

**SEXUALLY TRANSMITTED DISEASE
CORE GROUP MEMBERSHIP IN MANITOBA;
STRATEGIES FOR DEFINITION,
AND DESCRIPTION OF RISK MARKERS**

By Ann Jolly

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STRATEGIES FOR DEFINITION, AND DESCRIPTION OF RISK MARKERS**

BY

ANN JOLLY

**A Thesis/Practicum submitted to the Faculty of Graduate Studies of The University
of Manitoba in partial fulfillment of the requirements of the degree**

of

DOCTOR OF PHILOSOPHY

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Executive Summary

Chlamydia trachomatis and *Neisseria gonorrhoeae* are the two most frequently occurring bacterial sexually transmitted diseases (STD) in Canada. The burden and costs of both diseases are primarily due to the sequelae which include pelvic inflammatory disease, ectopic pregnancy and infertility. Although preventive programs have been largely successful at reducing the number of cases in the last two decades, a decrease in disease is no longer evident. If gonorrhea is to be eliminated and chlamydia incidence greatly reduced in Canada, new control strategies need to be implemented.

STD epidemiology is dominated by the concept that a small subset of the population known as the “core group” is essential in maintaining the endemicity of STD in a population. Through high numbers of partners, and long periods of infectiousness, core group members contribute disproportionately to STD spread. Mathematical formulae have been used to prove core group theory the equations have seldom, if ever, been solved.

The goal of this research was to define predictors for members of chlamydia and gonorrhea core groups using the mathematical equations. The proposed core group populations comprised individuals repeatedly infected with chlamydia, gonorrhea and with both organisms, and multiply named sexual contacts of cases from 1990 through 1992.

After substituting infection transmission probabilities and duration of infection estimates from the literature, and partner change rates from this research the results of the mathematical equations formulae strongly suggest that the proposed core groups do indeed encompass the true core groups. They also show that in a population with a high incidence of gonorrhoea, and where dual therapy for both gonorrhoea and chlamydia is practiced, combination therapy for chlamydia is effective and chlamydia will become a non-viable infection.

Last, the feasibility of constructing sexual networks from contact data for the purposes of better defining core groups was successful, and revealed an astonishingly large network of more than 900 connected people, the upper limits of which are still to be established.

Future investigation into the uses of social network analysis for both practical use by field staff and for the understanding of STD epidemiology is essential.

Table of contents

Chapter 1 Background

1.1	Burden of illness	1
1.2	Research goals	4
1.3	Review of existing control strategies	5
1.4	Risk behaviors for sexually transmitted diseases	11
1.5	Epidemiology of <i>Neisseria gonorrhoeae</i> and <i>Chlamydia trachomatis</i> infections	14
1.6	Critical review of mathematical “core group” theory of sexually transmitted diseases	19
1.7	Social network analysis, a new framework	35
1.8	Conclusion	41

Chapter 2 Methods

2.1	Study rationale and objectives	44
2.2	Hypotheses	45
2.2.1	Phase I, laboratory proven cases of sexually transmitted disease	46
2.2.2	Phase II, multiply named contacts of confirmed cases	49
2.3	Sample size and selection	54
2.3.1	Phase III, mathematical modelling and construction of sexual networks	56
2.4	Statistical methods	58

2.4.1	The use of statistical tests of whole populations	59
2.4.2	The effect of large sample sizes	62
2.4.3	Normality	63
2.4.4	Missing values	70
2.5	Outliers	72
2.6	Data sources	73
2.6.1.	Manitoba Health STD registry	75
2.6.1.1	Registering a case	76
2.6.1.2	Following up a case, treatment and partner notification	77
2.6.2	Manitoba Health Patient Registry File	78
2.6.3	Manitoba Health STD contact database	79
2.6.4.	Statistics Canada census data	80
2.7	Definitions	82
2.7.1	Individual	82
2.7.2	Laboratory confirmed	83
2.7.3	Laboratory confirmed case repeater	84
2.7.4	Individual with only one confirmed infection	86
2.7.5	Categories of disease; chlamydia, gonorrhoea and coinfection	87
2.7.6	Contact	89
2.7.7	Repeatedly named contact	90
2.7.8	Contact named only once	91
2.9	Conclusions	93

Chapter 3; data management strategies

3.1	Introduction	94
3.2	Phase I; laboratory-confirmed cases of gonorrhea and chlamydia	94
3.2.1	Selection of individuals with repeated infections	95
3.2.2.	Data cleaning; individuals with repeated infections	96
3.2.3	Classification of individuals with single infections.	101
3.2.4	Data cleaning; individuals with single episodes of infection	102
3.2.5	Sample selection of individuals with single episodes of infection	103
3.3	Phase II; Contacts named by laboratory confirmed cases	104
3.3.1	Classification of multiply named contacts	104
3.3.2	Sample selection; contact comparison group	109
3.3.3	Data cleaning; contact database	110
3.4	Definition of variables; Phase I, laboratory-confirmed cases of gonorrhea and chlamydia	112
3.4.1	Number of repeat events	113
3.4.2	Age	114
3.4.3	First Nations ancestry	115
3.4.4	Use of an alias	116
3.4.5	STD in pregnancy	116
3.4.6	Postal codes	117
3.4.7	Number of sex partners	117
3.4.8	Presence of symptoms	118

3.4.9	Duration of symptoms	119
3.4.10	Recorded therapy	119
3.4.11	Income quintile	122
3.5	Phase III Contact tracing data of case and contact repeaters and comparison groups	123
3.5.1	Numbers of sexual partners	123
3.5.2	Construction of sexual networks	124
3.6	Conclusions	125
Chapter 4; Chlamydia confirmed cases and contacts - results and discussion		
4.1	Introduction	127
4.2	Comparison of chlamydia repeater cases and comparison group	128
4.3	Introduction; contacts of chlamydia infection	142
4.4	Comparison of chlamydia repeat contacts and comparison group	144
4.5	Comparison of chlamydia, gonorrhea, and coinfecting repeaters	148
4.5.1	Comparison of coinfecting repeat cases with chlamydia repeater cases	148
4.5.2	Comparison of gonorrhea repeat cases with chlamydia repeater cases	155
4.6	Comparison of multiply named chlamydia, gonorrhea and coinfecting contacts	161
4.6.1	Comparison of coinfecting repeat contacts with chlamydia repeat contacts	161
4.6.2	Comparison of chlamydia repeat contacts with	

	gonorrhea repeat contacts	164
4.7	Comparison of repeat cases and repeatedly named contacts	168
4.7.1	Comparison of chlamydia case repeaters with multiply named contacts of chlamydia	169
4.8	Conclusion	174
 Chapter 5; gonorrhea cases and contacts - results and discussion		
5.1	Introduction	176
5.2	Comparison of gonorrhea repeater cases and comparison group	177
5.3	Comparison of gonorrhea repeat contacts and comparison group	186
5.4	Comparison of multiply named contacts of gonorrhea and comparison group	187
5.5	Comparison of chlamydia, gonorrhea, and coinfecting repeat cases.	188
5.5.1	Comparison of coinfecting repeat cases with gonorrhea repeat cases	189
5.5.2	Comparison of gonorrhea repeat cases with chlamydia repeater cases.	194
5.6	Comparison of the contact repeaters with chlamydia, gonorrhea and coinfection	194
5.6.1	Comparison of coinfecting repeat contacts with gonorrhea repeat contacts	195
5.7	Comparison of repeat cases and repeatedly named contacts	198
5.7.1	Comparison of gonorrhea repeat cases with multiply named contacts of gonorrhea	199
5.8	Conclusions	201

Chapter 6; Coinfected cases and contacts - results and discussion

6.1	Introduction	203
6.2	Comparison of coinfecting repeater cases and comparison group	203
6.3	Analysis of contacts of coinfecting cases	211
6.4	Comparison of coinfecting repeat contacts and comparison group	211
6.5	Comparison of chlamydia, gonorrhea, and coinfecting repeaters.	215
6.5.1	Comparison of coinfecting case repeaters with chlamydia case repeaters	215
6.5.2	Comparison of coinfecting case repeaters with gonorrhea case repeaters	216
6.6	Comparison of the contact repeaters with chlamydia, gonorrhea and coinfection	216
6.6.1	Comparison of coinfecting repeat contacts with gonorrhea repeat contacts	216
6.6.2	Comparison of coinfecting repeat contacts with chlamydia repeat contacts	217
6.7	Comparison of repeat cases and repeatedly named contacts	218
6.7.1	Comparison of coinfecting repeaters with multiply named contacts of coinfecting cases	218
6.8	Conclusions	223

Chapter 7; Predicting case and contact repeaters - results and discussion

7.1	Introduction	225
7.2	Predictive model for individuals with repeated exposure to chlamydia	229
7.3	Predictive model for individuals with repeated exposure to gonorrhea	236
7.4	Predictive model for individuals with repeated exposure to gonorrhea and chlamydia coinfection	240
7.5	Conclusions	244

Chapter 8; Numbers of partners and estimation of core group parameters - results and discussion

8.1	Introduction	246
8.2	Results of comparisons between case repeaters and comparison groups	248
8.2.1	Chlamydia case repeaters and comparison group	249
8.2.2	Gonorrhea case repeaters and comparison group	252
8.2.3	Coinfected case repeaters and comparison group	253
8.3	Chlamydia, gonorrhea and coinfecting case repeaters	253
8.4	Results of comparison between contact repeaters and the comparison groups	255
8.5	Comparison of chlamydia, gonorrhea, and coinfecting contact repeaters	258
8.6	Conclusions; analysis of numbers of partners	259
8.7	Use of sex partner data in mathematical formulae for the reproductive rate of infection	261
8.7.1	Calculations of formulae for the reproductive rates of chlamydia	262

8.7.2	Calculations of formulae for the reproductive rates of gonorrhoea	267
8.7.3	Calculations of formulae for the reproductive rates of chlamydia and gonorrhoea coinfection	270
8.8	Conclusions; calculations of R_0	273
8.9	Social network analysis	276
8.9.1	A brief introduction to social network analysis	277
8.10	Results of network construction	284
8.11	Conclusions	292
 Chapter 9; Conclusions		
9.1	Summary	294
9.2	The nature of the core groups	301
9.3	The reproductive values of the core groups	309
9.4	Sexual networks	311
9.5	Practical applications	312
9.6	Limitations of the research	315
9.7	Conclusions	318
 Bibliography		320
 Appendix I		354

List of Figures

Figure 2.1	Flow chart of hypothesis testing	53
Figure 2.2	Normal probability plot of ages of cases with one episode of gonorrhoea	65
Figure 2.3	Normal probability plot of ages of gonorrhoea repeaters	65
Figure 2.4	Normal probability plot of ages of cases with one episode of coinfection	66
Figure 2.5	Normal probability plot of ages of coinfecting repeaters	66
Figure 2.6	Histogram of ages of gonorrhoea repeaters	69
Figure 2.7	Histogram of the natural log of ages of gonorrhoea repeaters	69
Figure 2.8	Hierarchy for classifying repeaters and comparison groups	92
Figure 3.1	Data management plan	98
Figure 3.2	Results of cross referencing case and contact databases	108
Figure 4.1	Probability of repeat chlamydia compared with single infections	141
Figure 4.2	Probability of multiply named contacts of chlamydia compared with those named once	145
Figure 4.3	Probability of repeated coinfection compared with repeated chlamydia	151
Figure 4.4	Probability of repeated gonorrhoea compared with repeated chlamydia	158
Figure 4.5	Probability of being a multiply named contact of gonorrhoea	

	compared with repeated chlamydia	167
Figure 4.6	Probability of repeated chlamydia infection compared with being a multiply named contact	171
Figure 5.1	Probability of repeat gonorrhoea compared with single infections	181
Figure 5.2	Probability of repeated coinfection compared with repeated gonorrhoea	193
Figure 5.3	Probability of a multiply named contact of coinfection compared with being a multiply named contact of gonorrhoea	197
Figure 6.1	Probability of repeated coinfection compared with single infections	210
Figure 8.1	Histogram of number of partners of chlamydia, gonorrhoea, and coinfecting repeaters	254
Figure 8.2	Histogram of number of partners of chlamydia, gonorrhoea, and coinfecting multiply named contacts	258
Figure 8.3	Network of ten friends	279
Figure 8.4	Network of ten employees of a company	280
Figure 8.5	Network of adjacency matrix	281
Figure 8.6	Network of a bridge	283
Figure 8.7	Small network from feasibility study	285
Figure 8.8	Coinfection network showing those testing positive; negative and those not tested	286
Figure 8.9	Coinfection network showing diffusion of infection over time	287

Figure 8.8	A portion of the largest network	289
Figure 8.9	A portion of the largest network, showing individuals by diagnosis	291
Figure 9.1	Proportions of First Nations people in chlamydia, gonorrhea, and coinfected repeaters and comparison groups	302
Figure 9.2	Proportions of income quintiles of chlamydia, gonorrhea, and coinfected repeaters and comparison groups	303
Figure 9.3	Proportions of people using aliases in chlamydia, gonorrhea, and coinfected repeaters and comparison groups	304
Figure 9.4	Proportions of people with symptoms in chlamydia, gonorrhea, and coinfected repeaters and comparison groups	305
Figure 9.5	Diagram of core group continuum	308

Chapter 1

Background

1.1 Burden of illness

Chlamydia trachomatis and *Neisseria gonorrhoeae* are the two most frequently occurring bacterial sexually transmitted diseases in the world, and in Canada.¹⁻³ *Chlamydia trachomatis* is an intracellular parasite, and is primarily transmitted sexually or congenitally.⁴ *Neisseria gonorrhoeae* is a bacteria closely related to *Neisseria meningitidis*, and is also sexually transmitted. Both organisms infect the columnar epithelial cells of the urethra in men and the endocervix in women, causing inflammation, epithelial ulceration and scarring. The pathogenesis of chlamydia is less well understood than that of gonorrhea. Gonococcal infection produces symptoms in 50%⁵ of women, although ranges of 20% to greater than 75% have been cited.⁶ The different proportions depend on the populations studied and the reasons for presentation. The proportion of incident asymptomatic gonococcal infection in men has been estimated at between one and three percent. The incubation period for gonorrhea is between two and seven days.⁵ Only 50% of people with chlamydial infection are symptomatic.⁷ Clinical symptoms of gonorrhea and chlamydia are similar. Both cause urethritis, epididymitis, and proctitis in men. The most common symptoms in women are; cervicitis, acute urethral syndrome,

bartholinitis, and salpingitis. Conjunctivitis, and disseminated infections are suffered by both genders.⁸

The cost of *C. trachomatis* genital infection in Canada has been estimated at between \$89 million annually (base cost) and \$123.1 million (1990 dollars).⁹ Estimates for the direct and indirect costs of chlamydial infections in the United States were as high as US\$2.18 billion in 1990. The rise in incidence of chlamydia, now the most frequently occurring reportable sexually transmitted disease (STD),^{1,2,10} is of concern on its own, but particularly because of its role in causing pelvic inflammatory disease (PID) or salpingitis, involuntary infertility and ectopic pregnancy.^{11,12} Women with a positive serology test for IgG antibodies to *Chlamydia trachomatis* have five times higher risk of ectopic pregnancy than women who have negative chlamydia serology. The pediatric sequelae of maternal chlamydial infection are also substantial. Associations between preterm birth, premature rupture of membranes, intrauterine growth retardation and presence of chlamydia has also been found, although the pathogenesis has not been elucidated.¹³⁻¹⁶ Additionally, in a study of commercial sex workers with equivalent numbers of partners and similar rates of condom use in Nairobi, those with chlamydial infection had an almost fourfold increased risk of seroconversion to HIV, when compared with women who had no chlamydial infections¹⁷. The high cost and burden of illness due to chlamydia is primarily due to the high incidence and prevalence of infection, both of which are higher than those of gonorrhea. In addition, because gonorrhea is more often symptomatic, patients are treated more often and more promptly, before sequelae develop.

While infection with *N. gonorrhoeae* is associated with a substantial disease burden, there are far fewer cases and the organism is less often isolated in patients with sequelae of STD than is chlamydia.¹⁸ However, a substantial proportion of gonorrhea cases in women are asymptomatic, and infection does ascend into the upper genital tract, causing pelvic inflammatory disease, ectopic pregnancy and infertility. These sequelae are the most costly, although sequelae in men which are rare include epididymitis and infertility. Costs of gonococcal infection include billings for physician office visits; hospitalization costs for sequelae, infertility therapy, drug costs and loss of productivity for time off work. The cost for males with gonorrhea was estimated at \$10.2 million in 1990, and the cost for females was 43.8 million. Because the incidence of sequelae is unknown, the total costs for males and females could be as high as \$11.7 million and \$62.6 respectively.⁹

In an effort to reduce the cost and burden of illness of both these infections legislation, policy guidelines, and programs have been implemented in the developed world.

Gonorrhea has been a notifiable disease requiring treatment and management of sex partners in many jurisdictions for a long time.¹⁹ Chlamydia was added more recently, but in both cases, the legislation allows for the gathering of statistics, sex partner notification, and monitoring of management of the infections. Policy guidelines on the diagnosis, treatment and management of gonorrhea and chlamydia have been published regularly in the United States and Canada. Screening programs to detect asymptomatic patients with disease have also been also advocated.²⁰

Gonorrhea incidence declined in the 1980's in Manitoba, ²¹ Canada, ² and in the United States.^{22,23} In Canada, the number of cases of gonorrhea has decreased ten-fold in the last 15 years from 56,330 in 1981 to 5,500 in 1995.²⁴ After the introduction of the chlamydia screening program in Manitoba, incidence rates in women had initially decreased by half, from 778.1/100,000 in 1988 to 393.1/100,000, in 1994. However, the decline in rates slowed in from 1993 to 1995,²¹ and positivity rates for women have levelled off to 3.6% in 1992 through 1994. Rates have also declined, then levelled off in other jurisdictions.^{25,26}

There is no doubt that part of the reduction in chlamydia and gonorrhea incidence is due to the implementation of screening programs and the attendant partner notification which occurs after finding a positive case. However, because of the decline in the incidence of chlamydia and gonorrhea, and the need for reducing health care costs, the value of screening large numbers of individuals who may be at very low risk of infection has been questioned.^{27,28} Control strategies other than those currently employed may need to be implemented if gonorrhea is to be eliminated and if chlamydia incidence is to be greatly reduced in Canada. The factors which affect diagnosis, screening and partner notification are reviewed in section 1.3.

1.2 Research goals

The goal of this research is to develop methods to better describe populations in need of enhanced gonorrhea and chlamydia control in Manitoba in the years 1990 to 1992. This

project will also define risk markers (predictors) of those individuals who are at high risk of transmitting chlamydia and gonorrhea infections. The description and prediction of individuals at high risk of chlamydia and gonorrhea infection, if consistent over time, will enable public health staff to distinguish between individuals with higher and lower risk behaviors and therefore set appropriate priorities for interventions. In addition, they may also provide enhanced education and prevention services to those clients at particularly high risk. By designing control programs which are appropriate for these populations, declines in gonorrhea and chlamydia rates may be achieved more rapidly and efficiently than with current control strategies alone.

1.3 Review of existing control strategies

Active prevention and control programs have contributed to the decrease in gonorrhea incidence. These programs may not be automatically adaptable to the prevention and control of chlamydia. Selected populations within Canada such as First Nations people, and those living in low socioeconomic areas continue to have high rates of gonococcal infections.^{3,29} In addition, reports of infections with antibiotic resistant strains of *N. gonorrhoeae* increased in Canada in the early 1990's. Although the number of isolations had dropped since then, importation of these strains into Canada will continue. National goals for the elimination of locally acquired gonococcal infections have been recognized as achievable by the year 2010. The emphasis on strategies for achievement has changed. Previously, selective screening, and partner notification were the secondary prevention

methods advocated, but now that gonococcal infection is becoming rare more selective screening is warranted, and services and research should be concentrated on those populations in which the incidence of gonorrhoea is relatively high.³

Chlamydia was made reportable nationally in Canada in 1990. Prior to 1990, many laboratories throughout Canada voluntarily reported chlamydia cases. Only nine provinces including Manitoba required reporting of chlamydial infections; therefore the true incidence of *C. trachomatis* for the whole of Canada was not known.³⁰ Since 1992, all provinces in Canada provided data on positive laboratory tests for chlamydial infection, and notifiable disease reports of chlamydia currently make up 84% of all notifiable sexually transmitted diseases.²

In order to decrease incidence, prevalence and costs of chlamydial infections, many jurisdictions introduced screening programs for women.^{20,25,26,31} In Manitoba, a screening program was initiated in 1987; chlamydia was added to the list of notifiable diseases under the Public Health Act and its regulations, and protocols for the management of chlamydial infections, which included partner notification, diagnosis and treatment, were introduced.³² A review of the Manitoba chlamydia screening program in 1995 (unpublished, Ann Jolly, Cadham Provincial Laboratory), revealed that since routine testing has been available in Manitoba, the number of positive test results has risen annually from 391 in 1984 to 6,683 in 1988. (The difference in the number of positive tests almost certainly reflects the increased use of the tests rather than the true incidence of disease.)

The strategy of screening women for chlamydia genital infection may have reached the point of diminishing returns. Not only has the cost for each case identified risen, but the practice of screening and rescreening women who are being reinfected by their male partners may result in artificially increased rates of detection in women, while failing to effectively reduce the size of the epidemic. Because chlamydia infection rates in males are one third of those in females, focussing control efforts on underdiagnosed male partners of women with chlamydia should prove a more effective and efficient control strategy, than continuing to screen low risk women.

The lack of adequate diagnosis and treatment in male sex partners of women with confirmed chlamydial infection which in turn leads to lack of adequate partner notification, is caused by a number of related factors. The first of these is that many men are reluctant to undergo a painful urethral swab, and secondly that the enzyme immunoassay test method (Chlamydiazyme Abbott Laboratories, Chicago) in men is less sensitive than in women, and leads to unexpectedly low positivity rates.

By far the majority of men tested for chlamydia at Cadham Provincial Laboratory (which completed more than 95% of testing for chlamydia in Manitoba) in 1990 were aged 15-39, and would have undergone testing either because they had symptoms of an STD or were contacts of a laboratory-confirmed case of chlamydia. A review of studies on transmission shows that 22% - 47% male contacts of female index cases with chlamydia are concordantly infected.^{2,18,33-36} The above studies diagnosed infection mostly by culture, but

one study used the direct fluorescent antibody method.³⁶ In groups where all men had symptoms, the likelihood of detecting *C. trachomatis* would be even higher. A positivity rate of 9.77% for all chlamydia tests in males in 1994, for example, therefore seems unexpectedly low. (Review of the chlamydia screening program in Manitoba, Ann Jolly, May 1995, unpublished report.) Poor specimen collection,³⁷ and/or low sensitivity of the enzyme immunoassay (EIA) tests for males, which is widely reported, are the most likely reasons for the low positivity rate.⁸

Public health nurses and physicians in the province note that men who are contacts of women with laboratory-confirmed chlamydia often test negative. (Personal communication, Ms. Kathy Mestery, May 1995, and Dr. Robert Brunham, April 29, 1997). This causes physicians in some cases to refuse to prescribe antibiotics. Secondly, physicians are reluctant to encourage a male partner to undergo an uncomfortable urethral smear to be submitted for an insensitive laboratory test. In cases where physicians do prescribe therapy for chlamydia, in the absence of a laboratory test or with a negative test result, male patients may not be convinced that they are infected and tend not to comply with therapy.³⁸ Both the lack of testing and poor sensitivity of the test in males lead to reinfections or "ping-pong infections" in female sexual partners. The diagnosis of repeated "ping-pong" infections in women whose male partners have not been adequately tested and treated for chlamydial infection artificially inflates incidence rates.

In addition to the above problems in the existing chlamydia screening and control program in Manitoba, a recent survey from Ontario indicated that only one third of physicians in a downtown Toronto family practice teaching units were aware of the "1989 Canadian Guidelines for Screening for *Chlamydia trachomatis* infection."³¹ Of those that were aware, only 39% followed the guidelines for selective screening. Thirty-five percent of respondents stated that they routinely screened all sexually active female patients.

While screening programs may be very effective in the early stages of infectious disease control, they become less effective as the number of cases diminishes.²⁷ Once the majority of prevalent cases have been diagnosed and treated, the people most likely to sustain the epidemic are less likely to have contact with the health care system.

There is evidence that the sequelae of chlamydial infection are caused in part by immune responses to *C. trachomatis*.^{11,39} Therapy for chlamydial infection, while effective in eradicating the organism, may not be effective in controlling the anatomical changes due to immunopathological responses.^{34,40,41} This hypothesis is supported by epidemiologic evidence in Manitoba which shows a rise in hospitalizations for ectopic pregnancy and in physician office visits for PID, despite a reduction in gonococcal infections, during the 1980's and early 90's.²⁹

If therapy is effective only early on in infection, which is often asymptomatic, traditional methods of secondary prevention such as screening may not be adequate in preventing

further infection and sequelae. Although a recent randomized controlled trial revealed that selective screening for women with demographic and behavioral markers of higher risk reduced diagnosis of PID (pelvic inflammatory disease) by more than 50%, it did not eliminate PID. The rate in screened women still remained eight confirmed cases per 10,000 woman months,⁴² and due to methodological problems in the study design, it is debatable whether significantly reduced rates of infection existed. The methodological issues raised in letters to the editor were that one third of women who were assigned to the screening group actually received no screening at all, and that women assigned to the screening group were followed-up more vigorously for appearance of PID than women who were assigned to the usual care group.⁴³⁻⁴⁶ Also, the study was conducted in an HMO in Washington State in the United States. A study on sequelae of STD in a population such as this may represent only those members of the population with higher educations or incomes, creating a type of self selection bias. Such a population which may contain women with infections acquired in the past, (prevalent infections), may fail to include individuals at most risk of incident, repeated or prolonged chlamydial infections, or those at most risk of gonorrhea and chlamydia coinfections. Repeated chlamydial infections have been associated with higher rates of sequelae,⁴⁷ which may be less amenable to screening programs.

Research into more effective primary prevention strategies is necessary in order to decrease the burden of chlamydial infections and their sequelae.

1.4 Risk behaviors for sexually transmitted diseases

In modern Western society, the challenge of STD has been addressed as a health issue. The management of STDs has been delegated to the medical and public health professions. From this background, three important factors are thought to be the most important in determining risk (probability of infection) for individuals and for populations and in preventing infection. These factors are: numbers and selection of sexual partners, (and the rate of acquisition), frequency of intercourse, and type of intercourse.⁴⁸ Frequency of intercourse may only apply to those individuals whose partners are infected, and quantifies the risk to an uninfected partner. Type of intercourse, (penile-vaginal, or penile-anal) is important in defining risk of specific sexually transmitted infections, as are attempts to account for whether barrier contraceptives are used. Aral and Holmes emphasize the importance of the precise use of the term “risk factor”. “Risk markers” is a more appropriate term than “risk factor” when characteristics such as ethnic group, or income level are described. These may be proxy indicators for other sexual risk behaviors.⁴⁸

With the advent of HIV infection and in order to gain a better understanding of populations at risk for sexually transmitted disease, attempts to describe classical risk factors were driven by the need to justify, design, implement and evaluate appropriate prevention efforts in a focussed manner.⁴⁹⁻⁶¹

Some elaborate analyses of population surveys of risk behavior have been conducted in order to arrive at estimates of the number of people exposed to STD, and those at high risk for HIV. One Canadian and one American study showed that condom use decreased with increased risk of STD, (through having high numbers of partners.)^{49,51} Another analysis from the US estimated the number of women exposed to higher risk of STD both through their own activities, and also those of their partners.⁸ These estimates take into account the number of partners women have, and how many partners their male partner is likely to have had. Expectedly, the researchers had to estimate to what extent women's partner choice is random, or to what extent women choose men who have similar numbers of partners as themselves, i.e., belong to the same sexual activity classes. Estimates using both scenarios showed that the percentage of women exposed to multiple partners in the last 12 months ranged between 26.5% and 38.7% of all American women.

The general conclusions which can be drawn from the studies are that men tend to have more partners than women; that the highest rate of partner change occurs in the younger age groups, (teenagers and early twenties), and that use of condoms is reported slightly more often by men, but generally in both genders, and in women, their use decreases with increasing numbers of partners. Frequency of intercourse is highest in people in their early twenties, reflecting steady partners, fewer child care duties, and lowest in people over age seventy. Decreases in age at first intercourse and increases in the total number of lifetime sexual partners over time have also been documented.⁶¹ The latter trend is observed despite the lack of comparable "opportunity" over time (i.e., from first intercourse to time

of survey), in which to recruit partners. Most of the increases in numbers of partners were reported by people born in the 1930's through the 1950's. Double the proportion of men compared with women report more than five lifetime sex partners over all birth cohorts from 1930's to the 1960's.⁶¹

The methodological problems in questionnaire research were commented on by all of the above cited authors. These surveys are usually affected by self-selection bias, which may result in over representation of persons of higher socioeconomic status. The sampling frame may also have excluded certain groups of people, for example the institutionalized and homeless in national surveys.⁵⁴ Sampling frames using school children would exclude dropouts, who would tend to be of lower socioeconomic status and be at greater risk of sexually transmitted diseases. In answering questionnaires, people may be subject to social acceptability bias, where men may exaggerate their numbers of partners, and where women minimize theirs.⁵⁰ Efforts were taken to maintain confidentiality and anonymity in the more intimate questions,^{50,54} In addition, new methods have been developed to describe non-responders more accurately,⁵⁰ but the drawbacks of questionnaire research remain to some extent.⁶¹

The catalogue of numbers of partners, frequency of sex, and condom use does not provide a coherent portrait of population risk for STDs. The phenomena described are merely the sexual practices of individuals who consent to participate in a survey. If risk behaviors were both necessary and sufficient causes of chlamydial and gonococcal infection, the

enumeration of risk behaviors, (such as number of sex partners), to define risk of STDs would be appropriate. However, “risky” sexual behavior is neither necessary nor sufficient in order for infection to occur, but rather represents a contribution toward risk, which may be more or less quantifiable. This concept has obviously been recognized by Kost and Forrest who attempted to quantify the proportion of American women who have more than one partner during the past 12 months, and those who are exposed to more than one partner through their partner’s activities.⁵¹ Risk of STD depends not only on an individual’s sexual practices and those of their partners, but also on those of the partners of those partners, and on the prevalence of infection within the whole group of people linked by sexual relationships.

1.5 Epidemiology of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections

Another common epidemiologic method used to describe populations at risk of gonococcal and chlamydial infection is to define the characteristics of people diagnosed with these infections.

Clients with gonorrhea have been described generally as belonging to ethnic minorities, located in inner cities, having low income and being young and male.^{18,62-67} There have been some exceptions to this; high rates of gonorrhea have also been described in rural areas in the United States,⁶⁸⁻⁷⁰ and in the north of Canada,² although in both countries the rural areas under study were inhabited by ethnic minorities.

Characteristics of women with chlamydial infection have also been described, although the epidemiology is more complex than that of gonorrhea. Two review articles state that *C. trachomatis* infection occurs at all socioeconomic levels.^{22,62} This assumption seems to be borne out by research done in the United States. Two studies done in a clinic serving lower socioeconomic groups and working class families, cite prevalences of 15.3%⁷¹ and 25.4%;⁷² another in a middle class neighborhood shows a rate of 12%,⁷³ and yet a fourth in a middle class and upper-middle class neighborhood reveals a rate of 14.5%⁷⁴. A Canadian study done in a low to middle income area of Montreal revealed a prevalence rate of 7.1%, in 1985/86,⁷⁵ and in 1984/85, female university students were shown to have a prevalence rate of 8.1% dropping to 3.2% after a "safer sex" education campaign.⁷⁶ It is assumed that university students may not be accurately classified as belonging to a "low" socioeconomic group as they are in the process of becoming highly educated. Yet another Canadian study on middle class patients revealed rates of 11% in women seeking care from general practitioners.⁷⁷

Studies in Canada and in the United States have revealed that North American Indians and Inuit suffer disproportionately from both gonorrhea and chlamydia when compared with non-aboriginal people.^{29,78-80} Manitoba's reported annual provincial chlamydia rates for 1988 were 50/100,000, but the rate for Aboriginal males was 379/100,000 and for Aboriginal females it was 1,026/100,000, (eight and 20 times higher respectively.)⁸¹

Associations between urban and/or rural residence and risk of chlamydial infection have not been consistent; one study in Canada suggests that rural populations have rates of infection (11%)⁷⁷ comparable with those of an adjacent urban population (7%),⁷⁵ and another suggests that urban populations have higher rates than the rural population.⁸² Another study in the United States revealed comparable rates in both urban and rural areas in Pennsylvania.⁸³ Rates of 9% were found in pregnant women in rural Tennessee⁸⁴ and 21% in rural women in Georgia - higher rates than in urban women in the same state.⁸⁵ Prevalence rates are available for populations served by certain clinics, usually in urban areas.^{86,87} However, there are no data comparing those rates with those of adjacent less populated areas, and certainly none where access to chlamydia testing is comparable in both urban and rural areas.

Differences in socioeconomic, demographic³⁶ and behavioral patterns⁸⁸ of clients with gonorrhea and chlamydia were found in research from the United States. People with chlamydia were more likely to be white, and younger than those patients with gonorrhea. Cases were distributed more evenly than gonorrhea cases, which tended to be concentrated in a small geographic area.³⁶ Male patients with gonorrhea were significantly more likely to report a new, casual or multiple sex partners in the previous 30 days than men with chlamydia. In comparing women with chlamydia and gonorrhea, those with chlamydia were significantly more likely to be under age 20.⁸⁸ In Australia, similar socioeconomic differences were found, with high rates of gonorrhea in Australian

aborigines, but low rates of gonorrhea and higher rates of chlamydia being prevalent in white, single, middle class individuals.⁸⁹

Research in Manitoba comparing sociodemographic characteristics of women with chlamydia, gonorrhea, and coinfection with both organisms, revealed striking differences in characteristics between women with gonorrhea or coinfection and controls, but not many differences between controls and women with chlamydia.²⁹ A study of differences in sexual behavior between clients with gonorrhea and those with chlamydia by Hook et al. showed no differences in behavior between female STD clinic attendees who had positive chlamydia tests and those who had negative chlamydia tests.⁸⁸ Young age was associated significantly with laboratory-confirmed chlamydial infection in Manitoba,²⁹ but unlike in women with gonorrhea, and coinfection with gonorrhea and chlamydial, neither household income nor urban residences were associated with chlamydial infection. This may indicate that the sample size was not adequate to detect differences, or that no differences exist. Another explanation for this finding could be that the chlamydial infections detected were prevalent infections indicative of past risk factors which are no longer present, whereas the gonococcal infection and coinfections were more likely to be symptomatic and incident, associated with current risk factors.

Yet a third possibility involves homogeneity of members in sexual mixing patterns. If sexual contacts tend to be similar to the index case as shown in the choice of steady sex partners in Gothenburg, Sweden, (similar sexual activity, geographic area and income

level),⁹⁰ then differences in demographic characteristics between clients with chlamydia and those with gonorrhea may indicate differences between the individuals who participate most in transmitting gonococcal and chlamydial infections. The “core” group has been defined as a group of individuals who, through high numbers of partners, and possibly through lengthy durations of infectiousness, transmit infections with a frequency which is disproportionate to their small numbers. These core groups may be responsible for transmitting the majority of gonococcal and chlamydial infections. If the group of individuals who transmit chlamydia efficiently differ from those who transmit gonorrhea, this may indicate that the descriptors used in the Manitoba study were inappropriate, or that there are two core groups operating in transmission of *C. trachomatis* infection. One of these may overlap to a large extent with that which is responsible for transmission of gonorrhea, and individuals may in fact often be coinfecting with both organisms. The second core group may not be similar to the first as suggested by the Swedish research which showed that sex partners of cases of either gonorrhea or chlamydia are usually alike. The existence of two core groups in chlamydia transmission is suggested in research which has found high levels of chlamydial infection in youth of upper middle class and middle class neighborhoods,²⁹ but low rates of gonorrhea. Research showing differences in behavior, geographic area of residents, socioeconomic status and ethnic group for chlamydia and gonorrhea clients is not consistent with theories that high rates of chlamydia, like gonorrhea, are found only in lower socioeconomic or inner city groups.^{36,62,63}

Research into the dynamics of the epidemics will reveal important avenues for intervention. The advent of gene amplification technology and single dose therapy in the context of shrinking resources, make core group members a high priority for prevention efforts. Because core group members initiate sexually transmitted infections more commonly than other clients, concentrated intervention in these groups will bring about a sharper drop in disease rates, than interventions which are currently prioritized equally for all STD clients.

In order to fully appreciate the research objective of defining core groups in Manitoba, some knowledge of the development of core group theory in mathematical epidemiology is necessary.

1.6 Critical review of mathematical “core group” theory of sexually transmitted diseases

The concept of a "core group" first arose in the context of mathematical models which were being developed for describing the epidemiology of gonorrhea in 1976.^{91,92}

The use of mathematical models may seem academic at first glance. However, they provide an excellent framework for understanding, discussing and researching both STD and other communicable diseases. This may be because they facilitate a very clear description of the questions which need to be answered. The major goal of mathematical

models is to; "...further understanding of the interplay between the variables that determine the course of infection within an individual, and the variables that control the pattern of infection within communities of people."⁹³ In describing the dynamics of how diseases move through populations, one can define points at which prevention is possible, where it should be focused and sometimes, what type of intervention is appropriate. Forecasting the effects of possible intervention strategies assists public health professionals in setting priorities for interventions, and in evaluating the effects of interventions.^{51,94,95}

The first concrete description of the "core group" occurred in 1978. It was stimulated by the discovery that when screening for gonorrhea was introduced in the United States, the detection of an additional 10% of gonococcal infections in women resulted in a 20% decrease of infections in the years immediately following.⁹⁶ The concept that incidence of gonorrhea is a dynamic equilibrium, determined by its epidemiological characteristics, was explained. Changes in incubation periods, asymptomatic infection, duration of infection, resistance to treatment, treatment types, screening and partner notification would all affect the equilibrium of disease positively or negatively.

When the incidence of disease was stable for a period of time, it was postulated that the epidemiologic characteristics are stable or compensate for each other. Theoretically, epidemiologic characteristics of infection could change, resulting in ever increasing prevalence. An infinite rise in prevalence is not possible due to the saturation effect.

When an infectious individual has sexual contact with a person who is already infected by

a different source, the occurrence of a new infection is preempted. It was determined that a group which has a prevalence of gonorrhoea high enough that substantial pre-emption effects exist, would be known as a "core group". The prevalence of gonococcal infection in the core group where substantial pre-emption effects exist, was estimated at 20%.⁹⁶

The effect of "removing" the possibility of infection in the core group, (by a hypothetical vaccine, for example), would have great effects on the incidence of infection in the rest of the population. The authors theorize that gonorrhoea would eventually die out. The existence of a saturated subpopulation with a high rate of infection, in which an average member must have disease twice annually or more, is essential to maintain an epidemic of gonorrhoea.

A summary of the work of Yorke et al. in 1981⁹⁷ reinforced the original intention of describing the gonorrhoea epidemic mathematically and the intention to provide important insights into gonorrhoea transmission for public health professionals. The identification of contacts who were responsible for infecting high numbers of cases was thought to be of great value in identifying core group members; whereas identifying those who are infected by the index case was not as useful.⁹⁸ For practical contact identification and partner notification purposes, the distinction is not made, and all sexual contacts of the index case in the preceding weeks are asked to be identified.⁹⁹ Indeed, unless one has global knowledge of all individuals' activities it may be difficult to determine at the time of the interview which contacts are likely to play a major role in transmission of infection.

In 1983, Rothenberg described the characteristics of a core group and attempted to validate Yorke's hypothesis.⁶⁵ Reported cases of gonorrhea were converted to rates occurring in Standard Metropolitan Statistical Areas. Nine percent of the population, concentrated in one geographic area, was responsible directly or indirectly for 50% of reported cases. Rates of gonorrhea in the core group area were twice those of other areas, at 1822/100,000. The tendency of core group cases to have contacts from the same area was high - 75% of contacts were made in the same core area. The incidence in the 15 - 24 year old core group area was 20%; Yorke had previously estimated this rate.⁹⁶ Core group areas had high population density, and low socioeconomic status. Rothenberg noted then that more intense intervention and education should be concentrated on people from core areas, which in this case, was well defined by geographic area of residence. This would give the most cost-effective method of disease control.

Rothenberg's work is very important in defining core group characteristics. In 1989 an investigation into epidemic penicillinase-producing *Neisseria gonorrhoeae* revealed the existence of similar patterns exhibited by gonococcal infections in low income, inner cities inhabited by ethnic minorities.¹⁰⁰ However, Yorke's epidemic equilibrium formula contained the important variable of partner change rates, which Rothenberg did not address, but which would be key to maintaining productive chains of transmission. In addition, the practical application of readily identifying core group individuals for intense interventions is absent from this analysis. It may be unreasonable to require that all public

health jurisdictions duplicate Rothenberg's study in order to arrive at a portrait of their core group.

Mathematical models were developed further in the last two decades. The basic formula for describing the "success" of a disease in a population, (i.e., whether it propagates or dies out), is;

$$R_0 = \beta c D$$

R_0 is the "average number of secondary infections produced when one infected individual is introduced into a host population where everyone is susceptible"⁹³, known as the reproductive number of infection. If it is greater than one, the disease will spread in population; if it is consistently less than one, the disease will cease to exist in the population.¹⁰¹ Because R_0 is an average measure, it takes into account the whole of the population under study, giving a number which reflects group experience.

