

Gonorrhoea reinfection in heterosexual STD clinic attendees: longitudinal analysis of risks for first reinfection

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Sex Transm Infect 2003;**79**:124–128

Objectives: Gonorrhoea is associated with adverse reproductive health outcomes, including pelvic inflammatory disease and increased HIV transmission. Our objective was to determine the association of demographic factors, sexual risk behaviours, and drug use with incident gonorrhoea reinfection among public STD clinic clients.

Methods: A retrospective cohort study conducted from January 1994 through October 1998, of heterosexual public STD clinic attendees age ≥ 12 years having at least one gonorrhoea infection in Baltimore, MD. The outcome was first incident gonorrhoea reinfection over a maximum 4.8 years, compared in STD clinic clients with or without sexual risk behaviours and drug use at initial gonorrhoea infection.

Results: 910 reinfections occurred among 8327 individuals and 21 246 person years of observation, for an overall incidence of 4.28 reinfections per 100 person years (95% CI 4.03 to 4.53). Median time to reinfection was 1.00 year (95% CI 0.91 to 1.07 years). In multivariate Cox regression, increased reinfection risk was associated with male sex, younger age, greater number of recent sex partners, and having a sex partner who is a commercial sex worker. Injection drug use and coming to the clinic as an STD contact were protective. Among risk factors that differed significantly between men and women, injection drug use was protective of reinfection in men, and "any" condom use was a risk factor for reinfection in women.

Conclusions: Reinfection represents a significant proportion of STD clinic visits for gonorrhoea. Prevention counselling and routine screening for patients at high risk for reinfection should be considered to maximally reduce transmission and resource utilisation.

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Accepted for publication 16 September 2002

There are an estimated 650 000 cases of gonorrhoea annually in the United States,¹ costing approximately \$1 billion (direct and indirect costs).² The sequelae of untreated gonorrhoea infections have been well described, and in women include pelvic inflammatory disease (PID) and subsequent increased risk of tubal infertility and ectopic pregnancy.³ Gonococcal infection has been shown to increase the risk of HIV acquisition⁴ in a large variety of populations, including STD clinics.^{5–6}

Recent data from the CDC Gonococcal Isolate Surveillance Project (GISP) found that 17.2% of men tested in 1999 reported having had a gonorrhoea infection in the previous year.⁷ Similarly, 14.8% of 608 patients with gonorrhoea at a public STD clinic in rural North Carolina were reinfected over a 2 year observation period.⁸ Similar proportions of repeat infections were reported among 14–35 year olds over a 5 year observation period in San Francisco.⁹

It is likely that people with repeated gonorrhoea infections have different risk behaviours than those who do not,^{10–11} which would have important implications for design of focused interventions. Our objective was to quantify the proportion of gonorrhoea visits attributed to reinfection, and determine demographic or behavioural factors associated with first occurrence gonorrhoea reinfection in STD clinic patients.

METHODS

This study was a record based historical cohort study. The cohort consisted of heterosexual patients diagnosed with gonorrhoea at either of the two public Baltimore STD clinics between January 1994 and October 1998. Risks at first gonorrhoeal infection were compared for patients with gonorrhoea

reinfection and patients who did not have gonorrhoea reinfection. This study was approved by the Johns Hopkins University School of Medicine Joint Committee on Clinical Investigations and the Baltimore City Health Department.

Data collection and analysis

Information regarding demographics, reason for visit, and behavioural risks were collected using a standardised clinical encounter form entered by scanning into a clinic database. Routine data collection included reason for visit to the clinic, number of sexual partners in the past month (< 2 or ≥ 2), condom use ("any" or "none"), exchanged sex for drugs or money ever ("exchange sex"), injection drug use (IDU) ever, non-injection cocaine use ever, and sexual partner's risks, including ever having sexual contact with someone who uses injection drugs, exchanged sex for drugs or money, or was known to be HIV infected. Over 95% of clinic attendees are African-American, and therefore we did not analyse race.

