In conclusion, this study demonstrates that PPNG infections have mainly spread within Central and South American window prostitutes and their clients and not within drug addicted prostitutes and their clients. Since window prostitutes originating from countries in Central and South America are transient in Amsterdam, prevention activities targeted at these prostitutes and their clients should be continued to limit the spread of PPNG and other STDs within these groups. In addition, the future occurrence of gonorrhoea caused by PPNG and non-PPNG strains should be
closely monitored, to observe whether there are new potential core groups in order to control the spread of these infections.

The authors thank the staff of the STD clinic of the Municipal Health Service of Amsterdam for the valuable assistance and cooperation in conducting this study.

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