The second parameter is β , which is the measure of transmission from one infected individual to another. The measurement of this parameter has been attempted for gonorrhea and chlamydia, although those measurements for chlamydia are less reliable than those for gonorrhea.^{101.102}

The measurement of contact between infectious individuals and susceptible individuals is

c .

$$c = m + \frac{\sigma^2}{m}$$

For gonorrhea and chlamydia, this translates as the average number of partners exposed per unit of time, weighted by the extent of heterogeneity in numbers of partners. The above equation assumes that people randomly select partners. The only constraint on the selection process is that people will select partners proportionate to the number of partners each is likely to have. Other, more complex formulae have been devised which describe the effects of different criteria in choosing sexual partners. It is obvious that a large number of people will not have sufficient numbers of partners to sustain a disease in a population. Those few who do have very large numbers of partners can easily sustain an epidemic in a population. Therefore the mathematical equation representing c , describes not only the average number of partners, but the spread (variance) in the population.^{103,104}

The importance of the variance in number of sexual partners is illustrated by the survey data at one US college, where the average number of partners with whom male respondents had ever had sex was 11.2, the mode was 4.0, and the range was 1 - 240. In females the respective values were 5.6, 3.0, and 1 - 100.⁵⁰ Those with the extremely high numbers of partners are far more likely to acquire and then to spread STDs, and as such, can maintain the viability of a STD in a population.¹⁰⁵

The last parameter in the equation is D , which denotes the duration of infectiousness. For chlamydia, this parameter is not well-known, as many infected individuals are asymptomatic, and incident infections are not easily distinguished. One early study found that women who were not treated with antimicrobial agents were still infected 16 to 17 months after first culture.¹⁰⁶ For gonorrhea and chlamydia this "natural" duration of infectiousness may be meaningless to some extent, as screening, case-finding and symptoms usually result in treatment.

The challenge for the design of these models concerns human behavior. The number of partners which an individual chooses to have is one variable in the maintenance of disease in a population. Obviously of more concern are those who are "superspreaders",¹⁰³ as that group of individuals is responsible directly or indirectly, for the progression of disease through a population. The problem then becomes how to represent with whom they are likely to have contact. If they mix only among themselves, presumably there would be no disease outside that group. If they mixed only with people outside of the core group, the infection would die out, because non-core group members do not have enough sexual partners during the infectious period to pass it on. These ranges are known respectively as assortative and disassortative mixing patterns, and are measured using number of sexual partners in different sexual activity classes of individuals.¹⁰⁷ For example, one class would have more than 10 partners a year, the next would have between five and 10, and a third would have between two and four. The class with the lowest number of partners would have one per year. The extent to which the class with the lowest number of partners

mixes with the class of the highest determines the magnitude of R_0 , as do the interrelationships of all the other classes.^{108,109}

Unfortunately, there is a substantial lack of information on sexual mixing patterns. Only three have been described so far; one in homosexual males in Iceland¹¹⁰, and one in heterosexuals in Sweden¹¹¹, and a third in Australia.¹¹² One other study applied the mathematical formula of partner mixing patterns to geographically defined core groups of Rothenberg and Potterat and concluded that for gonorrhoea, patterns of partner mixing were mostly assortative, taking place between individuals living within the geographically defined high incidence core areas of cities. A number of researchers in this field have remarked upon the inadequacy of partner mixing matrices because of the lack of data.^{95,108,113}

The lack of data hampers the estimation of the reproductive rate substantially,¹¹⁴ and usually several models are given depending on varying amounts of assortative and disassortative mixing.^{109,113,115,116} Midway between these two extremes is proportionate mixing. This matrix of sexual partner mixing allows for the fact that people in higher sexual activity classes "offer" more sexual liaisons than do those at lower classes, hence they have a higher likelihood of being selected as sex partner. Apart from this one condition, partner selection is usually assumed to be random, dependent on no other factor than the availability of willing partners.^{109,112} The effect of proportionate mixing on an epidemic is to both lengthen and heighten it over time, so that the epidemic is larger in

total and but grows more slowly. Assortative mixing predicts a short epidemic with a steeper rise in cases initially, and a longer period of persistence of the disease due to transmission only within the high sexual activity groups.

Another practical detail which has hampered research is that of the possible unreliability of contact tracing data, as clients are asked not only to divulge the numbers of partners, but also their names.^{108,113} Although the complexity of gathering such data from contact tracing studies is substantial, and some clients are unwilling to divulge the names of partners, it must be remembered that we gain information on contacts from two sources. The first is the index case, and the second - the contact - if infected, will usually name the index case as well. The reliance on information from only one source does not seem to make good use of the data. It is recognized that a substantial amount of work may have to be done in linking contacts' case files with index cases, in order to arrive at a more complete picture of sexual liaisons. However, if the records are computerized, this may be possible.

Mathematical models have become more sophisticated in recent years, reflecting not only characteristics of the host, but also of the environment and agents. Adaptations have been made in the models to allow for partial immunity of the population to some strains of *C. trachomatis* and *N. gonorrhoeae*¹¹⁶ and for the success of particular strains,¹¹⁵ the ages of sex partners¹¹³, and population growth and fertility.^{95,107} Models based on core group theory which estimate the relative effectiveness of proposed control strategies have also

been developed.^{28,117-119} Kretschmar et al. employ a complicated model which assumes random, repeated partnership formation based on age classes. By repeatedly running simulations, they estimate the effectiveness of contact tracing, (with varying amounts of success), screening with various target populations, and condom use by certain segments of the population. This is one of the more user-friendly models to understand if one is interested in applying it directly to public health data.

While surveys of sexual behavior and new attempts at describing partner mixing matrices may supply the necessary parameters for mathematical equations, there remain some additional drawbacks intrinsic to the models themselves.

While mathematical models may show the concept of "a core group" to be a valid phenomenon, practical methods of identifying members have not been described. Defining the core group by the effects of its elimination is not very helpful in identifying core group members for increased prevention efforts. Defining core group members by their previous histories of STD (i.e. repeaters) may also not be accurate, as the incidence of "ping-pong" infections may be high. These are infections which occur as a result of reinfection from contacts who may be asymptomatic or are untreated for whatever reason. Although the individual has a previous history of STD she may have the same sexual partner throughout. Therefore her contact is more likely to be a member of the core group, and more capable of transmitting infection rapidly than she is herself. The precise

identification of infection rates in a suspected core group would be useful in the description of the group, rather than the arbitrary figure of 20%.

A useful catalog of other definitions has been completed by Thomas and Tucker.¹¹⁴ Many of these overlap, such as “prostitutes”; people who have a high rate of partner acquisition, or those who name a large number of sexual contacts. Many of the definitions attempt to define core group membership in terms of the mathematical equations, (such people who, on average generate more than one new case of infection.) Although the mathematical formulae have focussed on the precise components which determine STD rates, that in itself precludes direct practical application of the abstract concept to a particular individual. Attempts to define core group members by their behaviors (e.g, high rates of partner change) are not very helpful in disease control programs. Although the behaviors are those which public health professionals are seeking to change, they cannot be determined for each potential core group member *a priori*. Most important, the above definitions were derived from data and mathematical models of gonorrhea epidemiology, and they were not intended to define a possible core group for chlamydia.

In general, the description of gonorrhea core groups has been somewhat successful, as these infections seem to cluster in geographically adjacent areas.^{36,64-66} However, the assumption that certain areas contained core groups was made first, and the application of the mathematical formula was not intrinsic to their discovery. Core groups for infections which are not maintained within defined, administratively distinct geographic areas, such

as chlamydia, would be more difficult to describe using Rothenberg's method. Another interesting, and possibly a confounding factor in the description of geographic core groups is that of social disintegration.¹²⁰ The removal of essential municipal services such as fire prevention and school services from some areas of New York city caused forced removals of large numbers of people into unfamiliar neighborhoods. Combined with increasing poverty, these movements caused social disruption, and loss of community institutions. The social institutions, such as community church groups and youth centers, which promoted socialization of individuals were also lost, and increases in behaviors such as drug taking and prostitution occurred. This cycle formed a negative feedback loop, where increasing deviance led to further withdrawal of resources, and yet more fragmentation of social structures.

Focusing on changing the rate of infection in core groups may be an effective disease control measure. However, new methods are necessary to define these groups and their members. Numbers of partners whether measured by population surveys or by numbers of named sex contacts, and partner mixing matrices in mathematical models may only be risk markers for other factors. These as yet unknown factors may be key to how people are recruited into core groups, how they pass out of them, (possibly as a function of age), and how stable the core groups are.

One solution to the practical problem of calculating an average reproductive rate for a proposed core group is to select two distinct sets of people hypothesized to be at higher

(core group) and lower risk of STD, and then attempt to calculate the reproductive rates of gonorrhea and chlamydia. Should the calculations for the high risk group show that R_0 has a value of greater than one, then the hypothesis that the high risk group is the core group or contains a high proportion of core group members is proven. Having mathematically proved the existence of the core group and compared it with a non-core group, multivariate models can be developed to describe and predict the individual demographic and behavioral characteristics common to core group members. Of course, the above strategy is viable only if groups at high and low risk for STD have different characteristics. Should the core group members be similar to those at lower risk of STD, the mathematical theory is moot for all practical purposes. The remaining task is to propose a group of individuals at high risk of becoming infected with and transmitting an STD.

Yorke et al. suggested that individuals with repeated infections in the space of one year may be core group members, and interventions with them would prove effective in reducing gonorrhea rates.⁹⁶ A few other authors have also studied repeaters,^{121,122} and most of them agree with Yorke that intervention with these individuals may be a very effective method of disease control.^{79,123-125} Rothenberg's early research in 1978 demonstrated the disproportionate effect which repeaters may have on seasonal oscillations in cases of gonorrhea in an ecological study¹²⁶. The research of Kinghorn et al., who also studied repeaters, predated Anderson and May's differential equation, therefore making the calculation of R_0 impossible.¹²⁷ Another group interested in

repeaters, (Richert et al.) do not show any data which would allow the calculation of R_0 .

¹²⁸ McEvoy et al. also do not present data which would allow the calculation of the reproductive rate in these repeater groups, and in the introduction to the paper, the assumption is made that repeaters are core group members.¹²⁹ Plummer and Brunham raise the problem of immunity to gonorrhoea among people repeatedly exposed to it, which needs to be taken into account if mathematical models for gonorrhoea are to be accurate.¹³⁰ Concerning sex partners of cases, one interesting comment by Richert et al. acknowledges the importance of the partners of the repeaters; ...”even if the patients with repeated infections are not core group members, their partners may be.”¹²⁸

A handful of studies on chlamydia repeaters has also been completed, and again, there is agreement that repeated screening is necessary, but nothing which relates the repeater status to core group theory.^{125,131,132} Serotyping of *Chlamydia trachomatis* was performed in two studies and indicated that a proportion of the study participants were not reinfected by an existing partner, but may have suffered a relapse.^{124,133} There are four available studies on gonorrhoea and chlamydia coinfection, and once again, although there are indications that these individuals may be at very high risk for STD, there are no suggestions that these individuals form part of a core group.¹³³⁻¹³⁶

In addition to the practical difficulties in applying the models, there are theoretical deficiencies in the models. One of these deficiencies is that the parameters on which they are based are measured in a population at one point in time. Should the parameters

change, the reproductive rate changes and the model may no longer be valid. The parameters, such as sexual partner mixing, have to be re-measured for the whole population and new models drawn up. Researchers have attempted to take into account some changes such as deaths due to AIDS affecting the number of available partners. This has led to a theory of supply and demand, which is not based on actual data.¹⁰⁹

A second theoretical deficiency relates to the problem of context. We have successfully measured the proportion of individuals who seem to have high numbers of partners; we have not made sufficient allowance for an individual's chances of encountering a partner who is also infected. Garnett and Anderson concede the importance of factors other than numbers of partners in determining R_0 in a population,¹¹⁶ but due to the point prevalence approach of the mathematical formula, populations with historically very high prevalence rates and assortative sex partner mixing patterns may not be adequately described by the equation. Lastly, Wallace has vehemently and justifiably criticized the mathematical epidemiology which has so "medicalized" the HIV epidemic that it has divorced it completely from the context in which it has occurred, and recommends that more attention be paid to the disintegration of social and community networks in inner cities.¹²⁰

This problem of context is illustrated in a study of women in Tennessee,¹³⁷ where sexual behavior for Black and White women was described as being similar. However, the prevalence of infection in Black women was 36.7% when compared with that among White women which was 27.1%. The likely reason for higher rates in Black women was

that their chance of having sex with an infected man was higher. This illustrates the point that the use of numbers of partners only, can lead to incorrect assumptions of disease risk, and that mixing matrices based on numbers of partners may also be inadequate to describe a pattern which relies on race and not just sexual activity class. It is important to acknowledge the social influences on network formation. In this case, networks are formed on racial lines. The fact that Blacks have higher rates of STDs, and that they form a distinct group in American society⁶⁷ is important to one's understanding of risk of gonorrhea in Black women attending a STD clinic in Tennessee. Another study which produced puzzling results revealed that crack cocaine use by adult males was associated with syphilis and gonorrhea infections.¹³⁸ No such association was evident in adolescent males with gonorrhea, who had similar numbers of sex partners, but were also much less likely to have syphilis and did not use crack. Partner mixing matrices based on numbers of partners, do not take into account these kinds of social phenomena.

The theoretical problems presented by mathematical models are less easily overcome than the practical ones. Once a core group has been successfully identified by calculation of R_0 , and reliable descriptive models have been completed, other methods should be sought which give similar results. Such methods should be more easily used than the differential equation of Anderson and May, and should allow for changes in core groups over time. The study of network formation used in sociology may provide us with the most sensitive theoretical constructs which can define who propagates infection, and perhaps why they do so.

In a short review of core group theory in 1991, Brunham theorizes that the core group concept is generalizable to STD's other than gonorrhoea, although not as well studied.⁶³ In addition, the challenge to define markers of a core group member which can be easily used by field staff to identify and intervene actively in core group transmission of sexually transmitted disease, still remains.^{114,139}

1.7 Social network analysis, a new framework

Traditional epidemiologic STD risk factor literature and mathematical modelling literature have provided us with some of the answers as to how individuals and groups interact in transmission of STD. In order to design control programs which are effective, root causes of high risk behavior which lead to acquisition of STDs are yet to be defined. Both individual and societal contributions to high risk behavior have to be taken into account, and the causes for these determined, if lasting changes are to be made. In addition, more specific mechanisms have to be identified for defining core groups.

The only framework I could find which accounts for individual behavior, social traditions, and the way that individuals interact within social groups is that of social network theory.^{140,141} It also has the advantage of allowing for the use of existing partner notification (contact tracing) data which are available in public health departments.

The initial introduction of social network analysis to health professionals concerned with infectious diseases was that of an analysis of the original cases of AIDS.¹⁴² This study added substantially to the evidence that AIDS was caused by an infectious agent, and that individuals with AIDS who reported sexual contact with each other were not connected solely by chance.

A network is defined as a set of nodes connected together by links which represent social relationships (e.g., kinship, friendship) or interactions (e.g., sexual, monetary exchanges.)¹⁴³ In the study of STDs, the nodes represent people and the links between them, sexual contact. The analysis of networks has been accomplished by graphical depiction of them.

Social network analysis has developed relatively recently since its initial description in the 1930's. While the notion that social interactions and relationships are important to our understanding of society may seem obvious, it was not until the methods of representing and measuring social structures were developed in the 1950's that the focus on social relationships increased. The branch of mathematics known as graph theory allowed social networks to be displayed and also provided mathematical methods of analyzing properties of the networks.¹⁴⁴ Once the concept of a network operating as a complex system was accepted, the first mathematical models were used by Anatol Rapaport to describe the diffusion of disease through populations. Algebraic methods for network analysis were further developed in the mid-1960's, and new developments followed even more rapidly with the advent of more powerful computers. Conventional biostatistical methods cannot be

used in the analysis of social networks because they violate the basic assumptions of statistical theory. Because the attributes being measured are dyadic or relational, such as the existence or lack thereof of sexual contact between two people, the assumption of independence of observations is violated. A factor related to this, is that the attributes studied are not selected at random and probably are related to other individuals in the same set.

In the AIDS analysis a third dimension was added so that incidence of disease in a group of individual can be shown over time.¹⁴² The links between people show clearly how many infections were due to the activity of any single individual. Mathematical equations can also be used to measure the likelihood that all these individuals are linked together by chance. In addition, matrix algebra also provides some objective measures of more concentrated interaction between some members of a network than others (centrality measures) and between some subgroups of analysis than others (cliques analysis).¹⁴⁴ These measures could be very useful in the meaningful definition of STDs core groups, (whom Anderson refers to as "superspreaders").

Networks have been described previously in regard to the spread of HIV in homosexual populations.^{110,145,146} These studies show that partner mixing patterns, which had been assumed to be primarily assortative, were disassortative in these groups. They have also been used in studies on risk behaviors and social environments of drug injectors at risk for HIV, which confirm the fact that syringe sharing and sexual relationships of injection drug

users take place within the network of social, economic and kinship contacts which have been in existence for long periods of time.^{147,148}

Only a small number of studies have used social network analysis to further our knowledge of infectious diseases other than HIV. The first and perhaps largest of these was a prospective questionnaire survey, the Colorado Springs study, which recruited commercial sex workers, injection drug users and their associates. More than 600 individuals were found to be connected to each other, with an average distance from HIV infection of only three acquaintances away.^{143,149} These authors were among the first to explore the uses of different algebraic network measures in epidemiologic concepts of disease transmission.¹⁵⁰ Correlations of sexual network structure with the molecular typing of organisms have also been attempted. One network of people with gonorrhoea and their partners involved 1,272 people over two years.¹⁵¹ Molecular types of *N. gonorrhoeae* and the sexual network data coincided for the most part, although phenotyping may not be as accurate as genotyping, particularly in individuals who have been exposed to more than one strain, allowing recombination of the organism. Analyses of linked individuals was performed, but there was no attempt to correlate parameters with those suggested by mathematical epidemiologists.

Describing networks also has direct implications for disease control. For example, in preventing disease spread from one large network to another the point of intervention may become clear, when a small set of individuals is depicted as bridging two networks.

Networks may define discrete groups with higher STD rates, such as the group of Black men and women in Tennessee, and interventions can be far more clearly focused. In one epidemic, intervention was extended to social and not only sexual contacts of individuals with syphilis. This approach doubled the yield of confirmed cases of syphilis identified in the outbreak,¹⁵² and has been employed in other settings.¹⁴⁰ Sexual networks also are proposed as the reason differences in STD incidence occur along age subclasses, and were associated with use of crack cocaine, and the lack thereof, in younger and older men, respectively.¹³⁸

Network theory has also been used in generating mathematical equations which take into account sexual network processes as well as those parameters of mathematical epidemiology, reviewed above. Therefore they may be used to explain epidemic trends in disease. Epidemics with multiple peaks are usually the result of a disease breaking through from one network into another susceptible population, with swift increases in cases.^{142,153} Network theory may also explain the descriptive epidemiology of certain STD. In one personal network study, it was noted that the highest number of people with whom highly paid, highly educated people have (non-sexual) contact is much greater than those who are less well educated. If education and income levels of individuals are indicative of the size of their personal social networks, they may also be indicative of the size of their sexual networks. A study in Colorado of both sexual and social networks showed that 24% of all relationships reported, were sexual.¹⁴³ Unfortunately, anonymous sexual relationships were not reported, although they may carry higher risk than those in which

the partner is known. Not the least important is how networks reflect the ages of their participants, which, as the population survey research shows, is highly predictive of STD transmission.

Like mathematical epidemiology, social network analysis can also be used to predict risk of disease transmission. Use of network measures and individuals' risk of infection with HIV have been evaluated in a simulated population, using real parameter values of numbers of partners and geographic location gathered from network interviews.¹⁵⁴

Intensity of sexual contact, (frequency of intercourse) can also be taken into account in the description of networks, by weighting the links between nodes, as can the cultural traditions and social norms in which it is based. Network patterns in Africa show different mechanisms of discrete grouping, for example, tribal affiliation, but the structure is still meaningful.

This area of research is still in its infancy, and more data for the description of large networks is needed,¹⁴² but network theory has the potential to add much to the current understanding of STD transmission.^{27,111,141}

1.8 Conclusion

In this review I have attempted to summarize and criticize the tools epidemiologists currently use to describe the transmission of STD. The preoccupation of epidemiologic methodology on quantitative measures has precluded the investigation of some very important individual and social factors contributing to STDs, including age dependent subcultures. This may be partly due to the highly technical and sometimes somewhat abstractly worded documents arising from epidemiologic and social science literatures. While the pursuit of the reproductive number has helped to refine the search for determinants of STD transmission in populations, the debate has distanced us from an humane definition of core groups which is necessary in order to plan effective interventions. The ideal definition of a core group would satisfy the mathematical equation ($R_0 > 1$), allow for the effects of social context on individuals, and recognise the active participation of undiagnosed and perhaps unknown individuals in maintaining endemicity. The concept of a core group I had at the start of this research resembled Yorke's in three respects. First, the concept stemmed from working with notifiable STD databases in which the importance of repeaters seemed undeniable. Second, named sexual contacts of cases who seldom became confirmed cases seemed to be crucial in maintaining chains of transmission. This concept is similar to Yorke's "upstream contacts" who were more important in transmitting infections compared to those infected by the index case. Last, the idea that population prevalence comprises two rates, one of which is higher in the core group, and another which is lower in non-core population, inspired the study

design. The methodology used in this research validates the existence of a core population which is distinct from a non-core population in demography, behavior and social characteristics, and in the critical reproductive number. My concept of the core group evolved as the research progressed, and was influenced greatly by oral and written reports of daily encounters between public health staff and STD clients themselves. I do not believe that a constant, highly sensitive and highly specific definition is achievable due to inaccuracies in precise measurement of complex systems. However, it is evident that a core group is a group of people who are closely (sexually) or loosely connected (socially) and through whom transmission of STD is facilitated to a greater or lesser extent by the sexual and health care seeking behavior of members, the practices of health care providers and the social and economic circumstances in which core group members live. Core group membership is not a binary phenomenon; it is continuous (see Chapter 9.) People may contribute more or less to the maintenance of disease in a population and it is important to note that the “contribution” is not necessarily self-determined. My concept of the whole core group is close to that of a complex organism, in which the parts interact and react constantly, producing pulses of infection through the organism. Therapy and prevention are only partially effective when applied to each individual part of the organism, and their application serves to concentrate infection in segments of the organism which are less accessible to intervention, making eradication of the infection more difficult as the disease diminishes.

Other authors have reached the conclusion that we need new methods to describe the epidemiology of STD and its determinants.^{111,142} This critique provides a logical progression through epidemiologic investigations into STDs, to issues usually of concern to social scientists, but which are crucial to interpreting transmission of STDs in context. Both the disciplines of epidemiology and social science are required to understand the transmission of sexually transmitted diseases, and to provide strategies for effective control.^{27,117,140} This research is a first attempt at using both methodologies to gain further knowledge of the transmission of *Neisseria gonorrhoeae* and *Chlamydia trachomatis*.

Chapter 2

Methods

2.1 Study rationale and objectives

This research will identify, describe and compare core groups for gonococcal and chlamydial genital infections. An historic prospective cohort study which compared members of core groups with non-core members with gonorrhea or chlamydia or coinfection over a period of three years was proposed. In order to differentiate between core groups for chlamydia and gonorrhea, the two core groups were also compared.

This research furthers the understanding of mathematical epidemiology of STD and core group theory. It is original in three respects. First, some research has revealed the risk factors for core group transmission of *N. gonorrhoeae*, and some research has suggested behavioral and epidemiologic differences between the two diseases.^{36,88} None to date has addressed the possibility of core group transmission of *C. trachomatis*. This research will reveal whether a unique core group for chlamydial infections exists, and attempt to broaden the core group theory beyond gonococcal infection. Second, the strategies described below to define core groups have not, to my knowledge, been used previously. They have the advantage of being simple and may be used by public health officials who have computerized STD datasets. Third, the scope of the project has the advantage of

describing core groups of STD patients for the whole of the province, over a three year period. This is the largest and most complete STD population from which core group dynamics has ever been described. This research will provide evidence necessary for mathematical and other theoretical concepts of core group dynamics. Lastly, this research will test the feasibility of constructing sexual networks from computerised contact tracing data routinely gathered by physicians and public health nurses.

2.2 Hypotheses and study design

Because of the complexity of the hypotheses and study design, this study was conducted in three phases. The analysis of individuals with laboratory-confirmed infection comprised Phase I. Individuals with repeated laboratory-confirmed infections during the study period, 1990 - 1992 were compared with those who had only one infection in that time. In order to minimise misclassifying repeaters as people with only one episode of STD, repeaters who had a first disease episode in the two years prior to 1990 and who had a repeat event in the three years following that were included. However, people who may have had repeat episodes in the two years following the study period may have been misclassified. Individuals with repeated gonorrhoea, repeated chlamydia and with repeated episodes of coinfection were also compared, in order to establish whether the proposed core groups of the three disease categories were similar. In Phase II of the research similar analyses were completed for the multiply named sex partners of cases with confirmed chlamydia, gonorrhoea and coinfection. In Phase III multiply named contacts of

cases were compared with individuals who had repeated infections with chlamydia, gonorrhea and coinfection, in order to establish whether the proposed core groups of the each disease group are similar, and whether different proposed core groups for chlamydia and gonorrhea exist.

2.2.1 Phase I: laboratory proven cases of sexually transmitted disease

Those individuals with repeated chlamydial, gonococcal or both infections in three years, and those who have been named multiple times as sexual contacts of chlamydia, gonorrhea or both infections are hypothesized to form the whole, or at least a large part of the core groups for each disease. Because individuals suffer repeated infections they conform with the definition of core groups as being a subset of the population in which sexually transmitted infections are viable. Because repeaters have had more than one infection during that time, they have probably had an increased probability of transmitting the infection as well as acquiring it. Not only have they had the infection more than once, but because of the multiple infections, they will probably also have had a longer total duration of infectiousness, when compared with someone who has been infected only once in three years. However, there are circumstances in which a repeatedly infected individual may be only the recipient of infection, because that individual is continually exposed to an untreated, infected partner.

If repeatedly infected individuals form core groups which are responsible for maintaining an infection in the population, the revelation is useful only insofar as its members are

distinct from non-core individuals who may also be infected. The first priority in this research therefore, is to compare individuals with repeated infections with gonorrhoea and/or chlamydia in three years with those who have had only one infection. Likewise, sexual contacts of cases of chlamydia and/or gonorrhoea who have been repeatedly named will be compared with those named only once. Only if these groups are proven to be distinct would it be valuable to proceed to compare the proposed core groups of gonorrhoea and chlamydia. The null hypotheses for the first phase of research was that there was no difference between individuals repeatedly infected with chlamydia and/or gonorrhoea, and the remaining STD population, who had only one episode of infection in three years reported to Manitoba Health. The null hypothesis for the contacts was that there were no differences between multiply named contacts and those named only once. If differences are found, the null hypothesis would be rejected in favour of the alternative, which is that there were significant differences between the proposed core group members of repeaters and multiply named contacts, and non-core group members of individuals with only one infection and those named as contacts only once.

The hypothesis that core groups exist for chlamydia, gonorrhoea, and gonorrhoea and chlamydia coinfection whose members have definable characteristics, must include the alternate possibility that they do not exist. If we suspect that clients repeatedly infected with both gonorrhoea and chlamydia were different from those repeatedly infected with chlamydia only, this should be taken into account in classifying patients and defining appropriate comparison groups. If all chlamydia core group members were also core

group members for gonorrhea, the null hypothesis is that statistical analysis will show no differences between the two groups. Conversely, if the chlamydia core group members were different from core group members with gonorrhea or with coinfection, this would indicate the existence of a measurably distinct core group for chlamydia only.

The Manitoba Health STD registry data were used as a basis for describing individuals with repeated episodes of gonorrhea, chlamydia and coinfection during a three year period, from 1990 - 1992. All laboratory-confirmed cases with multiple episodes of infection were divided into four groups; those who had repeated laboratory-confirmed chlamydia, those with repeated gonorrhea, those who had at least one episode of gonorrhea and at least one episode of chlamydia infections at different points in time, and those who ever had a coinfection with both organisms simultaneously or had a coinfection followed by repeated infections with either gonorrhea and/or chlamydia. Individuals with multiple chlamydial infections in three years were compared with a random sample of those with only one episode of chlamydia in three years. The random samples were stratified by year of infection, gender and disease (chlamydia, gonorrhea, coinfection or alternating infections.) According to the study design, and power estimates, the ratio of repeaters to those with single infections was approximately 1:1. Household income, gender, age, status or non-status Indian, urban or rural residence, antimicrobial therapy, numbers of contacts and symptoms of cases with multiple infections were compared with those cases who had only one episode of infection. This comparison was repeated for individuals with multiple episodes of gonorrhea, and for those with coinfection, resulting

in three separate analyses for each group of cases with chlamydia, gonorrhea and coinfection, as shown in Figure 2.1. The classification of those individuals with episodes of chlamydia interspersed with gonorrhea infections is discussed in Chapter 3.

2.2.2 Phase II: multiply named contacts of confirmed cases

The inclusion of multiply named contacts as proposed core group members is justifiable in three ways. The first is that defining core group members by their previous histories of STD may not be that accurate. Although an individual has a previous history of STD, she may have the same sexual partner throughout and may never transmit disease. However, her contact is more likely to be a member of the core group, and more capable of transmitting infection more frequently than she is herself. Therefore, including only those individuals with repeated laboratory documented infections excludes those individuals who may be the actual primary sources of infection. Second, the actual proof of infection in an individual is secondary to “core group” status. Being a member of a core group should not be dependent on laboratory confirmation of infection in an individual. In fact, “core group” members may be more efficient at disease transmission in the absence of laboratory confirmation, as lack of a laboratory result allows for a long infectious period without treatment. Some studies which attempt to define core group members have included only those individuals with laboratory-confirmed infections,¹³⁹ and are incomplete as a result. Last, and most important, the specific cause of repeated exposure and repeated transmission of STD to others is the risk behavior of core group members. Whether repeated sexual intercourse with an infected case results in infection or not, the fact

remains that if a person has been named numerous times as having had sex with individuals with confirmed gonorrhoea, for example, it stands to reason that the chances of infection are high, and that the ability to transmit infection is obvious. The measurement of high risk sexual activity should not be hampered by unrelated factors, such as poor performance of chlamydia EIA testing in men, or our inability to locate, test and treat contacts. This last factor may play an important role, as some “core group” members may not wish to be found due to other high risk and/or illegal activities. For these reasons I hypothesize that multiply named contacts are probable core group members. The possibility that sex partners named multiple times by individuals with confirmed sexually transmitted diseases are members of the proposed core group is even higher than the probability for those contacts named only once.

STD registry data at Manitoba Health were used to describe all named sex partners (contacts) of index cases with chlamydia, or gonorrhoea or coinfections. Contacts who were named more than once during the three year study period, were separated from the others named only once. As with the repeaters, separate analyses were completed for multiply named contacts of gonorrhoea, chlamydia and coinfecting cases. Age, average household income, gender, treaty status, urban or rural residence of frequently named contacts were compared with those named only once. Because information on treaty status and postal code were not routinely entered in the database, treaty status for each contact was collected and entered using the patient registry file at Manitoba Health. Postal code information was collected based on the address of the contact at the time of

the notification to Manitoba Health and was also entered. Socioeconomic descriptors from the Statistics Canada census database were attached to each contact's file.

The next step was to compare the characteristics of the repeater populations with gonorrhea, chlamydia and coinfection in order to discover whether the proposed core groups differ. The reason for the separation of coinfecting repeaters from those with chlamydia and gonorrhea alone was to prove the similarity or dissimilarity of the core group for gonorrhea to that maintaining chlamydia endemicity. Once the three groups of repeatedly named contacts were shown to differ from those named only once, the multiply named contacts of chlamydia, gonorrhea and coinfection were compared (see Figure 2.1.) The analysis would show whether multiply named contacts of chlamydia and gonorrhea coinfection differed from multiply named contacts of chlamydia or gonorrhea cases only.

Lastly, the three groups of repeatedly named contacts were compared with the three groups of laboratory-confirmed repeaters. The analysis would confirm whether multiply named contacts of the three disease categories were sufficiently similar to their counterpart repeaters with laboratory-confirmed infection as to be considered the same population. If the repeaters with chlamydia, gonorrhea or coinfection could be considered similar to those multiply named contacts, they would be pooled together, comprising the whole proposed core group for that disease. Then logistic regression models which accurately predict multiply named contacts and repeatedly infected individuals who form the core group would be designed for the use of public health staff and physicians.

All hypotheses were tested with an α error of 5% and a β error of 20%. The chances of incorrectly adopting the alternative hypothesis that differences between the two groups exist, was only 5%, while the chance of rejecting the alternative hypothesis when it is correct was 20%. This design included a large number of comparisons were made. While the chances of finding a significant difference is high when many hypotheses being solved for the same dataset, these comparisons are being made each time between different datasets.¹⁵⁵ Also, the hypotheses were hierarchical. If the hypothesis that the individuals with repeated STD could not be differentiated from those with only one episode of STD, any further inquiry would cease. Last, although there is extensive literature on errors associated with statistical methods, there was none on the topic of conducting multiple logistic regressions on different datasets.

Flow chart showing the process of hypothesis testing

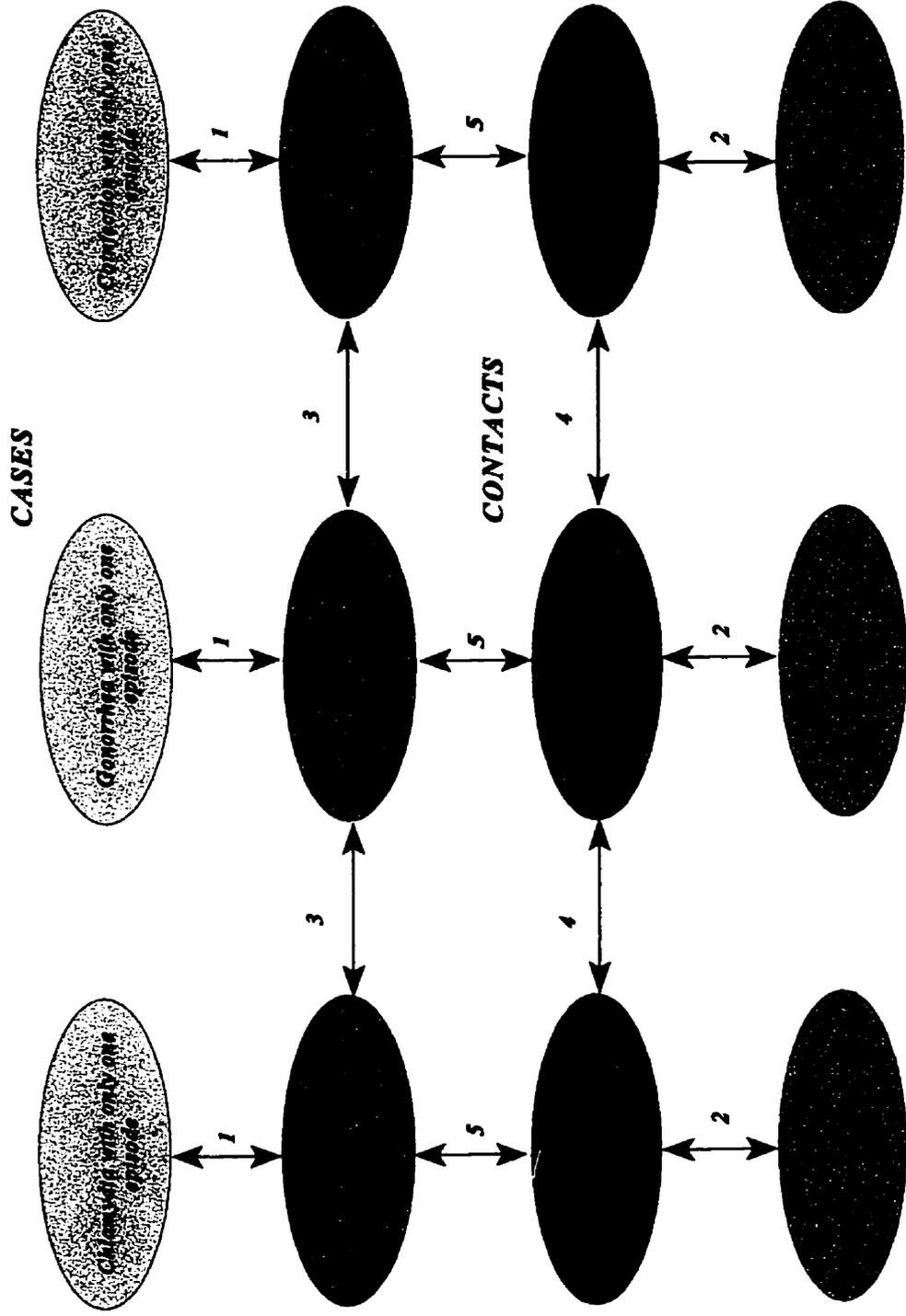


Figure 2.1 Diagram of hypothesis testing showing the order in which the hypothesis were tested adjacent to the arrows.

2.3 Sample size calculation and selection

A major consideration in defining study population size was to allow a period of time long enough to select a stable core group. If one were to use only six months worth of data, a considerable number of core group members may be missed because they would not have been identified as a case or contact in that short space of time.^{47,79,123,151,156} One study in the United States revealed that only two thirds of repeaters may be identified in one year, while another third may have repeated infection in the following two years.¹²⁸ In addition, constructing coherent sexual networks over a three year period would be more informative than those for only a one year period. This is why a study period of three years was proposed.

Sample sizes were calculated on the basis of proportions of genders and ethnic groups in all STD cases in Manitoba. These proportions approximate the "exposure" in the control group of non-core group STD cases. These estimates were conservative, allowing for the fact that once the core group members were removed from the general STD population, proportions of females and Status Indians would be lower.

The formula for estimating sample size was taken from Hassard's text on biostatistics:¹⁵⁷

$$n=2P.I.^2(\bar{p}(1-\bar{p})/(p_1-p_2)^2)$$

Where the power index (P.I.) = α , two-tailed (1.94) + β , two-tailed (0.84), using the probabilities for α and β cited below.

\bar{p} = the mean proportions of the variable of interest for both study populations

p_1 = the proportion of the variable of interest in one of the study populations

p_2 = the proportion of the variable of interest in the other study population

Assuming that the proportion of First Nations in the non-core group STD population was 35%, a power of 80% (beta) and a confidence level of 95% (alpha), the number of "cases", (i.e., core group members) would have to be 420 to detect a significant odds ratio of 1.5. The estimate of 35% was deliberately conservative; a random sample of women with laboratory-confirmed chlamydia at Cadham Provincial Laboratory in 1988 revealed that 42% of women were Status Indian.²⁹ Assuming that 73% of cases of chlamydia were female, that the confidence level was 95%, the power 80%, and the odds ratio was 0.66 of an individual being a core group member and being female, the required number of "case" individuals to produce statistically significant results would have been 447. The odds ratio of 0.66 was to be expected, because core groups usually contain more men than women as men tend to report more partners than women.^{79.124.128.129} Women would

be in the majority for the non-core group chlamydial infections, as they are screened for chlamydia and hence have a higher chance of the infection being detected.

As this type of research had never before been conducted, it was impossible to estimate the size of the core group (individuals with repeat STD or those who were multiply named sex partners), or "cases". However, as the core group was drawn from all notifications for chlamydia or gonococcal infection in Manitoba over the space of three years for a total of 3,223 gonococcal infections, and 11,242 chlamydial infections, the core groups identified are not a sample, but are the actual core groups in Manitoba. Therefore the results of this study will be valid for these diseases in Manitoba and probably for prairie provinces.

2.3.1 Phase III, mathematical modelling and construction of sexual networks

In order to explore possible differences in core groups between gonorrhoea and chlamydia, repeatedly named contacts of cases and repeatedly infected individuals with the two diseases will also be compared.

Available data from these groups can be placed into the mathematical equations;

$$R_0 = \beta c D$$

and

$$c = m + \frac{\sigma^2}{m}$$

then we can attempt to solve for c and R_0 . Note that data on numbers of partners are available from STD repeaters from both the index case and the contact when he or she is confirmed as a case. The use of the sex partner data from this study in these equations will be used to prove mathematically whether or not the groups of multiply named contacts of chlamydia, gonorrhea and coinfection and those repeatedly infected do actually form a substantial proportion of the core group(s).

The feasibility of constructing contact tracing trees for a sample of repeaters and multiply named contacts would also be explored. This method is adapted from network studies in sociology. The method has the advantage of showing clear connections between people with STD as well as defining those individuals who are most successful in propagating the infections.^{142,150} In discussions with staff who worked with the data, the majority of networks was estimated at two or three individuals, and the remainder would consist of at most 20 (personal communication, December 1994, Ms. E. Sherman, Program Specialist,

Manitoba Health.) Therefore this exercise was an unknown quantity initially, and the information which could be derived from it would depend wholly on its feasibility. The first study employing a similar methodology was published only in 1996, hence no literature on the subject was available for guidance.¹⁵¹ To whatever extent would prove possible, measurements of the number of infections caused directly or indirectly by individuals were to be calculated.

2.4 Statistical methods

Initially, chi-squared tests, T-tests and other univariate techniques were used to explore the differences in the "core groups" of gonorrhoea and chlamydia and the respective non-core comparison groups. Only those variables significantly associated with the outcome were entered into logistic regression models. These multivariate techniques are essential in building a predictive model, which can be used to assess the likelihood of a certain STD patient being a core group member. In addition, logistic regression models disentangle the effects of each of the independent (predictor) variables, so that the additional risk associated with that variable alone can be measured.¹⁵⁸ For example, being of First Nations ancestry may carry with it an added risk of STD diagnosis. However, on univariate analysis alone, it is impossible to estimate how much of this risk is attributable to lower socioeconomic status, commonly suffered by aboriginal people. The added risk of STD diagnosis may also be associated with youth, as a higher proportion of aboriginal people are younger than other Canadians. Logistic regression analysis will provide odds

ratios of all three of these variables separately; low socioeconomic status, First Nations ancestry and age, which represent the added risk contributed by each variable on its own. This multivariate technique was also used to compare the different characteristics of gonorrhoea core group members and chlamydia core group members, and of those coinfecting with both.