The observation period was from 3 January 1994 to 20 October 1998. Entry into the cohort began with a visit in which gonorrhoea was diagnosed. Gonorrhoea infection was defined as a positive genital culture. The outcome measure for this analysis was incident first reinfection with gonorrhoea, which was defined as a diagnosis of gonorrhoea at a visit at least 3 months subsequent to the first visit in which gonorrhoea was diagnosed. The following patients were excluded: patients who were initially gonorrhoea culture positive within 3 months before the end of the observation period; patients whose reinfection occurred within 3 months of the previous infection; patients < 12 years of age; and patients with missing information on sex.

Table 1 Trends over time for gonorrhoea positive patients, 1994–8

	1994 No (%)	1995 No (%)	1996 No (%)	1997 No (%)	1998 No (%)	p Value non-parametric trend test
Number of visits*						
One visit only	2033 (80.9%)	1812 (74.0%)	1289 (71.6%)	1377 (75.7%)	906 (78.9%)	
Repeat visit	480 (19.1%)	638 (26.0%)	511 (28.4%)	442 (24.3%)	243 (21.1%)	<0.01
Mean age (years)	27.8	26.7	25.5	21.9	22.5	<0.01
Patients that were male	1993 (79.3%)	1975 (80.6%)	1495 (83.1%)	1467 (80.7%)	920 (80.1%)	0.31
Patients having ≥ 2 sex partners in past month	1040 (41.4%)	1033 (42.2%)	787 (43.7%)	771 (42.4%)	476 (41.4%)	0.69
Patients used injection drugs "ever"	199 (8.3%)	177 (7.5%)	117 (6.7%)	88 (5.0%)	49 (4.5%)	<0.01
Patients used inhaled cocaine "ever"	465 (19.6%)	350 (14.9%)	259 (14.9%)	221 (12.7%)	150 (13.7%)	<0.01
Patient engaged in "exchange sex" ever	90 (3.8%)	86 (3.7%)	62 (3.7%)	59 (3.5%)	58 (5.6%)	0.14
Sexual contact ever with someone who used injection drugs	170 (7.9%)	127 (5.8%)	114 (7.0%)	84 (5.1%)	74 (7.1%)	0.06
Sexual contact ever with someone who engaged in "exchange sex"	301 (13.2%)	324 (14.3%)	208 (12.4%)	202 (12.2%)	108 (10.4%)	0.01

*"One visit only" indicates patients who appeared in the entire data set only once. "Repeat visit" indicates patients who had more than one visit.

We calculated incidence by dividing the number of people with gonorrhoea reinfection by the number of person years at risk. Observation times were calculated as the time from the first infection to individual's first reinfection or the end of the follow up period if they did not become reinfected. We assumed STD clinic clients who were not subsequently diagnosed with gonorrhoea in the STD clinics were free of gonorrhoea throughout the observation period.

Descriptive analyses included frequencies, χ^2 tests, and non-parametric trend tests. Exploratory analysis included log rank test for equality of survivor function to assess statistical significance and direction of differences in observed compared with expected number of gonorrhoea reinfections between groups. Variables significant at the $p < 0.05$ level by log rank test were entered in Cox proportional hazards regression, to assess the risk of gonorrhoea reinfection over time by characteristics at initial gonorrhoea infection. The assumption of proportionality for Cox proportional hazards was assessed graphically for each independent variable. In addition to analysing the sample population as a whole, men and women were analysed separately. Data were analysed using STATA 6.0 for Windows (Stata Corporation, TX, USA).