Analysis of these data presented two interesting and highly debated statistical questions. The first of these was the value of performing statistical tests on whole populations, where extrapolation from a random sample to the rest of the population may be irrelevant as the whole population has been selected. The second issue involved the use of very large sample sizes, in which almost all comparisons would be statistically significant, although not necessarily epidemiologically relevant.

2.4.1 The use of statistical tests on whole populations

In the first sets of analyses, which compare individuals with repeated disease episodes with those who have only one episode, and multiply named contacts of STD cases compared with those named only once, the question of whether to use statistical tests was easily resolved. The whole populations of non-repeater comparison groups were not used in these analyses, because of the amount of work involved in ascertaining the correct classification of each individual into the repeater or non-repeater groups. The use of random sampling for the comparison group of people with only one episode of infection in the three-year period reduced the number of records which had to be individually

examined from 10,000 to 3,000. So, although the repeater populations were the complete populations of all individuals with reported repeated gonorrhoea, chlamydia or coinfections over the three year period, the comparison populations were not, hence the need to use biostatistical methods and the need to estimate confidence limits.¹⁵⁸

In other analyses, where the whole populations of repeater individuals in different disease categories were compared, there are no random samples involved. Differences in proportions and means are absolute, and there are no uncertainties of the sample failing to represent the sampling frame. However, I have used the statistical methods for several reasons.

The first of these is in an attempt to make the data more generalizable, both in time and space. Other than special considerations of medical service delivery, there is little to suggest that the populations under study would differ substantially from those of Alberta and Saskatchewan, and possibly from similar populations in the rest of Canada. Should a reader wish to relate these results to other populations, at least some parameters are available for assessment of applicability. In addition to spatial generalizability, there is also a consideration of generalizability through time. Once again, there is no reason to suppose that STD repeaters from 1990-1992 differed significantly from those in 1989 or 1993, although the samples are not from those years. Theoretically, it is possible and indeed likely, that the study results are indicative of circumstances just before and after the study period. Therefore, the treatment of these populations as “samples” of those from other

years is warranted. (Unpublished lecture; "Statistics for large databases; implications for public health" K. C. Carriere, 1995.) Last, and probably most important, is that the infections reported to Manitoba Health are a subset of all those that really exist. The use of statistical methods at least provides some guide as to how analyses of reported cases may apply to those cases not reported to Manitoba Health.

Second, the capability of multivariate analysis to separate the quantity of variation of a population due to several independent variables such as age, gender, income level and ethnic group allows the estimation of effects of each of these characteristics. In order to better understand and describe the causes of repeated STD, it is essential to separate the effects of individual characteristics from each other in order to design adequate prevention strategies which involve the appropriate groups. One of the more important uses of logistic regression in the following analyses is to show that low income is a risk factor for repeated STD, but being registered as a treaty Indian carries additional risk, over and above that associated with low income. Programs which attempt to lower repeat STD rates in low income populations may therefore neglect the added needs of First Nations people, who may require particular language and cultural adaptations of prevention programs.

Lastly, logistic regression can be used as an instrument for prediction. Knowing several characteristics of an individual, it may be possible to build a model which can predict the probability of that individual being an STD repeater. This model would differ from others

in that it's main purpose is to predict, rather than to describe. Therefore, the characteristics of the individuals entered into the model would have to be those which are immediately obvious or can be very easily determined. A descriptive model, which attempts to describe preexisting characteristics affecting risk of disease in an individual includes any characteristic which is supposed to have a causative effect, although it may not be immediately accessible.

Discriminant function analysis is usually used to predict group membership, and was used in one study.¹²⁷ However, due to the fact that all but one of the independent variables in this analysis are categorical, discriminant function analysis was not advisable, as it relies heavily on continuous data to define cutoff points for group membership.¹⁵⁹ (Personal communication, Ms. Mary Cheang, Biostatistical Consulting Unit, June 1997.) In addition, multiple logistic regression techniques were used to differentiate repeatedly infected individuals from others, in the three most recent studies on repeaters.^{125,128,131}

2.4.2 The effect of large sample sizes

The most striking feature of these analyses is the effect of large sample sizes on measures of statistical significance. Not only do minute differences become statistically significant, but tests of normality which are influenced by large sample sizes, are also affected.¹⁶⁰ For example, in comparing mean ages of individuals with repeated chlamydial infections and those with only one episode, a difference of only 1.18 years was statistically significant on univariate analysis ($p < 0.001$), as well as when all other variables were controlled for in a

logistic regression analysis. This small age difference may have a logical explanation, but it is also possible that the difference may not be epidemiologically relevant. I have not taken the liberty of imposing artificial standards on which differences should be considered as clinically relevant or epidemiologically important.^{161,162} All results which are statistically significant at the 95% level have been noted as such, and the reader may make his or her own judgements on the importance of the differences.

One concept which may be useful in evaluating the importance of age differences is related to the common practice of reporting STD rates by five year age groups, which are also used in chlamydia screening guidelines. Since a difference of over 2.5 years will place an individual in another 5 year age category, a difference of such a magnitude may be more relevant for public health staff and physicians, than differences of only one year. This is shown in the comparison of individuals with repeated episodes of gonorrhea with those with repeated episodes of chlamydia. The mean difference in age was three years, indicating that the gonorrhea repeaters were noticeably older than chlamydia repeaters (mean ages 24.5 and 21.5 respectively).

2.4.3 Normality

Histograms of ages of repeat cases and those of the comparison group who had only one episode of chlamydia in three years were examined and looked non-normal. On data screening, the data on age were tested for normality, and that assumption was rejected using the Martinez-Iglewicz, Kolmogorov-Smirnov and D'Agostino skewness tests.

Despite this, two tailed t-tests were still used to compare differences in mean ages because skewness tests are greatly influenced by large sample sizes. Even when a small amount of kurtosis or skewness was detected in the larger samples, which did not significantly affect analysis, the normality tests showed the data distribution to be non-normal. When sample sizes differed greatly, such as in the comparisons between individuals with repeated episodes of chlamydia, (n=1,956) and those with repeated episodes of gonorrhoea (n=565), the Aspin-Welch Unequal variance t-test was used.¹⁶³

Although age was non-normally distributed in all populations, non-parametric equivalents of the t-test were not an option because neither Epi Info nor Number Cruncher Statistical System could perform the Mann-Whitney U test which compares relative ranking of the ages, because sample sizes were too large. This was not of great concern, as tests of normality are highly sensitive when sample sizes are too large. In a large sample, a variable which deviates from normality does not do so enough to result in a realistic difference in the analysis,¹⁶⁰ and a sample size of 100 or more will approximate normality.¹⁶³ The following are the normal probability plots for the groups repeatedly infected with gonorrhoea, chlamydia and coinfection and the comparison groups with only one infection.

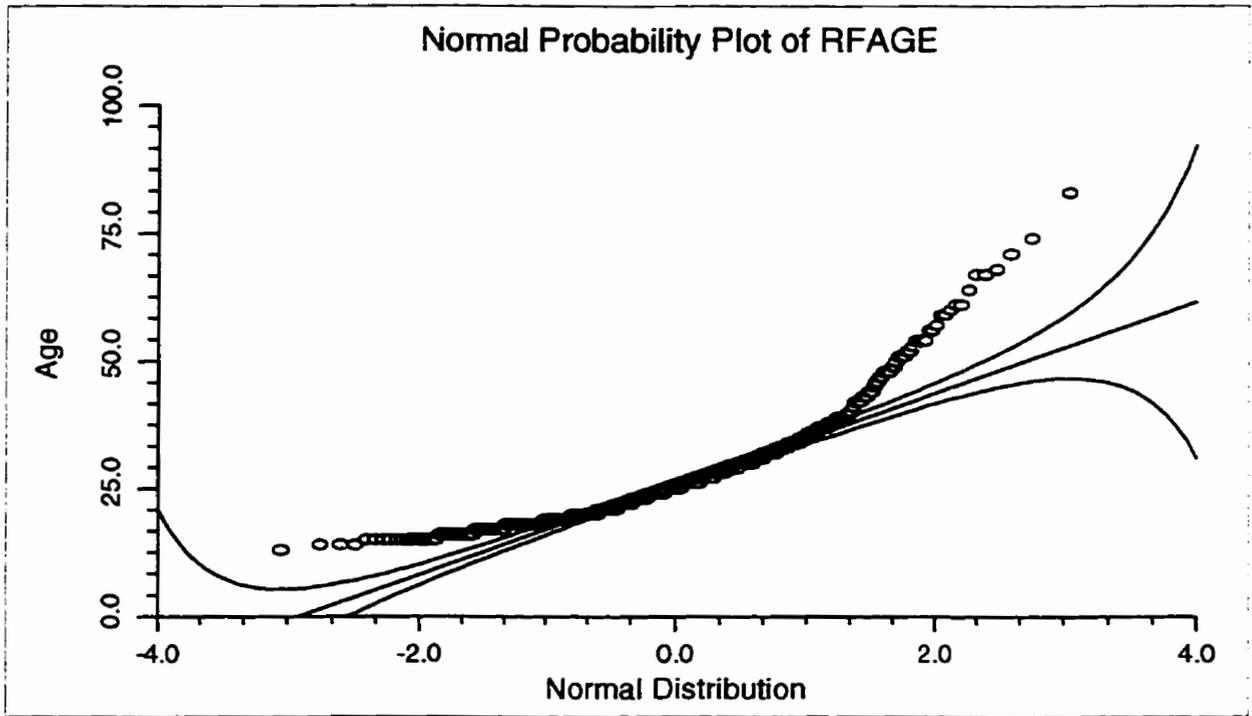


Figure 2.2 Normal probability plot of ages of individuals with one episode of gonorrhea

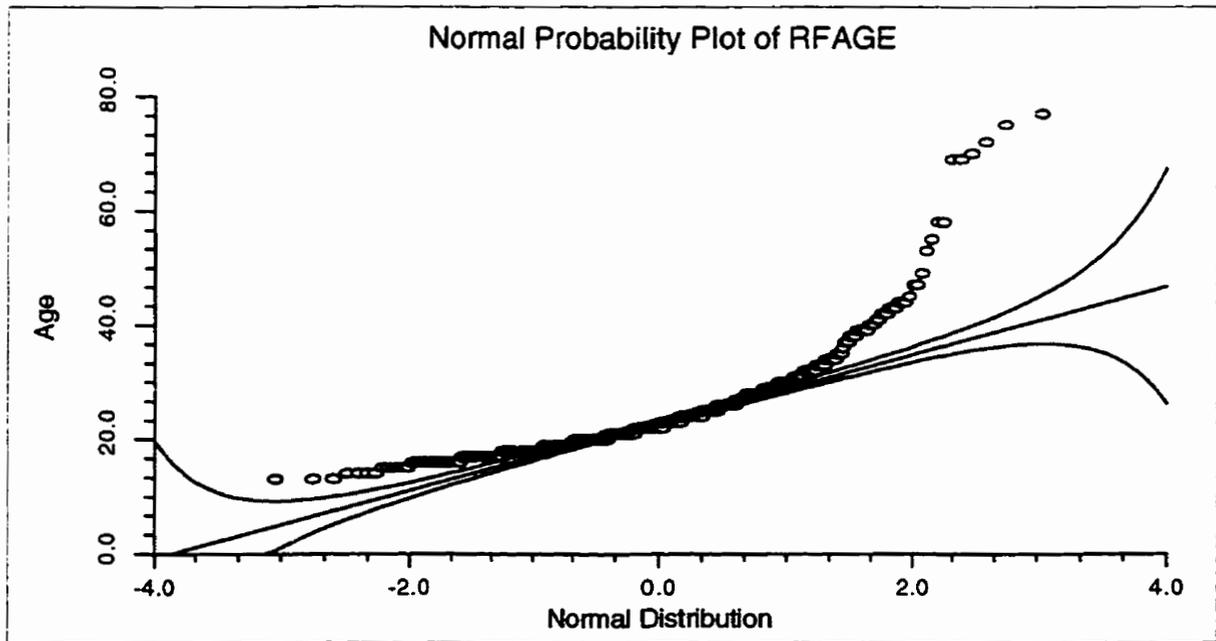


Figure 2.3 Normal probability plot of ages of individuals with more than one episode of gonorrhea

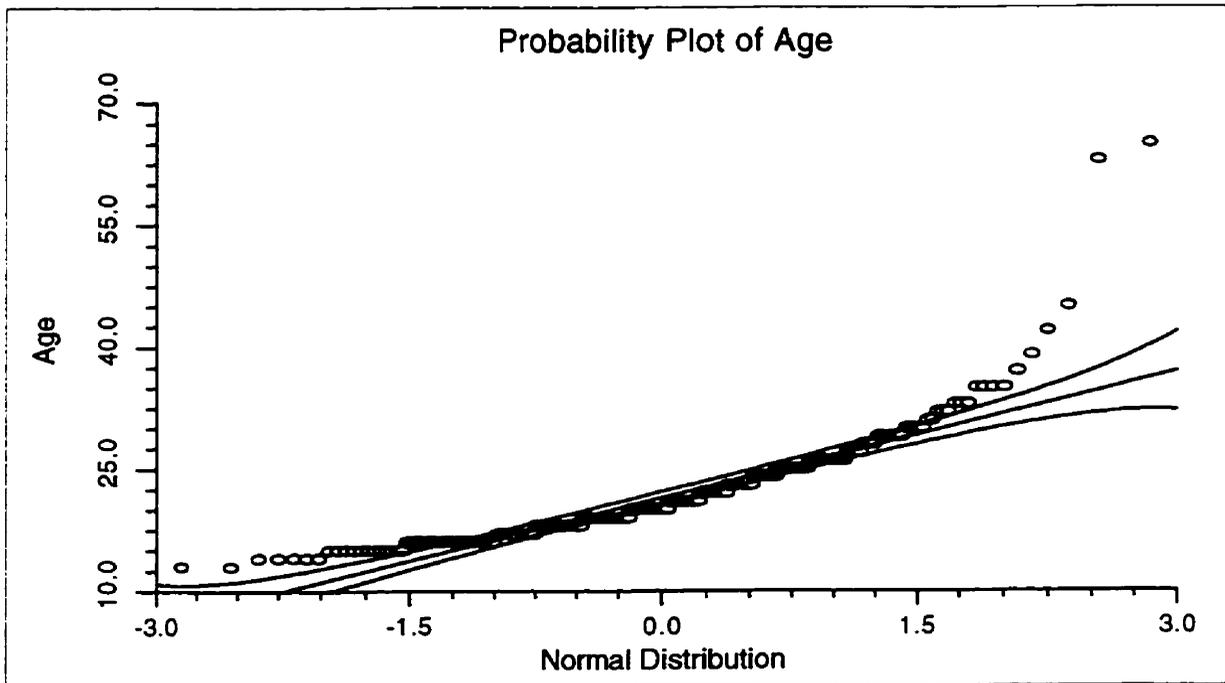


Figure 2.4 Normal probability plot of ages of individuals with one episode of gonorrhea and chlamydia coinfection

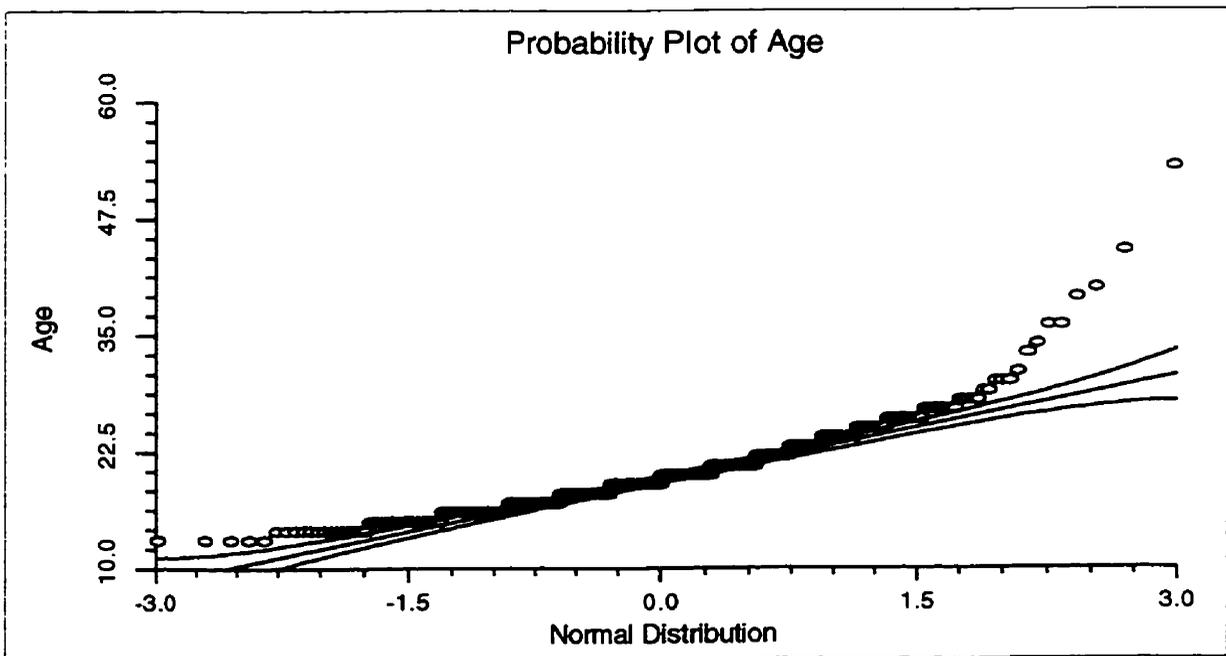


Figure 2.5 Normal probability plot of ages of individuals with more than one episode of gonorrhea and chlamydia coinfection

The probability plots for the ages of individuals with laboratory-confirmed chlamydia, (n=3,835) are not available as there are so many that the statistical program, NCSS could not plot all the points.

The effects of large sample size are evident in these plots. The confidence limits (green lines) on either side of the normal straight line (blue) are very narrow. The plots of the ages also show diversions from the normal at the low and high ends. The causes for this are evident from the frequency distributions of ages of all case and contact groups analysed, and from tests of the assumption that the age data are distributed normally. Although sample sizes of above 100 will approximate normality, it was not clear whether this would extend to samples of that size which are subjected to multivariate analysis. Multivariate analyses usually require larger sample sizes than univariate analyses, as the analysis of samples is divided into “cells” of individuals who share each possible combination of the predictor (independent) variables. While many of the logistic regressions comparing comparison groups with repeater groups were large, the number of multiply named gonorrhoea contacts was only 158.

In order to compare the smaller groups with others, the age variable was transformed to the natural log of the age. The square root of the age was also tested, and reduced the skewness, but not the kurtosis.¹⁶⁰ The transformation which produced test results closest to those of a normal distribution was the logarithm of the age. This transformation

“normalized” the data flattening the distribution and pulling it slightly to the left, (see Figures 2.6 and 2.7), and improved the results of tests of normality.

All of the age data were transformed to the natural log so that consistent comparisons between groups could be made. The transformation provided more accurate descriptions of STD risk in older individuals. Graphs which show the odds of the outcomes at various ages are provided to describe the effect of age on the likelihood of the outcome.

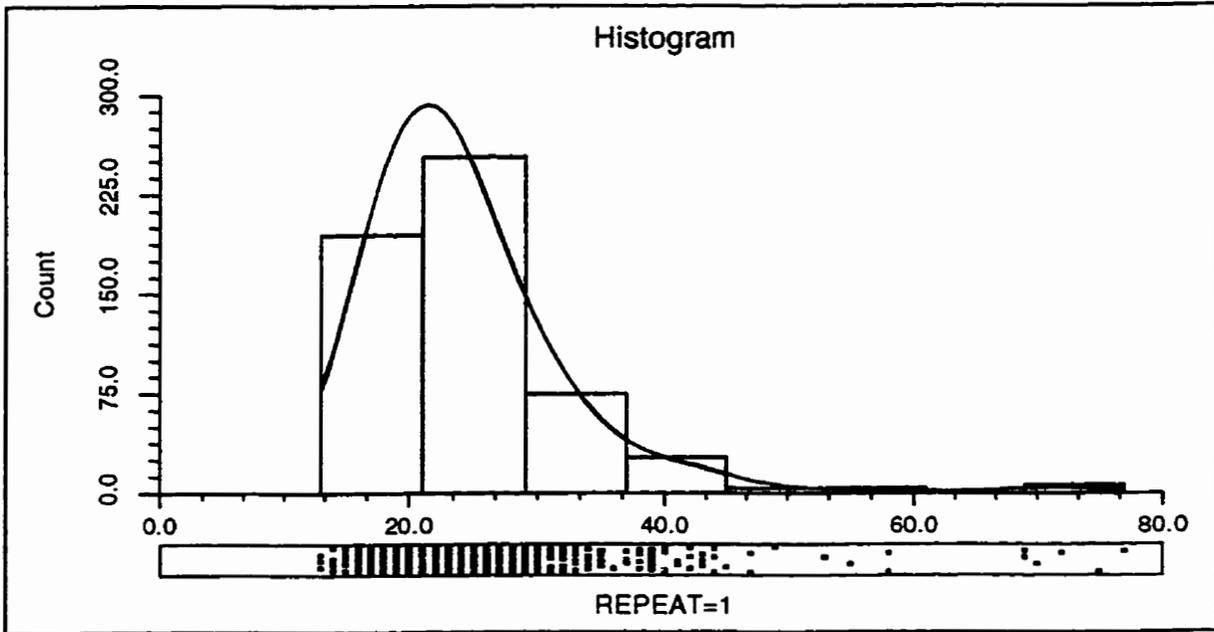


Figure 2.6 Frequency distribution of ages of individuals with repeated episodes of gonorrhea.

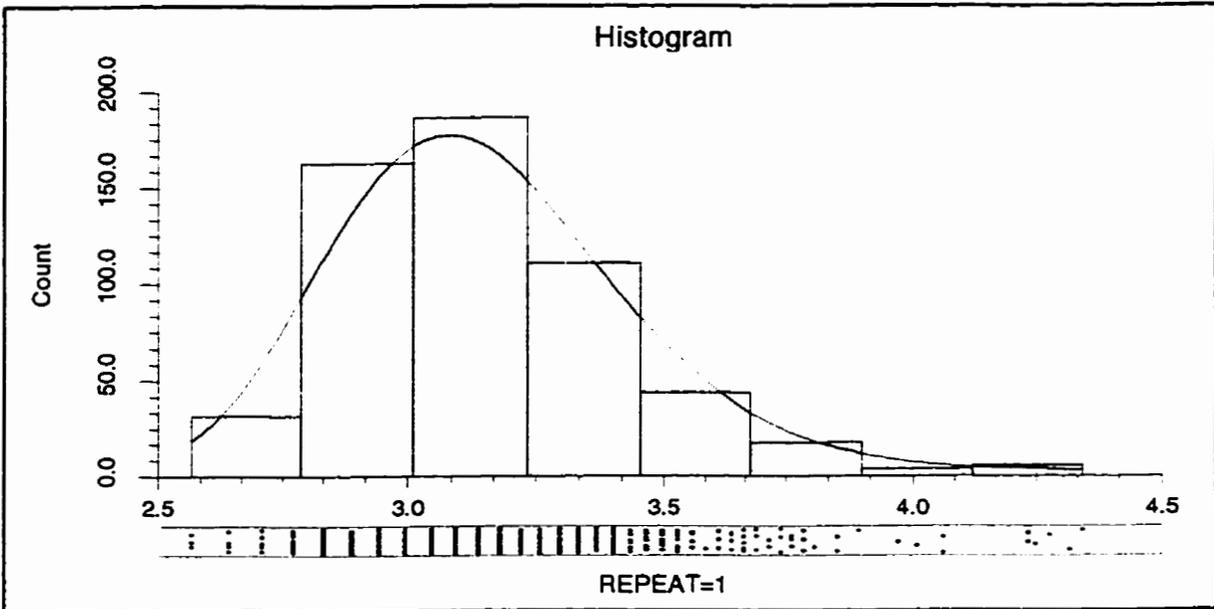


Figure 2.7 Frequency distribution of the natural log of ages of individuals with repeated episodes of gonorrhea

2.4.4 Missing values

The amount and distribution of all missing values was measured in all analyses. Because missing data were almost always associated with other independent variables and/or the outcome variable on univariate analysis, missing value substitution was used in order to perform unbiased analyses.

Missing independent variables in logistic regression analysis, such as income quintile, serve to exclude the whole record of the individual from the analysis. This may not be serious, if the variables which are missing are spread randomly throughout the data set. If they are not randomly distributed, the analysis is biased in favour of those contacts we know most about. This is not desirable, as people with missing data are very often the people whom we have trouble identifying and locating.

In some cases the proportion of missing data seemed high (Table 2.1) As there are no guidelines on how much missing data is acceptable for a given sample size,¹⁶⁰ and as these sample sizes were very large, the remaining data in the sample were adequate to permit valid estimates of the missing variable. Multivariate normal estimation techniques were used. This method estimates the most likely value for a missing value using multiple regression analysis. The variables of all other records with non-missing values are the independent variables in the equation, and the dependent variable is calculated from those.¹⁶³ For example, in performing the logistic regression comparing individuals with

multiple chlamydia infections with those infected only once, data on whether the individual resided in an urban or rural residence were missing in 33.5% of records. The missing variables were estimated from 1,287 other records - more than enough to yield a valid substitution. Although most of the missing data were dichotomous or ordinal in nature, the multivariate normal estimation still produces a reasonable estimate of what the missing value should be, even though it is not absolutely precise. (Personal communication, Dr. Tom Hassard, Director Biostatistical Consulting Unit, October 1996.)

The following tables show the amount of missing data in all analyses. Missing value estimation is accomplished using the total number of individuals in the analysis.

Table 2.1. Missing data of all cases with repeated disease episodes; multiply named contacts and comparison groups.

	Cases					
	Chlamydia		Gonorrhea		Coinfection	
	(n=3,835)	%	(n=1,134)	%	(n=770)	%
Urban/rural residence	588	15.3	179	15.8	104	13.5
Income quintile	666	17.4	213	18.8	130	16.9
Chlamydia therapy	45	1.2			3	0.4
Gonorrhea therapy			7	0.6	3	0.4
	Contacts					
	Chlamydia		Gonorrhea		Coinfection	
	(n=1,935)	%	(n=331)	%	(n=726)	%
Urban residence	648	33.5	87	26.3	235	32.4
Income quintile	694	35.9	96	29.0	261	36.0
Ages	129	6.7	15	4.5	39	5.4

2.5 Outliers

The problem of outliers was evident in the frequency distributions of age. A small number of individuals with reported ages of more than 72 were verified by chart review. Because these records were correct and presumably contribute to our understanding of core group membership, I was reluctant to delete the observations.¹⁶⁰ Transforming the age variable to the log of the age was another option which minimizes the effects of outliers at the

extreme end of the distribution. The remainder of the variables were categorical. All variables where categories of data were split by more than 90% and less than 10% were excluded from analysis as categories of less than 10% of the values have a disproportionate influence on the analysis.¹⁶⁰ In the case of income quintiles, where cell sizes became too small, higher income quintiles were grouped together.

2.6 Management of STD in Manitoba and data sources

Sexually transmitted diseases in Manitoba are diagnosed and treated by primary care providers in Manitoba. Physicians and nurses practicing in medical clinics and hospitals, and nurses employed by Health Canada, Medical Services Branch in health centers on Indian reserves screened, diagnosed, and treated patients with STD. There are no designated STD clinics in the province. Primary care givers and laboratories were responsible for reporting both chlamydial and gonococcal infections to CDC at Manitoba Health. They may also have interviewed clients to obtain information on their sex partners, and completed the management of sex partners. However, the interviewing and partner notification was often completed by public health nurses employed either by the City of Winnipeg, the Province of Manitoba, or by Medical Services Branch of Health Canada, depending on the jurisdiction of the client's residence. Partner notification was completed in one of three ways. Names of the contacts were reported to Manitoba Health, CDC for follow up by local public health nurses, or they were managed by the primary care giver. Alternatively the case, if judged competent, may have been able to

inform his or her own partner(s) of their exposure. In the latter case, the health care provider still may have noted the names to ensure that the partners presented for testing and treatment, (the practice known as “contracting”). If this failed to occur, the provider in some instances located and notified the partners herself. If the client was assumed to be capable of locating and notifying his or her own partner(s), it was possible that the provider may not have noted the names of the contacts, and we may never have known whether they presented to a medical clinic for care. Of course, if this was the case, Manitoba Health would not have had a record of the name of the contact at all.

At the time a person presented to a medical office with symptoms of an STD or as a contact of case, epidemiological treatment for both gonorrhea and chlamydia was recommended, in the absence of a laboratory result. In addition, dual therapy for chlamydia and gonorrhea was also recommended for those individuals who had a positive laboratory test for gonorrhea.

A screening program for chlamydia had been established in Manitoba in 1987. Selective screening was recommended for all women with multiple sex partners or a recent history of or exposure to an STD, and for women undergoing therapeutic abortion or intrauterine device insertion. Screening was not recommended for women presenting for annual or prenatal examination who did not fall into the above categories.²⁹ Partner notification for women with chlamydia detected by screening was probably not as thorough as those

detected by diagnostic testing, as infection may have taken place months previously, complicating the location of previous sex partners.

2.6.1 Manitoba Health STD Registry

The primary source of data was the computer and paper sexually transmitted disease registry kept by Manitoba Health on each case of laboratory proven or, in very few cases, (see section 2.7.3) clinically diagnosed infection with *N. gonorrhoeae* and *C. trachomatis*. Under the Public Health Act and regulations, all cases of chlamydial and gonococcal infection are reportable to public health officials at Manitoba Health.

Both the paper system and computerised databases were designed to fill the dual purposes of recording epidemiologic data on gonorrhea and chlamydia cases, and to provide a reference source for client and contact care. This included provision of patient addresses and other information to public health nurses in order to interview those patients for sexual contacts, provide general education, and encourage compliance with testing and treatment.

Laboratories which tested individuals for these two organisms reported routinely to Manitoba Health. Cadham Provincial Laboratory (CPL) completed approximately 95% of testing for *Chlamydia trachomatis* in Manitoba and electronically reported all instances of chlamydia detection. All case reports and laboratory reports are recorded in the sexually transmitted disease registry. Reporting of *Neisseria gonorrhoeae* infections by CPL and

other laboratories was also believed to be complete, as contact follow-up had not revealed previously tested individuals who are unknown to public health officials. However, the individuals who may have been diagnosed clinically as having chlamydia or gonorrhea, and treated, but who were not tested, may never be reported to Manitoba Health as having infection, and no record of them will be found in the sexually transmitted disease registry. Some of these cases may be included as named contacts. Groups of people who may not have been tested and may not have been named as contacts, may also exist. An example of such people may be partners of commercial sex workers, whose name or locating information may not be known to the sex worker, and who may wish to avoid testing and the notification process.

2.6.1.1 Registering a case

When a laboratory report confirming chlamydia and/or gonorrhea in an individual in Manitoba was generated by a laboratory, the laboratory report was forwarded to Manitoba Health. Staff in the Communicable Disease Control (CDC) Unit, in the Public Health Branch of Manitoba Health searched the paper files for the individual's record. The paper files on disease episodes were maintained for each individual, with the separate reports of disease episodes attached. They were stored for the current year and the two previous years. If a previous record of STD in that individual was found, the patient's previously assigned identification number was assigned to the case, as well as sequence letter indicating the number of the repeat episodes. An "A" was assigned for a first episode, "B" for a second, "C" for a third and so on. If there was no previous record of

that individual in the paper filing system, the person was assigned a new identification number, and the sequence number “A”. Patients who had a reported laboratory-confirmed infection with STD and did not have another episode for three or more years, but then had another infection were recorded with a new identification number and sequence number “A”. The lack of information on individuals with repeat episodes three or more years apart may have affected the current research. However, there was no way to examine these records. The laboratory information, the individual’s demographic data, the symptoms and treatment data, and the assigned identification number were then entered into the computer.

2.6.1.2 Following up a case: treatment and partner notification

Once a positive laboratory report has been received at CDC, the responsible public health unit was informed, and the public health nurse responsible contacted the physician. The physician completed the sexually transmitted disease report form with information on whether the patient has been treated. If the physician wished, he or she may have interviewed the case in order to obtain information on their sex partners. If the physician requested, the interview may have been completed by a public health nurse and the sexual contact information was filled out on the notification form by the public health nurse. The form was forwarded to Manitoba Health, and the information entered on the computer along with the laboratory and demographic data.

The computerised database contained one record for each notification of a disease episode to Manitoba Health. Each record contained detailed demographic, laboratory, contact, treatment, symptom and health care provider information for each client. Three years of data from these files, from January of 1990 to December of 1992, inclusive, were used in the present analysis.

2.6.2 Manitoba Health Patient Registry File

Continuous validation of the computerised information occurred as each individual's demographic information for each new episode was checked against the Manitoba Health Patient Registry file. The patient registry was and is still the file of the demographic information of all residents of Manitoba who are eligible for publicly funded health care services. Because the health insurance system does not require the payment of premiums and provides universal health insurance, including all basic inpatient and outpatient services, nearly all residents of Manitoba are registered.

Data in the patient registry file underestimates the number of Indians with treaty status. If the patient was of First Nations ancestry, the band with which they were affiliated was entered into the registry. In 1987, lists of all newly registered treaty Indians were forwarded routinely to Manitoba Health so that the registry file could be reconciled and updated with federal files. The original purpose of this was to allow for health care services delivered to First Nations people to be flagged for payment by the federal government. However, in 1990, registration clerks merely asked the individual if he or she was a status Indian. If the individual omitted to state this fact, then he or she was not

registered as having treaty status. Likewise, if an individual regained treaty status under Bill C31 which allowed women who had married non-treaty Indian men, and their children to reapply for their treaty rights, the registry file may not reflect the fact that the individual is now entitled to treaty rights. The effect of this on the current research is to underestimate the odds ratios of increased risk of repeated sexually transmitted disease in First Nations people. Also, addresses for some people change frequently, and may not have been updated in the registry file. In these cases, the STD registry would have more accurate information on addresses than the registry file.

2.6.3 Manitoba Health STD contact database

Information on the sexual contacts from the STD notification form was entered into a second database used in this study - the contact database. This database contained all the names of the sexual partners of cases which were reported to Manitoba Health. Data within this database were not as complete or as accurate as that contained in the case database. The name, birth date, age, gender, and address, were recorded as well as whether the contact was located, tested, treated, the date on which the exposure took place, and the disease to which the contact was exposed.

During the years 1990-1992 the contact file was "closed off," an activity which was later halted due to staff cuts. "Closing off" meant that the reports of the outcome of each contact investigation were entered into the computer for those years, recording whether the contact had been found, tested and/or treated. For the purposes of this study,

information on a sex partner who had laboratory-confirmed infection was gained from the STD case registry, as the information contained in that database was more specific than that of the contact database.

2.6.4 Statistics Canada Census Data

An additional source of information on average household income and rural or urban residence used in this study was gathered by Statistics Canada for the Census of 1991. The data on average annual household income are gathered on the Census form 2B commonly known as the "long form," which is filled out by a 20% stratified, random sample of Canadians. These data are summed and averaged for each enumeration unit in Manitoba. Data definitions and information on data quality were available from Statistics Canada. Household was defined as the following: "...a person or group of persons (other than foreign residents), who occupy the same dwelling and do not have a usual place of residence elsewhere in Canada."¹⁶⁴

There were 100 census tracts in Manitoba, which were divided into 1,406 smaller enumeration units, each of which had an average of 272 households with a sum of about 600 people in each. For the purposes of attaching socioeconomic indicators to individual case records, census data were aggregated by these enumeration units. Enumeration units correspond approximately with 25,315 postal code areas in the province of Manitoba. Only 348 enumeration areas in Canada were not linked to a postal code, which represents a population of 10,844 Canadians.¹⁶⁵

A study of the error rate in postal code geographic linkage with enumeration areas was conducted by Statistics Canada. Erroneous linkages were defined as those where a postal code was linked to an enumeration area of which the boundaries excluded the postal code area entirely, or where the linkage was not made, but the postal code area was included in the boundaries of the enumeration area. Forty-six (6.7%) enumeration areas were incorrectly linked with postal codes. Another limitation of these data in rural areas is related to physical location of residence and postal code area. Postal codes in rural areas straddle many geographic boundaries, and therefore represent where the person collected their mail, not necessarily where they resided.

In order to link the postal code areas directly with the enumeration area, each postal code has to belong to only one enumeration area. (Computers cannot link multiple values of variables such as postal code to multiple values of the enumeration area, for example. There must be a unique value of postal code to which an enumeration area can be attached.) In the urban areas where postal codes straddle enumeration area boundaries, Statistics Canada has determined which enumeration area “best” fits the postal code. This was done by calculating where the highest number of addresses fell, and assigning that enumeration area to the postal code. In rural areas, the enumeration area in which the post office was located was assigned to the postal code.

The urban/rural indicator was assigned to each enumeration area. Urban areas were defined as “continuously built-up areas having a population concentration of 1,000 or

more and a population density of 400 or more per square kilometre based on the previous census.”¹⁶⁵

2.7 Definitions

In order to select patients eligible for study and classify the study groups and comparison groups consistently, the following definitions were used.

2.7.1 Individual

Because this study involved taking records of specific events and converting them to one all inclusive record on each individual, criteria on which to decide which records belonged to one individual were necessary.^{79,143}

Records of events were considered to belong to an individual if the following criteria were met in each of three situations;

1. The first name and surnames or alias matched exactly **and**;
 - a) two of three components (the day, month and year) of the birth date were identical **or**,
 - b) the month and day were identical but reversed **or**,
 - c) the address, (including the house or apartment number) were identical.

Nonspecific addresses such as “The Pas” were not considered to be matched addresses.

2. The first name was shortened, or the last name was spelled differently, for example “Michael” shortened to “Mike”, or “Taylor” was spelled “Tailor”
and
 - a) the above criteria for matching birth dates and addresses applied.

3. Those contacts named by laboratory-confirmed cases of STD whose last names were spelled differently, and/or whose first name was shortened, the above criteria for birth dates and addresses would apply, **or**,
 - a) the confirmed case who named the contact matched **or**,
 - b) the ages of the two records matched, allowing for the year in which the events were reported **and**
 - c) the address matched exactly.

2.7.2 Laboratory-confirmed

Virtually all cases of gonorrhoea and chlamydia reported to Manitoba Health have been tested and confirmed as positive in a laboratory. Forty-nine of 15,639 records of notifiable infection from 1990-1992 contained in the computerised database were missing information on laboratory tests. Nine of these diagnoses were noted as having been made on the basis of clinical

symptoms. This was often done where patients refused testing. Eighty-five percent of all tests for chlamydia were conducted at Cadham Provincial Laboratory, where enzyme immunoassay was used. (Chlamydiazyme, Abbott Labs. Chicago). Tests used by other labs included; direct immunofluorescent assay (Microtrak) for chlamydia diagnosis. Gonorrhoea was diagnosed by culture, enzyme immunoassay and gram stain.

2.7.3 Laboratory-confirmed repeater - case repeater

The term repeater was used instead of the traditional term “recidivist” because it is less pejorative. Recidivist means “a person who relapses into crime”,¹⁶⁶ which implies voluntary behavior on the part of the recidivist, which was inappropriate for a surprisingly large proportion of individuals who may have been prescribed inadequate therapy for their infections. In addition, it is not the intention of this work to label individuals who may have had little choice in their own circumstances.

The first task in defining repeat episodes is to differentiate new infections from continuing infections. This problem of classification has been addressed in previous studies.¹⁵⁶ Some have the advantage that tests of cure were required, therefore a new infection was one which immediately followed a negative laboratory test.¹²⁷ In those jurisdictions which did not require tests of cure, designations of three days,⁷⁹ seven days¹²³ or two

weeks,^{124,128} were used to differentiate new infections from old ones.

Designations were also made on the basis of re-exposure to an untreated contact,¹²⁷ and on whether therapy was adequate¹²⁸ Staff who worked with these data daily during 1990 - 1992, indicated that in each case where infections occurred immediately after a previous one the Program Specialist for sexually transmitted diseases in Manitoba reviewed the case and determined whether the case was a new infection or the continuation of an existing one. She did this by reviewing the named contacts, and notes on compliance with treatment and other notes on the paper file. The separation of new infections from continuing ones was supported by the very low percentage of infections recorded as less than 28 days apart. Only 3.3% of 781 records for which adjacent dates of infection were known, occurred within 28 days of the laboratory specimen date of the previous infection. The mean time to new infection for repeaters was 280 days with a range of six days to 977 days.

The use of 28 days to estimate the shortest possible time to acquire a new infection is reasonable. The incubation period for gonorrhoea ranges from 1-14 days.⁶ For a conservative estimate one can use 14 days as the outside estimate of incubation period. The time taken for treatment depended on the therapy itself, usually, 10 days.¹⁶⁷ Adding the two times together

allows for 24 days from the time of infection and 10 days for cure, after which it is possible to clearly define a new infection.

Repeat disease episodes were defined by CDC staff as those where an individual was reported to have another STD within the two years previous to the first event. Should an individual have had a repeat episode three or more years previous to the start of the study period in 1990 and none since then, then there was no record of the individual having a repeat episode.

For this study, a case repeater was any individual with a first laboratory-confirmed disease episode occurring in the two years before the start of the study period or during the study period **and** who had one or more repeat episodes reported to Manitoba Health between 1990 and 1992.

2.7.4 Individual with only one laboratory-confirmed infection, (case comparison group)

The repeatedly infected individuals were compared with those who had been reported to Manitoba Health as having only one episode of laboratory-confirmed infection during the study period. The designation of having only one episode could have been incorrect if the individual's first episode took place three or more years before the start of the study period, then the individual subsequently had another episode during the study period and was selected as part of the comparison sample. However, the

effect of this on analysis would be to underestimate odds ratios, which is a more conservative approach than to overestimate the differences.

2.7.5 Categories of disease; chlamydia, gonorrhea and coinfection

The grouping of individuals into disease categories was one of the most important in this study. Because of the epidemiological and behavioral differences between chlamydia and gonorrhea, and the need to compare possible core groups for the two diseases, individuals with these two infections and contacts exposed to the two infections were placed into separate groups. Therefore there were clear distinctions between individuals repeatedly infected or contacts exposed repeatedly to gonorrhea and those repeatedly infected with or exposed to chlamydia.

Individuals with coinfection were defined as those who ever had the ICD9 diagnostic code for chlamydia as well that for gonorrhea in the same record for one disease episode. In addition to the staff at CDC evaluating each case as to whether it was a new case of disease, or a continuation of an existing infection, I conducted an additional validation to ensure that people classified as coinfecting had both gonorrhea and chlamydia within a short period of time. The dates of a selection of laboratory reports of positive tests for both organisms in the same individual were reviewed. In

170 (95.5%) of 178 cases, infection was confirmed within one day, with the maximum length of time between dates being 27 days.

There were two reasons for separating individuals who ever had been coinfecting with gonorrhea and chlamydia from those with only one STD. First, previous research completed in Manitoba revealed that women infected with chlamydia only were similar to those who tested negative for both gonorrhea and chlamydia and differed substantially in socioeconomic status from women with gonorrhea only and from women with gonorrhea and chlamydia coinfection.²⁹ In order to test the hypothesis that the group responsible for transmitting gonorrhea is the same as that transmitting chlamydia it was necessary to separate the two groups in order to compare them. Second, it seemed logical that individuals who had ever been coinfecting were likely to have higher numbers of sexual partners, or have higher risk sex partners since they had contracted two sexually transmitted diseases, and not just one. In order to define the core groups as precisely as possible, individuals who had ever been coinfecting and previously or subsequently had either chlamydial or gonococcal infections were compared with the gonorrhea and chlamydia repeaters.

Included within the “coinfecting repeater” group were those individuals with repeated episodes of infections with or exposures to chlamydia

alternating with gonorrhea, occurring at different points in time. There was no statistical difference between the serially coinfecting group and those who had simultaneous chlamydial and gonococcal infections/exposures, so they were grouped together as “coinfecting” (see Chapter 6.) Because they were not statistically different no statistical effect would be apparent after the two groups were joined. The comparison group for coinfecting repeaters consisted of individuals with only one recorded episode of simultaneous infection with, or exposure to gonorrhea and chlamydia. The algorithm for the classification of the study groups is shown in Figure 2.8, below.

2.7.6 Contact

A contact was defined as a person who has been named by a confirmed STD case as having had sex with that infected individual and who has likely either been exposed to infection, or has transmitted infection. Each individual with a sexually transmitted disease was interviewed by public health staff from the City of Winnipeg, Manitoba Health or a physician. According to procedure guidelines, sexual partners were considered to be contacts if they had sex with the case since and just before symptoms started and before the case had been treated, or in the absence of specific information, had had sex with a case in the last three months.³²

2.7.7 Repeatedly named contact, or contact repeater

Contacts who had their names referred to Manitoba Health more than once for location, testing and treatment during the period 1990 to 1992 were multiply named contacts. Historic records on contacts were not stored at CDC as they were for cases, therefore all repeated reports of names occurred during the study period regardless of how many times they were named prior to 1990.

Because contacts who are multiply named have the potential for repeated acquisition or transmission of STD in the absence of a positive laboratory result, they were classified as proposed core group members, **even if** they had one laboratory-confirmed infection, see section 2.2. Therefore, ever having been named multiple times as a contact took precedence for placing a person into the repeatedly named contact group, over having one laboratory-confirmed infection. Consequently, the comparison groups of individuals with only one confirmed infection exclude all individuals who were multiply named contacts which suggested high risk behavior (see Figure 2.8).

2.7.8 Contact named only once, contact comparison group

Repeatedly named contacts were compared with individuals who had been reported to Manitoba Health as having been named by a laboratory-confirmed case only once in the three year study period.

Figure 2.8 shows the algorithm used to classify mutually exclusive case and contact repeaters, and the comparison groups. Of all the cases and contacts registered with Manitoba Health's Communicable Disease Control Unit, the first group selected was that of the laboratory-confirmed repeaters. They were separated into a further four groups as shown in steps a, b, c, and d. Individuals who had ever had coinfection were separated from the other three groups. Repeaters with chlamydia diagnosed at one episode and gonorrhoea at another were classified as serially coinfecting, and were analysed as outlined in Chapter 3. Note that being a multiply named contact took precedence over being a case with only one proven infection. Also note that all samples were mutually exclusive. For example, if a case with only one episode of infection was also contact named only once, the record was purged from the contact sample, according to the hierarchy in the diagram. However, if the same case was a multiply named contact, then the case was placed in the "multiply named contact group" as this group had a higher priority (Step 2) than the non-repeater cases (Step3).

HIERARCHY FOR CLASSIFYING STUDY AND COMPARISON GROUPS

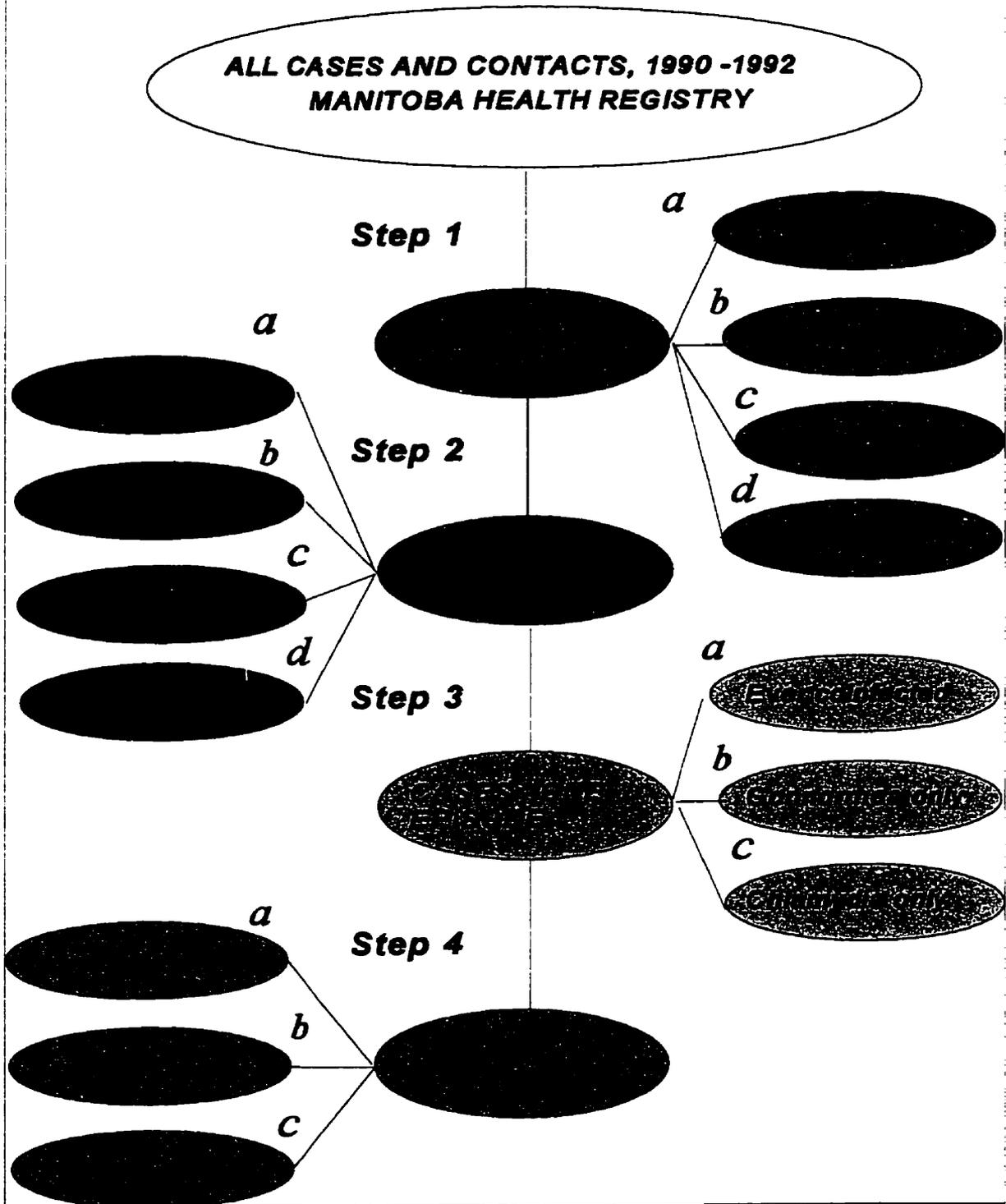


Figure 2.8 The algorithm used to classify mutually exclusive case and contact repeaters and comparison groups

2.8 Conclusions

This chapter has outlined the methods and some definitions used in this research. The use of statistical methods, despite the fact that whole populations were studied, is justified.

The full effects of large sample sizes on statistical tests of significance are evident in the following analyses. However, some suggestions have been made as to how decisions of clinical and epidemiological relevance can be made.

The registry data used in this study are secondary sources, and were never intended for use in answering sophisticated research questions. Therefore a considerable amount of time had to be spent exploring inaccuracies in the data, estimating their effects, in some cases correcting records, and also in looking up and entering missing data on ethnic origin and postal code. In effect, each record was individually groomed before selection and analysis. The following chapter elucidates the data cleaning, the building of historic records from multiple events of each individual, and the implementation of the above methods.

Chapter 3

Data management strategies

3.1 Introduction

This chapter describes the implementation of the methods outlined in Chapter 2 to select individuals with repeated infections, contacts who were multiply named, and the comparison group of individuals who had been infected only once, and those contacts who had been named only once. In addition, the data were examined for errors, which were corrected wherever possible. Although the data were computerised, which facilitated data cleaning, the process was time-consuming. However, data cleaning is essential in obtaining reliable and valid results from statistical analyses.¹⁶⁸

3.2 Phase I: laboratory-confirmed cases of gonorrhoea and chlamydia

The total number of records of each reported episode of STD for the years 1990 through 1992 was 15,639. Of the total number of infections 4,132 were repeat episodes. The total number of records decreased slightly from 1990-1992, as the number of reported infections decreased; 5,322 records were from 1990, 5,595 from 1991 and 4,722 from 1992.

3.2.1 Selection of individuals with repeated infections

Each record in the STD database denoted a separate episode of infection, and not a separate individual. However, there was allowance in each record for the entry of two infections in one individual simultaneously, representing one disease episode. The data management plan for both repeater and non-repeater cases is shown in Figure 3.1, below. All records of repeated episodes since 1988, (as shown by their sequence number, see Chapter 2, section 2.7.1.1) were selected and exported in an ASCII file from Dbase into Epi Info v. 6.02, (Centers for Disease Control, Atlanta, Georgia). In addition, another variable in the database which indicates a repeated infection within one 12 month period was reviewed, and nine individuals who had incorrect sequence numbers but had had repeated events were included in the repeater group.

In order to build an historic record containing all disease episodes for each individual repeater, a unique identifier for each individual was created. This served the following purposes: a) to identify and eliminate errors in identification of individuals in multiple records of different disease episodes, b) to ensure the correct classification of repeaters and comparison group, and c) to provide a unique value for each individual on which to build a history of repeated infections, treatments, and symptoms over time. A unique identifier which consisted of the patients' first names, last names and birthdates was developed and frequencies of all unique identifiers were compiled. Duplicates occurred when the person had an identification number assigned in error, or had a reported infection in one year, and had not had another reported infection for a 12 month period or longer.

and then had a second identification number assigned to them by staff at the Communicable Disease Control unit (CDC), Manitoba Health. For the purposes of this study, the earlier identification number was adopted and the later one deleted. Changes were made to the record indicating the additional infection, if appropriate.

Once the individual identifiers were established, frequencies of the identification number showed 35 duplicate records of the identical disease episode in the same individual. In order to allow for the counting of cases with reported pelvic inflammatory disease (PID), these cases were recorded twice; once as cases of gonorrhoea and/or chlamydia, and again as recorded with PID as the diagnosis. These duplicate records were deleted. There were 19 other duplicate records of the same event which were deleted; in one case the infections reported were only three days apart. The reports were assumed to be of the same event, and this individual was not classified as a repeater. Six records of infections had a number entered instead of a sequence letter. One of these was deleted, as it was impossible to classify him/her as a repeater or not; the remainder were corrected according to information in the paper files. At this point names and addresses were then stripped off the file containing only the records of repeat disease episodes and stored in accordance with Manitoba Health policy.

3.2.2 Data cleaning: individuals with repeated infections

In order to “clean” the remainder of the data, frequencies of each variable were reviewed, as well as combinations of variables. The gender field contained one entry of “0” instead

of an “F” or “M”; but the lab sample was recorded as cervical, hence this person was assumed to be female. Birth dates which seemed improbable were verified. All birthdates earlier than 1925 were examined, and several were verified in the paper files which had not yet been purged, as being correct. The remainder, therefore were also assumed to be correct. Two children under age 13 with repeated infections were deleted from the study population because sexual activity at that age was assumed not to be indicative of personal choice or behavior.

Six records did not contain a postal code. This was due to unknown addresses, out of province addresses, or non-Canadian residence of the individual. One individual was recorded in the computerized database as having 91 contacts, higher than all others by a magnitude of 10. The paper file for that individual had been purged. However, in consultation with staff at CDC responsible for data entry, and in accordance with statistical methods,¹⁶⁰ the value was assumed to be a typographical error and was left blank.

One person had no diagnostic code which designates infection with chlamydia or gonorrhea, but she was assumed to have chlamydia as she had a positive laboratory report for it. Fifty-four individuals had no test result recorded. Two of these also were missing information on sample site and had been treated on the basis of symptoms. Three of the 54 records also had missing data on the type of test used in diagnosis of STD, but other data were present to allow for the verification of a diagnosis. Two of the 54 people were recorded as having negative test results. However, information contained in the diagnosis field is more reliable than any of the other variables indicating test type, site and result. (Personal Communication, Ms. Linda Graham, CDC, February, 1994). The remaining forty-nine had no test result, test type or sample type, but did have a diagnosis which indicated a clinical diagnosis. I checked nine of these against the paper files, and confirmed the diagnoses of six of them. The remainder of the files had been purged. Because of the results of the validation and on the advice of the staff at Communicable Disease Control, the 54 individuals were assumed to truly have the diagnoses which were recorded in the database.

Forty-eight individuals were recorded as being male but had cervical smears; these were corrected after verification of the name, which indicated the gender of the person. Forty males had been noted as having cervicitis, being pregnant or having an abortion (hence the reason for being tested); these were coding errors in the symptom field and were deleted after the gender of the client had been verified.

One hundred and eleven records had no treatment entered in the treatment fields. This could have occurred under one of the following circumstances; the health care provider did not fill in information on the drugs used in treatment; there was no treatment provided at the time of testing; and/or the health care provider did not return the request for updated treatment information; or the public health nurse engaged in patient follow-up could not ascertain whether the patient had been treated. It was also possible that a data entry clerk merely omitted to enter the information.

There were two fields in which the band and treaty numbers of First Nations people who were registered as status Indians were entered. The field containing the alias was sometimes used to show the First Nations band with which that the person was registered. Therefore each entry in the alias field was reviewed (n=810), and the band information deleted, leaving only the alias information behind.

Once the validation of basic information recorded in the database was complete, the history files recording each individual's history of STD were constructed. All second infections which occurred between 1990 and 1992 were selected and placed in a file with the unique identification number. All third infections were stored in another file, and the fourth infections in yet another. Then the files were merged using the unique identifier to attach second, third and fourth infections of the same individual, forming a long horizontal record of the history of infections. There were 2,988 individuals in the repeater file at this point. After cross referencing of identification numbers from the non-repeater case file

was completed, eight additional individuals were found to have had repeat events. These were added to the repeater file for a total of 2,993 individuals.

The repeaters were divided into four separate disease groups; those infected repeatedly with chlamydia only, those with gonorrhea only, those who had repeated coinfections and those who had episodes of chlamydia alternating with episodes of gonorrhea (serially coinfecting.) The serially coinfecting individuals were compared with those coinfecting repeatedly, and the two groups were found not to be significantly different, (see results in Chapters 4, 5, and 6). Therefore, the serially coinfecting repeaters were combined with the simultaneously coinfecting group, and all further hypotheses were tested with the pooled group of coinfecting individuals.

3.2.3 Classification of individuals with single infections.

After all non-Manitoba residents were deleted (n=20), 11,282 records of individuals whose first disease episodes occurred between 1990 and 1992 remained. This group of people still contained the first episodes of disease from the repeater population. Once the historical, individual-based records of repeater populations had been constructed and cleaned, these were linked with the database containing first episodes. All records of repeater individuals which were successfully linked were deleted from the comparison group. Sixty children and infants less than 13 years of age were also removed from the database. After these corrections had been made 9,853 records of single episodes of disease remained.

The same procedure of identifying possible duplicate records used for repeaters above was undertaken for all those individuals with single events. A frequency distribution of the identification number assigned by staff at Manitoba Health was completed. Fifty-seven records with duplicate identification numbers were found. This occurred for any of the following reasons; one identification number was assigned to two different individuals in error; duplicate records were stored for counting an STD infection as well as another for PID, duplicate records on the same person were entered in error, and lastly, repeated infections were incorrectly recorded as being the first infection of that individual.

Individuals who had duplicate records which indicated repeated infections within the study period were deleted from the comparison group and added to the repeater group, and all other duplicate records were deleted. Those individuals who had been assigned the same identification number as another case, were assigned a new identification number, and added to the repeater or comparison database, as appropriate. After all deletions and additions of individual records were made, 9,823 individuals remained in the group of people with only one laboratory-confirmed infection over the three year study period.

3.2.4 Data cleaning; individuals with single episodes of infection

Only one of the comparison group patients had missing birthdates. Eighty-nine individuals had no treatment recorded. One hundred forty-one males were recorded as having cervical and vaginal swabs submitted for testing; these were corrected to urethral swabs after the gender had been verified. One hundred and thirteen males were recorded as having cervical and vaginal symptoms; these were also corrected. One male was recorded

as being pregnant; this value which was entered in the symptom field was deleted, but the rest of the record was valid and remained in the comparison group. Nine patients had no test results recorded, although five were diagnosed clinically. As with the repeater group, these patients were assumed to have the diagnosis recorded in their fields, in the absence of test results.

Not one record in the comparison group had missing postal code data. As with the repeater group, all entries in the alias field were verified as being *bona fide* aliases and not comments. People with birth dates earlier than 1925 were also verified and found to be correct according to the paper files, and the Manitoba Health insurance patient registry file.

3.2.5 Sample selection of individuals with single episodes of infection

Because of the large number of patients, and time necessary to perform statistical measures on such a large group of records (n=9, 823), a random, stratified sample of records was drawn from the comparison group with only one reported STD in the study period. Samples were stratified by year of episode, gender and disease group (chlamydia only, gonorrhea only, or coinfection.) The ratio of sampled records to the repeater groups was 1:1. Of course, there was no comparison group for those individuals who had chlamydia infections alternating with gonorrhea. Therefore all individuals who had one episode of gonorrhea and chlamydia coinfection simultaneously were selected as the comparison group for the coinfecting repeaters (see section 3.2.2.)

3.3 Phase II: Contacts named by laboratory-confirmed cases

All contacts who had been named by laboratory-confirmed cases from 1990 to 1992 were selected from the contact registry at CDC, Manitoba Health. There were 19,387 records which, like those of the laboratory-confirmed cases, represented events of notification, and not individuals. In order to maintain accurate numbers of contacts, even those who were not identified were recorded. For example, there were many entries with “unknown” entered as the surname. For the purposes of describing a supposed “core group” these records were not useful, and 2,618 were deleted. The structure of this database was unlike that of the laboratory-confirmed cases, in that it did not contain an identification number for each individual contact.

3.3.1 Classification of multiply named contacts

The initial task was that of classifying people into two groups; one of those who had been repeatedly named and one that contained individuals who had been named only once. All contacts were sorted by last name, first name and birthdate, so that records of individuals who were named more than once would be adjacent. A field which indicated whether an individual had been repeatedly named was defined. All records were reviewed and people who had two or more adjacent records were noted in the “repeat” field. Resolution of which records belonged to a single individual was made as outlined in Chapter 2. At the same time, spelling of the person’s name was standardized. For example, the name “Michael Taylor” may appear “Mike Tailor”, in which case the following entries were

changed in order to be identical. All reported aliases were checked and records for each individual were changed so that they all bore the same name. In addition, all Scottish surnames starting with “Mac..” were recoded and compared with those which began “Mc” in order to ensure that both spellings of repeatedly named individuals were standard.

All contacts who had been recorded multiple times were sorted by notification date. A program in Epi Info then calculated the frequency of combinations of first names and last names of each contact repeater and assigned a sequence number to each record. This process was repeated twice in order to ensure that the all records of repeat contacts were appropriately counted, and no names with irregular spellings remained. There were 1,946 individuals who had been reported 4,779 times by cases. Eleven thousand nine hundred and ninety individuals remained who had been named only once in the three year period.

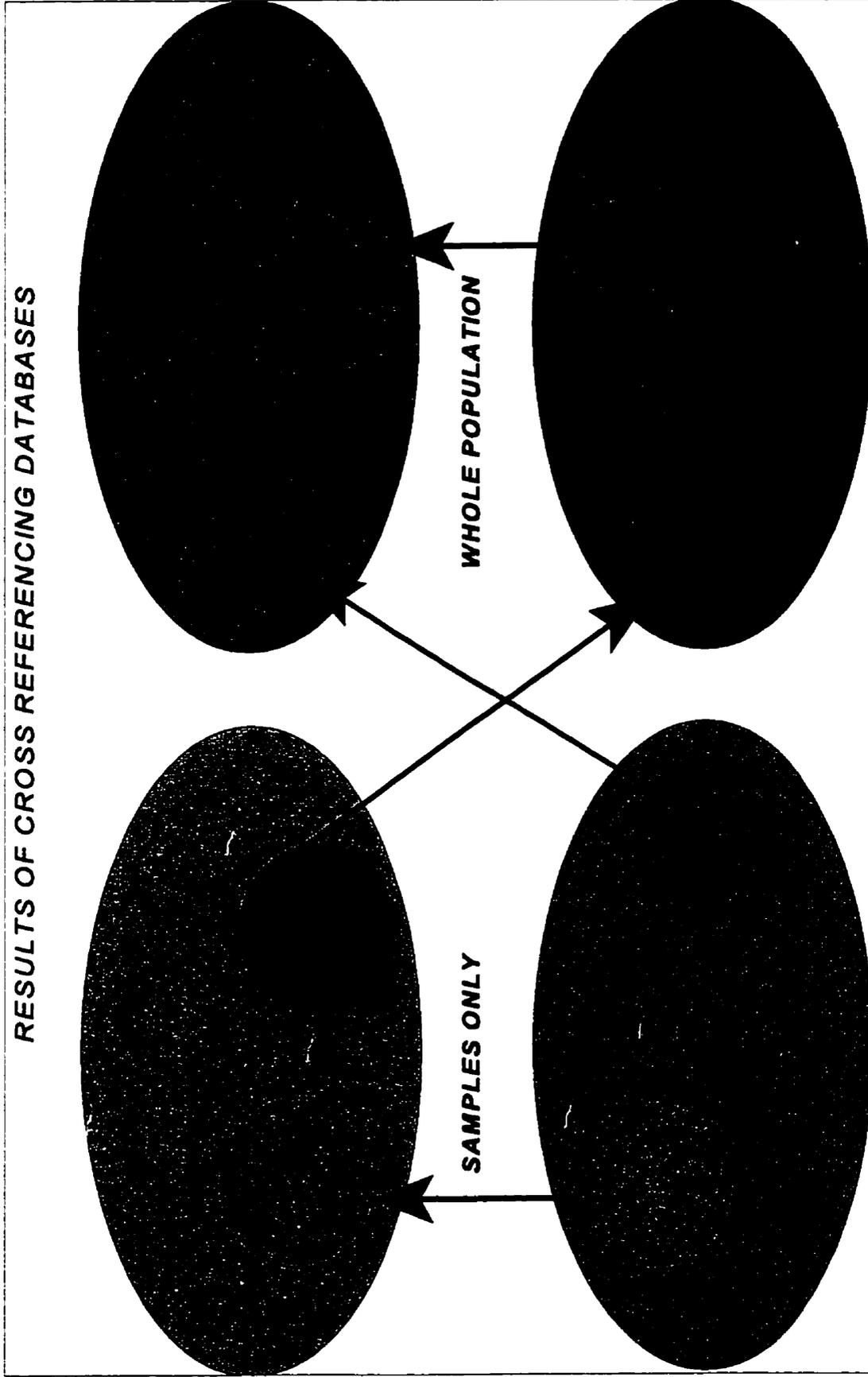
In order to build an historical record containing all the events during which each individual had been named as a contact, a unique identifier for each individual was constructed. Frequency distributions verified that each unique identifier was in fact unique. The records of each event for each individual were linked horizontally to form a history of reports to Manitoba Health. Records were sorted by the date of report to Manitoba Health, so that the resulting history file recorded the events in chronological order.

The case repeaters and the case comparison groups were cross referenced with the multiply named contacts. Thus the multiply named contact group excluded those cases

who had been confirmed to be repeatedly infected, and the number of repeatedly named contacts who had episodes of laboratory-confirmed infection was revealed. Because more accurate demographic and other information was present in the file of laboratory-confirmed cases than in the contact file, this information was used in the analysis of contact repeaters who became cases. As names, birthdates and addresses varied, much of this matching was done manually using the criteria outlined in Chapter 2. Finally, 494 repeatedly named contacts (25.8%) were found to be cases who had only had one disease episode in three years (see Figure 3.2) Five hundred and fifty-two (28.8%) had laboratory-confirmed repeated STD episodes. The remaining 874 (45.6%) had no evidence of laboratory-confirmed infection during the study period. This is remarkable, as it reveals that almost half of repeatedly named contacts are never confirmed as having disease. Some may in fact have been tested, and had a negative result, but this is unlikely for the majority of cases. Some, if located, should have received epidemiological treatment. But of course, many may never have received treatment, and if they did, may not have been motivated to comply. They may form a reservoir of infectious individuals who are likely to be asymptomatic, and have long durations of infectiousness during which they may transmit it to many partners.

Figure 3.2 shows the number of contacts present in the case databases. The case and contact databases were not mutually exclusive. The color of the subsets and the direction of the arrows indicate the larger group to which the subgroup was assigned. For example, 155 of 494 individuals who had been named as sex partners multiple times were also

randomly selected cases with only one infection, and were deleted as comparison cases, and included with the multiply named contact group.



RESULTS OF CROSS REFERENCING DATABASES

Figure 3.2 Results of cross referencing the case and contact databases.

For the purpose of this study, those multiply named contacts who were reported as having laboratory-confirmed infection only once in the study period (n=346) were included as repeatedly named contacts, see Chapter 2, section 2.2. The reason for this is that due to repeated exposure they have the potential to repeatedly acquire and transmit of chlamydia and gonorrhea, they are hypothesized to form part of the “core group.”

3.3.2 Sample selection: contact comparison group

Those who had been named only once in three years comprised the comparison group for the multiply named contacts; n=11,980. Because of the time taken to clean the data, and analyze large populations, random samples of this population were selected of those named only once. The number of contacts selected was equal to the number of repeatedly named contacts. The samples were stratified by year of reporting to Manitoba Health, by disease, and by gender. In order to provide a sufficiently large comparison group for the repeatedly named individuals who were exposed to chlamydia and then subsequently to gonorrhea in separate events, all contacts of coinfecting cases who had been named only once were selected.

After the comparison sample population was selected (n=1,955), the records were cross-referenced with those of laboratory-confirmed cases (see Figure 3.2.) One hundred twenty-nine (6.6%) contacts who had been named only once were laboratory-confirmed case repeaters and were deleted from the contact comparison sample. Two hundred and fifty-eight of the contacts were cases with one episode of infection; only 89 (4.6%) of

which were common to both the sample databases of comparison STD cases and contacts. These were also removed from the contact comparison database, leaving 1,737 remaining in the sample of contact named only once. The ratio of individuals in the comparison group who were named only once to repeatedly named contacts was a little over 1:1 in most strata.

3.3.3 Data cleaning: contact database

A large amount of information, (such as treaty status and postal code), which had been present on the case database, was missing from the contact database. In order to be able to make meaningful comparisons between repeatedly named contacts and cases with multiple infection, more demographic data were needed. Information on whether the contacts were registered status Indians was entered from searches on the Manitoba Health Patient Registry file. All the postal codes of the contacts were searched for in the registry file were entered manually.

Internal validation was completed for all contacts with very young ages. If the person was recorded as never located, tested or treated, then the age was assumed to be incorrect. This was done on the advice of Ms. Linda Graham (CDC, Manitoba Health,) who said that it was almost impossible for contacts under age 13 not to be investigated thoroughly. Incorrect ages were converted to blanks, in the absence of any reliable data.

The variable containing information on symptoms was validated internally. If information indicated that the contact had not been located, the entry in the field containing symptoms was assumed to be erroneous and was converted to a missing value denoting “unknown.”

Although there was a field which noted whether the contact had been treated, this field was not comparable to that variable present in the case database, which itemized exactly which drug(s) were used. Because the type of drug was not reported in the contact database, the assumption of efficacy could not be made.

The disease categories were classified so to be consistent with those individuals who were reported to Manitoba Health as confirmed STD patients. All those who were named as contacts to a coinfecting individual were coded as such; all those who had been in contact with a person with gonorrhoea were coded as gonorrhoea, and those who had been exposed to chlamydia as chlamydia. Those individuals who had been named repeatedly as contacts of both of a case infected with gonorrhoea and in a separate event as contacts of chlamydia were coded as serially coinfecting. There is no assumption that all contacts of cases are infected. However, the action of sexual intercourse with a confirmed case which exposes them to disease is the risk factor under study. The reason for the similar categories for contacts as those of the cases is that contacts and cases of each disease group may be similar, and in the case of the repeaters, may form separate core groups for gonorrhoea and chlamydia.

3.4 Definition of variables: Phase I - laboratory-confirmed cases of gonorrhoea and chlamydia

In order to derive data which accurately distinguishes the STD history and behavior of the repeater individuals from individuals infected or named only once, data from all episodes had to be considered.

This research describes various demographic and behavioral measures which may be associated with being a multiply named contact of chlamydia and/or gonorrhoea, or an infected repeater . These may be potential risk factors for core group membership. In addition, a model of risk markers which predicts the likelihood of individuals contributing disproportionately to disease transmission was developed. The two are subtly different in terms of their occurrence in time. For the risk factor to be genuine it has to occur prior to the risk behavior, while risk markers may have no causative role in behavior, but are mere proxies for other factors which cannot be easily measured. Therefore, two values were derived for each mutable variable. The risk factor variables were those recorded at the first repeat event, while for the predictive model, I used the value most commonly reported while the individual was a repeater.

For example, the postal code for the address of an individual at the first repeat event is more closely associated with the initiation of repeater behaviour, while the address at which he/she resides subsequently is more predictive of the state of being a repeater itself.

The distinction may not reflect real differences in predictive models, but is consistent with the epidemiological and statistical uses of the models.

What follows are the definitions and logic for the independent variables for both the descriptive and predictive models which were used to compare case and contact repeaters and those individuals infected only once.

3.4.1 Number of repeat events

In order to accomplish any of the above, a variable defining the number of infections/exposures of each individual was developed. In creating this variable, another problem surfaced. Some individuals had a second infection and a fourth infection, for example, but no record of the third. This hampered the calculation of how many infections a person had, and therefore affected the averaging of the number of contacts the person may have named across episodes, or the percentage of times they had been prescribed inappropriate drugs. A program was written which would identify these individuals, (n=8), and the corrections to these records were made according to the original paper files. Numbers of repeated infections were calculated by subtracting the first infection occurring in the study period from the last repeat infection in the study period. For multiply named contacts, the number of times they were recorded as being named was easily calculated by adding the number of reported exposures.

3.4.2 Age

Age for the descriptive models (“risk factor” models), was defined as the age at first infection/exposure occurring within the study period. In the case of the repeatedly infected individuals, and multiply named contacts, the age was calculated from the date of the first report of disease or exposure and the birth date; that is, the time at which the individual became a *de facto* repeater. If the birthdates recorded at all repeat events was not identical, then that recorded most often was assumed to be the correct birthdate. If all the birthdates were different then the correct birth date was obtained from the Manitoba Health patient registry file.

Ages for both the repeatedly named contacts and the comparison group were calculated by subtracting the date of birth from 15th of the month on which the first report was made to Manitoba Health. It may have been more accurate to use the date on which the exposure to the case took place, but some of these reflected years of sexual activity, and was not a precise enough indicator of recent events to be used to calculate age. If no date of birth was present, the age of the contact entered into the database was used. Seventeen of the repeaters were missing ages, but 11 were found using the Manitoba health patient registry file and were entered. The ages of case and contact repeaters for the predictor or “risk marker” model were calculated as being the mean ages between first and and last repeat

infection/exposure. Of course, those of the comparison group with only one infection/exposure was the age at first infection with chlamydia and/or gonorrhea.

3.4.3 First Nations ancestry

First Nations ancestry was determined from the presence of either a treaty or a band number at any reported infection in the history of a repeater. The band and treaty variables were similar to those found in the Manitoba Health Insurance Patient registry file against which the STD registry data was verified. The band and treaty numbers in the patient registry file represent an underestimate of the total number of people who are registered as treaty Indians. The registration of Indian women and their children who had been excluded after the women had married non-status Indians was not reflected immediately in the patient registry file, therefore there may be people who are actually registered as status Indians in these data, but who were not recorded as such. There was no information recorded in the databases as to whether a person was a non-status Indian. The effect of this omission is to underestimate the odds ratios of risk associated with being aboriginal and having more than one episode of STD.

For contacts, First Nations status was not always recorded. This information was gathered from the Manitoba Health Insurance patient registry, and entered for each contact. A contact was recorded as being status Indian if they had ever had a band number at any time.

3.4.4 Use of an alias

Use of an alias was defined similar to the above, where either cases or contacts who had used an alias at any point in his/her history (recorded in the STD registry and also in the Manitoba Health patient registry), were defined as using an alias or had a “street name”. When clients was being interviewed for their sex partners they are asked whether the contact uses another name. There is a specific place on the notification form to record the use of an alias. The role of aliases in sexually transmitted disease epidemiology has not been well described. However, use of an alias complicates the identification of an individual, its use may indicate those most at risk of STD. One third of commercial sex workers in the Colorado Springs study used aliases.¹⁴³ The fact that a client uses an alias may also affect client identification, location and therefore treatment. For these reasons, use of an alias was determined to be a valid descriptor of repeatedly infected or repeatedly named individuals.

3.4.5 STD in pregnancy

In cases of confirmed chlamydia and/or gonorrhoea, pregnant females were recorded. However, the proportion of pregnant women was too low for any meaningful statistical analysis and was discarded during data screening.

3.4.6 Postal codes

The postal codes provided an indication of geographic area and were used to link the Statistics Canada income data and rural or urban indicator with each individual's record. Two postal codes were derived for each case with repeated episodes of STD or contacts who were multiply named. The code for use in the descriptive model of repeaters would be the postal code at first repeat event, while the postal code for the predictive model was defined as the postal code in use at the second infection if there were two, or the most commonly used postal code if there were more than two repeat infections. If there were four or more different postal codes, the one of the most central event would be taken (i.e. if there were five infections the postal code at the third infection would be used). For cases who had only one infection and contacts who had been named only once, only one postal code was available.

3.4.7 Number of sex partners

The number of sex partners named at each reported infection was noted. This information was gathered by public health nurses interviewing clients for the names of their contacts. If symptoms were present, they would ask for the names of all sexual contacts since one month before the onset of symptoms.¹⁶⁹ If the date of exposure to another infected case was known, then the names of all contacts since that date would be requested. If there was no known exposure date and no symptoms, the nurses would usually request the names of all contacts within the

last three months.³² The number of contacts was therefore not requested for a similar time period for all cases, and would not have included contacts whose names were not known to the index case. In the absence of better information, these data were used to describe the numbers of reported contacts of repeaters. The variable was the average number of partners reported per episode, that is; the total number of contacts reported over the study period divided by the number of reported infections. This variable could not be used in the predictive model, as public health nurses do not have access to that information prior to locating and interviewing the individual.

3.4.8 Presence of symptoms

Symptoms were recorded in the original Manitoba Health CDC database. The coding of them was problematic. It had changed between 1990 and 1991, so that in 1990, all records not containing a symptom code were coded as "0". This was ambiguous, as it did not differentiate between symptoms reported as being absent, or simply not reported at all. In 1991 and 1992, this appeared to have changed, as a much lower proportion of "0" entries were made, but some were still present. Initially, for these to be meaningful descriptors of the repeater population, they were "averaged" over all events in which symptoms were recorded. However, very few had been coded as having symptoms over 50% of the time, making analysis of the variable unstable because of small cell sizes. Therefore symptoms were finally coded as never being recorded (0) or ever being recorded (1). This

variable was not included in the analysis of contacts, due to the large amount of missing data.

3.4.9 Duration of symptoms

Sixty-seven percent of individuals had no information on duration of symptoms recorded, therefore coding of this variable was not feasible for analysis, due to the large amount of missing data.

3.4.10 Recorded therapy

The type of drug with which the patient was treated was also entered in the STD database from the STD notification form, filled out by the health care provider. However, on cursory examination it appeared that many of the regimens prescribed would not have been effective against the infection which the patient had. The effectiveness of chemotherapy is central to the present topic of who may be an STD repeater and why. Patients who receive ineffective therapy are not only prone to remain infected, but also to transmit infection. Some may have a temporary remission of disease, and then subsequently be recorded as having a separate, repeat infection. In any event, as the focus of this study is individuals who contribute disproportionately to STD incidence, individuals who have longer periods of infectiousness due to inadequate treatment should be taken into account. In order to measure the effects of inadequate therapy, two variables defined the number of times a patient received ineffective treatment for gonorrhea

and for chlamydia. The algorithm depended on the complications of infection which the patient had, (for example, disseminated gonorrhoea), and on which drug had been prescribed. If patients had both gonorrhoea and chlamydia, both variables would contain information on adequate treatment.

In making the decision on effective treatment, it was assumed that all drugs had been prescribed at the correct dosage. Of course, there was no assurance of compliance. All drugs recommended for gonorrhoea of all sites and chlamydia in the following publications were defined as adequate treatment. The treatments recommended by Manitoba Health for uncomplicated gonorrhoea were; Ampicillin, (3.5 mg orally), or Aqueous Procaine Penicillin (4.8 million unit IM) and Probenecid (1.0 mg orally) and Tetracycline (500 mg orally Q.I.D. for seven days).¹⁶⁹ The recommended treatments for chlamydia during 1990 to 1992 were Tetracycline (500 mg orally Q.I.D. for seven days), Doxycycline (100 mg orally B.I.D. for seven days) or Erythromycin (500 mg orally Q.I.D. for seven days.) If the drug prescribed was not recommended in any of the following publications, Dr. Robert Brunham judged whether it would have been effective or not.

1. 1989 Sexually transmitted diseases treatment guidelines.¹⁷⁰
2. 1988 Canadian guidelines for the treatment of sexually transmitted diseases in neonates, children adolescents and adults.¹⁷¹

3. Canadian guidelines for the prevention, diagnosis, management and treatment of sexually transmitted diseases in neonates, children and adults.⁵
4. 1989 Canadian guidelines for the diagnosis and management of sexually transmitted diseases by syndrome in children, adolescents and adults.¹⁶⁷
5. 1993 Sexually transmitted diseases treatment guidelines.¹⁷²
6. Sexually transmitted disease control guidelines, (Manitoba Health) ¹⁶⁹

As shown later in Chapters 4 and 5, most of the treatment for chlamydia classified as ineffective was penicillin or derivatives thereof, and for gonorrhea, erythromycin and tetracycline. The variables indicating ineffective treatment for gonorrhea and chlamydia were coded as "0" for treatment which was adequate for less than 66.7% of disease episodes, and "1" for those that were inappropriate for more than 66.7% of all episodes. The coding of this variable is not split 50%- 50% because this coding did not take into account the natural peaks of the histogram of the percentages of episodes inappropriately treated. The comparison group with only one episode was coded "0" or "1" depending on whether that one episode was treated adequately or not. Episodes which had no treatment recorded, were coded as appropriate treatment, under the assumption that the correct treatment had been given, but had not been documented. While this may be unlikely, it was decided to afford health care providers the benefit of the doubt, in the absence of any report to CDC.

3.4.11 Income quintile

Income data from Statistics Canada was available for the enumeration areas where people with laboratory-confirmed infection and contacts lived. The data was gathered for each enumeration area, which can be linked to the postal code of each record. The average household income was attached to each individual's record, as well as the urban rural indicator. Urban residence was indicated by the value "1" and rural by a "0". Income quintiles were developed using the average household incomes and population statistics for all enumeration areas in Manitoba. The enumeration areas containing one fifth of the population earning an income of under \$29,572 in the province were assigned an income quintile of "1"; the next highest earning under \$35,870 but \$29,572 over were assigned a quintile of "2" and so on. (This method was adapted from that of Dr. Cam Mustard, Manitoba Centre for Health Policy, University of Manitoba.) The postal code conversion file was linked with the income quintiles and urban/rural indicators were attached to each individual record containing a postal code. The following table shows the population of Manitoba from the 1991 census divided into fifths and the income levels associated with the quintile. The absolute values of the income were not used as these tend to vary widely in rural enumeration areas of the province. (Dr. C. Mustard, "Units of observation and measurement of socio-economic status", unpublished, Manitoba Centre for Health Policy and Evaluation, 1991.) By categorizing the data, these variations are minimized, without losing the sensitivity of the measure of average household income.

Table 3.1 Income quintile divisions in Manitoba, 1991 data

Population	Population(cum.)	Income cutoff
Quintile 1	203,290	\$29,572
Quintile 2	406,580	\$35,870
Quintile 3	609,870	\$44,027
Quintile 4	813,160	\$52,992
Quintile 5	1,016,450	\$145,515

Other variables present in the database which may have been valid descriptors of STD were the sexual orientation of the patients and their marital status. However, after records had been constructed for each individual, these proved to be of little importance as over 90% were recorded as single, and heterosexual.