RESULTS

Study population

From January 1994 to October 1998, 9145 individuals had 10 801 visits (range 1–15 visits) in which gonorrhoea was diagnosed at the two STD clinics. Ten infections occurred in people with missing information on age, three were missing information on sex, 509 initial infections occurred within 3 months of the end of the observation period, 296 reinfections occurred within 3 months of the initial infection; these records were rejected from the analysis. Of the remaining 9845 visits, 474 second to 14th reinfections were also excluded from the longitudinal analysis (log rank test and Cox proportional hazards regression). Analyses were based on 8327 (91.1%) individuals completing 9731 (90.1%) visits in which gonorrhoea was diagnosed. Of these, 7417 (89.1% of patients) patients had gonorrhoea on one occasion. The other 2314 (23.8% of all gonorrhoea visits) visits were accounted for by 910 (15.8%) patients.

The proportion of clinic visits with gonorrhoea attributable to reinfections was 19.1% in 1994, increasing to 28.5% in 1996, and 21.2% in 1998 (table 1). The mean age at initial infection for people who were subsequently reinfected decreased from 27.8 years in 1994 to 22.5 years in 1998 ($p < 0.01$, non-parametric trend test). The prevalence of IDU decreased from 8.3% in 1994 to 4.5% in 1998 ($p < 0.01$), inhaled cocaine use from 19.6% in 1994 to 13.7% in 1998 ($p < 0.01$), and sexual contact with someone who engages in exchange sex from

13.2% in 1994 to 10.4% in 1998 ($p = 0.01$). The proportion of patients who were male, had ≥ 2 sex partners in the past month, or reported exchange sex did not vary over time.

Characteristics of patients are shown in table 2. Almost 80% of patients were male, and 83% of all patients presented to the clinic because of symptoms. Only 9.5% of patients stated they use "any" condoms, and 42% of patients reported ≥ 2 sex partners in the past month. Cocaine use was common among patients (16%), as were sexual partner risk behaviours (table 1). As information regarding sexual partner's HIV status was missing in 24% of cases, this variable was excluded from further analysis.

The incidence of 910 gonorrhoea reinfections over 21 246 person years at risk was 4.28 per 100 person years (95% CI 4.03 to 4.53). Median time to reinfection was 1.00 year (95% CI 0.91 to 1.07 years). Table 2 shows results of log rank tests for differences in observed and expected number of reinfections. The observed number of gonorrhoea reinfections was statistically significantly greater than the expected number of reinfections if the patient was male, ≤ 25 years of age, had ≥ 2 sex partners, came to the clinic for symptoms, reported no condom use, or ever had sexual contact with someone who engages in "exchange sex." The observed counts were statistically significantly lower than the expected counts for IDU and coming to the clinic as an STD contact or for an HIV test.

Cox proportional hazards regression

Cox proportional hazards modelling was used to calculate the hazard ratio (HR) of first gonorrhoea reinfection associated with demographic and behavioural risks. Graphical inspection showed no violation of the assumption of proportionality for each independent variable. In univariate Cox regression (table 3), the risk of reinfection estimated by the HR was higher for patients who were male, ≤ 25 years of age, had ≥ 2 sex partners in the past month, and sexual contact "ever" with someone who engages in "exchange sex." Reporting contact to an STD as the reason for clinic visit, "any" condom use, and IDU were protective of reinfection.

In multivariate Cox regression, male sex, younger age, ≥ 2 sex partners in the past month, and sexual contact "ever" with someone who engages in "exchange sex" remained statistically significant predictors of gonorrhoea reinfection (table 3). Conversely, IDU and reporting "contact to an STD" as the reason for clinic visit were statistically significantly protective of gonorrhoea reinfection. In multivariate analysis, "any" condom use was associated with an increased risk of gonorrhoea reinfection.