3.5 Phase III Contact tracing data of case repeaters, contact repeaters and comparison groups.

An important part of this work is to attempt to describe numbers of sex partners and sexual interrelationships which may define core group members.

3.5.1 Numbers of sexual partners

In order to compare differences in numbers of sex partners between case repeaters and cases with only one infection in the study period, random samples of the repeater cases and comparison cases were drawn. An initial feasibility study was completed in order to estimate the sample sizes. In order to assess the sample sizes needed to demonstrate

differences in numbers of partners, all contacts who had been named once in the total sampling frame database, and those named repeatedly, were sorted alphabetically by last name and first name. The first 41 of the comparison group and the first 48 of the repeatedly named group were selected.

The program Rsample in Epi Info, version 6.01 (Centers for Disease Control, Atlanta, Georgia) was used to generate the random samples of approximately 60 individuals in each sample. Random samples were drawn from the contacts who had been repeatedly named, and from those who had been named only once. The samples were stratified by disease category only. At this point, contacts who were named as contacts of a case with chlamydia, then with gonorrhea on separate occasions (serially coinfecting), were evaluated. Their characteristics did not differ from those who were named repeatedly by coinfecting individuals by univariate analysis. Therefore, there were only three disease categories; those named repeatedly as contacts of cases with chlamydia, of cases with gonorrhea, and of cases with coinfection. Samples selected from each disease category of the individuals with repeated laboratory-confirmed infections and the comparison group of those infected only once, resulted in a total sample of cases of 382.

3.5.2 Construction of sexual networks

The feasibility of constructing sexual networks was unknown. In order to construct a network for each individual, the identification number of the case was used to extract the contacts named by the case from the contact database. If any contacts were named more

than once, then their names were searched for the identification number of laboratory-confirmed case who named them. In addition, the name of each contact was searched for in the STD registry file, to determine if that contact had become a case. If the records were determined to belong to same person, then the sex partners named by that individual were also recorded in the network. This process was repeated until no more new repeat contacts or repeat cases with named contacts could be found.

3.6 Conclusions

This chapter describes how the STD registry data, the contact data and the Statistics Canada data were redesigned for analysis, and the justification for such changes. Because these data were not intended for use in this kind of research, a substantial amount of data cleaning was necessary. With very minor changes to the databases, and some routine checks on the accuracy of data entry, useful data such as the number of patients with symptoms, the number of patients treated with the correct drugs, and the total number of contacts per case, can be easily extracted from these data.

It is important to note that this type of research, particularly on the sex partners who were not confirmed as having infection, can contribute much to our knowledge of chlamydia and gonorrhoea transmission. Despite this, research on repeaters and on sex partners has been rare, due to the lack of easily accessible data. The forethought and planning of the staff at Manitoba Health who developed these databases is to be admired, not only for the value of

these data for research, but for their use in the management of STD patients and their sex partners.

Chapter 4

Chlamydia cases and contacts: results and discussion

4.1 Introduction

Those individuals with repeated infections with chlamydia in three years and those who have been named multiple times as sexual contacts of chlamydia are the proposed core group members. The following analyses will describe the repeater group in as much detail as possible, using all available data. Not only will the analyses distinguish those with repeat episodes from those individuals with only one infection, but may also provide insight into sociological and psychological risk factors for repeated chlamydia infection which underlie demographic and economic conditions.

These analyses will also explore differences between proposed core groups for chlamydia, gonorrhea and coinfection. STD clients who have multiple infections with both gonorrhea and chlamydia are probably responsible for transmitting chlamydia along with gonorrhea. If all gonorrhea core group members are core group members for chlamydia, then statistical analysis will show no differences between the two groups. Likewise, if chlamydia core group members are different from core group members with gonorrhea or

with coinfection, then this indicates the existence of a measurably distinct core group for chlamydia only.

4.2 Comparison of chlamydia repeater cases and comparison group

On univariate analysis, chlamydia repeater cases were more likely to reside in rural areas of less than 400 people per km² (Table 4.1.) However, this variable was not retained in the multivariate analysis as it was correlated with having treaty status (Table 4.2)

Table 4.1 Univariate analysis of chlamydia repeat cases (n=1,956) and comparison group with only one infection (n=1,879)

	Comparison		Repeaters		p value
	% or mean	n	% or mean	n	
Age	22.7	1,879	21.5	1,956	<0.001
Urban	78.2	1,247	69.0	1,141	<0.001
Treaty status	16.7	313	36.0	704	<0.001
Used alias	13.9	262	23.8	465	<0.001
Inappropriate therapy	26.0	489	35.6	680	<0.001
Female	80.9	1,519	81.1	1,586	n.s.
Symptoms noted	53.4	1,004	58.5	1,145	0.002

	Comparison		Repeaters		p value
	% or mean	n	% or mean	n	
Income					
Quintile 1					
<\$29,572	35.6	558	51.1	818	
Quintile 2	20.5	321	15.8	253	
Quintile 3	17.8	280	15.5	248	
Quintile 4	14.3	224	9.8	157	
Quintile 5	11.9	186	7.8	124	<0.001
Number of named partners					
1	73.6	1,229	73.6	1,244	
2	20.1	336	21.5	364	
3-4	5.2	86	4.5	76	
>4	1.1	18	0.4	7	n.s.

Chlamydia repeaters were as likely to be female as those individuals who infected only once (Table 4.1). This partly reflects the nature of the chlamydia screening program in Manitoba, and the high proportion of asymptomatic infections in women. Approximately 60,000 women per year are tested, with the overwhelming majority being screened at routine physical examinations. The chances of discovering chlamydia infections in these women and those with repeated infections may therefore be a function of being screened. These results may also indicate under diagnosis of repeat infections in men; due to poor

test sensitivity,⁸ reluctance on the part of physicians to take a urethral swab,³⁷ and reluctance on the part of the patient to undergo the process. Also, in the presence of symptoms, or knowing that the patient has been exposed, physicians may treat them without testing. This result differs from that found in the work of Orr et al also from Manitoba, but the populations studied are not similar. Their study population included patients with gonorrhea in addition to chlamydia, whereas the population in the above analysis had only chlamydia.⁷⁸

Individuals with repeated chlamydial infections did not name significantly more partners per episode than those with only one infection. This may be the result of a number of factors. The first of these is that public health nurses and physicians, who interview patients to elicit the names of their partners, may not persist in requesting more names after the client has already named one partner. As women (who comprise 80% of chlamydia repeaters) may have been diagnosed on screening, infections may have taken place months before. In the absence of symptoms, public health nurses enquire about partners for a three month time period before a positive test. This time period may be too short to include more than a current partner in most cases. Last, it should be noted that the number of partners named may not reflect the total number of partners which the client had. For this reason, Phase III of the current project was designed to evaluate the number of partners named by the case and also those who named the case, hence using partner information from two sources. Although this method may not yield all partners of the case, it will give more accurate information on numbers of partners than using only those

data given by the case. This result agrees with findings in the literature where the number of partners of repeater patients has not been significantly different from those patients with only one disease episode.^{125,132,156,173} In one study, female adolescents with only one partner were at higher risk of repeat chlamydial infection in the first year of the longitudinal study than were patients with only one infection.¹⁵⁶ This was due to poor follow up and treatment of sex partners of the patients,^{125,156} which led to reinfection of the young women.

Table 4.2 Logistic regression comparing chlamydia repeat cases (n=1,956) and comparison group with only one infection (n=1,879)

Variables	Odds ratio	Lower 95% C.I.	Upper 95% C.I.	p value
Intercept	8.24			<0.001
Treaty status	2.42	2.06	2.83	<0.001
Used alias	1.66	1.39	1.97	<0.001
Treated	1.44	1.25	1.67	<0.001
inappropriately Symptoms	1.25	1.10	1.43	0.001
noted				
Log Age	0.39	0.29	0.54	<0.001
Income quintile				
Quintile 1	1.60	1.31	1.95	<0.001
<\$29,572				
Quintile 2	1.14	0.93	1.39	0.20
Quintile 3	1.14	0.90	1.44	0.29

Both univariate and multivariate analyses of these data indicate that an individual being registered as eligible for benefits under the treaties with First Nations people has a risk of being a chlamydia repeater which is more than double that of an individual who does not have treaty status. This increase in risk, once all other factors including age and income level are accounted for, should not be interpreted as being directly related to membership in the North American Indian racial group. A more complex and more realistic interpretation includes differences in sexual behaviour, whether it be numbers of partners; selection of partners, frequency of intercourse, differences in health care seeking behaviors, differences in the behavior of health care providers, or most likely, a combination of all the above. Previous work has shown that people with treaty status are more likely to receive a specific diagnosis of STD rather than a non-specific diagnosis such as cervicitis, on medical claims records which physicians use for billing the health care insurance plan in Manitoba.¹⁷⁴ Therefore part of the increase in risk of aboriginal people may reflect the reluctance on the part of health care providers to label non-aboriginals with the diagnosis of STD, and reluctance to order appropriate tests. This difference in health provider behavior lends credence to the inference that some of the First Nations' increased risk in this area may be attributed to poor interactions between First Nations providers and patients, which may have a negative effect on the relationship between provider and patient. Language differences leading to problems in communication may also play a role in increased risk for aboriginal people. Lastly, the fact that care is delivered to many First Nations people through the nursing stations, where

diagnostic and reporting procedures are more rigorous than in a private medical clinic, also influences rates of reported disease.

Increased risk of repeated sexually transmitted infections in ethnic minorities has been recorded in Alaska, although only in the incidence of recurrent gonorrhea.^{79.123} African Americans have also been noted as having increased risk on univariate analysis,^{125.156} and also on multivariate analysis.^{47.131} First Nations people in Manitoba formed a higher proportion of repeaters than did other Manitobans in a study completed two years ago.⁷⁸ However, the analyses of repeated chlamydia in ethnic minorities in Canada and in the United States were not accompanied by any measures of education or economic status, which usually are collinear with ethnic status; hence one cannot conclude that rates of repeated chlamydia were associated exclusively with ethnic status and not with socioeconomic status. While this particular analysis does not provide any data on possible differences in sexual behavior and ethnic groups, other research suggests that higher disease rates should not be automatically ascribed to sexual behavior differences in ethnic minorities. Historically high prevalence rates of this disease which were never reduced to levels of the non-aboriginal population affect the epidemiology of STD in minority populations.¹⁷⁵ This was shown in a study of women in Tennessee.¹³⁷ Sexual behavior for Black and White women were described as similar. However, the prevalence of infection in Black women was 36.7% when compared with that of 27.1% in White women. The likely reason for higher rates in Black women was that their chances of having sex with an infected Black man were higher. This illustrates the point that using only the numbers of

partners can lead to incorrect assumptions of disease risk, and that mixing matrices may also be inadequate to describe a pattern which relies on race and not on sexual activity class.

Use of an alias was associated with being a chlamydia repeater compared with those individuals with only one infection over the three year period on both univariate and multivariate analyses. The use of an alias has been noted in other research as a complicating factor in identification, notification and follow-up of sex partners and index cases.¹⁴³ Use of an alias may also be an indicator of illicit activity involving prostitution, gang activity and/or illegal drugs. Apart from the obvious risks of repeated STD in selling sex, these illicit activities in themselves reflect higher thresholds of acceptable risk of individuals, and have been associated with STD core groups in other studies, however defined, and of increased rates of STD.⁶⁶ Not only may use of an alias reflect involvement of an individual in illegal activities, but also may indicate sexual contact with other individuals who also have deviant behavior, forming a sexual network in which individuals are at high risks of STD.

Individuals who were recorded in the Manitoba STD registry as having received inappropriate treatment for chlamydia were at significantly higher risk of having a repeated chlamydia episode than those who received correct treatment for the disease. Once other variables are held constant in the logistic equation, people who were recorded as having

inappropriate treatment for chlamydia were 44% more likely to have a repeated chlamydia episode in the three year study period.

Because chlamydia is a disease notifiable to the Ministry of Health under the Public Health Act and regulations, a legal responsibility is conferred on the province to ensure that the individual receives adequate care, and the public health is protected. Inadequate therapy for chlamydia is serious, but mechanisms to detect it and alert physicians can be easily be developed. The following table represents disease events of all individuals with repeated chlamydia, and may include individuals later eliminated from present analytical study, hence the totals will not balance with the study results presented above.

Table 4.3 Recorded treatment of disease episodes of chlamydia repeaters, 1990 - 1992, Manitoba STD registry.

Therapy	Urethral/			Total
	Cervical	**Epididymitis	PID	
No treatment recorded	107		4	111
* Ceftriaxone	7			7
Ceftriaxone + tetracycline	69	1	6	76
Ceftriaxone+ erythromycin	61		1	62
* Ceftriaxone+ proamp	1		2	3
Ceftriaxone + doxycycline	67		2	69
Ceftriaxone + other	1			1
Tetracycline	201		4	205
Tetracycline + erythromycin	308		2	310
Tetracycline + proamp	205		5	210
Tetracycline + spectinomycin	1			1
Tetracycline + doxycycline	4			4
Tetracycline + cefixime	76		4	80
Tetracycline + ofloxacin	3			3
Tetracycline + APPG	2			2
Tetracycline + Other	1			1
Erythromycin	762		10	772
Erythromycin + proamp	33			33
Erythromycin + spectinomycin	31		1	32
Erythromycin + TMP/SMX	3			3
Erythromycin + doxycycline	4			4
Erythromycin + cefixime	10		6	16
Erythromycin + ofloxacin	22		1	23
Erythromycin + APPG	1			1
*Proamp	573		5	578
*Proamp + spectinomycin	28			28
Proamp + TMP/SMX	4			4
Proamp + doxycycline	4			4
*Proamp + cefixime	9			9
Proamp + ofloxacin	6			6

Therapy	Urethral/			
	Cervical	**Epididymitis	PID	Total
*Spectinomycin	3			3
*Spectinomycin + Cefixime	10		1	11
Spectinomycin + Ofloxacin	1			1
*Bicillin	1			1
TMP/SMX	2			2
TMP/SMX + doxycycline	1			1
TMP/SMX + cefixime	0			0
Doxycycline	147			147
Doxycycline + cefixime	1			1
Doxycycline + APPG	4			4
Doxycycline + other	1			1
Ciprofloxacin	1			1
*Cefixime	265	1	15	281
*Cefixime + Ceftriaxone	2			2
Cefixime+ ofloxacin	15		4	19
Ofloxacin	3			3
I.V. Clindamycin, gentamycin and penicillin			1	1
TOTAL	3061	2	74	3137

* Asterisks indicate inappropriate therapy for chlamydia

** Epididymitis cases also included as urethral cases.

The highest proportions of recorded therapies deemed inappropriate were Proamp alone and cefixime alone, with the others being combinations of these. The therapies prescribed were entered in to the computer from each STD notification form, required under the regulations of the Public Health Act. If one of these forms was not filed, staff at Communicable Disease Control, Public Health Branch would request it of the health care

provider after receiving the laboratory report confirming the patient is infected. It is possible this analysis overestimates the amount of incorrect therapy, as amendments to treatment regimens after the forms had been filed may not have been forwarded to Manitoba Health.

A Canadian study on treatment received for sexually transmitted diseases revealed that only 5.5% of patients were inadequately treated, although “inadequate” treatment included incorrect dosages, whereas we assumed that all prescriptions were filled for the correct dosage.¹⁷⁶ Also, the physicians who were selected for the study were all between 30 and 40 years old, and were chosen because they may be more familiar with current practices than older physicians. This selection would therefore overestimate the proportion of adequate therapy given for STD by the general physician population. The high proportion of individuals recorded as receiving inadequate therapy in this study (29.4%) indicates irregularities in the prescription of drugs for chlamydia. In addition, the finding that a higher risk of repeat infections is associated with inappropriate therapy, indicates that further investigation into causes for inappropriate prescription and validation of prescription data is essential.

The fact that some of the repeater population may have repeat infections due to inadequate therapy affects the interpretation of possible core group characteristics. If one accepts that a core group is a group of people where the reproductive rate of infection is greater than one, then it is immaterial whether the predisposing behavior is that of the core

group member or of his or her health care provider. (Thesis committee meeting, October 1996.) Inappropriate therapy leads to longer periods of infectiousness which results in higher transmission rates, which in turn facilitates core group propagation of infection. If a core group lies within the chlamydia repeater group, we may be able to lower rates in the general population considerably, merely by ensuring that therapy for this group is consistent with that currently recommended. This study is unique in including the effect of therapy on possible core group membership.

Once all other variables were controlled for, individuals with repeated chlamydia infections were 25% more likely to have symptoms noted on any of the reports of disease episodes compared with those individuals who had only one episode in the study period. Increased reporting of symptoms may be due to a number of reasons. First, it is possible that health providers were more assiduous in completing notifiable disease forms on repeater cases than they were on single cases. Second, it is also possible that repeater cases were more likely to recognise symptoms as they had previous disease episodes than clients with only one infection. Last, the increase in reporting of symptoms may be part of a pathophysiological response to repeated infections with chlamydia, either with the same serovar or a different one. A higher proportion of women reporting symptoms has been associated with repeated infection on univariate, but not on multivariate analysis.¹³² Increased rates of sequelae have been noted in women with recurrent episodes of chlamydia,⁴⁷ which may indicate that repeated assaults on the immune system may

stimulate a more severe response as the organism causes more disruption in tissue which has already been damaged.

The difference in mean ages of the repeater and non-repeater group is only 1.2 years, which although statistically significant, is of unknown clinical or epidemiological significance.

The use of the natural log of age to normalize the variable in the logistic regression complicates the interpretation of the risk associated with this variable. Therefore, I have converted values back to the original ages. Figure 4.1 shows the probabilities of being a repeater for selected five year age groups, once all other variables in the equation are held constant at zero. The probability of having repeated chlamydia declines from 39.5% at age 15 to 18.9% at age 45. Another way to interpret the probabilities is to convert them to odds ratios. Thus, an individual aged 15 had increased odds of being a repeater of 1.26 (26% higher), when compared with that of the study mean of 22 years.

It is interesting to note that the repeaters were slightly younger than those individuals with only one infection. Because the ages of the repeater group were calculated at the first repeat episode, which was the second disease episode, it seems that sexual activity would have to begin early in life for a client to acquire chlamydia, and further, to have repeat episodes by age 16, for example. This corroborates the results of other studies which identify young age at first intercourse as a risk factor for repeated episodes of

chlamydia.^{78,128,132} The decrease in risk over the lifetime indicates that sexual activity likely to result in a STD is age dependent. While sexual behavior surveys have shown this pattern of sexual activity in the general population, it is interesting that the pattern of risky sexual activity in youth is maintained in possible core group members, and that increased “opportunities” to become repeatedly infected do not increase with age. The other factor contributing to the increased risk of younger clients is that of absence of immunity. *Chlamydia trachomatis* infection spontaneously resolved in a small proportion of untreated patients reported by Parks et al. Spontaneous resolution was significantly associated with older age, suggesting a host immune response in some patients.¹⁷⁷

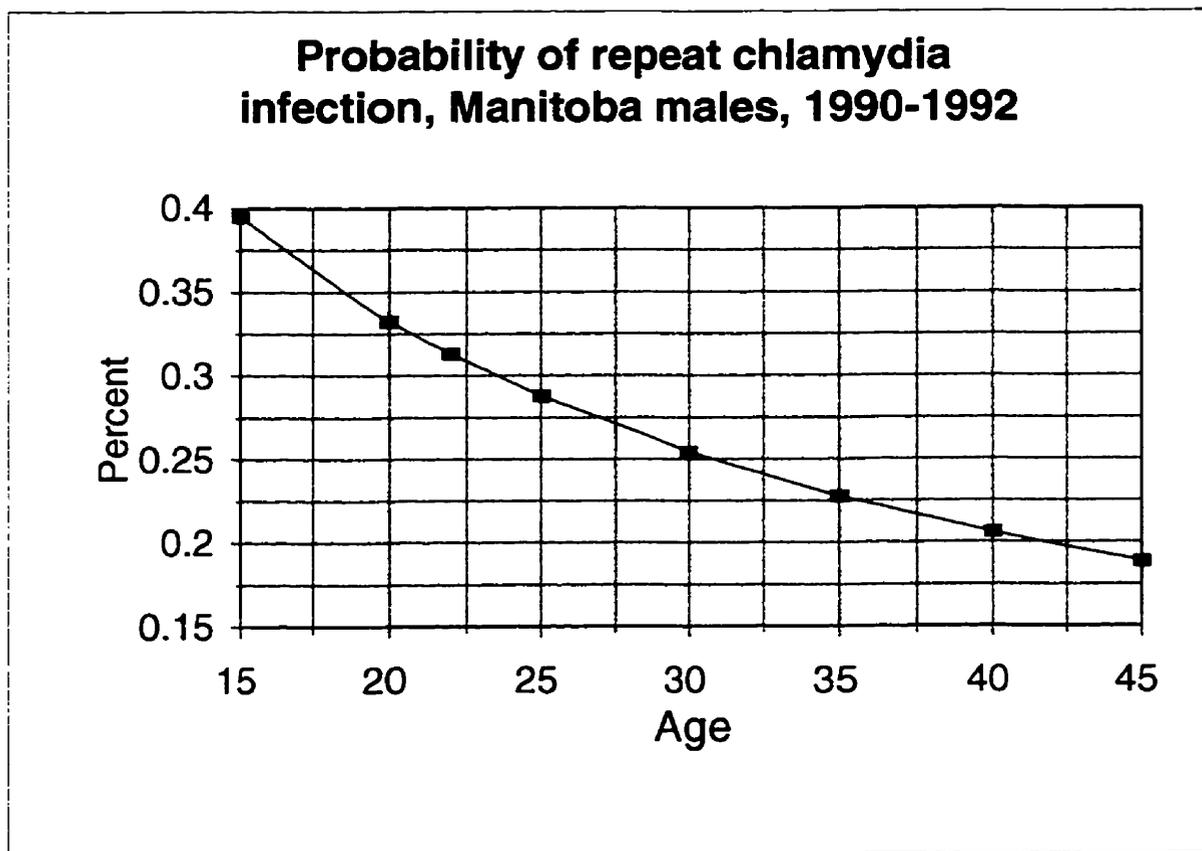


Figure 4.1 Probabilities of repeated chlamydia infection by age, for a non treaty male with no symptoms who has been treated appropriately, does not use an alias and lives in an area in which the average household income is greater than \$52,992.

On both univariate and multivariate analysis, income levels were found to be significantly different for chlamydia repeaters compared to those people with only one chlamydia infection. A higher proportion of repeaters had household income levels of less than \$29,000, when compared with non-repeaters. Household income in dollars was not a normally distributed variable. Therefore the variable was converted to a categorical variable of income quintiles (see Chapter 3, section 3.4.11.) The logistic regression analysis reveals an increased odds of 1.6 associated with repeated chlamydia of individuals in the first income quintile when compared with the reference categories, quintiles four and five. Although no other research has measured socioeconomic status and its possible association with repeated STD, studies on other proposed core groups also show high incidence rates of infections in individuals in areas with lower incomes.^{36,64-66,84,178}

4.3 Introduction: contacts of chlamydia infection

Analysis of available information on the sex partners of individuals with confirmed chlamydia gonorrhea, and coinfection is essential in attempting to describe potential core group populations, (see Chapter 2, Section 2.2.2.)¹²⁸ While we lack proof of laboratory-confirmed STD in many of these people, this may be due to reasons entirely unrelated to the actual spread of disease in the population. Schacter et al have described the effects of testing and test methods on the epidemiology of the disease;¹⁷⁹ it is important not to fall

into the trap of allowing test phenomena or idiosyncrasies of the public health system to dictate the epidemiology of the disease, especially when the basic biology of STD transmission is well known. Many factors may interfere with obtaining laboratory confirmation of infection in sex partners. There is a reluctance to perform urethral swabs in males,³⁷ and males resist having them. There is also a tendency to treat epidemiologically without testing, which reduces the likelihood of compliance with treatment, particularly if there are no symptoms.³⁸ Many urethral swabs are taken incorrectly,^{5,37} which increases the false negative rate, which in turn also affects treatment compliance. Lastly, sex partners of individuals with chlamydia are not pursued as thoroughly as they are for gonorrhea,¹⁸⁰ and health care providers tend to rely on the index case to notify his or her own partners. Because most cases are women, this places the burden on them to notify their partners, which may not occur. We cannot afford to ignore the role of undiagnosed contacts of cases in disease transmission merely because we are unable to establish proof of infection in these individuals.

Sex partners of laboratory-confirmed cases of chlamydia are probably far more important in terms of maintaining endemic disease than are contacts of gonorrhea cases. Females are diagnosed, either by screening or diagnostic testing, and because of the under diagnosis in men, women form two thirds of confirmed cases.²¹ In addition, a higher proportion of men with chlamydial infection are asymptomatic than those with gonococcal infection, therefore detracting from the motivation to be tested.

The following section describes the univariate and multivariate comparisons between multiply named contacts of chlamydia with those named only once during the study period, which established whether multiply named contacts are a definable group, distinct from those named only once. In addition, differences between multiply named contacts of confirmed chlamydia, gonorrhoea and coinfection were assessed, which would indicate whether the potential core groups are similar or not. Lastly, repeater contacts were compared with repeater cases, in order to determine whether the repeater populations for chlamydia, gonorrhoea and coinfection were similar.

4.4 Comparison of chlamydia repeat contacts and comparison group

There was less information recorded on sex partners on the computerized contact registry at Manitoba Health than there was on cases. Table 4.4 shows the results of the univariate analysis of contacts of cases of chlamydia named more than once during the period 1990 through 1992, and those named only once in that time.

As with laboratory proven chlamydia repeater cases and non-repeater cases, the mean age of the contact repeaters was lower than those who were named only once. This difference was significant both on univariate and multivariate analysis, (Table 4.5.) The actual ages for the contacts are generally higher as most contacts are men, who tend to choose partners (cases) younger than themselves. Figure 4.2 shows the decreasing probabilities of being multiply named as a chlamydia contact of selected five year age groups. The odds

of a fifteen year old being named repeatedly as a contact of a chlamydia case was 1.38 times that of a 27 year old.

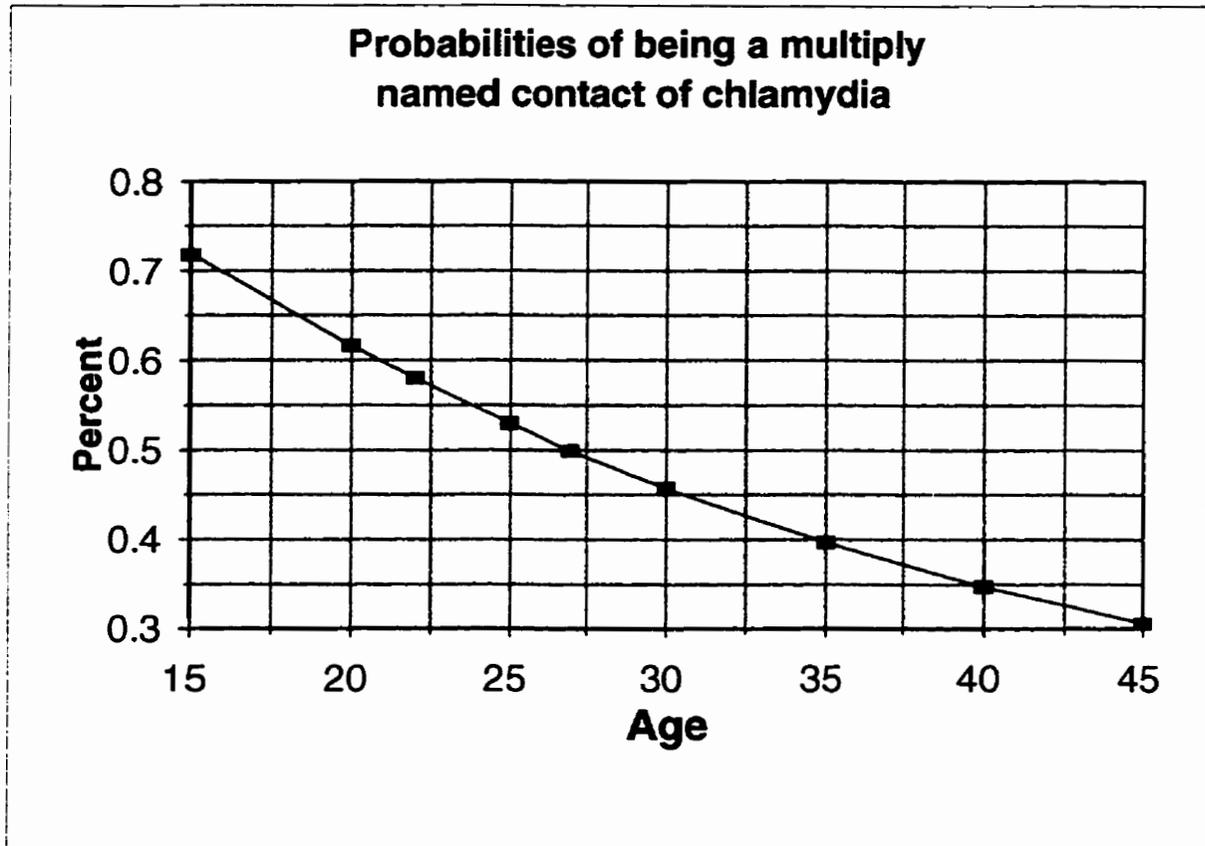


Figure 4.2 Probabilities of being a multiply named contact of chlamydia infection by age, for a non-aboriginal male who lives in an areas in which the average household income is greater than \$52,992

Although rural residence was associated with being named repeatedly as a contact of a chlamydia case on univariate analysis, it did not add significantly to the explanatory power of the multivariate model.

Table 4.4 Univariate analysis of chlamydia repeat contacts (n=761) and comparison group with only one infection (n=1,174)

	Comparison		Repeaters		p value
	% or mean	n	% or mean	n	
Age	23.7	1,056	22.6	750	<0.001
Urban	72.9	742	65.5	545	0.005
Treaty status	14.0	1,174	26.1	789	<0.001
Female	14.6	1,174	12.1	761	n.s.
Income level					
Quintile 1					
<\$29,572	37.0	264	50.5	266	
Quintile 2	22.3	159	16.7	88	
Quintile 3	16.4	117	18.0	95	
Quintile 4	13.4	96	8.5	45	
Quintile 5	10.9	78	6.3	33	<0.001

Being registered as a treaty Indian was associated with an 80% additional risk of being named as a contact repeater over all other individuals. This resembles the situation of the chlamydia cases, where treaty status also bore a significant additional risk. Possible reasons for this increased risk are the same as for cases, i.e., that disease prevalence and incidence are truly higher in aboriginal peoples, and that interactions with health providers may lead to more complete documentation of disease episodes and partner information. It is also possible that aboriginal people may be more willing to provide information on sex partners than non-aboriginals to health providers. The only research involving ethnic

minorities and sex partner was done in the 1980's and showed that Black males formed the majority of contacts named by women with gonorrhea in Colorado Springs.¹⁸¹

Table 4.5. Logistic regression comparing chlamydia repeat contacts (n=761) and comparison group named only once (n=1,174)

	Odds ratio	Lower 95% C.I.	Upper 95% C.I.	p value
Intercept	6.11			0.01
Treaty status	1.80	1.42	2.30	<0.001
Log Age	0.43	0.28	0.68	<0.001
Income level				
Quintile 1				
<\$29,572	1.96	1.41	2.73	<0.001
Quintile 2	1.16	0.85	1.58	0.35
Quintile 3	1.61	1.09	2.38	0.02

Having an income level in the first and third quintiles was significantly associated with an increased risk of being named repeatedly as a contact of chlamydia, compared with individuals who were only named once. Risks were 96% higher and 61% higher respectively, than those individuals in the fourth and fifth quintiles who had household incomes of more than \$52,992. The association of higher risk with lowest income quintile is similar to that of chlamydia case repeaters. The risk associated with the third income quintile is not an artifact of the substitution of normally distributed income levels, determined by multivariate predictions for missing data; all of the values of income quintile three exist in the original data. The increased risk associated with the third income quintile suggests that men who have relatively high income levels are repeatedly

named more often as contacts of chlamydia cases than those named only once. This supports other evidence that chlamydia is more of a “middle class” STD than gonorrhea is, and that the multiply named males are the reservoir of the infection.¹⁸² Ramstedt found similar evidence that higher income asymptomatic males form a reservoir of chlamydial infection.¹⁸ She also found that another group of male partners with lower incomes also existed, and were named by lower income women who were more dependent on social welfare.

4.5 Comparison of chlamydia, gonorrhea, and coinfecting repeaters.

This section addresses the hypothesis that if the populations of individuals with repeated confirmed chlamydial infections forms a core group for chlamydia only, this group may differ from the core group responsible for maintaining gonorrhea or from that responsible for propagating both infections simultaneously.

4.5.1 Comparison of coinfecting repeat cases with chlamydia repeater cases.

In order to assess whether a core group for chlamydia exists within the repeater population and whether it is the same as that of the coinfecting repeater population, the two populations were compared (Table 4.6).

As with the analysis of chlamydia repeaters and non-repeaters, the large numbers allowed for small differences between the populations to be detected. The mean ages showed a

difference of just 1.4 years, which is clinically irrelevant, but which was statistically significant on univariate, and multivariate analysis (Table 4.7). The difference in age, though small, does show a gradient of increasing youth, from gonorrhoea repeaters, (mean age 24), chlamydia repeaters (21.5), with coinfecting repeaters having the lowest mean age. This suggests that the younger the individual, the higher the risk factors for coinfection, which must include sufficient numbers of partners to encounter two infections, high susceptibility to infection, and probably more efficient transmission.

Table 4.6 Univariate analysis of coinfecting repeat cases (n=471) and chlamydia repeat cases, (n=1,956)

	Chlamydia		Coinfecting		p value
	repeaters	n	repeaters	n	
	% or mean		% or mean		
Age	21.5	1,956	20.1	471	<0.001
Urban	69.0	1,141	68.2	274	n.s.
Treaty status	36.0	704	51.6	243	<0.001.
Used alias	23.8	465	34.0	160	<0.001
Inappropriate	35.6	680	19.0	89	<0.001
therapy (Ct)					
Female	81.1	1,586	71.5	337	<0.001
Symptoms	58.5	1,145	80.5	379	<0.001
noted					

	Chlamydia		Coinfected		p value
	repeaters	n	repeaters	n	
	% or mean		% or mean		
Income					
Quintile 1					
<\$29,572	51.1	818	65.0	249	
Quintile 2	15.8	253	10.2	39	
Quintile 3	15.5	248	12.3	47	
Quintile 4	9.8	157	6.8	26	
Quintile 5	7.8	124	5.7	22	<0.001
Number of					
named partners					
1	73.6	1,244	60.9	265	
2	21.5	364	31.5	137	
>3	4.5	83	6.0	33	<0.001

The probabilities of repeated coinfection for selected 5 year age groups are shown in Figure 4.3. Assuming all other variables are held constant at zero, the relative odds of a 15 year old being a coinfecting repeater is 2.89 - almost triple that of a 27 year old.

On multivariate analysis, being registered a status Indian was associated with a 73%

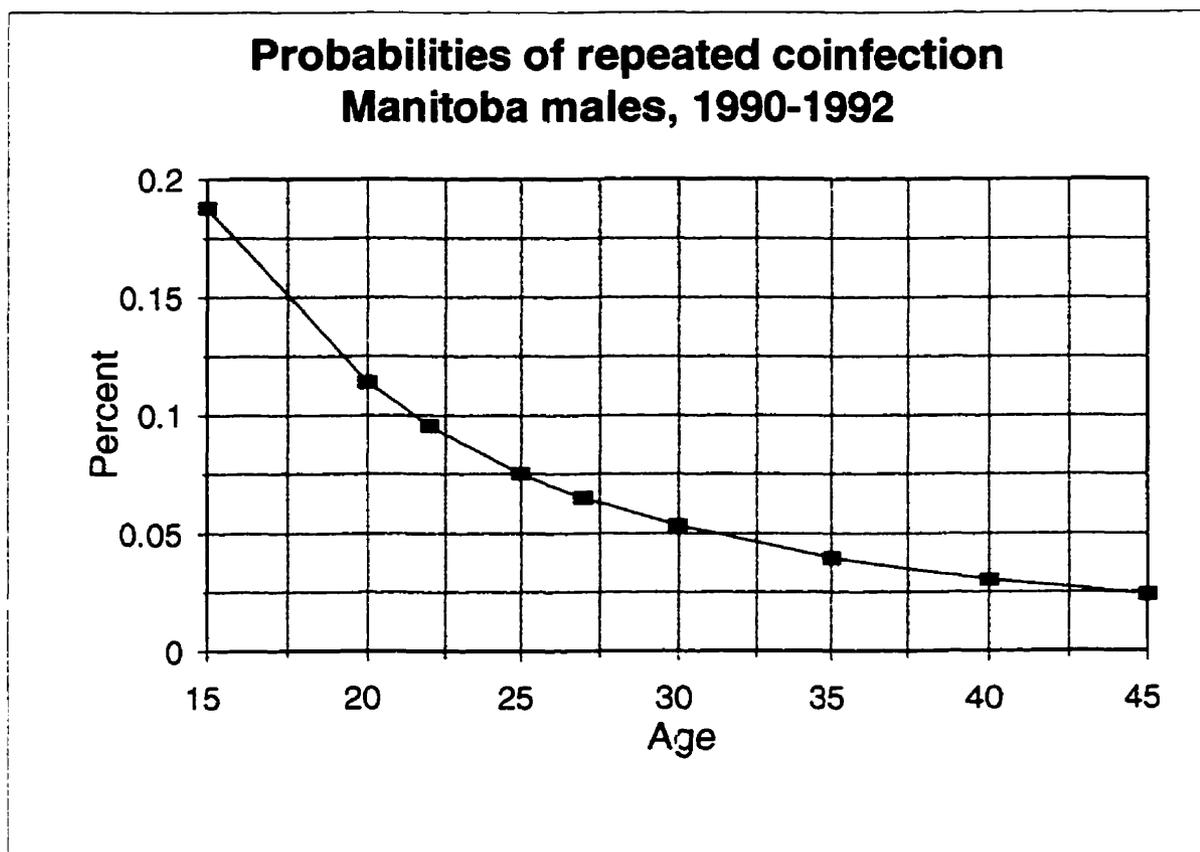


Figure 4.3 Probabilities of repeated coinfection, compared with repeated chlamydial infection by age, for non-aboriginal males, living in an area in which the average household income is \$44,027 who were treated appropriately for chlamydia, reporting no symptoms, and with one or no sex partners in the last three months.

higher risk of having repeated coinfections compared with having repeated chlamydial infections. This finding is consistent with a previous study in Manitoba, which found that people with repeated gonorrhoea, and concomitant infection with chlamydia were more likely to be aboriginal.⁷⁸

Table 4.7 Logistic regression comparing coinfectd repeat cases (n=471) and chlamydia repeater cases (n=1,956)

Variable	Odds ratio	Lower 95% C.I.	Upper 95% C.I.	p value
Intercept	58.55			<0.001
Treaty status	1.73	1.39	2.15	<0.001
Used alias	1.53	1.21	1.94	<0.001
Inappropriately treated (Ct)	0.43	0.33	0.56	<0.001
Female	0.59	0.45	0.76	<0.001
Symptoms noted	2.58	2.00	3.32	<0.001
Log Age	0.13	0.07	0.24	<0.001
Income level				
Quintile 1				
<29,572	1.46	1.02	2.10	0.04
Quintile 2	0.94	0.64	1.39	0.77
Quintiles 3,4,5	0.87	0.55	1.38	0.56
Two or more contacts named	1.61	1.28	2.04	<0.001

The use of an alias was associated with an increased risk of repeated coinfection when compared with repeated chlamydia infection. Those individuals with repeated chlamydia do not seem to use aliases as often as those with repeated coinfection (53% less).

The most interesting result of this analysis is the differences in proportions of coinfectd repeaters treated adequately for chlamydia when compared with individuals repeatedly

infected with chlamydia alone. Chlamydia repeaters were inappropriately treated for two thirds of their episodes 2.33 times more than were coinfecting repeaters. The high proportion of inappropriately treated chlamydia repeaters has already been described, (section 4.2), but the fact that coinfecting repeaters were given correct therapy more frequently indicates that the health care system treats them differently. First, gonorrhea is one of the oldest notifiable STD's and the one with the most symptoms. It is regarded as a higher priority for management than is chlamydia.¹⁸⁰ Public health nurses and physicians are more diligent in ensuring that patients are managed correctly, and sex partners are notified and tested. In arranging for testing, public health nurses are more careful to recommend clinics which are familiar with management of STD to the patient, hence they receive better care. In addition, because gonorrhea has been notifiable longer, physicians may be more familiar with its treatment. However one may interpret the difference, the implications are unavoidable. It is possible that once the management for repeated chlamydial infections is improved, the population who continue to have repeated chlamydial infections may be similar to the coinfecting repeaters, who, despite a high incidence of symptoms; better therapy, and concentrated attention from public health nurses, continue to have high risk sexual behavior and therefore acquire repeated infections.

Males were 1.79 times more likely to be coinfecting repeaters than they were to be chlamydia repeaters. This is probably due to the under diagnosis of chlamydia in men, mentioned above. The higher rates of symptoms in gonococcal disease in men also affect

this analysis, as those with suspected gonorrhea are more likely to be tested and treated for chlamydia. In addition, symptoms may motivate more patients to be tested than if symptoms are not present.

The presence of symptoms was two and a half times more likely to be noted on the STD notification form if the patient was repeatedly coinfectd, compared with being repeatedly infected with chlamydia only. This is due to the more symptomatic nature of gonococcal disease. However, it is also possible that infection with gonorrhea may cause the chlamydia infection to be more severe, or symptomatic. Third, it may also be due to the health care provider being more thorough in interviewing the patient and then completing the notification form, because the patient has two notifiable infections, not just one.