There were three statistically significant interaction terms. Although coming to the clinic as an STD contact was protective of reinfection in the base model, ever engaging in "exchange sex" and coming to the clinic as an STD contact had an HR of 6.23 (95% CI 2.17 to 17.8, $p < 0.001$). Also ever

Table 2 Descriptive analysis of characteristics associated with gonorrhoea reinfection

Characteristic at initial infection	Total number of people	Number of gonorrhoea reinfections observed	Number of gonorrhoea reinfections expected	p Value log rank
	No (%)			
Sex				
Female	1717 (20.6%)	122	193	<0.001
Male	6610 (79.4%)	788	717	
Age above or below median				
Age <25 years	4186 (50.3%)	506	446	<0.001
Age ≥25 years	4141 (49.7%)	404	464	
Reason for visit				
None recorded	406 (4.9%)	45	45	<0.001
STD symptoms	6893 (82.8%)	805	752	
STD contact	692 (8.3%)	36	75	
Previous positive STD test result	93 (1.1%)	8	12	
HIV testing	28 (0.3%)	2	4	
Check up	215 (2.6%)	14	22	
Number of sex partners in past month				
<2	4813 (57.8%)	457	530	<0.001
2 or more	3514 (42.2%)	453	380	
Condom use				
Any	787 (9.5%)	67	84	0.056
None	7540 (90.5%)	843	826	
Injection drug use ever				
No	7467 (93.1%)	823	804	0.016
Yes	553 (6.9%)	46	65	
Non-injection cocaine use ever				
No	6717 (84.1%)	735	726	0.402
Yes	1272 (15.9%)	135	144	
Engaged in exchange sex ever				
No	7501 (96.1%)	812	817	0.386
Yes	302 (3.9%)	37	32	
Sexual contact ever with an IDU				
No	6937 (93.5%)	764	756	0.262
Yes	480 (6.5%)	46	54	
Sexual contact ever with someone who engages in exchange sex				
No	6739 (87.6%)	698	738	0.001
Yes	951 (12.4%)	145	105	
Year of initial infection				
1994	2368 (28.4%)	335	349	0.497
1995	2107 (25.3%)	295	270	
1996	1441 (17.3%)	152	158	
1997	1481 (17.8%)	104	108	
1998	930 (11.2%)	24	25	

engaging in “exchange sex” and having no reason recorded for clinic visit had an HR of 1.25 (95% CI 1.22 to 1.81, $p < 0.001$), and having no reason recorded for clinic visit and having ≥ 2 sex partners in the past month had an HR of 1.70 (95% CI 1.15 to 2.51, $p = 0.007$). Limiting the analysis to individuals who had at least 1 year of follow up produced the same model as described above in terms of magnitude, direction, and significance of hazard ratios, (results not shown).

Sex stratified cox proportional hazards regression

Among women, univariate Cox regression showed that having ≥ 2 sex partners in the past month, using “any” condoms, and ever engaging in “exchange sex” increased the risk of gonorrhoea reinfection (table 4). Coming to the clinic as an STD contact was protective of gonorrhoea reinfection. Inhaled cocaine use, ever having sexual contact with an IDU, coming to the clinic for other reasons for visit, and ever having sexual contact with someone who engages in “exchange sex” were not statistically significant in univariate analysis. Only seven women reported HIV testing as reason for visit, and it was excluded from analysis. “Any” condom use, ≥ 2 sex partners in the past month, and coming to the clinic as an STD contact remained statistically significant in stepwise multivariate Cox regression (table 5).

Although “any” condom use was a risk for gonorrhoea reinfection in the final multivariate model for women, 31% of

women who reported “any” use of condoms had ≥ 2 sex partners in the past month compared to 18% of women who reported no condom use. Additionally, 62% of women who ever engaged in “exchanged sex” reported using “any” condoms compared to 45% of women who did not report “exchange sex”, and 62% of women who ever engaged in “exchange sex” had ≥ 2 sex partners in the past month compared to 22% for women who did not report “exchange sex” ($\chi^2 p < 0.001$, each).