Living in a neighborhood with an average household income of less than \$29,572 was associated with an increased risk of 1.5 of repeated coinfections compared with repeated chlamydial infections. The logistic regression suggests that the two populations have significant social differences. The reasons for this may be that the group of repeaters with chlamydia only would be educated enough to be aware of symptoms if they had any and act on them, and would probably live in higher income neighborhoods.

Because so few individuals named more than three partners these were combined into one category of two or more partners named to avoid categorical outliers on multivariate analysis. A higher proportion of repeatedly coinfectd individuals named two or more sex

partners than individuals with repeated chlamydial infections, once all other factors are controlled. It is likely that physicians would be more likely to involve public health nurses in interviewing and following up patients when a patient is coinfectd than if they have chlamydia alone. Through experience and training, public health nurses are usually able to extract more complete information from clients than are physicians.^{183,184} It is also possible that both nurses and physicians may be more thorough in getting information from patients with two infections rather than only one. Finally, it is also likely that coinfectd repeaters do in fact have more partners than people with repeated chlamydia. This last explanation is consistent with the lack of appropriate treatment for a large proportion of chlamydia repeaters. Reinfection from the same partner or relapse of infection is probably a lot more common in inadequately treated chlamydia repeaters, while coinfectd repeaters become reinfected from new partners. It is important to note that this variable measures only the number of partners named by the case. However, patient interviews cannot all be completely accurate, and it is likely that many sex partners are not named, and analysis of these data should be considered as indicating differences in numbers of partners, and not as defining absolute numbers of partners.

4.5.2 Comparison of gonorrhea repeat cases with chlamydia repeater cases.

This section describes the differences found between the chlamydia and gonorrhea repeaters. Differences between coinfectd repeaters and chlamydia repeaters have been established, despite the fact that the groups had one disease in common. Therefore, it is not surprising that differences also exist between chlamydia and gonorrhea repeaters.

There was a significant difference in age of three years between gonorrhoea and chlamydia repeaters. Probabilities of being a chlamydia repeater decreased with age, compared with being a gonorrhoea repeater, which increased significantly with age ($p < 0.001$, Figure 4.4.) A forty-five year old has an increased odds of 1.53 of being a gonorrhoea repeater compared with a twenty-seven year old, assuming all other factors are held constant. These age differences may be attributed to increased susceptibility of younger people to chlamydia; partially effective immune responses to chlamydia increasing with age, and differences in the populations affected by the two diseases. The difference in age remained significant on multivariate analysis, (Table 4.9.)

Table 4.8 Univariate analysis of gonorrhoea repeat cases (n=565) and chlamydia repeat cases, (n=1,956)

	Gonorrhoea		Chlamydia		p value
	repeaters	n	repeaters	n	
	% or mean		% or mean		
Age	24.5	565	21.5	1,956	<0.001
Urban	67.4	481	69.0	1,141	n.s.
Treaty status	46.9	565	36.0	704	<0.001.
Used alias	22.7	565	23.8	465	n.s.
Inappropriate therapy (Ct)	34.6	565	35.6	680	0.007
Female	37.9	565	81.1	1,586	<0.001

	Gonorrhea		Chlamydia		p value
	repeaters	n	repeaters	n	
	% or mean		% or mean		
Symptoms noted	72.9	565	58.5	1,145	<0.001
Income Quintile 1					
<\$29,572	69.2	317	51.1	818	
Quintile 2	13.5	62	15.8	253	
Quintile 3	9.4	43	15.5	248	
Quintile 4	4.1	19	9.8	157	
Quintile 5	3.7	17	7.8	124	<0.001
Number of named partners					
1	66.8	324	73.6	1,244	
2	25.0	124	21.5	363	
>3	5.4	37	4.5	83	0.006

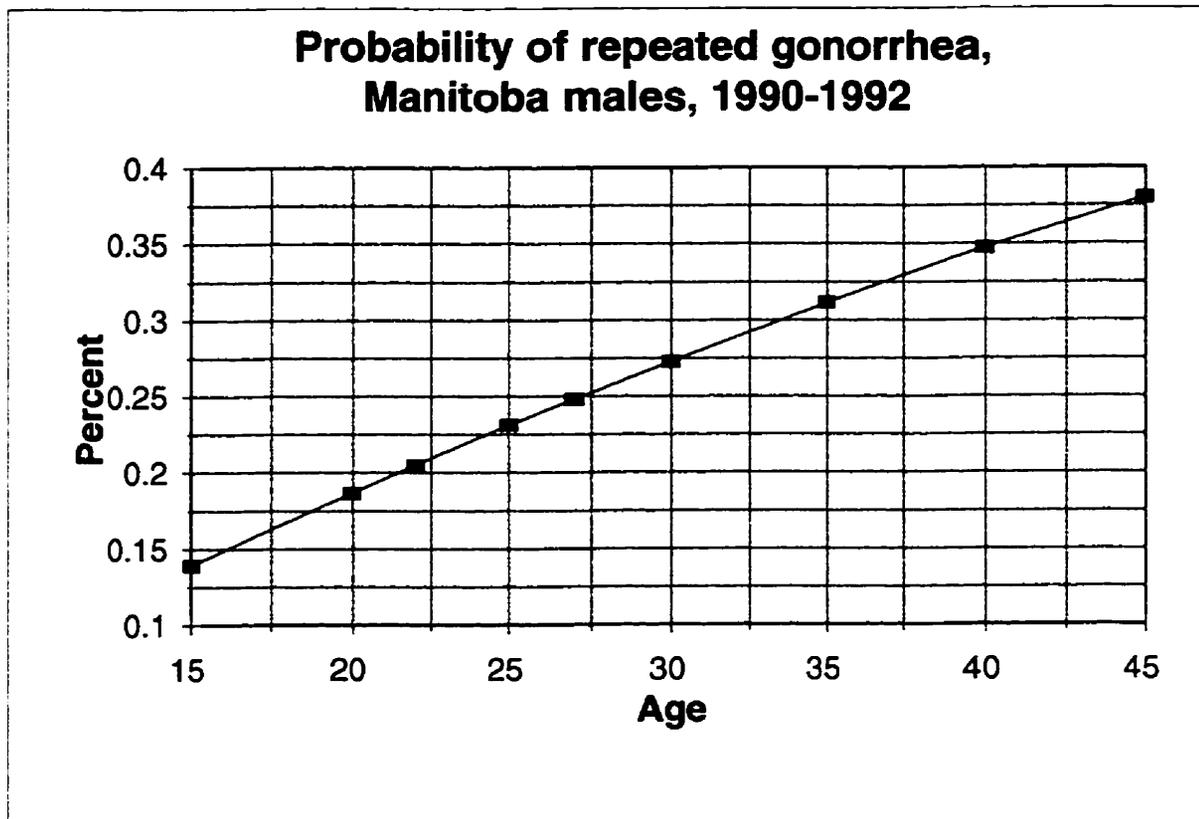


Figure 4.4 Probabilities of repeated gonorrhoea infection compared with repeated chlamydial infection, by age, for non-aboriginal males with no symptoms noted, one or no sex partners named and who live in an area with an average household income of greater than \$35,870.

Aboriginal people were 55% more likely to have repeated episodes of gonorrhoea compared with non-aboriginals with chlamydia. This is probably due to a number of factors including more complete reporting of cases in First Nations people, higher rates of laboratory testing and diagnosis, rather than epidemiologic treatment, and last, historically high rates which, although sexual behavior may be similar to non-aboriginals, predispose the population to higher rates of repeated infection. Ethnic differences between people with gonorrhoea and chlamydia (though not specifically among repeaters), have been noted in Australia,¹⁸² the United States,³⁶ and in Canada,²⁹ with the ethnic minority forming a higher percentage of the gonorrhoea patients than the chlamydia patients.

Table 4.9 Logistic regression comparing gonorrhoea repeat cases (n=565) and chlamydia repeater cases (n=1,956)

Variable	Odds ratio	Lower 95% C.I.	Upper 95% C.I.	p value
Intercept	0.006			<0.001
Treaty status	1.55	1.25	1.93	<0.001
Female	0.17	0.13	0.21	<0.001
Symptoms noted	1.64	1.30	2.05	<0.001
Log Age	3.37	2.10	5.40	<0.001
Income level				
Quintile 1				
<\$29,572	2.50	1.66	3.76	<0.001
Quintile 2	1.74	1.14	2.66	0.01
Quintile 3,4,5	1.09	0.65	1.82	0.74
Two or more				
contacts named	1.28	1.00	1.62	0.05

Males were 5.9 times more likely to have repeated gonococcal infection than females were to have a repeated chlamydial infection. This does not mean that men are invulnerable to repeated chlamydial infections, it is merely due to the more effective diagnosis of men with gonorrhoea and higher proportions of men who experience symptoms. When compared with repeated chlamydial infections where women make up 81% of the population, women comprise only 38% of the gonorrhoea repeater population. The higher proportion of men in this population also corroborates data from sexual behavior studies which show higher proportions of men with high numbers of partners, and relatively few women with

high numbers of partners.¹⁸⁵ The sex partner ratio therefore cannot be even, as more sexually active men have sex with few highly active women.^{49,53}

Symptoms were 64% more likely to be noted on the records of gonorrhea repeaters than they were for chlamydia repeaters. This reflects the differences in symptom rates common to the two diseases, and the bias due to more complete reporting of gonorrhea cases than of chlamydia cases (reporting bias).¹⁸⁵

A substantially greater proportion of gonorrhea repeaters resided in areas with the lowest income quintiles in Manitoba, when compared with chlamydia repeaters. The differences in the chlamydia and gonorrhea populations may be explained by the tendency of people to select partners similar to themselves. It is unlikely that as many social interactions occur between populations which differ ethnically, economically and in age, as within them. It is important to note that this is the only logistic regression analysis which showed differences in proportions at the second income quintile, as well as the first, which suggests that the income gap measured between gonorrhea and chlamydia repeaters is wider than any other populations analyzed heretofore. The difference in income levels of clients with gonorrhea and chlamydia has previously been shown, although not in repeater populations.^{29,182}

Gonorrhea repeaters were 1.28 times more likely to name 2 or more sex partners than were chlamydia repeaters. This is partially due to more complete gathering of information

in cases of gonorrhea, than from cases with chlamydia. In addition, the higher proportion of people with inadequate therapy for chlamydia, makes reinfection from the same partner or relapse more likely, therefore lowering the number of sex partners necessary for transmitting infection. Caution should be used in interpreting this analysis, as discussed in Section 4.5.1. Increased numbers of sex partners have been collected from cases with gonorrhea than from with chlamydia only,^{29,182} although in other studies numbers of partners have not been a distinguishing factor.^{125,182}

4.6 Comparison of multiply named chlamydia, gonorrhea, and coinfecting contacts

In order to establish whether possible core groups for chlamydia, gonorrhea and coinfecting transmission were the same, it was necessary to compare the multiply named contacts, similar to the analysis of the STD cases.

4.6.1 Comparison of coinfecting repeat contacts with chlamydia repeat contacts

Table 4.10 shows the results of the univariate analysis of differences between the multiply named contacts of chlamydia cases and those named multiply as contacts of coinfecting cases. If these differed, then the multiply named contacts, may indeed form separate core groups for the chlamydia alone or for gonorrhea and chlamydia coinfection.

Table 4.10 Univariate analysis of coinfecting repeat contacts (n=294) and chlamydia repeat contacts with only one infection (n=761)

	Chlamydia repeaters		Coinfecting repeaters		p value
	% or mean	n	% or mean	n	
Age	22.6	750	22.1	292	n.s.
Urban	65.5	545	55.3	125	0.009
Treaty status	26.1	789	40.1	118	<0.001
Female	12.1	761	20.0	59	0.001
Income level					
<\$29,572					
Quintile 1	50.5	266	75.8	163	
Quintile 2	16.7	88	9.3	20	
Quintile 3	18.0	95	8.4	18	
Quintile 4	8.5	45	3.3	7	
Quintile 5	6.3	33	3.3	7	<0.001

Missing variables were found not to be associated with the outcome or any other variable, hence missing variable estimation was not necessary. Therefore, total populations do not match those of the univariate analysis.

Urban residence was significantly associated with being repeatedly named as a contact of a chlamydia case, whereas coinfecting contact repeaters were more likely to reside in rural areas. This variable was not significant on multivariate analysis after all other variables

entered into the equation. This is probably because many First Nations people live in rural areas, so that the two variables were collinear.

Table 4.11 Logistic regression comparing coinfecting repeat contacts (n=294) and chlamydia repeat contacts (n=527)

Variable	Odds ratio	Lower 95% C.I.	Upper 95% C.I.	p value
Intercept	0.16			<0.001
Female	1.63	1.05	2.52	0.03
Treaty status	1.43	1.01	2.03	0.04
Income level				
Quintile 1				
<\$29,572	3.02	1.96	4.66	<0.001
Quintile 2	1.24	0.67	2.29	0.50

Females had a 63% additional risk of being repeatedly named as a contact of a coinfecting case, than being repeatedly named as a contact of a chlamydia case. Although proportions of females in both populations are small, the additional risk may reflect that of the increased risk of female commercial sex workers to be coinfecting, and be named as a source for both diseases. Commercial sex workers themselves may not be as able to name clients as clients are to name them. Aliases used by sex workers are maintained on the STD registry, but clients who may give no name at all would not be able to be identified as contacts.

Individuals who are registered as treaty Indians have a 43% higher risk of being named repeatedly as contacts of coinfection than of chlamydia alone. This is probably due to higher rates of gonorrhea in that population compared with other Canadians, and the tendency of health care providers to report sexually transmitted diseases, (at least in medical billing data), in that population more readily than in non-aboriginals.

There were so few individuals living in areas with income levels greater than \$44,027 that they were combined in one reference category which included income quintiles three, four and five. Residing in an area where the average household income was less than \$29,572 was associated with a tripling of risk for being repeatedly named as a contact of coinfection, when compared with individuals with chlamydia only who resided in higher income neighborhoods. Once again, this corresponds closely with the analysis of repeatedly coinfecting cases, a higher proportion of whom live in low income areas. The magnitude of risk is different, probably because of the other variables available for analysis for cases, which are not collected on contacts.

4.6.2 Comparison of chlamydia repeat contacts with gonorrhea repeat contacts

Multiply named contacts of chlamydia and gonorrhea were compared in order to test the hypothesis that the two groups are similar. Table 4.12 shows the results of the univariate analysis of the two groups.

Table 4.12 Univariate analysis of chlamydia contacts (n=761) and all gonorrhoea contacts (n=331)

Variables	All gonorrhoea contacts		Chlamydia repeaters		p value
	% or mean	n	% or mean	n	
Age	23.9	316	22.6	750	0.001
Urban	61.9	151	65.5	357	n.s.
Treaty status	36.6	121	26.1	199	<0.001
Female	43.5	144	12.1	92	<0.001
Income level					
<\$29,572					
Quintile 1	71.6	167	50.5	266	
Quintile 2	11.5	27	16.7	88	
Quintile 3	10.2	24	18.0	95	
Quintile 4	2.1	5	8.5	45	
Quintile 5	5.1	12	6.3	33	<0.001

Although ages were significantly different on univariate analysis, the difference is small (six months), and may not be of any clinical or epidemiologic relevance.

Table 4.13 Logistic regression comparing gonorrhoea repeat contacts (n=316) and chlamydia repeat contacts (n=750)

Variables	Odds ratio	Lower 95% C.I.	Upper 95% C.I.	p value
Intercept	0.005			<0.001
Female	0.04	0.00	3.41	0.15
Treaty Indian	1.38	1.01	1.89	0.04
Log Age	2.80	1.30	6.02	0.01
Income level				
<\$29,572				
Quintile 1	2.61	1.68	4.04	<0.001
Quintile 2	1.58	1.02	2.46	0.04
Interaction				
Female*Log Age	5.46	1.23	24.15	0.03

An interaction between age and sex was found to be significant and was included along with the main effect variables. The effect of age on the risk of being a repeatedly named contact of gonorrhoea was interdependent on gender. Although the risk of being a repeatedly named contact of gonorrhoea increased with age, the probabilities differed substantially for males and females. Figure 4.5 shows the different probabilities of being a multiply named contact of a gonorrhoea case for selected age groups by gender. Note that the tendency to be a gonorrhoea contact repeater increases with age, whereas with chlamydia, it decreases (see section 4.6.1.) Odds ratios for differences in probabilities are similar. A 45 year old female has an increased risk of being repeatedly named as a contact of gonorrhoea, and a male of the same age has a risk of 1.5 when compared with the risk of a 27 year old.

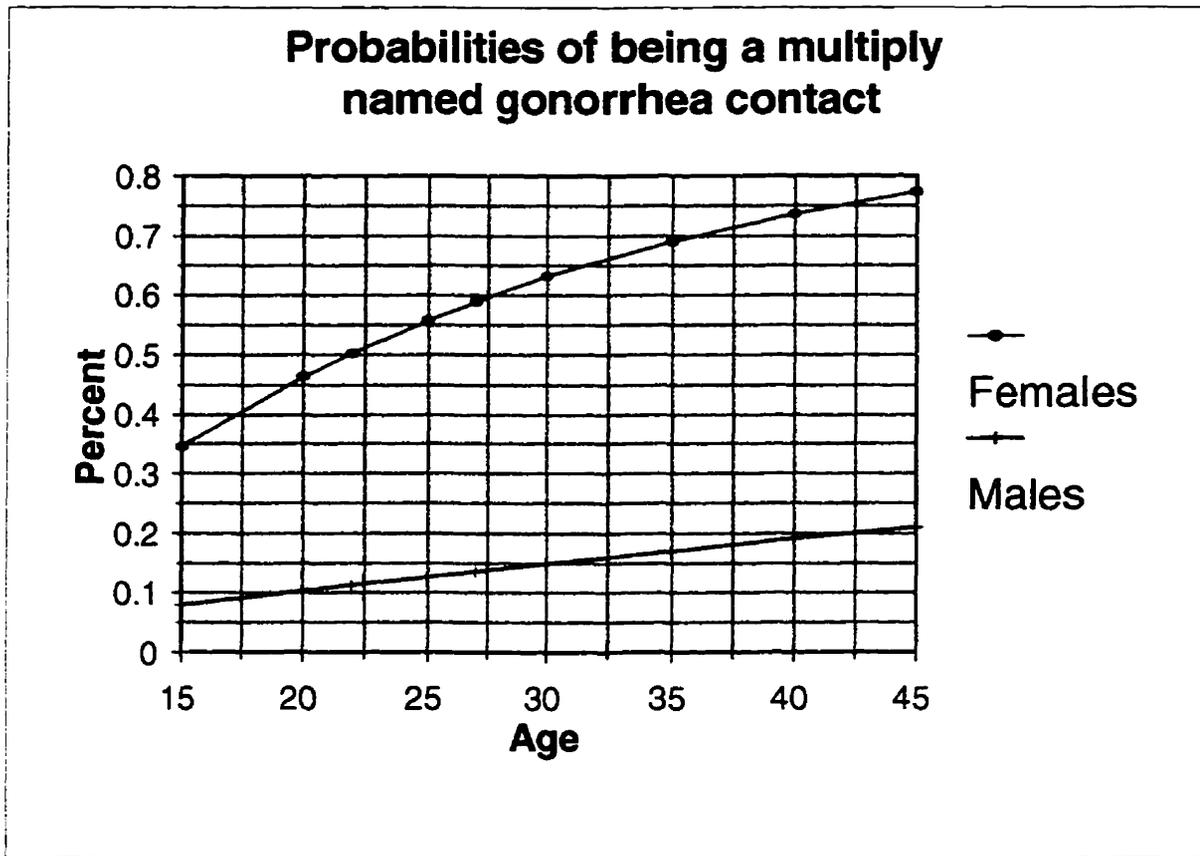


Figure 4.5 Probabilities of being a multiply named contact of gonorrhea by age, for male and female contacts, compared with being a multiply named contact of chlamydia.

Individuals with treaty status were 35% more likely than other residents of Manitoba to be repeatedly named as contacts of gonorrhea. This corresponds with the analysis of gonorrhea and chlamydia repeater cases, mentioned above.

Residing in an area with a low household income was significantly associated with being repeatedly named as a contact of gonorrhea. Individuals living in areas with average household incomes below \$29,572, and between \$29,572 and \$35,870 had increased risks of being gonorrhea repeat contacts of 2.61 and 1.58 respectively, compared with people

living in areas with an average household income of greater than \$35,870. The doubling of risk associated with living in income quintile one is independent of ethnic origin, which carries its own additional risk. This finding also supports that found in comparing gonorrhea and chlamydia repeat cases. The odds ratio of being a multiply named contact of gonorrhea increases with decreased income quintile suggesting that risk increases with decreasing income.

4.7 Comparison of repeat cases and repeatedly named contacts

The following analyses were designed to detect differences, if any, between the multiply named contacts of chlamydia and the repeatedly infected individuals who are proposed as containing the subset of the core groups. It has already been established that the repeater groups of gonorrhea, chlamydia and coinfection are different, and that the repeater groups differ from those contacts named once and those with confirmed infection only once.

Therefore the multiply named contacts of chlamydia were compared with the cases who had repeated infections over the three year period. The hypothesis that the case and contact repeaters for chlamydia are similar will be tested. If the differences are minimal, or are artifacts of health care practices and not due to inherent characteristics of the disease or the people it affects, this would suggest that a core group should also include the multiply named contacts, not only the group of repeat cases.

In addition to the above hypothesis testing, the second valuable outcome of the analysis is the identification of specific health care practices and technologies which prevent contacts, even though they have been named as sex partners multiple times, from becoming laboratory-confirmed repeaters after they have been named multiple times.

4.7.1 Comparison of chlamydia repeat cases with multiply named contacts of chlamydia

The following table shows the results of the univariate comparison of contacts repeatedly named by individuals with laboratory-confirmed chlamydia.

Table 4.14 Univariate analysis of chlamydia repeat cases (n=1,956) and repeatedly named chlamydia contacts (n=761)

	Case repeaters		Contact repeaters		p value
	% or mean	n	% or mean	n	
Age	21.5	1,956	22.6	750	<0.001
Urban	69.0	1,141	65.5	545	n.s.
Treaty status	36.0	704	26.1	789	<0.001
Female	81.1	1,586	12.1	761	<0.001
Income					
Quintile 1					
<\$29,572	51.1	818	50.5	266	
Quintile 2	15.8	253	16.7	88	

	Case repeaters		Contact repeaters		p value
	% or mean	n	% or mean	n	
Quintile 3	15.5	248	18.0	95	
Quintile 4	9.8	157	8.5	45	
Quintile 5	7.8	124	6.3	33	n.s.

Age was significantly associated with whether a multiply named contact of chlamydia was ever confirmed as being a case, although the difference in ages of only one year cannot be considered to be clinically or epidemiologically relevant. Large sample sizes are the only reason for the statistically significant finding. On univariate analysis, cases appeared to be slightly younger than repeatedly named contacts. On multivariate analysis, increasing age was actually associated with a higher probability of becoming a case, independent of the effects of gender (Table 4.15.) The probabilities for males of being confirmed as a case of chlamydia are shown for selected ages in Figure 4.6. The relative odds of a 45 year old male having laboratory proven infection with chlamydia is 1.3 times higher than that of a 27 year old. There are two likely reasons for the increase in probability of becoming a case with age. The first is that the longer an individual has had chlamydia, the more times he is likely to be named as a contact, therefore the more likely there are to be multiple efforts to locate, notify and test him. The second reason, equally likely for the increase in laboratory-confirmed infections with age, is due to the development of symptoms. In section 4.2, repeated cases of chlamydia were shown to have symptoms noted on the

report form 25% more of the time than those with only one episode of infection. It is possible that contacts who are repeatedly named may be experiencing multiple infections

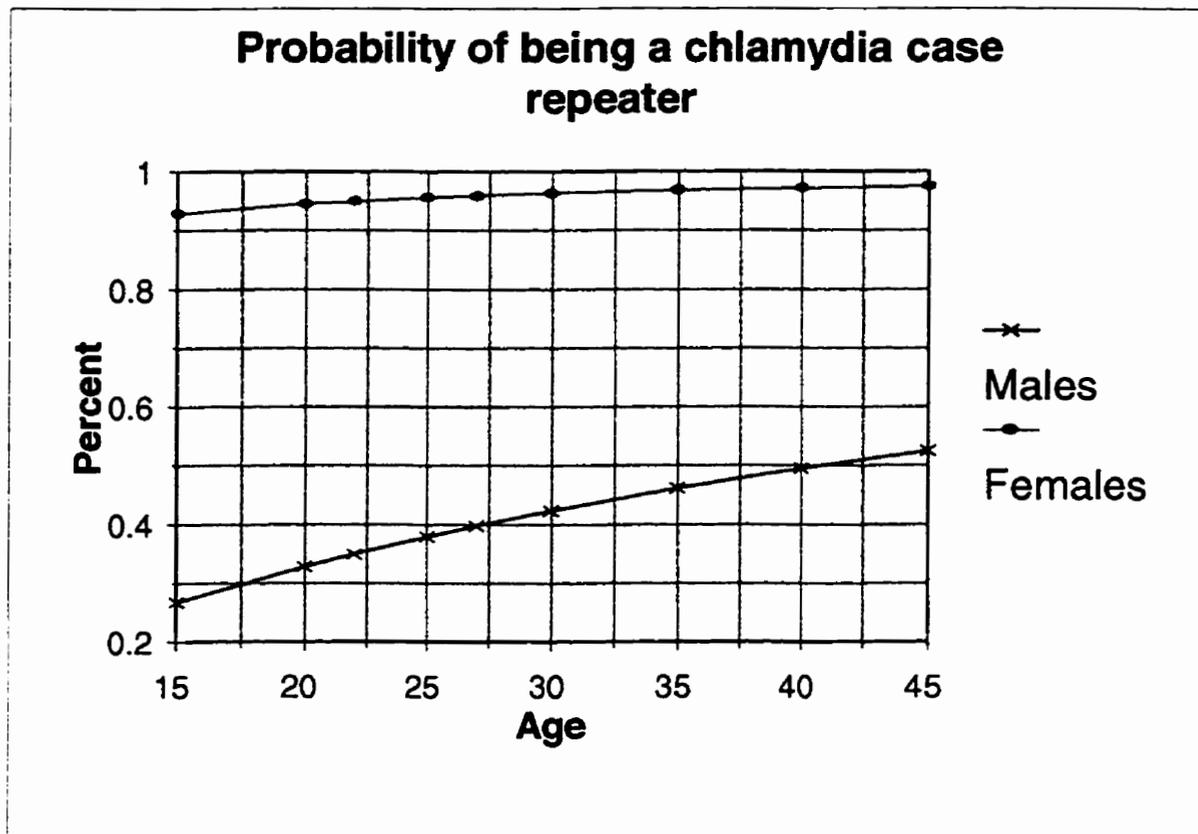


Figure 4.6 Probabilities of a multiply named contact of chlamydia becoming a case with repeated chlamydial infections, compared with being a multiply named contact.

with chlamydia, and are then more likely to show symptoms as time goes on.¹³²

Experiencing symptoms is likely to prompt the individual to seek care and be tested, thus resulting in a laboratory-confirmed case.

Table 4.15 Logistic regression comparing chlamydia repeat cases (n=1,956) with cases being the outcome, and chlamydia repeat contacts (n=750)

Variable	Odds ratio	Lower 95% C.I.	Upper 95% C.I.	p value
Intercept	0.02			<0.001
Female	35.64	27.47	46.25	<0.001
Log Age	2.74	1.58	4.76	<0.001

The strikingly high odds ratio of the likelihood of women to have laboratory-confirmed disease is due to several factors, some related to health care practices and some related to sociological dynamics.

The screening program for women introduced in Manitoba in 1987 produces a higher rate of diagnosed cases in women with chlamydia than in men. Also, the sensitivity of the chlamydia enzyme immunoassay (EIA, Abbot Laboratories, Chicago) in men is notoriously low (see Chapter 1, Section 1.3.) Collection of specimens for chlamydia after voiding; after specimen collection for gonorrhoea, insertion of the swab in the distal urethra, rather than the proximal,³⁷ all of which are common, adversely affect specimen quality. The lack of sensitivity of the EIA test in men may also discourage physicians from collecting samples, as the procedure itself causes discomfort, and the test is seen to be suboptimal (personal communication, Dr. R. Brunham, April 1997).

Women testing positive after screening may have been asymptotically infected for a long period of time. Because of the lack of symptoms, and the inability to establish a date of infection, sex partners of positive women may be excluded from the partner notification

process. In addition, many physicians send extra medication home with the women, to give to their current sex partners. In these cases, where the male may be asymptomatic, there may be no compliance with therapy,³⁸ and the woman is obliged to tell her partner that she tested positive. This occurs despite the fact that it may be the male who infected his female partner, and not the other way around. This second factor may incline her not to pass on the medication, and/or simply end the relationship, simply because she is vulnerable to blame for infecting the male, as well as for possible infidelity. (Discussion, City of Winnipeg and Province of Manitoba Sexually Transmitted Disease Teams, June 1997.) The practice of sending medication home with the female index case also fails to establish the chain of infection from a third person through either the male or the female into the partnership, leaving the couple, and the public at large, susceptible to reinfection from the third party. However, both city and provincial STD public health nurses agree that the wider perspective of spread of disease to the public is not considered by most physicians, who regard only the original individual patient as their responsibility.

In conclusion, the logistic regression shows a striking similarity between the repeatedly infected cases, and multiply named contacts. The most valid explanation for the only differences - age and gender - are that they are artifacts of testing which create diagnostic bias, and by the increasing likelihood of multiply named cases to become confirmed cases as time passes. These minimal differences indicate that the two groups are actually very similar, particularly in socio-economic and ethnic composition. This is not surprising, as the individuals repeatedly infected with chlamydia and those who are multiply named as

contact of chlamydia cases have the same risk behavior - that of repeated sexual intercourse with a high risk of chlamydia transmission.

4.8 Conclusion

The proposed core group responsible for transmitting chlamydia consists of repeatedly named contacts of chlamydia and those with repeated confirmed infections. Incrementally, these analyses show that individuals with repeated confirmed infection can be distinguished from those infected only once, and that multiply named contacts are different from contacts named only once. This is important because if the repeaters were indistinguishable from the non-repeaters, the core group, while it may exist, could not be defined. The second set of hypotheses investigated whether the proposed core group of case and contact repeaters of chlamydia was different from the core groups maintaining gonorrhoea or both chlamydia and gonorrhoea. Again, the differences in the three groups suggest that there is a role for the maintenance of chlamydial infection alone by a core group which is somewhat different from that of gonorrhoea and coinfection.

The comparison of the multiply named contacts of chlamydia with the individuals with repeated infections shows that the two groups are very similar, if not exactly the same. The only differences between the groups likely relate to biases in testing and the increased likelihood of confirmation of multiply named contacts over time, neither of which are characteristics inherent to the individuals themselves. The fact that case and contact

repeaters are very similar indicates that a core group comprising these two components is a distinguishable entity. If the calculation of the reproductive rate is successful in showing that R_0 is greater than one in this population, then the group of combined case and contact repeaters may comprise a core group, according to Anderson and May's mathematical definition.

In addition to the resolution of the research questions, the comparison of the case and contact repeaters suggests that health care technology and sociosexual dynamics in this culture affect the confirmation of chlamydial infection in men. Although the reasons for the lack of testing, partner notification and diagnosis of chlamydial infection in men are debatable, the results are that effective control of the disease is prolonged and men are excluded from responsibility in maintaining their own health and from contributing to the health of the public.

Chapter 5

Gonorrhea cases and contacts:

results and discussion

5.1 Introduction

The following analyses will distinguish those with multiple infections from those individuals with only one infection, and will examine differences between gonorrhea repeat cases and repeat contacts, and chlamydia and coinfecting repeat cases and repeat contacts. If the gonorrhea repeaters are different from chlamydia and coinfecting repeaters, then this would suggest that the core group responsible for maintaining gonorrhea in communities is not the same as those existing for the other two.

Lastly, the repeat gonorrhea cases will be compared with the multiply named contacts. This analysis will indicate whether or not the two groups are sufficiently similar to be regarded as the core group for gonorrhea.

5.2 Comparison of gonorrhoea repeater cases and comparison group

Table 5.1 shows the results of the univariate comparison of individuals with repeated episodes of gonorrhoea in the three year study period with those who had only one infection.

Table 5.1 Univariate analysis of gonorrhoea repeat cases (n=565) and comparison group with only one infection (n=569)

	Comparison		Repeaters		p value
	% or mean	n	% or mean	n	
Age	27.4	569	24.5	565	<0.001
Urban	71.7	474	67.4	481	n.s.
Treaty status	27.6	569	46.9	565	<0.001
Used alias	13.4	569	22.7	565	<0.001
Inappropriate therapy	40.2	569	34.6	565	0.06
Female	40.2	569	37.9	565	n.s.
Symptoms noted	72.9	569	72.9	565	n.s.
Income					
Quintile 1					
<\$29,572	58.5	271	69.2	317	
Quintile 2	14.0	65	13.5	62	

	Comparison		Repeaters		p value
	% or mean	n	% or mean	n	
Quintile 3	13.4	62	9.4	43	
Quintile 4	7.1	33	4.1	19	
Quintile 5	6.9	32	3.7	17	0.004
Number of named partners					
1	67.6	319	66.8	324	
2	25.0	118	25.0	124	
3-4	6.1	29	5.4	26	
>4	1.3	6	2.3	11	n.s.

Differences in the proportions of registered status Indians in the gonorrhea repeater group and the comparison group with only one disease episode were striking. Being of First Nations ancestry doubled the risk of being a repeater (Table 5.2.) This effect could not be attributed to poverty or young age, as the logistic regression equation takes into account both the effects of household income level and age. Higher risk for aboriginal peoples may be due to higher numbers of partners, differences in health care services and/or differences in interactions with health care providers. As with chlamydia, some of the higher rates may be due to health care providers' predilection for more candid diagnoses in aboriginal people than in non-aboriginals.¹⁷⁴ Historically high prevalence rates which were never reduced to levels of the non-aboriginal population affect the epidemiology of

gonorrhoea in minority populations.¹⁷⁵ This is also the case with non-aboriginal ethnic minorities; African Americans have been noted as being at increased risk of being repeaters in other studies.^{124,125,128,129} Only one of these studies showed that ethnic group still carried an increased risk of being a gonorrhoea repeater after low socioeconomic status was taken into account. However, these researchers also found that the Black Americans did not report significantly more sex partners than did White Americans. This makes the supposition of increased risk due to different behaviors of African Americans unlikely, so that ethnic group is merely a proxy risk factor for other as yet unexplored factors.¹²⁴ Aboriginal people living in Alaska, and aboriginals in Manitoba, two years prior to this study,⁷⁸ were also found to be at higher risk than non-aboriginal people of repeated episodes of gonorrhoea, although this was not shown to be independent of education or income level.^{79,123}

Table 5.2 Logistic regression comparing gonorrhoea repeat cases (n=565) and comparison group with only one infection (n=569)

Variables	Odds ratio	Lower 95% C.I.	Upper 95% C.I.	p value
Intercept	6.89			0.005
Treaty status	1.96	1.51	2.53	<0.001
Used alias	1.59	1.15	2.20	0.005
Log Age	0.44	0.29	0.67	<0.001
Income quintile				
Quintile 1	1.57	1.12	2.19	0.009
<\$29,572				
Quintile 2	1.41	0.98	2.03	0.063

Individuals who were ever recorded as having an alias during the study period were 60% more likely to have repeated episodes of gonorrhoea than those who did not use aliases. The use of an alias or “street name” has been documented in the study of other STD and indicates involvement with the illegal drug trade, the sale of sex, or other illicit activities. It is also possible that the uses of a family surname or spouse’s surname interchangeably may be a factor in this analysis.¹⁴³

The three year difference in mean ages of the repeater and the comparison group is large enough to be of epidemiologic, and perhaps of clinical, significance. The usual age breakdown for describing STD’s is by five year age group. A three year difference places the average repeater individual in the 20 - 24 year old category, the age group with the highest proportion of cases, whereas the mean of the comparison group is the age group 25 - 29. As with chlamydia, risk of repeated episodes of gonorrhoea decreases with age, see Figure 5.1. The probability of a 15 year old having a repeat episode of gonorrhoea is 35% higher than that of a 27 year old, which is the mean of the comparison group with only one infection with gonorrhoea in three years. Because the ages of repeater individuals used in this analysis was the age at first repeat event, this means that the individual would have to have had one episode prior to the first recorded repeat episode. Young age has been reported in five studies as an important difference between gonorrhoea repeaters and non-repeaters in the United States,^{79,123,124,128,186} and in aboriginal people in Manitoba.⁷⁸

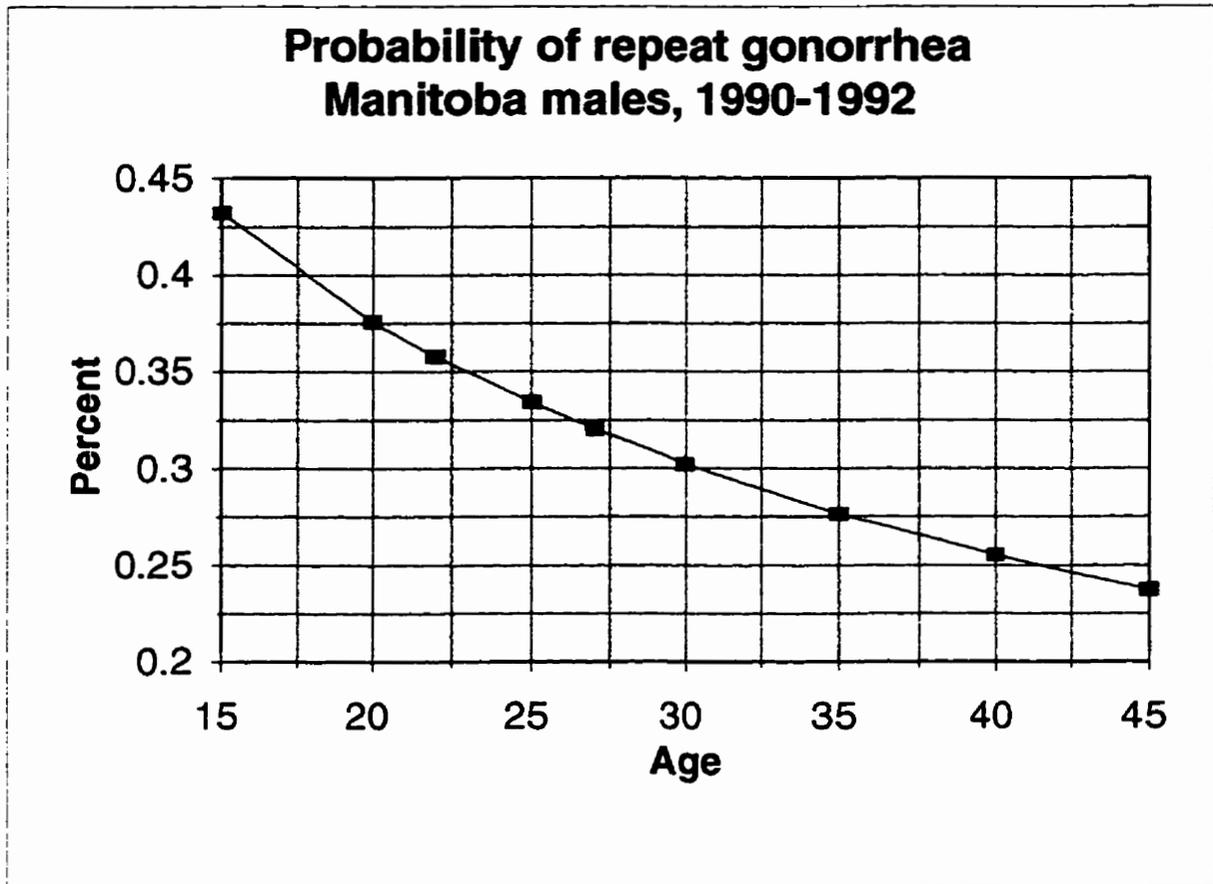


Figure 5.1 Probabilities of repeated gonorrhea infection compared with those with only one episode, by age, for a non-treaty male with no symptoms, who has been treated appropriately, does not use an alias, and lives in an area in which the average household income is \$44,027 or over.

For the purposes of multivariate analysis, the third, fourth and fifth income quintiles were combined in order to avoid splits of less than 10% which are outliers. Individuals with household income levels of below \$29,572 had a 57% increased risk of having a repeated episode of gonorrhea, compared with those with income levels above \$44,027. It is possible - even probable - that low average income is a marker of low education levels. However, because part of the study group are under the age for school graduation, or the completion of any other advanced education, it would not be realistic to apply those

indicators to individuals who could not possibly accomplish them. A previous study addressing education and income in gonorrhea repeaters showed that repeaters were significantly more likely to live in lower socioeconomic areas, not have completed high school, and were more likely to be employed. With regard to this last characteristic, it is noteworthy that this study was completed in the mid 1970's, when employment rates were high.¹²⁴

Most of the therapies considered inappropriate for the treatment of gonorrhea were tetracycline or erythromycin and combinations thereof. Although numbers of gonorrhea cases were small, a study on the management of sexually transmitted diseases by 49 family physicians in Canada revealed that of nine patients with gonorrhea, seven were treated with tetracycline alone.¹⁷⁶

On univariate analysis, inappropriate treatment for 35% and 40% of gonorrhea repeaters and comparison group, respectively, was entered into the STD computerised registry from the STD notification form, (Table 5.3.) The proportion of cases inappropriately treated is high, although it is probable that at least a portion is due to the fact that patients may be treated initially for chlamydia when presenting with symptoms, or as a contact of a chlamydia case. Later, on receipt of a positive laboratory result, individuals may be treated with another regimen. However, it is unknown how much of the information on additional therapy was forwarded to Manitoba Health. Note that Table 5.3 records all

disease episodes of individuals repeatedly infected with gonorrhea from 1990 - 1992, therefore totals will not balance with Table 5.2.

Table 5.3 Recorded treatment of all disease episodes of all gonorrhea repeaters, 1990 - 1992, Manitoba STD registry.

Therapy	Ureth/ Cerv.	Pha- rvnx	Rec- tal	Epidid.	PIDDissem.	PPNG
*No treatment recorded	22				2	
Ceftriaxone	71	3	2			1
Ceftriaxone+Tetracycline	138		2	1		4
Ceftriaxone+Erythromycin	46				1	
Ceftriaxone+Proamp	4				1	1
Ceftriaxone+Doxycycline	113	1	1		6	1
Ceftriaxone+Ofloxacin	1					
Ceftriaxone+Other	3					
*Tetracycline	77	1	2			
*Tetracycline+ Erythromycin	272		1		1	
Tetracycline+Proamp	88	1	1		1	
Tetracycline+Spectinomycin	6					
Tetracycline+TMP/SMX	3					
*Tetracycline+Doxycycline	1					
Tetracycline+Cefixime	86	1		1		
Tetracycline+Ofloxacin	4					1
Tetracycline+APPG	2					
Tetracycline+Other	1					
*Erythromycin	42	2	1			
Erythromycin+Proamp	7					
Erythromycin+Spectinomycin	29				1	
Erythromycin+TMP/SMX	2					
Erythromycin+Cefixime	1					
Erythromycin+Ofloxacin	21				1	3
Erythromycin+Other	1					
Proamp	23					

Therapy	Ureth/ Cerv.	Pha- rvnx	Rec- tal	Epidid.	PIDDissem.	PPNG	
Proamp+Spectinomycin	20				1		
Proamp+Doxycycline	16						
Proamp+Cefixime	2		1				
Proamp+Ofloxacin	12						
Proamp+APPG	2						
Spectinomycin	15						
Spectinomycin+TMP/SMX	1						
Spectinomycin+Cefixime	11						
*Bicillin	4						
TMP/SMX	2						
TMP/SMX+Doxycycline	1						
TMP/SMX+Cefixime	2						
Doxycycline	10						
Doxycycline+Spectinomycin	1						
Doxycycline+Ofloxacin	2						
Doxycycline+APPG	2						
Cefixime	22		1	1	5	1	
Cefixime+Ceftriaxone	1		1		1		
Cefixime+Ofloxacin	35		1		5		
Cefixime+APPG	1						
Ofloxacin	14		1		1	1	
Ofloxacin+TMP/SMX	1						
APPG	1						
TOTAL	1242	9	15	3	27	2	12

* Asterisks indicate inappropriate therapy

** Epididymitis also included as urethral cases.

Although the effects of the treatment variable were not large enough to be retained in multivariate analysis, it is interesting that on univariate analysis, gonorrhea repeaters were

recorded as having fewer incidences of inappropriate therapies than those with only one episode ($p=0.06$). This may indicate that gonorrhoea repeaters received care from physicians more familiar with the treatment of gonorrhoea, than those with only one infection.

Individuals with gonorrhoea once in three years named similar numbers of sex partners per episode as those with repeated infections. This may be an indication that control efforts have reduced the level of gonorrhoea to an extent that the populations of repeaters and non-repeaters have become more homogenous over time. Another explanation for the similarity is that the clients with repeated episodes were unwilling or unable to divulge the names of more sex partners, or that nurses believed that the numbers of partners given were sufficient. In one other study on gonorrhoea repeaters, they were shown to have similar numbers of sex partners as those individuals who did not have repeated episodes of gonorrhoea.^{124,125} However, gonorrhoea repeaters reported more recent unprotected sex with possibly infected individuals, and also had sex significantly more often than the non-repeater populations.¹²⁴ Another important factor which is usually not considered in these studies is not the quantitative measures of behaviors and partners, but the type of partners which high risk (repeater) individuals are likely to choose.

A statistical difference in those reporting symptoms is conspicuous by its absence. Two studies where symptoms were studied have found that symptoms were experienced, and/or recognised as such, more often by gonorrhoea repeaters than by non-

repeaters.^{124,186,187} Mechanisms for higher proportions of symptoms in repeaters is unknown, but it is possible that having been sensitized to a strain of *N. gonorrhoeae*, humoral or cellular responses to infection contribute to symptoms. Data from Kenya also suggest that strain specific immunity may develop.¹³⁰

Differences in proportions of females were not found between gonorrhoea repeaters and non-repeaters. This corroborates evidence of at least one study,⁷⁹ but others did find that a higher proportion of repeaters tended to be men.^{123,124,128,129}

5.3 Comparison of gonorrhoea repeat contacts and comparison group

Comparison of the sex partners of individuals with confirmed chlamydia and their contacts proved that the groups were similar, regardless of whether the individuals had laboratory-confirmed infection. The reasons for examining the named partners as a potential core group are contained in Chapter 2, section 2.2, Chapter 4, section 4.3. In attempting to define core groups who contribute disproportionately to infections within the community, case repeaters who have more than one documented infection in three years were included. Similarly, sex partners of cases (contacts), who have been named more than once are more likely, if infected, to have greater opportunities to transmit infection than those cases with only one infection or contacts named only once.

The following section describes the univariate and multivariate comparisons between multiply named contacts of gonorrhoea with those named only once during the study period. These analyses were completed in order to establish whether multiply named contacts are a definable group, distinct from those named only once.

5.4 Comparison of multiply named contacts of gonorrhoea infection with those named only once

No differences between repeatedly named contacts of gonorrhoea cases and those named only once were found on univariate analysis, (Table 5.3). Therefore, none were eligible for entry into a multivariate model.

Table 5.5 Univariate analysis of gonorrhoea repeat contacts (n=158) and comparison group with only one infection (n=173)

	Comparison		Repeaters		p value
	% or mean	n	% or mean	n	
Age	23.9	160	23.8	156	n.s.
Urban	60.8	73	62.9	78	n.s.
Treaty status	32.4	56	41.1	65	n.s.
Female	46.8	81	39.9	63	n.s.
Income level					
<\$29,572					
Quintile 1	70.4	81	71.6	86	

	Comparison		Repeaters		p value
	% or mean	n	% or mean	n	
Quintile 2	9.6	11	13.3	16	
Quintile 3	13.0	16	7.5	9	
Quintile 4,5	7.0	8	7.5	9	n.s.

The lack of differences between these two groups is remarkable and proves that the two groups are homogenous at least at the level of these broad socio-demographic characteristics. This homogeneity of all gonorrhoea partners, (n=331), establishes that all sex partners of cases of gonorrhoea are similar, regardless of whether they had been multiply named or not. The fact that they were never proven to be cases during the study period suggests that if they were infected, they are ideal candidates for core group membership.

5.5 Comparison of chlamydia, gonorrhoea, and coinfecting repeat cases.

This section addresses the hypothesis that should the repeater population comprise the core group for gonorrhoea then it may be similar to the core groups responsible for maintaining chlamydia in the population. If significant differences exist between the coinfecting repeaters; the chlamydia repeaters and gonorrhoea repeaters, then the core groups for the infections may indeed be different.

5.5.1 Comparison of coinfecting repeat cases with gonorrhoea repeat cases

Table 5.6 shows the univariate analysis of differences between the coinfecting repeaters and the gonorrhoea repeaters.

Table 5.6 Univariate analysis of coinfecting repeat cases (n=471) and gonorrhoea repeat cases. (n=565)

	Gonorrhoea repeaters		Coinfecting repeaters		p value
	% or mean	n	% or mean	n	
Age	24.5	565	20.1	471	<0.001
Urban	67.4	481	68.2	402	n.s.
Treaty status	46.9	565	51.6	471	n.s.
Used alias	22.7	565	34.0	471	<0.001
Inappropriate therapy (Gc)	34.6	565	26.7	468	0.007
Female	37.9	565	71.5	471	<0.001
Symptoms noted	72.9	565	80.5	471	<0.005
Income Quintile 1					
<\$29,572	69.2	317	65.0	249	
Quintile 2	13.5	62	10.2	39	
Quintile 3	9.4	43	12.3	47	
Quintile 4	4.1	19	6.8	26	

	Gonorrhea		Coinfected		p value
	repeaters		repeaters		
	% or mean	n	% or mean	n	
Quintile 5	3.7	17	5.7	22	n.s.
Number of					
named partners					
1	66.8	324	60.9	265	
2	25.0	124	31.5	137	
3-4	5.4	26	6.0	26	
>4	2.3	11	1.6	7	n.s.

Proportions of gonorrhea and coinfecting repeaters differed by gender, inappropriate therapy for gonorrhea, use of an alias and having symptoms noted on univariate analysis.

The gonorrhea repeaters were also significantly older than the coinfecting repeaters, where the difference of means was 4 years. These variables were entered into the logistic regression analysis, where inappropriate treatment for gonorrhea was dropped, as the variation explained by that factor did not add significantly to the model. Table 5.7 shows the results of the logistic regression analysis.

Table 5.7 Logistic regression comparing coinfecting repeat cases (n=471) and gonorrhoea repeater cases (n=565)

Variable	Odds ratio	Lower 95% C.I.	Upper 95% C.I.	p value
Intercept	749.9			<0.001
Used Alias	1.42	1.05	1.93	0.02
Female	3.13	2.36	4.14	<0.001
Symptoms noted	1.79	1.29	2.48	<0.001
Log Age	0.07	0.04	0.14	<0.001

Coinfecting repeaters were 42% more likely to use an alias than were people repeatedly infected with gonorrhoea. As with other analyses, this implies a greater involvement in illegal activities.

The hypothesis that many more coinfecting repeaters are commercial sex workers is supported by the fact that females are three times more likely to be reported as having repeated coinfections than they are reported as having repeated gonorrhoea alone. This may be due to the fact that they are more likely to contract both infections in the sex trade. It is related to the fact that coinfection in men is more difficult to confirm. Lastly, the reduced odds of repeated coinfection in men may be due to the fact that female sex workers may not be able to identify their clients sufficiently so that they may be notified and tested. However, men with symptoms may present at medical clinics and be tested and treated for gonorrhoea rather than for chlamydia.

Symptoms were noted more often on records of coinfecting repeaters than they were on those who had repeated episodes of gonorrhoea. This may be a result of increased attention to record keeping when an individual has two infections rather than one. It is probably also due to the fact that there is greater disruption of the tissues when two pathogens are present, causing a higher likelihood of symptoms, or more severe symptoms.

Increasing age was associated with a lower risk of repeated coinfection when compared with repeated infection with gonorrhoea. The difference in mean ages is pronounced. Figure 5.2 shows the probabilities of repeated coinfection by five year age group.

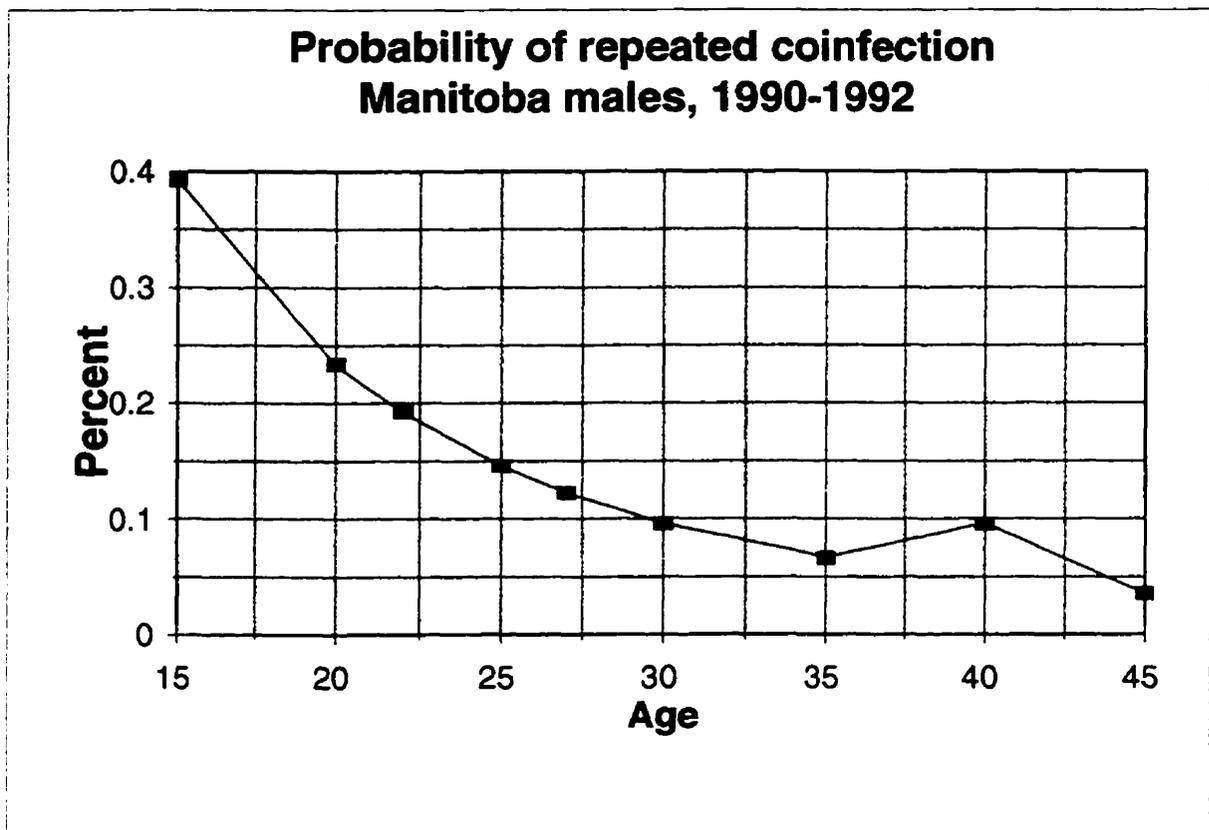


Figure 5.2 Probabilities of repeated coinfection compared with probabilities of repeated gonorrhoea of non-aboriginal males not using an alias and who did not report symptoms.

One explanation for these phenomena of repeated coinfection in youth could be physiological. Young women seem to be more susceptible to *Chlamydia trachomatis* infection than older women.^{77,87,188} Another possibility is that older gonorrhoea repeaters may have been repeatedly infected with chlamydia when younger, and developed an immune response which may be sufficient to suppress the infection to some extent,^{88,189} and decrease the likelihood of symptoms. It is possible that in some people the immune response may produce effective immunity. A third possibility is that infection with *Neisseria gonorrhoeae* provides competition for chlamydia or creates an environment which suppresses it. However, this explanation does not account for age differences, and is not biologically plausible, because chlamydia is an intracellular parasite, whereas

gonococci are usually extracellular parasites. Also, there has been recent evidence to suggest that gonococcal infection may reactivate chlamydial infection.¹³³ A fourth possible explanation for the difference in ages is that people who are older are members of sexual networks which are homogenous in age and where people tend to be infected with gonorrhea alone. Occasional sexual partnerships with commercial sex workers occurring outside the age cohort may occur, which explains the slight increase in risk at age 40. This kind of explanation related to age subclasses has been shown in different drug use behaviors in older and younger cohorts of people with different sexually transmitted diseases.¹³⁸

5.5.2 Comparison of gonorrhea repeat cases with chlamydia repeater cases.

The differences found between the chlamydia and gonorrhea repeater cases have already been explored in Chapter 4, section 4.5.2.) Differences were pronounced; chlamydia and gonorrhea repeater cases differed by age, ethnic group, gender, income level, in numbers of partners, and in the proportion who experienced symptoms.

5.6 Comparison of the contact repeaters with chlamydia gonorrhea and coinfection

In order to establish whether possible core groups for chlamydia, gonorrhea and coinfecting transmission were the same, it was necessary to compare the multiply named contacts, similar to the analysis of the STD cases.

5.6.1 Comparison of coinfecting repeat contacts with gonorrhoea repeat contacts

Table 5.8 shows the results of the univariate analysis of differences between repeatedly named contacts of coinfecting cases and all contacts of gonorrhoea cases.

Differences in mean age were very small and were detected only by virtue of large sample sizes. The difference of 1.8 years may not be a useful distinction between multiply named contacts of coinfection and gonorrhoea. This may also be a function of the increased susceptibility of younger people, who are more often likely to be cases, and hence name their sexual partners. It is interesting that this difference is detectable not only in cases, but also in their contacts, suggesting that the two groups have some characteristics in common.

Table 5.8 Univariate analysis of coinfecting repeat contacts (n=294) and all gonorrhoea contacts (n=331)

Variables	All gonorrhoea contacts		Coinfecting repeaters		p value
	% or mean	n	% or mean	n	
Age	23.9	316	22.1	292	0.001
Urban	61.9	151	55.3	125	n.s.
Treaty status	36.6	121	40.1	118	n.s.

Variables	All gonorrhoea		Coinfected		p value
	contacts	n	repeaters	n	
	% or mean		% or mean		
Female	43.5	144	20.0	59	<0.001
Income level					
<\$29,572					
Quintile 1	71.6	167	75.8	163	
Quintile 2	11.5	27	9.3	20	
Quintile 3	10.2	24	8.4	18	
Quintile 4	2.1	5	3.3	7	
Quintile 5	5.1	12	3.3	7	n.s.

Age remained a significant explanatory variable of coinfecting contact repeaters on multivariate analysis (see Table 5.9.) Figure 5.3 shows the decreasing probabilities of being repeatedly named as a contact to a coinfecting case with age. A 15 year old has 45% higher chance of being repeatedly named as a contact of a coinfecting case than a 27 year old, once all other variables are held constant.

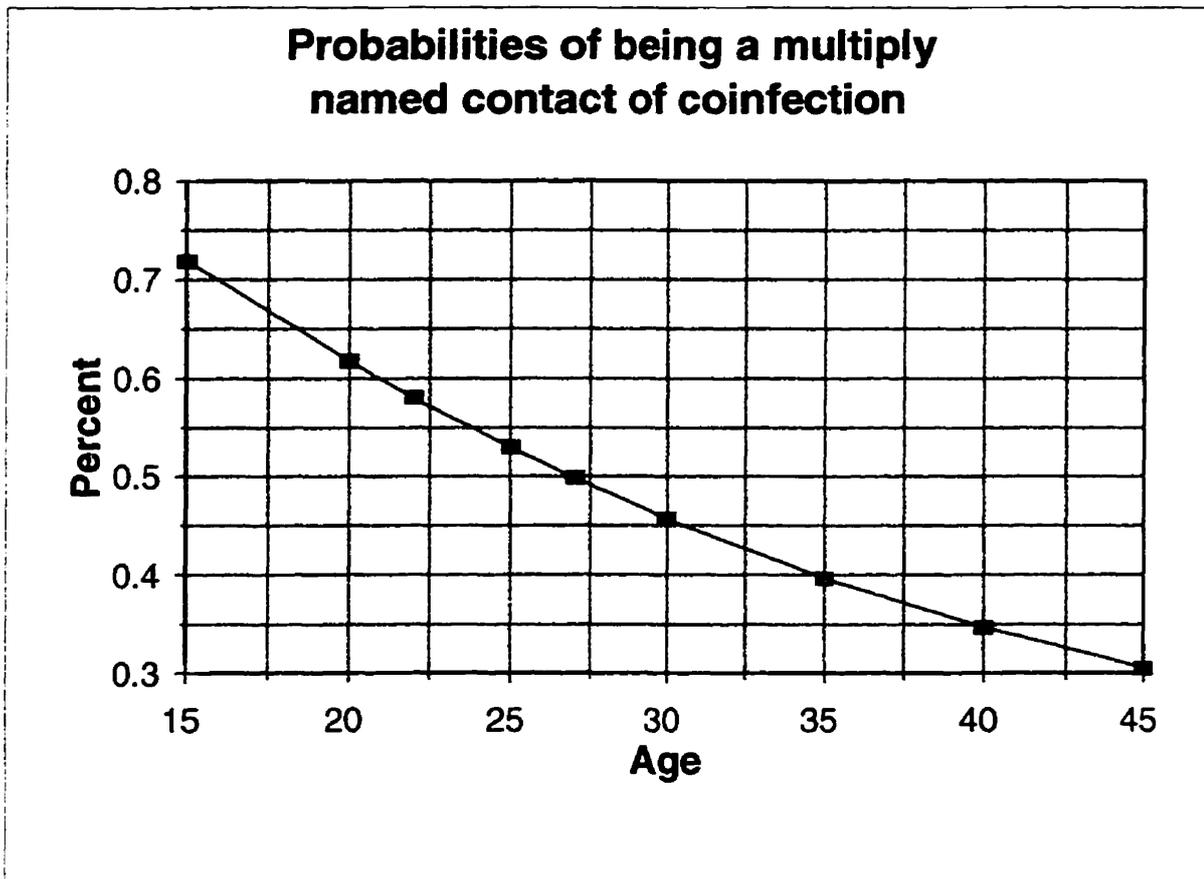


Figure 5.3 Probabilities of being a multiply named contact of coinfection by age for a male contact, compared with being a multiply named contact of gonorrhoea

Females are much less likely to be repeatedly named contacts of coinfecting cases than are males, when compared with all named contacts of gonorrhoea cases (O.R=0.28). The inverse of the odds ratio shows that males are named repeatedly as contacts of coinfecting cases 3.5 times more than females when compared with repeat contacts of gonorrhoea. This is due to the fact that chlamydia is under diagnosed in men (making them less likely to become cases), due to lower specimen collection rates³⁷ and insensitivity of the chlamydia EIA.⁸ The fact that these men are named repeatedly suggests that they have a long duration of infectiousness during which women are exposed. The tendency of some

populations of symptomatic males not to seek care has been noted previously.¹⁹⁰⁻¹⁹² It is also possible that these men may not be infected due to regular condom use or poor transmission of the bacteria from females to males. However, were that the case, it would not explain the continual the multiple times the men have been named as sexual contacts by infected partners over time.

Table 5.9 Logistic regression comparing coinfecting repeat contacts (n=292) and all gonorrhoea contacts (n=316)

Variable	Odds ratio	Lower 95% C.I.	Upper 95% C.I.	p value
Intercept	196.4			<0.001
Female	0.28	0.19	0.41	<0.001
Log age	0.20	0.10	0.40	<0.001

The results of the comparison of these two groups are interesting. If one is prepared to attribute the differences in the populations to the pathophysiology of the disease (as affecting younger people), and the lack of testing and insensitive testing in men, these two groups would have similar characteristics.

5.7 Comparison of repeat cases and repeatedly named contacts

The following analyses were designed to detect differences, if any, between the gonorrhoea repeater cases and contacts who are the proposed core groups. It has already been proved that the gonorrhoea repeater groups are different from those with chlamydia and coinfection. The only possible exception to this is the comparison of coinfecting multiply

named contacts and the gonorrhoea contacts. However, the repeater cases of the two groups did reveal other differences. If the differences between gonorrhoea repeater cases and contacts are minimal, or are artifacts of health care practices this would suggest that a core group should also include the multiply named contacts, not only the group of repeat cases.

In addition to the above hypothesis testing, the identification of specific health care practices and technologies which prevent contacts from becoming laboratory-confirmed cases will be elucidated.

5.7.1 Comparison of gonorrhoea repeat cases with multiply named contacts of gonorrhoea

Table 5.10 shows the results of the univariate comparison of all contacts of cases of gonorrhoea, and those who have repeated episodes of gonococcal infection. Because contacts of gonorrhoea who were named only once were the same as those named multiple times, all gonorrhoea contacts were included in this analysis.

Table 5.10 Univariate analysis of gonorrhoea repeat cases (n=565) and all named contacts (n=331)

	Case repeaters		All contact repeaters		p value
	% or mean	n	% or mean	n	
Age	24.5	565	23.9	316	n.s.
Urban	67.4	481	61.9	151	n.s.
Treaty status	46.9	565	36.6	121	0.003
Female	37.9	565	43.5	144	n.s.
Income					
Quintile 1					
<\$29,572	69.2	317	71.6	167	
Quintile 2	13.5	62	11.5	27	
Quintile 3	9.4	43	10.2	24	
Quintile 4	4.1	19	2.1	5	
Quintile 5	3.7	17	5.1	12	n.s.

There were no demographic differences between contacts named by gonorrhoea cases, and those with repeated laboratory-confirmed infections, other than the proportion who were status Indians, who were 53% more likely to have laboratory proven infection than non-aboriginal Manitobans.. Physicians may be more likely to test aboriginal patients than non-aboriginal patients, and to report infection. The predisposition of physicians to provide a non-specific diagnosis for non-aboriginal women rather than for aboriginal women even though all had laboratory-confirmed infection has been documented previously in

Manitoba.¹⁷⁴ Also, medical services are provided by nurses working with the Federal government on Indian reservations. The nurses, because they are more reliant on practice guidelines than physicians are, may be more likely to test and treat all patients than physicians. Another possible, although less likely, reason for the higher proportion of First Nations people being frequently diagnosed, is that they may represent a higher proportion of sex trade workers, whom health care providers would be anxious to test and treat. Lastly, aboriginal patients may be more compliant with diagnostic procedures and less likely to refuse testing than non-aboriginal patients.

The lack of differences between the individuals with repeated episodes of gonococcal infection and those who are repeatedly named as contacts indicate that these groups are similar. It is highly likely that the two groups are homogeneous and that the difference in proportions of First Nations people of 10% is found to be significant only because of large sample sizes and may be an artifact of the medical and public health care systems.

5.8 Conclusions

This chapter has examined the possibility that a distinctive core group of individuals with gonorrhoea alone exists. The incremental approach of proving differences between repeaters and non-repeaters, and then comparing the repeaters with the coinfecting and chlamydia repeaters showed that the proposed gonorrhoea core group is distinguishable from the other groups. This is important from a public health practice point of view, as it

demonstrates that the data which are collected on STD patients may be used to distinguish core group members from non-core group members. The final step in proving that the gonorrhea core group is contained within the case and contact repeaters will be the calculation of the reproductive rates of the infections in the repeater and non-repeater populations.

Chapter 6

Coinfected cases and contacts: results and discussion

6.1 Introduction

Individuals with repeated coinfections in three years and those who have been named multiple times as sexual contacts of coinfection are proposed core group members. The following analyses are the same as those completed for gonorrhea and chlamydia cases and contacts and will distinguish those with multiple infections from those individuals with only one infection. Investigation into the hypothesis that the core group for gonorrhea is the same as that for chlamydia should include the alternate hypothesis that they are different. The analyses will also explore differences between proposed core groups for chlamydia, gonorrhea and coinfection.

6.2 Comparison of coinfecting repeater cases and comparison group

This analysis was complicated by the fact that there were a number of individuals who had alternating chlamydia and gonorrhea infections (n=187). That is, they were not reported as ever having had two infections at once, but they may have had one episode of

chlamydia, then one of gonorrhoea and then another of chlamydia, during the three year study period. The serially coinfecting individuals did not differ from *bona fide* coinfecting individuals (n=284) on univariate analysis. Therefore the two groups were combined and became the coinfecting repeater group. Univariate analysis of the coinfecting individuals and those serially coinfecting was completed using a more stringent alpha value. This was calculated by dividing the usual 0.05 by the number of variables being compared (n=10), to produce a p value of 0.005.¹⁵⁵ It is necessary to raise the threshold for rejection of the null hypothesis (known as the Bonferroni adjustment) in order to compensate for the higher likelihood that in asking 10 questions, one or more H_0 are likely to be rejected due to sheer random chance.¹⁹³ Although serially infected individuals differed from coinfecting repeaters in the proportions who had symptoms (p=0.03), inappropriate treatment for chlamydia (p=0.05), and who were status Indians (p=0.02), none of these exceeded the 0.005 significance level which allowed for the testing of multiple hypotheses.

The comparison group for the combined serially coinfecting and coinfecting repeaters, comprised those individuals who had ever had one episode of laboratory proven gonorrhoea and chlamydia reported to Manitoba Health simultaneously, (see Chapter 2 section 2.8.5. for more detail). Although sample ratios of 1:1 were ideal, there were fewer individuals with one episode of coinfection (n=299) than the repeater group and the serially coinfecting together, so the entire population of coinfecting individuals was analyzed.

Table 6.1 Univariate analysis of coinfecting repeat cases (n=471) and comparison group with only one coinfection (n=299)

	Comparison		Repeaters		p value
	% or mean	n	% or mean	n	
Age	21.7	299	20.1	471	<0.001
Urban	68.6	264	68.2	402	n.s.
Treaty status	35.1	299	51.6	471	<0.001
Used alias	20.0	299	34.0	471	<0.001
Inappropriate therapy (Ct)	9.4	299	19.0	468	<0.001
Inappropriate therapy (Gc)	37.1	299	26.7	468	0.003
Female	59.9	299	71.5	471	0.001
Symptoms noted	60.2	299	80.5	471	<0.001
Income					
Quintile 1					
<\$29,572	60.7	156	65.0	249	
Quintile 2	12.5	32	10.2	39	
Quintile 3	13.6	35	12.3	47	
Quintile 4	6.6	17	6.8	26	
Quintile 5	6.6	17	5.7	22	n.s.

	Comparison		Repeaters		p value
	% or mean	n	% or mean	n	
Number of named partners					
1	62.8	164	60.9	265	
2	27.6	72	31.5	137	
3-4	5.4	14	6.0	26	
>4	4.2	11	1.6	7	n.s.

The proportion of coinfecting repeaters who were registered as entitled to benefits under the treaties with First Nations people differed significantly from those individuals who had only one episode of coinfection during the study period (Table 6.1, 35.1% and 51.6% respectively, $p < 0.001$). This variable remained significant in multivariate analysis (Table 6.2). The risk of having more than one episode of coinfection, or being infected with both chlamydia and gonorrhoea during the study period was double for aboriginal people compared with non-aboriginal people. The increased risk may indicate that aboriginal people have higher numbers of partners, or more frequent intercourse. Health care providers may be more willing to “label” aboriginal clients rather than non-aboriginal clients, which affects rates,¹⁷⁴ as does a possible lack of accessible health services. The increased risk of First Nations people for coinfection and repeated episodes of coinfection was noted in a previous study in Manitoba.⁷⁸ The multivariate analysis produces an odds ratio independent of the other variables in the logistic equation, therefore low average household income does not explain the increased risk of being a coinfecting repeater

among First Nations people. However, it is likely that coinfecting individuals, especially those with repeated or serial infections, are more likely to be involved in the sex trade, and if aboriginals form a higher proportion of sex trade workers, this may explain the increased risk. There have been no studies which contain data immediately relevant to this analysis.

Table 6.2 Logistic regression comparing coinfecting repeat cases (n=471) and comparison group with only one infection (n=299)

Variables	Odds ratio	Lower 95% C.I.	Upper 95% C.I.	p value
Intercept	6.62			0.12
Treaty status	1.92	1.40	2.64	<0.001
Used alias	1.69	1.18	2.43	0.004
Inappropriate				
therapy (Ct)	2.16	1.34	3.51	0.002
Female	1.50	1.07	2.10	0.02
Symptoms				
noted	2.71	1.92	3.81	<0.001
Log Age	0.38	0.18	0.80	0.01

Using an alias was also significantly associated with having repeated coinfections or serial infections with gonorrhoea and chlamydia during the study period, although the proportion of individuals using aliases was not very high. The reason for this is probably that aliases are used frequently by commercial sex workers, their pimps and their clients in order to evade the authorities.¹⁴³ It is also possible that increased use of aliases may contribute to repeat infections simply because it complicates patient follow-up, location, and notification of sex partners.

Having inappropriate therapy for chlamydial infection for more than two thirds of all chlamydia episodes was associated with a doubling of risk of having repeated coinfection or serial infections with gonorrhea and chlamydia. The drugs prescribed to coinfecting or serially infected individuals have already been shown in Chapters 4 and 5. It is possible that a proportion of patients will have received the correct drug on receipt of a positive laboratory result, and that the report of amended therapy was not forwarded to Manitoba Health. However, even if half of the 19% of repeaters were inappropriately treated most of the time, this warrants investigation. Inappropriate therapy will lead to longer periods of infectiousness, and as these individuals are sexually active enough to contract two STD, they are probably efficient transmitters. Coinfecting repeaters were more often treated correctly for gonorrhea than those with only one disease episode, suggesting that clients with repeated infection are treated by physicians who are more familiar with the disease, or more eager to report correct therapies.

Females were 50% more likely than males to be reported to Manitoba Health as having serial or repeated laboratory-confirmed infection with chlamydia and gonorrhea. This is disturbing, as it suggests under-diagnosis of men. If many of the cases are female sex workers, their clients may also be infected, and logically there should be more clients than sex workers. In addition, comparisons of genders for gonorrhea cases did not show a significant gender difference. This suggests that the only differences in the two diseases are problems of urethral sampling and obtaining positive test results for chlamydia in men.

Symptoms were noted on the STD report form and entered on the computer three times more often per episode for coinfecting repeaters or serially coinfecting individuals than for those coinfecting only once in three years. This may be an artifact of reporting bias, where information on repeaters is more likely to be reported than for those who are not already known to the public health nurses. It may also be due to the fact that individuals with repeated infections are better at recognising symptoms and report them as such. It is also possible that repeated coinfections damage the genital tract, which then causes symptoms to be more pronounced. In reality, the reason for the tripling of probability that symptoms are noted in coinfecting repeaters is probably a combination of all of the above.

Lastly, the natural logarithm of age was significantly associated with risk of repeated coinfection (Figure 6.1). The odds decreased as the age increased, so that with all other variables held constant, the risk of a 15 year old is 1.52 that of a 27 year old. As with gonorrhoea and chlamydia repeaters, a first repeat episode of coinfection would have to occur at an earlier age than in an individual with only one episode of coinfection (mean ages 20.1 and 21.7, respectively). Young age has also been noted as a characteristic of repeatedly coinfecting individuals in Manitoba.⁷⁸

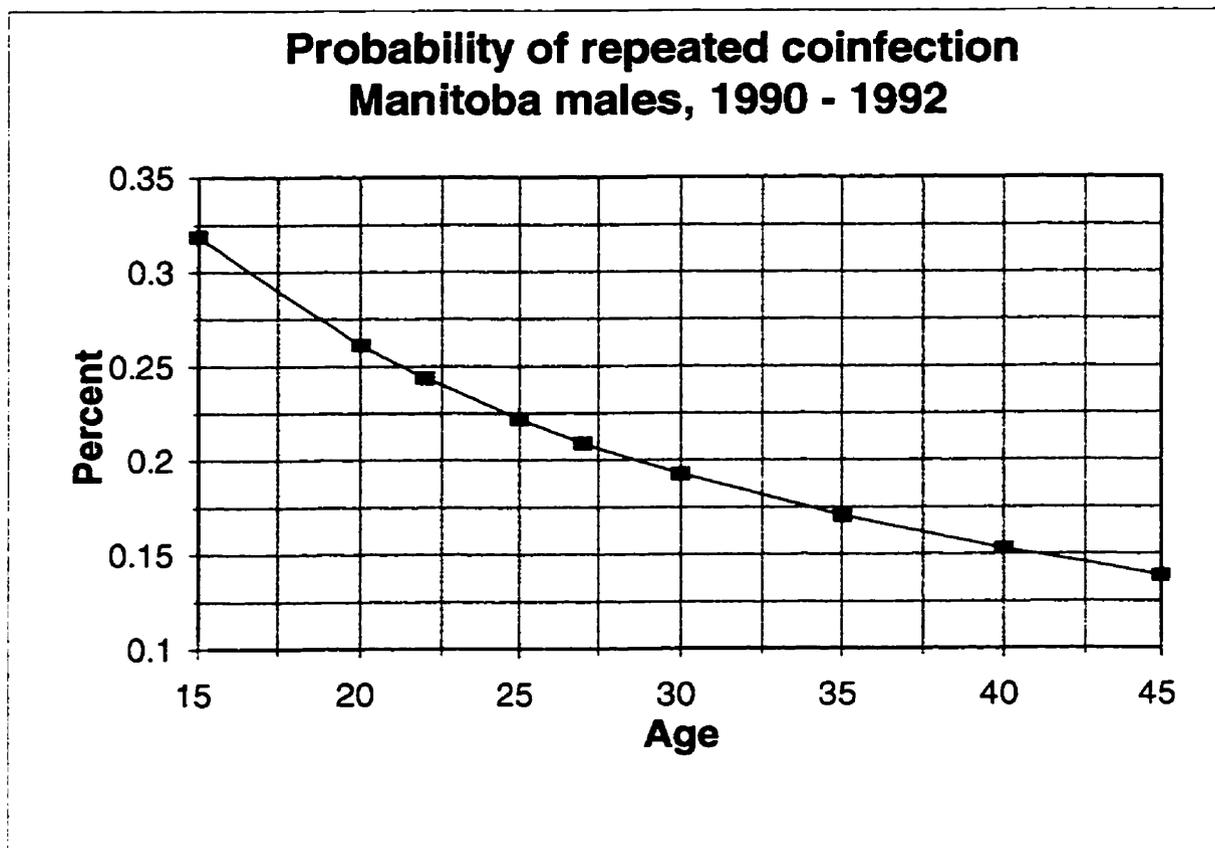


Figure 6.1 Probabilities of repeated coinfection by age, for a non-treaty male with no symptoms who has been appropriately treated for chlamydia and gonorrhea, and does not use an alias

Income quintiles and numbers of partners did not differ significantly when comparing coinfecting repeaters and non-repeaters. This is probably due to the fact that the population prone to both infections is homogenous to some extent in behavior and in socioeconomic status. The effect of infection with gonorrhea in research on pregnant women with chlamydia also suggests that gonorrhea is a marker for particularly low socioeconomic status which may nullify the effect of income level as a separate indicator in this analysis.¹³⁵

6.3 Analysis of contacts of coinfecting cases

Analysis of available information on the sex partners of individuals with confirmed coinfection is essential in attempting to describe potential core group populations.¹²⁸

While we lack proof of laboratory-confirmed STD in many of these people, this may be due to reasons entirely unrelated to the actual spread of disease in the population.

Contacts of cases who have been named more than once in three years, if infected, are more likely to have greater opportunities to transmit infection than those cases with only one infection or contacts named only once. The following analyses were completed in order to establish whether multiply named contacts are a definable group, distinct from those named only once.

6.4 Comparison of coinfecting repeat contacts and comparison group

As with the repeater coinfecting cases, there was a category of contacts of gonorrhea and chlamydia named repeatedly during the three year study period. Some were reported as exposed to both diseases simultaneously, while others were named, as contacts of chlamydia and gonorrhea alternately, at different points in time. The individuals named as contacts of serial coinfection posed a problem in terms of finding an appropriate control group. Neither those named as contacts only once of gonorrhea nor chlamydia cases only would be appropriate, as those are the two populations to which these were being compared. The most logical comparison group would be the contacts of coinfecting cases.

In order to assess the similarities between the multiply named contacts of coinfecting cases and those multiply named contacts of serial coinfection, the two groups were compared on univariate analysis. A more stringent p value was used, calculated by dividing the traditional 0.05 by the number of variables measured, ($n=5$) for a threshold value of 0.01. None of the proportions of gender, First Nations people, income levels or urban residence differed significantly. The difference in mean ages was evaluated by the Kruskal-Wallis test for differences in medians of two groups. This was used because of the non-normal age distribution; the heterogeneity of variances, and the fact that sample sizes were small (serial repeat contacts=159, coinfecting repeat contacts=133), which rendered the effects of the non-normality more severe than with larger sample sizes. Differences in ages were not significant either. Because of the lack of differences in the two populations of multiply named contacts of serial coinfecting cases and repeat contacts of coinfecting cases, the two groups were combined as the “coinfecting repeat contacts”. The use of the contacts named only once as exposed to coinfecting cases was therefore statistically, and logically justified.

Table 6.3 shows the results of the univariate analysis of multiply named contacts of coinfecting cases, and those named only once. Multiply named contacts differed from those named only once by gender and ethnic origin.

Table 6.3 Univariate analysis of coinfecting repeat contacts (n=294) and comparison group named only once infection (n=432)

	Comparison		Repeaters		p value
	% or mean	n	% or mean	n	
Age	22.6	395	22.1	292	n.s.
Urban	52.5	139	55.3	125	n.s.
Treaty status	24.3	105	40.1	118	<0.001
Female	31.2	137	20.0	59	<0.001
Income level					
<\$29,572					
Quintile 1	68.4	171	75.8	163	
Quintile 2	8.0	20	9.3	20	
Quintile 3	14.0	35	8.4	18	
Quintile 4	5.6	14	3.3	7	
Quintile 5	4.0	10	3.3	7	n.s.

The odds of a male being a multiply named contact of a coinfecting partner was 1.89 higher than that of a female. This is probably due to low levels of detection of chlamydial infection in men. Although epidemiologic treatment is provided for contacts, swabs may not be taken, and compliance may be low, especially where disease is asymptomatic.³⁸ This explanation is supported by the fact that there were no gender differences between repeatedly named gonorrhoea contacts, and those named only once. Therefore, it is likely that the gender differences in this analysis of coinfecting contact repeaters are due to the differences in the nature of chlamydial infection (asymptomatic), and in differences in

specimen collection and test sensitivity. Also, it is doubtful that the higher reliance on the patients with chlamydia to notify their own partners is as effective as the health provider referral more often used for gonorrhoea.^{183,184,194} For this reason, a higher proportion of male partners may not be notified, or tested.

Table 6.4 Logistic regression comparing coinfecting repeat contacts (n=294) and comparison group named only once (n=432)

Variables	Odds ratio	Lower 95% C.I.	Upper 95% C.I.	p value
Intercept	0.63			<0.001
Female	0.53	0.37	0.76	<0.001
Treaty status	2.11	1.52	2.91	<0.001

First Nations people eligible for treaty benefits were twice as likely to be repeatedly named as contacts as were non-aboriginal people. Once again, this can be attributed to higher levels of prevalent and incident infection within the population, more thorough interviews to elicit partner information, and perhaps increased willingness of First Nations people to give information on contacts. Only one study in the United States showed African Americans to be named more often as contacts of gonorrhoea cases than other ethnic groups, although coinfection with chlamydia was not considered in this study.¹⁸¹

This analysis shows that coinfecting repeat contacts are very similar, if not identical, to those individuals who have been named only once. Although it is tempting to combine the repeatedly named contacts together with those named only once, the more conservative

approach would be to examine differences between the contact repeaters for coinfection and those contact repeaters for gonorrhea and chlamydia, before pooling the two groups.