Among men, younger age, having ≥ 2 sex partners in the past month, and ever having sexual contact with someone who engages in “exchange sex” were statistically significant risks for reinfection in univariate Cox regression, while IDU was protective of reinfection (table 4). Non-injection cocaine use, sex partner who is an IDU, reasons for clinic visit, and year of initial infection were not statistically significant. In stepwise multivariate Cox regression, younger age, having ≥ 2 sex partners in the past month, and ever having sex with someone who engages in “exchange sex” were a risks for reinfection, while IDU dropped out of the model.

DISCUSSION

A significant proportion of gonorrhoea cases diagnosed in Baltimore City public STD clinic are attributable to reinfection. The risk for gonorrhoea reinfection was associated with male sex, younger age, and high risk behaviours. Paradoxically, IDU was protective of reinfection in men, and “any” condom use

Table 3 Univariate and multivariate Cox regression results: relative hazards of gonorrhoea reinfection

Variable	Univariate hazard ratio (95% CI) p value	Multivariate hazard ratio (n=8036) (95% CI) p value
Sex		
Male	1.74 (1.44 to 2.11) <0.001	1.83 (1.37 to 1.57) 0.001
Age above or below median		
≤25 years old	1.30 (1.14 to 1.48) <0.001	1.43 (1.23 to 1.66) <0.001
Reason for visit		
None recorded	–	
STD symptoms	1.06 (0.79 to 1.43) 0.692	
STD contact	0.48 (0.31 to 0.74) 0.001	0.59 (0.41 to 0.85) 0.005
Previous positive STD test result	0.64 (0.30 to 1.36) 0.246	
HIV testing	0.55 (0.13 to 2.27) 0.411	
Check up	0.62 (0.34 to 1.13) 0.116	
Number of sex partners		
≥2 past month	1.39 (1.22 to 1.58) <0.001	1.22 (1.06 to 1.41) 0.005
Reports “any” condom use		
Yes	0.79 (0.61 to 1.01) 0.057	1.61 (1.12 to 2.30) 0.009
Ever used injection drugs		
Yes	0.70 (0.52 to 0.94) 0.017	0.75 (0.55 to 1.03) 0.078
Sexual contact ever with someone who engages in exchange sex	1.47 (1.23 to 1.75) <0.001	1.51 (1.24 to 1.83) <0.001

Variables not significant at the p<0.05 level from univariate analyses that were not included: patient ever used non-injection cocaine, patient reports exchange sex ever, sexual contact ever with an IDU, and year of initial infection.

Table 4 Univariate Cox proportional hazards regression for women and men: relative hazards of gonorrhoea reinfection

Variable	Women hazard ratio (95% CI) p value	Men hazard ratio (95% CI) p value
Age ≤25 years	1.29 (0.89 to 1.89) 0.182	1.38 (1.20 to 1.59) <0.001
Reason for visit		
None recorded	–	
STD symptoms		
STD contact	0.48 (0.21 to 1.12)	
Previous positive STD result	0.091	
HIV testing		
Check up		
≥2 sex partners past month	1.78 (1.23 to 2.55) 0.002	1.24 (1.08 to 1.43) 0.003
“Any” condom use	1.61 (1.12 to 2.29) 0.009	
Exchange sex ever	1.83 (1.03 to 3.26) 0.040	
Injection drug use ever	0.53 (0.20 to 1.45) 0.217	0.70 (0.51 to 0.96) 0.026
Sexual contact ever with someone who engages in exchange sex		1.33 (1.11 to 1.60) 0.002

Variables not significant at the p<0.05 level from univariate analyses not shown: patient ever used non-injection cocaine, sexual contact ever with an IDU, and year of initial infection.

was a risk factor for reinfection in women, though closer inspection showed the relation between condom use and risk of reinfection was confounded by number of sex partners and engaging in “exchange sex.”

Several previous studies have examined factors associated with bacterial STD reinfection, specifically chlamydia, among adolescents and young adults. A longitudinal study of adolescents and young adults recruited from an urban STD clinic found that 53% of those who were “STD contacts” at enrolment had a subsequent STD.¹² Similarly, in our study exploration of

interaction terms showed that coming to the clinic as an STD contact was in general protective of reinfection, but among patients with high risk behaviours, this was a risk factor for reinfection. In contrast with our results, this same study found that being female increased the likelihood of subsequent chlamydia infection.¹² A large, retrospective cohort study of urban STD clinics in England found younger age, sexual orientation, ethnicity, and recent history of multiple sex partners were associated with an increased hazard ratio of STD reinfection, though not specific to gonorrhoea.¹³

Table 5 Stepwise multivariate Cox proportional hazards regression for men and women

Variable	Women (n=1640) hazard ratio (95% CI) p value	Men (n=6002) hazard ratio (95% CI) p value
Age ≤25 years		1.51 (1.29 to 1.76) <0.001
"Any" condom use	1.57 (1.08 to 2.27) 0.018	
≥2 sex partners past month	1.63 (1.11 to 2.40) 0.013	1.16 (1.00 to 1.35) 0.051
Reason for visit		
STD contact	0.56 (0.35 to 0.89) 0.014	
Sexual contact ever with someone who engages in exchange sex		1.51 (1.24 to 1.84) <0.001

This study had some limitations that primarily biased the measures of association towards the null. We observed several statistically significant changes in aggregated patient characteristics over time. However, data on risk status between positive visits or after the first positive visit were not available. Therefore we could not analyse change in an individual's risk over time and how that affects reinfection. Also, we did not have information on STD history. First recorded gonorrhoea positive visit in this data set may not have been the true first gonorrhoea infection, if the patient had been diagnosed before 1994 or outside of a city STD clinic. Thus some of the one time infections may have actually been gonorrhoea reinfections. Further, patients with one time infections in our database may have acquired subsequent infections and been diagnosed and treated elsewhere, leading us to underestimate gonorrhoea reinfection rate. Further, results of the analysis were limited by data collected through the medical record. Risk factor analysis may have produced different results had other variables been measured or had risks been measured differently (for example, frequency instead of "ever" or "any").

The historical cohort design allowed for evaluation of associations between exposures and outcome that were measured before the outcome, eliminating potential recall bias. Literature regarding the predictors of incident reinfections STDs is limited, especially regarding predictors specific to gonorrhoea reinfection and adult populations. The large sample size obtained over several years of observation provides a compelling foundation for the results of this analysis.

Our results demonstrate the substantial contribution of gonorrhoea reinfection to overall gonorrhoea morbidity. The large proportion of patients who experience reinfection suggests recommending routine screening for patients at high risk for infection. Specific factors associated with elevated risk for reinfection suggest possibilities for focused prevention interventions at the first gonorrhoea diagnosis. Targeting interventions to people at risk for reinfection may be an effective way of maximally preventing gonorrhoea transmission and reducing resource utilisation. Future research comparing reinfection rates among people at risk for reinfection with enhanced intervention to those who are not at risk for reinfection will be necessary to demonstrate this.

ACKNOWLEDGEMENTS

Sources of funding: JMZ was supported by NIH grants K24AI01633 and U19AI38533. AMR was supported by NIH grant A145724.

We thank the Baltimore City Health Department STD clinics for data collection, provision of data, and support of this analysis; Michelle Chung for cleaning the data; and Jonathan Ellen, MD, for reviewing statistical analysis methods.

CONTRIBUTORS

SDM developed the statistical analysis plan, analysed the data, and wrote the first draft of the paper; EJE participated in clinical data col-

lection and in database oversight through Baltimore City Health Department and also obtained approval for its use in this analysis, assisted SDM with interpreting the variables in the data set, assisted with the writing of the methods section, and reviewed and revised the manuscript; JMZ assisted with the writing of the background and discussion sections, guided SDM interpretation of the analysis and reviewed and revised the manuscript; AMR originated the objective of the paper, obtained the data for analysis, assisted interpretation and presentation of data analysis and results, and reviewed and revised the manuscript.

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