6.5 Comparison of chlamydia, gonorrhea, and coinfecting repeaters.

This section addresses the hypothesis that if the populations of individuals with repeated coinfection form a core group for chlamydia or gonorrhea, this group may be similar to that already described as responsible for maintaining gonorrhea or that responsible for propagating chlamydia. If substantial differences exist between the coinfecting repeaters and the gonorrhea and chlamydia repeaters, this would suggest that the groups are not identical, and that separate core groups may exist.

6.5.1 Comparison of coinfecting case repeaters with chlamydia case repeaters

The results of this analysis have already been described in Chapter 4 section 4.5.1. Briefly, coinfecting repeat cases differed greatly from chlamydia repeat cases in all attributes except age.

In view of the number of characteristics and the size of the differences between the two groups, we can logically conclude that coinfecting case repeaters differ significantly from chlamydia case repeaters.

6.5.2 Comparison of coinfecting case repeaters with gonorrhea case repeaters

This analysis was presented in Chapter 5, section 5.5.1. A high ratio of females to males indicated underdiagnosis of chlamydia in men, and the youth of the coinfecting repeaters may be due to higher susceptibility of young people to chlamydia. The large difference in age, and difference in uses of an alias may be due to different behaviors in age subclasses, which have been shown in previous research to harbor different sexually transmitted infections.¹³⁸

These differences preclude the assumption that all differences are artifacts of the health care system, and therefore combining the gonorrhea repeaters with the coinfecting repeaters was not justified.

6.6 Comparison of the contact repeaters with chlamydia, gonorrhea and coinfection

In order to establish whether possible core groups for chlamydia, gonorrhea and coinfecting transmission were the same, it was necessary to compare the multiply named contacts, similar to the analysis of the STD cases.

6.6.1 Comparison of coinfecting repeat contacts with gonorrhea repeat contacts

The description of the differences between repeatedly named contacts of coinfecting cases and all contacts of gonorrhea cases was presented in Chapter 5, section 5.6.1. Symptom

data were not available for contacts, but it is interesting to note that males who were likely infected with both gonorrhoea and chlamydia would probably have symptoms, but may not seek care promptly.

Coinfected contact repeaters differed from gonorrhoea contacts only with respect to age and gender. If one is prepared to attribute the differences in the populations to the pathophysiology of the disease (as affecting younger people), and the lack of testing and insensitive testing in men, these two groups would have similar characteristics. However, these differences are not echoed in the analysis of repeater cases, above. It is also possible that the age differences between the two populations are large enough to indicate that a different group of younger people who are susceptible to chlamydia are responsible for maintaining coinfection independent of the core group with gonorrhoea only.

6.6.2 Comparison of coinfecting repeat contacts with chlamydia repeat contacts

The results of the comparison of the coinfecting repeat contacts with the multiply named chlamydia contacts were shown in Chapter 4, section 4.6.1. Multiply named contacts of coinfection were more likely to be female (OR = 1.63), First Nations (OR=1.43) and live in the lowest quintile income areas in Manitoba, (OR=3.02). The higher risk of females to be multiply named contacts of coinfection indicates their involvement in the sex trade. Neither of the other two variables can be ascribed to differences in health care practices, therefore, it is reasonable to assume that the multiply named contacts of chlamydia and those who are named repeatedly as contacts of coinfection are not similar.

6.7 Comparison of repeat cases and repeatedly named contacts

The following analyses were designed to detect differences, if any, between coinfecting repeater cases and contacts proposed as containing the subset of the core groups.

Because it has already been established that the repeater groups of gonorrhea, chlamydia and coinfection are different, the multiply named contacts of coinfection will be compared with the cases who had confirmed coinfections over the three year period. If the differences are minimal, or are artifacts of health care practices and not due to inherent characteristics of the disease or the people it affects, this would suggest that a core group should include the multiply named contacts, not only the group of repeater cases.

In addition to the above hypothesis testing, the analysis will reveal the specific characteristics which prevent contacts, even though they have been named as sex partners multiple times, from becoming laboratory-confirmed repeaters.

6.7.1 Comparison of coinfecting repeat cases with multiply named contacts of coinfecting cases

The following table shows the results of the univariate analysis comparing coinfecting cases with repeated episodes of disease during the three year study period, and those who were named repeatedly as contacts of cases with coinfection. Income levels were of borderline significance, and were entered into the equation. Because proportions of people with

higher income levels were small, the third, fourth, and fifth income categories were combined.

Living in an urban area with a population density of 400 people or more per square kilometre was significantly associated with having laboratory-confirmed coinfection, on univariate analysis. This may be due to increased access to clinics with physicians who are familiar in dealing with sexually transmitted diseases associated with inner city, low income, ethnically diverse populations.

Table 6.5 Univariate analysis of coinfecting repeat cases (n=471) and multiply named contacts of coinfection (n=294)

	Case repeaters		Contact repeaters		p value
	% or mean	n	% or mean	n	
Age	20.1	471	22.1	292	<0.001
Urban	68.2	402	55.3	125	<0.001
Treaty status	51.6	471	40.1	118	<0.003
Female	71.5	471	20.0	59	< 0.001
Income					
Quintile 1					
<\$29,572	65.0	249	75.8	163	
Quintile 2	10.2	39	9.3	20	
Quintile 3	12.3	47	8.4	18	

	Case repeaters		Contact repeaters		p value
	% or mean	n	% or mean	n	
Quintile 4	6.8	26	3.3	7	
Quintile 5	5.7	22	3.3	7	0.055

When entered into the logistic regression model, shown in Table 6.6, an interaction effect was found between living in an urban area and being female. The odds of cases having laboratory-confirmed coinfection depended both on the gender and on the urban/rural residence of the individual. A female living in an urban area, had a probability of 0.93 of becoming a coinfecting case rather than a repeatedly named contact, whereas a rural woman had a probability of 0.77 of being diagnosed as coinfecting case compared with being a multiply named contact. This effect was independent of whether an individual was of First Nations ancestry, hence differences in care which may result in lower detection rates on rural Indian reserves do not affect this result. It is possible that increased rates of case detection in urban areas may be related to the sex trade which is more prevalent in urban areas, and more convenient access to health services such as walk-in clinics.

Males were five times less likely to be laboratory-confirmed as cases, than they were to be repeatedly named as contacts of laboratory-confirmed coinfecting repeaters. As with chlamydia repeat cases and contacts, this is due to poor test sensitivity, poor specimen quality, reluctance of physicians to obtain specimens, and reluctance of patients to provide

them. One other factor which lowers the likelihood of a positive laboratory test is the recommendation in the current STD guidelines for Manitoba that specimens for gonorrhoea are collected before those for chlamydia, if both are to be collected.³²

Tble 6.6 Logistic regression comparing coinfectd repeat cases (n=471) and coinfectd repeat contacts (n=294)

Variable	Odds ratio	Lower 95% C.I.	Upper 95% C.I.	p value
Intercept	0.72			0.28
Urban	1.16	0.71	1.91	0.55
Treaty status	2.16	1.49	3.13	<0.001
Female	4.63	2.59	8.26	<0.001
Income				
Quintile 1				
<\$29,572	0.46	0.27	0.76	<0.001
Quintile 2	0.40	0.23	0.71	0.002
Interaction				
Urban*Female	3.40	1.62	7.15	0.001

Being of First Nations ancestry doubled the likelihood of having a laboratory-confirmed diagnosis of coinfection(s), over those named repeatedly as contacts to coinfection.

Reasons for this are that physicians and other health care providers may be more reluctant to test and therefore notify Manitoba Health of infections in non-aboriginal people.

Physicians' predisposition to provide disease specific diagnoses for aboriginal women rather than a nonspecific diagnosis such as "cervicitis" for non-aboriginal women has been

previously documented in Manitoba.¹⁷⁴ It is also possible that aboriginal people may be more compliant with laboratory testing than non-aboriginal people.

Lastly, those people living in the lowest two income quintile areas in Manitoba were less likely to have laboratory proven infection than those living in income quintiles three, four and five, (ave. household income greater than \$44,027.) Those living in the first and second income quintiles were 60% and 48% less likely to have a confirmed laboratory diagnosis respectively, once gender, ethnic origin, and urban area of residence were taken into account. This may be due to a number of factors. First, contacts may change their residence more often, and therefore are more difficult to locate. Second, they may be more involved in illegal activities and be hiding from the authorities. In addition, they may use aliases more often. Both of these factors make location notification and testing of contacts more difficult. It is also possible that individuals with higher income are more likely to have more education, which in turn may motivate them to seek care if they suspect that they are infected or have symptoms.

This last analysis is more complicated than those which show the similarity of case and contact repeaters for chlamydia or gonorrhoea. In both those cases the analysis showed differences in only one or two characteristics which could easily be explained by idiosyncracies in the health care systems. This last analysis demonstrates a complex relationship between gender, use of aliases, First Nation ethnic group, urban residence and income level which indicates involvement with commercial sex. The fact that men are

less likely to become confirmed cases of coinfection suggests that either sex partners of the sex workers or the pimps may be the group of contacts who are less likely to become repeatedly confirmed cases. This is supported by the differences in income levels, which is significantly lower for cases than it is for contacts.

6.8 Conclusions

Exhaustive analysis of coinfecting cases and contacts has revealed differences between those repeatedly coinfecting and those with only one coinfection. There were also differences between chlamydia case repeaters and coinfecting repeaters, although there were fewer differences between coinfecting case repeaters and gonorrhoea case repeaters. Similar findings were shown for the contacts, although the only differences found were in proportions of First Nations, and gender. Analysis of the contact repeaters showed that coinfecting multiply named contacts were more similar to gonorrhoea multiply named contacts than multiply named contacts of chlamydia.

The comparison of the coinfecting case and contacts was interesting in that it suggested urban females are likely to be confirmed as having infection, while males of higher income are more likely to be known as contacts only. This can be explained by the different populations participating in commercial sex, which has implications for the prediction of groups at risk of coinfection, and for public health interventions with those groups.

Despite the differences in coinfecting case and contact repeaters, the potential that they form a core group who transmit both gonorrhoea and chlamydia is still possible. The final proof of this will be in the calculation of the reproductive rates of coinfection in both the repeater and non-repeater populations.

Chapter 7

Predicting case and contact repeaters: results and discussion

7.1 Introduction

One of the primary goals of this research was to test the feasibility of predicting the likelihood that an individual would have repeated episodes of gonorrhea or chlamydia or both, or would be named repeatedly as a sex partner of an individual with confirmed STD. If prediction was fairly simple, and reasonably sensitive and specific, then individuals at high risk of having repeated exposures to STD could be offered extra services, such as single dose therapy for chlamydia, cervical cancer screening, hepatitis B vaccination, enhanced STD education and HIV testing.

Because the risk behaviour under study is that of repeated exposure to chlamydia and gonorrhea, individuals with repeated laboratory-confirmed episodes of disease and those who were named repeatedly as sex partners of confirmed cases, were combined for these analyses. The comparison cases and contacts with only one episode were also combined.

Combining the cases and contacts may seem controversial. However, there are a number of reasons for it. The first is that, as mentioned in Chapter 2, section 2.2, repeated laboratory proven infection with chlamydia or gonorrhea is a function both of risky sexual intercourse, as well as the capability of the health care system to accurately diagnose disease. The appropriate intervention for preventing disease should occur because of the individuals' repeated exposure to disease, whether or not the medical care system is able to diagnose it. As we have seen from previous analyses, chlamydial infection in men is under diagnosed, both for technical and sociological reasons. Therefore, attempting to predict repeated positive STD tests in this group, by using only those individuals with laboratory-confirmed tests compared with those with only one positive test, compounds the biases already inherent in the medical system. Second, the analyses of gonorrhea repeater cases and contacts, and that of chlamydia repeater cases and contacts reveal that the contacts resemble cases to a large degree, despite the fact that some do not have confirmed infections. The only circumstance where combining the cases and contacts is questionable is that of the coinfecting repeaters, where contacts seem to differ on a number of characteristics which may be related to the sex trade. In order to assess the predictive models I have combined the coinfecting repeater case and contacts, but it is possible that such a model may not be practically applicable because of the differences in the populations. Third, other studies on repeater populations have noted the important role played by sexual contacts of repeaters in maintaining STD endemicity.^{128,129} Last, combining both cases and contacts in this analysis facilitates the application of the results in practical, everyday situations. If cases and contacts were analyzed separately, this

would mean producing six prediction tables, for gonorrhoea, chlamydia and coinfection. Collapsing the repeater cases and contacts for each disease category produces only three prediction tables.

Although more information is available on cases than on contacts, I have chosen predictor variables which are easily accessible and are available for both groups. For example, it is too difficult to ascertain income level of the postal code area in which an individual resides, but the individual's gender and reported age are more easily ascertained.

Although incorrect therapy for chlamydial infections was associated with repeated infections, this was not included in predictive models. Firstly, the information may not be readily available to public health nurses in the field; secondly, it is a circumstance which can be automatically flagged and corrected once the infection is reported to Manitoba Health; thirdly, because of its ease of correction, and because an evaluation of therapy is being conducted, inappropriate therapy should not be a continuing factor in chlamydia epidemiology in Manitoba.

The following logistic regression analyses are attempts to build a model based on individual characteristics which can be used for predicting a probability that an individual will have repeated exposures to disease or not. The result of the logistic formula is the log probability of the outcome event. Because the model is now being used to predict a binary outcome (repeatedly exposed/infected or not), a decision has to be made on the breakpoint below which the individual cannot be considered to be a repeater, and above

which the individual should be classified as a repeater. In order to obtain the sensitivity closest to 75% which would be acceptable for a screening test, and in combination with the most specific results, various values of this breakpoint were selected, and the resulting classifications reviewed. This exercise, if carried out for each breakpoint value of 1 - 100, would result in values of the receiver operating characteristic curves. However, in the following analyses, only the performance characteristics of the breakpoint values which produced sensitivities of about 75% were examined. The value which produced a sensitivity closed to 75% without allowing the specificity to drop significantly was selected. For example, in each analysis the breakpoint was varied, producing sensitivities of 73%, 74% 75% and 76%. The specificities would be for example, be 41%, 40%, 32% and 22%, respectively. In this case the breakpoint would be selected so that the sensitivity would be 74% and the specificity, 40% producing the optimal sensitivity and specificity.

The sensitivity, specificity, false positive rate and false negative rate were produced by the statistical analysis program NCSS. The predictive model with the selected breakpoint was tested against the data themselves, and the performance characteristics were calculated in a classification table, which clearly showed the proportion of true positives, true negatives, false positives and false negatives.

In order to develop a model which explained the highest proportion of variation in the study populations, a new variable was developed based on the general area of residence of the individual. The forward sortation areas where the proportion of repeaters and non-

repeaters differed by more than 5% were entered into the logistic model. The “high risk postal code prefix” was intended merely as an indicator or proxy for repeater status, rather than being a causative factor. Because of the large areas involved there was initially no supposition that physical presence in the area was causative of being a repeater. Had the areas been smaller, it is possible that individuals living in the “high risk area” would be more likely to meet and have sex with others in the area, facilitating a high incidence of STD. The possibilities of geographic area being a significant factor in the development of sexual networks and hence their role in repeated high risk exposures became evident only later in the last phase of the research.

7.2 Predictive model for individuals with repeated exposure to chlamydia.

Table 7.1 shows the univariate analysis of cases with repeated chlamydial infection and multiply named contacts of chlamydial infection, compared with individuals with only one episode of chlamydia and those who have been named only once.

Table 7.1 Univariate analysis of chlamydia repeat cases and contacts (n=2,717) and comparison group named only once, or with only one episode of infection (n=3,053)

	Comparison		Repeaters		p value
	% or mean	n	% or mean	n	
Age	23.1	2,935	21.9	2,705	<0.001
Alias	9.2	278	18.6	506	<0.001
Treaty status	16.0	489	33.2	903	<0.001
Urban	82.1	2,505	74.1	2,014	<0.001
High risk postal code prefix	28.0	761	45.8	2,623	<0.001
Female	55.3	1,688	61.8	1,678	<0.001

The above variables are not necessarily causative of repeated exposure to chlamydia, but were chosen because the information on a patient could be easily accessed - whether reported by a sex partner or from the Manitoba Health patient registry database. The risk factor data used in the descriptive models was derived differently from the sexually transmitted disease registry than that for risk markers. The primary differences were that the ages and postal codes were the most typical (for cases or contacts) during the study period. For a more detailed description of these variables, see Chapter 3, section 3.4.

The effect of large sample sizes is remarkable in the above analysis. An age difference as small as 1.2 years is highly significant, as is a difference in proportions of gender of only 6.5%. On multivariate analysis, gender was not significant and was not incorporated into

the model. Logistic regression results are similar to those found in the descriptive logistic models, with repeaters being younger than the comparison group, more likely to be of First Nations ancestry, and more likely to use aliases. The high risk postal code prefix is a variable derived from postal code data. The forward sortation areas selected were those where high proportions of repeaters but low proportions of non-repeaters lived. Because only the prefix is used, it applies to large general areas of the province which are easily distinguishable, and does not require knowledge of the individuals' precise address. For the purposes of chlamydia case and contact repeaters, the following postal code prefix areas contained higher proportions of chlamydia repeaters than non-repeaters; R0B, R2W, R2X, R3A, R3A, R3G, and R9A. Appendix I shows a map of the postal code prefixes in Manitoba and Winnipeg.

Table 7.2 Logistic regression comparing chlamydia repeat cases and contacts (n=2,717) and comparison group with only one infection (n=3,053)

	Odds ratio	Lower 95% C.I.	Upper 95% C.I.	p value
Intercept	6.17			<0.001
Treaty Indian	1.93	1.69	2.21	<0.001
Alias	1.87	1.59	2.20	<0.001
High risk postal code prefix	1.85	1.64	2.09	<0.001
Log Age	0.46	0.36	0.59	<0.001

The usefulness of the above logistic regression model in predicting whether or not an individual is likely to be repeatedly named or have repeated infections with chlamydia is

defined by the following parameters. The sensitivity (the ability of the model to accurately predict those who are repeaters), of the analysis was 76.9%; the specificity (the ability of the model to accurately classify those who are not) was 40.9%. The sensitivity was calculated by dividing the true positives by the true positives and false negatives, and the specificity was calculated by dividing the true negatives by the true negatives plus the false positives. The proportion of false positives (for whom the prediction was positive, but who are not actually repeaters) was 46.4% and that of the false negative (for whom the prediction is negative but the individual is actually a repeater) is 33.5%. The positive predictive value, given the period prevalence of repeaters during the study period was 31.3%. The positive predictive value is the proportion of all individuals classified as repeaters by the model, who truly were repeaters. In other words, using this model only one third of all the people predicted to be repeaters by this model actually were repeaters; the others were not. Lastly, the negative predictive value is 83.4%, meaning that of all the individuals the model predicted were not repeaters, 83.4% were in reality not repeaters, and the remaining 16.6% are repeaters.

I have not imposed a standard as to how high the sensitivity and specificity should be in order for this model to be useful to public health nurses and other medical staff. This dilemma was encountered in previous research.¹²⁸ If interventions were to be costly in terms of time and/or materials then many individuals (46.4%) would receive interventions which may not be necessary, as they are not at risk of being repeatedly exposed to chlamydia. It would be ideal to actually locate all patients who fall into the high risk

repeater category predicted by the model, and then ask further questions which would separate those at high risk from those who would otherwise be false positives. Such questions may relate to numbers of sex partners, education levels, frequency of intercourse or history of sexually transmitted disease, and would prove valuable when used in combination with the predictive model. Even without the second step (asking further questions) the sensitivity of the model is high, and the proposed interventions are reasonable and non-invasive, so although 46.6% of people would be offered enhanced prevention measures, the measures would benefit them, rather than cause harm. Of course, 23.1% of the repeaters would not be predicted by the model, and therefore they would miss any enhanced prevention efforts. In one study which attempted to predict the likelihood of individuals who would return with recurrent sexually transmitted diseases, 39% of those predicted to be at high risk returned with repeated infection.¹²⁸ This is comparable to the positive predictive value of the current research which is 31.3%. Another study predicting repeated infections failed to show any predictive characteristics at all,¹³¹ while a third showed a sensitivity for women of 82.7% for repeated gonorrhoea, a specificity of 62.2%, and a false positive rate of 32.2%.¹²⁷ The model for males in the study conducted in Sheffield, England in the late 1970's showed a sensitivity of 71.8%, a specificity of 64.4% and a false positive rate of 38.3%. The results from the English study are admirable, however, the culture and timing of the study are vastly different from that of Manitoba in 1990, so that comparisons may not be valid.

Table 7.3 shows the calculated risks of First Nations people, individuals using aliases, those living designated in high risk postal codes and combinations of these characteristics for various age groups. The shaded probabilities are greater than the cutoff point of 0.37 and individuals falling into these categories should be regarded as potential repeaters. The classification midpoint of 0.37 was selected from various models of the same data because it yielded the parameters with the acceptable sensitivities of around 75% without allowing specificity to drop drastically. The first column of the table shows selected ages of individuals, the second is the result of the logistic regression formula with the value of one for individuals who have First Nations heritage. The third column shows the probability given by the logistic formula. The fourth column shows the result of the logistic equation for individuals who do not have treaty status, and the fifth column shows the associated probability with the result. Residence in any of the following forward sortation areas, R0B, R2W, R2X, R3A, R3B, R3G, and R9A were predictive of a higher risk of being a chlamydia repeater.

Table 7.3 Probabilities of being a chlamydia contact or case repeater for individuals with different characteristics.

Age	Formula with		Formula with-	
	Treaty status	Probability	out Treaty status	Probability
15	1.47	0.43	0.76	0.37
20	1.17	0.34	0.61	0.30
25	0.99	0.28	0.16	0.14
30	0.86	0.24	0.14	0.12

	Formula with			Formula with-	
	Age	Treaty status	Probability	out Treaty status	Probability
Used Alias	15	2.75		1.43	
	20	2.20		1.14	
	25	1.85		0.96	
	30	1.61		0.83	
Residence in high risk postal code	15	2.72		1.41	
	20	2.18		1.13	
	25	1.83		0.95	
	30	1.59		0.82	
Both of the above	15	5.10		2.64	
	20	4.08		2.11	
	25	3.43		1.78	
	30	2.98		1.55	

The challenge in accurate prediction of chlamydia repeaters using well-defined characteristics compared with non-repeaters lies in a number of factors. Firstly, the epidemic may have been so pervasive that there is a large variation in the kinds of people affected. Widespread screening and testing began in Manitoba in 1988, and it is possible that in 1990, some prevalent rather than incident infections were diagnosed, so that the model is attempting to define both incident infections and those which may have been present in the individuals for months, if not years. Secondly, and more important, we are attempting to define people's behaviour by some very superficial characteristics such as age and gender. These are mere proxies for high risk sexual behaviors which have a host of psychological and sociological factors underlying them. The fact that the predictive

model may not be adequately specific indicates either that we are not collecting relevant data on chlamydia cases and contacts, or that those variables which would be predictive of repeated risky exposures are not easily accessible.

In order to make the use of this formula more practicable, and to raise the specificity, I suggest the above table be used in conjunction with another screening tool. The attributes of the client are available without contacting the patient, and an initial probability of repeater status established. On meeting the client, a question as to the client's number of partners in the last three months, frequency of intercourse, and use of condoms may help to further differentiate those at higher risk of being repeaters than other clients.

7.3 Predictive model for individuals with repeated exposure to gonorrhea

Laboratory proven cases of repeated gonorrhea infection were combined with individuals named as contacts. Contacts of gonorrhea cases who were named only once were not statistically different from those who had been repeatedly named, therefore these two groups were combined. Therefore, the analysis compared those people with one episode of laboratory-confirmed gonorrhea with all contacts of gonorrhea including those with repeated episodes of infection.

Table 7.4 Univariate analysis of gonorrhoea repeat cases and all contacts (n=896) and comparison group with only one infection (n=570)

	Comparison		Repeaters		p value
	% or mean	n	% or mean	n	
Age	27.4	570	24.4	881	<0.001
Alias	13.3	76	16.3	146	n.s.
Treaty status	27.5	157	43.1	386	<0.001
Urban	76.5	436	69.2	560	0.003
High risk postal code prefix	57.8	329	70.5	594	<0.001
Female	40.2	229	40.0	358	n.s.

As with the gonorrhoea case repeaters, this analysis shows that repeaters are younger, (by three years) and are more likely to be status Indians. On logistic regression, only age, being First Nations and living in a high risk area were associated with being a repeat case or contact of gonorrhoea.

Table 7.5 Logistic regression comparing gonorrhoea repeat cases and contacts (n=896) and comparison group with only one infection (n=570)

	Odds ratio	Lower 95% C.I.	Upper 95% C.I.	p value
Intercept	20.0			0.01
Treaty status	1.69	1.34	2.13	<0.001
High risk postal code prefix	1.67	1.33	2.10	<0.001
Log Age	0.38	0.26	0.55	<0.001

The above analysis yielded a sensitivity of 79.4%, and specificity of 40.2%. Although the model correctly classifies almost 80% of gonorrhoea repeaters, it classifies only 40% of non-repeaters correctly. The false positive rate using this model is 32.4% and the false negative rate is 44.7%. Use of this model would therefore mean that 32.4% of individuals would falsely be classified as repeaters, and 44.7% of all repeater individuals would be classified as non-repeaters. A study on gonorrhoea repeaters in England yielded comparable results; model of repeated gonorrhoea showed a sensitivity for women of 82.7%, a specificity of 62.2%, and a false positive rate of 32.2%.¹²⁷ The model for males in the study, conducted in Sheffield, England in the late 1970's showed a sensitivity of 71.8%, a specificity of 64.4% and a false positive rate of 38.3%.

Using the real prevalence of gonorrhoea repeaters during the study period, the positive predictive value, (the proportion of individuals classified as repeaters who truly are repeaters), 42.4% and the negative predictive value (the proportion of individuals classified as non-repeaters who truly are not repeaters), is 77.8%.

One of the possible reasons for the lack of distinction between individuals with only one episode of gonorrhoea and those with multiple episodes or those who named as contacts, is that the control program for gonorrhoea in Manitoba has reduced the pool of individuals with gonorrhoea to the extent that they are homogenous. Therefore, any demographic difference is not highly predictive of being a gonorrhoea repeater. The other possible reason for this is that the demographic variables to which we have easy access are not accurate proxies for high risk sexual behaviour.

As with the model of chlamydia repeaters, the addition of a simple question about sexual practices or education level may be able to substantially increase the usefulness of the model by raising the specificity. At least the model, as it stands, provides some advance guide as to which contacts or cases would be more likely to transmit disease. Once again, it is left to the discretion of the reader to decide how this model could be most useful.

Areas in which there were higher proportions of gonorrhoea repeaters included the following postal code prefix areas; R0B, R2G, R2W, and R7A (Figure 7.1). Probabilities of being repeaters for individuals with certain characteristics are provided in Table 7.6. The classification midpoint which provided the most acceptable sensitivity and specificity was 0.55. Once the natural logarithm of the age, and the indicators for treaty status (treaty status=1, no treaty status=0) and use of an alias (ever used alias=1, no alias=0) were placed in the logistic equation, the third and fifth columns were calculated, and the probabilities of repeater status were derived from those.

Table 7.6 Probabilities of being a gonorrhea contact or case repeater for individuals with different characteristics.

	Formula with			Formula with-		
	Age	Treaty status	Probability	out Treaty status	Probability	Probability
	15	2.53		1.50		
	20	1.92		1.14		0.53
	25	1.55		0.92		0.48
	30	1.30		0.77		0.44
	35	1.12		0.66		0.40
Used Alias	15	4.23		2.51		
	20	3.21		1.90		
	25	2.59		1.53		
	30	2.18		1.29		
	35	1.88		1.11		0.53

7.4 Predictive model for individuals with repeated exposure to gonorrhea and chlamydia coinfection

The following analysis was intended to differentiate individuals with only one episode of gonorrhea and chlamydia coinfection and those who were named only once, from multiply named contacts and those with multiple infections. Those with repeated exposure to coinfection would be more likely to be infected, and secondly, to transmit infection to others.

Table 7.7 Univariate analysis of coinfecting repeat cases and contacts (n=765) and comparison group with only one infection (n=731)

	Comparison		Repeaters		p value
	% or mean	n	% or mean	n	
Age	22.3	694	21.2	762	<0.001
Alias	9.3	68	22.0	168	<0.001
Treaty status	28.2	206	47.2	361	<0.001
Urban	71.5	523	70.1	536	0.53
High risk postal code prefix	71.2	521	74.2	566	0.21
Female	43.2	316	51.8	396	0.001

Differences in frequencies of coinfecting repeat cases and contacts and those named only once, or named only once were observed in the following postal code prefix areas; R0B, R2R, R2V, R2W, R3B, R3C, R3E and R1A. However, this variable was not significant on univariate analysis.

As shown in the analysis of coinfecting cases and contacts, a higher proportion of repeaters are of First Nations ancestry, with almost half of the case and contact repeaters being status Indians, although they comprise only 7% or less of the population of Manitoba, allowing for the undercounting of status Indians in the Manitoba Patient Registry File.¹⁹⁵ Use of an alias also increased the risk of being repeatedly infected, or repeatedly named as a contact to gonorrhoea and chlamydia coinfection. Interestingly enough, the ages of

coinfected repeaters and non-repeaters did not differ as much as the repeaters and non-repeaters with gonorrhoea. This may be due to the increased susceptibility of younger people to chlamydia, and the homogenous high risk behaviors of all individuals exposed to coinfection, whether they were repeatedly exposed or not.

Table 7.8 Logistic regression comparing coinfecting repeat cases and contacts (n=765) and comparison group with only one infection (n=731)

	Odds ratio	Lower 95% C.I.	Upper 95% C.I.	p value
Intercept	2.66			0.16
Treaty status	2.12	1.71	2.64	<0.001
Alias	2.40	1.76	3.27	<0.001
Log Age	0.64	0.41	1.01	0.05

The preceding model yielded a sensitivity of 79.4% and a specificity of 40.2%. The proportions of false positives were 32.4% and false negatives were 44.7%. While this model is reasonably sensitive in its ability to correctly detect coinfecting repeat cases and contacts, it lacks a high degree of specificity. The use of an additional screening tool is advocated in order to increase the specificity. Using the real incidence of repeatedly named cases and contacts of coinfection from 1990 - 1992, the positive predictive value of the test was 42.4% and the negative predictive value is 77.8%. This means that at the current rates, 58.6% of all individuals would be incorrectly classified as repeatedly coinfecting cases and contacts. These findings are comparable to those in previous reports.^{127,128} The exception to this, is the higher specificity found in the study of gonorrhoea repeaters in England.

The fact that the model lacks specificity may be due to the fact that individuals who are named contacts of cases with both gonorrhoea and chlamydia, or have confirmed coinfection, are similar. Demographic indicators for coinfecting repeaters were different from those with only one infection, although the contacts were similar. It is therefore possible that both case and contact repeaters with coinfection are part of a core group which has sufficient rate of partner change both to transmit two infections, become symptomatic, (more likely with two infections than with only one), be treated and then become re-exposed and reinfected. The increased likelihood of symptoms, and the increased diligence with which coinfecting cases and their contacts are followed up, suggests that the cycle of cure and reinfection is more rapid among this group, than among people with chlamydia only. Complicating this analysis, is the recent evidence of reactivation of chlamydial infection after infection with *N. gonorrhoeae*.¹³³ Of course, it is also possible that the demographic information which we find easy to collect, is not indicative of the behaviour which leads to exposure to coinfection, and that we need to collect other information. It is equally possible that there may be no easily collectable, proxy indicators for such risk.

Because of the relatively high sensitivity of this predictive model, it does provide a valuable strategy for initial separation of individuals who may become repeaters and those who probably will not. Prediction tables are contained in Table 7.9. The classification midpoint which yielded the highest sensitivity without allowing specificity to fall drastically was 0.42. All client characteristics and combinations thereof which are shaded

indicate that the individual should be considered at high risk of being a repeater, or core group member.

Table 7.9 Probabilities of being a coinfecting contact or case repeater for individuals with different characteristics.

	Formula with			Formula with-		
	Age	Treaty status	Probability	out Treaty Status	Probability	Probability
	15	1.71		0.81		
	20	1.51		0.71		
	25	1.37		0.64		0.39
	30	1.26		0.59		0.37
	35	1.18		0.55		0.36
Used Alias	15	4.10		1.93		
	20	3.61		1.70		
	25	3.27		1.54		
	30	3.02		1.42		
	35	2.82		1.33		

7.5 Conclusions

This first attempt at using demographic characteristics to classify risk of repeated infection and/or exposure to STD has been fairly successful. High sensitivities allow for the detection (or prediction), of most repeaters. It is proposed that the above predictive models be used in conjunction with another screening tool, such as questions on numbers of sex partners, or education level, and use of condoms to decrease the number of non-

repeaters to whom enhanced intervention measures would be offered. Although repeaters have been considered very important in the transmission of sexually transmitted infections,¹³⁹ only three research groups have ever attempted to predict repeater groups. None of these studies included information on the contacts of repeat cases, although their impact on endemicity was recognised.^{127,128,131}

The following chapter contains analyses of number of partners of repeater and non-repeater groups. The average number of partners over a period of time, the duration of infectiousness, and the probabilities of transmission of a pathogen which are central to the concept of core groups and STD risk, will be described.^{110,196} In order to evaluate the role of repeater cases and multiply named contacts in maintaining viable infections in the community, the reproductive rates of the repeaters and non-repeaters will be calculated.

Chapter 8

Numbers of partners, estimation of core group parameters, and sexual networks: results and discussion

8.1 Introduction

Defining the number of partners of core group members is an important step in describing transmission of pathogens within the core and between the core and the rest of the population. The unreliability of contact tracing data has hampered research, as clients are asked not only to divulge the numbers of partners, but also their names.^{108,113} Although gathering such data from contact tracing studies is complex, and some clients are unwilling to divulge partners, it must be remembered that we gain information on contacts from two sources. The first is the index case, and the second is the contact who, if infected, will usually name the index case as well. Although information provided by clients on sex partners may not be complete, this analysis includes sex partners named by the index case, and also those infected sex partners who named the index case over a period of three years.

All named sex partners of all individuals with chlamydia and gonorrhoea are recorded in a database maintained Manitoba Health (see Chapter 2) Unfortunately, the databases of

named contacts and laboratory proven cases were maintained separately, and there was no indicator to link a contact who was investigated and was subsequently found to be infected with his or her record as registered in the case database. Identifying information such as birth date and address of contacts was more likely to be incomplete, and of course treaty numbers or MHSC numbers are not known to public health staff until after the contact is found to be a case. Decisions as to whether a case record and a contact record both referred to the same individual were made according to the criteria outlined in Chapter 2.

In order to estimate the numbers of partners of chlamydia, gonorrhea and coinfecting repeater cases, random samples of the repeater and comparison groups in the previous chapters were selected. The samples were taken from the case and contact repeater groups, and compared with the contacts who had been named only once, and with cases who had only one episode of infection. They were drawn using the Rsample program in Epi Info, version 6.01 (Centers for Disease Control, Atlanta, Georgia). The samples were stratified by disease; chlamydia, gonorrhea, or coinfection (see Chapter 2, section 2.7.5.)

In addition, the values for c and σ in the formulae

$$R_0 = \beta c D$$

and

$$c = m + \frac{\sigma^2}{m}$$

are calculated from these data.

8.2 Results of comparisons between case repeaters and comparison groups.

The following comparisons were made initially using univariate techniques. The total number of partners of an individual was calculated by adding the number of individuals named by the case and the number of individuals who had named the case. If the individual had repeated episodes of chlamydia, the number of total partners was divided by the number of episodes, averaged, and rounded to a whole number (see Chapter 3, section 3.4.7.) Univariate analysis of differences in numbers of partners between chlamydia cases who had repeated episodes of disease during the study period and those who had only one episode was completed using Epi Info, version 6.01. (Centers for Disease Control, Atlanta, Georgia). As distributions were non-normal, the non-parametric equivalent of Student's t-test, the Mann-Whitney U test for measuring differences in means of two samples was used.

In order to assess the unique effect of numbers of partners on whether an individual had repeated STD episodes, the numbers of partners were divided into categories for multivariate analysis. Categories were made up of not less than 10% of the samples and the reference group comprised those individuals with zero partners per episode.

8.2.1 Chlamydia case repeaters and comparison group.

Table 8.1 shows the results of the comparison between individuals with repeated episodes of confirmed infection with chlamydia and those with only one infection.

Table 8.1 Univariate analysis of chlamydia repeat cases (n=64) and comparison group with only one infection (n=71), including data on numbers of partners who named the case and who were named by the case.

	Comparison		Repeaters		p value
	% or mean	n	% or mean	n	
Age	22.0	71	21.0	64	n.s.
Urban	85.9	61	70.3	45	0.03
Treaty status	18.3	13	39.1	25	0.012
Used alias	11.3	8	32.8	215	0.003
Inappropriate therapy	38.0	27	36.5	23	n.s.
Female	81.7	58	78.1	50	n.s.
Symptoms noted	50.7	36	54.7	35	n.s.

	Comparison		Repeaters		p value
	% or mean	n	% or mean	n	
Income					
Quintile 1					
<\$29,572	36.1	22	46.2	24	
Quintile 2	23.0	14	21.2	11	
Quintile 3	11.5	7	17.3	9	
Quintile 4 & 5	29.5	18	15.4	8	
Number of named partners					
0	14.1	10	4.7	3	
1	57.7	41	54.7	35	
2	21.1	15	20.3	13	
>3	7.0	5	20.3	13	0.055

Recoding the partner data into a categorical variable resulted in loss of power. The analysis of actual rounded numbers of average partners per episode of infection by Kruskal-Wallis test showed a significant difference in numbers of partners, $p=0.02$. Once these data were transformed into four categories the p value for differences between chlamydia repeaters and non-repeaters dropped to 0.055, on the edge of significance. The mean, median and variance of numbers of partners of chlamydia non-repeaters were 1.2, 1.0, and 0.73; and of repeaters they were; 1.75, 1.0, 1.91, respectively.

The difference in numbers of partners was not detectable on multivariate analysis. Because the number of partners of an individual is a phenomenon which has a direct effect on the likelihood of infection, instead of the other demographic variables which are proxy indicators of behavior, the dummy variables for numbers of partners were forced into the logistic equation. Despite this, numbers of partners were not associated with any significant improvement in the model. This may indicate that no differences in numbers of partners exist beyond those which are already explained by ethnic group, and use of an alias in the logistic regression. It is also possible that the difference is so small that it requires a larger sample size to be detected on multivariate analysis. Another logical, and more likely explanation of the lack of importance of numbers of partners, was already mentioned in Chapter 1. The measurement of numbers of partners may not be adequate to describe risk of repeated chlamydial infection; what may be more important is who the partners are.

Associations between numbers of partners and recurrent chlamydial infection on univariate analysis have been found in two previous studies, but did not remain in the multivariate statistics.^{125,132} Mosure et al found that predictors of repeated chlamydial infection in female adolescents did not differ from predictors of adolescents with only one infection, and these predictors included having a new partner within the last 60 days.¹³¹ Lastly, Blythe et al actually found that remaining with the same partner was predictive of shorter time to recurrent chlamydia diagnosis, which was probably due to reinfection from an untreated partner.¹⁵⁶

Analyses of other variables which were significant on univariate analysis of the smaller samples are not presented, because the larger population from which these samples were taken has already been analyzed in Chapter 4. Because the number of people in the earlier analysis is so large, those results are far more accurate than any analysis of these smaller samples would produce.

8.2.2 Gonorrhea case repeaters and comparison group.

Although numbers of partners of gonorrhea repeaters differed from those individuals with only one confirmed gonococcal infection by Kruskal-Wallis testing ($p=0.007$), the variable did not remain significant after transformation into categories for multivariate analysis.

This finding is in agreement with previous studies, in which no association was found on univariate analysis between higher numbers of sex partners and repeated gonococcal infections.^{124,125,127,186} The mean, median and variance for gonorrhea non-repeaters were; 1.13, 1.0, and 0.94, and for gonorrhea repeaters they were; 1.67, 1.0, and 1.42, respectively.

Because numbers of partners were not significant on univariate or multivariate analysis, the tables of data are not presented. The other information gained from the univariate analysis is a repetition of that already presented in Chapter 5 with the whole population of repeaters, and hence that analysis is more accurate.

8.2.3 Coinfected case repeaters and comparison group

Numbers of partners per episode did not differ on univariate or multivariate analysis when individuals repeatedly infected with gonorrhea and chlamydia were compared with those coinfecting only once. The mean, median and variance of the coinfecting non-repeaters were 1.3, 1.0, and 0.89, and for the coinfecting repeaters were 1.7, 1.0, and 2.3, respectively. Again, tables of univariate statistics are not presented here, as they duplicate the analysis of the larger samples in Chapter 6.

8.3 Chlamydia, gonorrhea and coinfecting case repeaters

Differences in numbers of sex partners between the repeatedly infected chlamydia, gonorrhea and coinfecting clients were also evaluated. If we assume that repeaters comprise part or all of the core groups, then this analysis would reveal whether differences in the core groups for gonorrhea and chlamydia exist.

Kruskal-Wallis tests for more than two groups were used to assess differences in numbers of partners between chlamydia, gonorrhea and coinfecting case repeaters.

There were no significant statistical differences in the numbers of partners among all three repeater groups, (see Figure 8.1.) Average numbers of partners per episode for all disease categories were similar; 1.75 for chlamydia, 1.67 for gonorrhea and 1.69 for

coinfection. Variances of numbers of partners from all three disease categories were also similar, (1.9, 1.4, and 2.3 respectively) as were medians, which all equalled one.

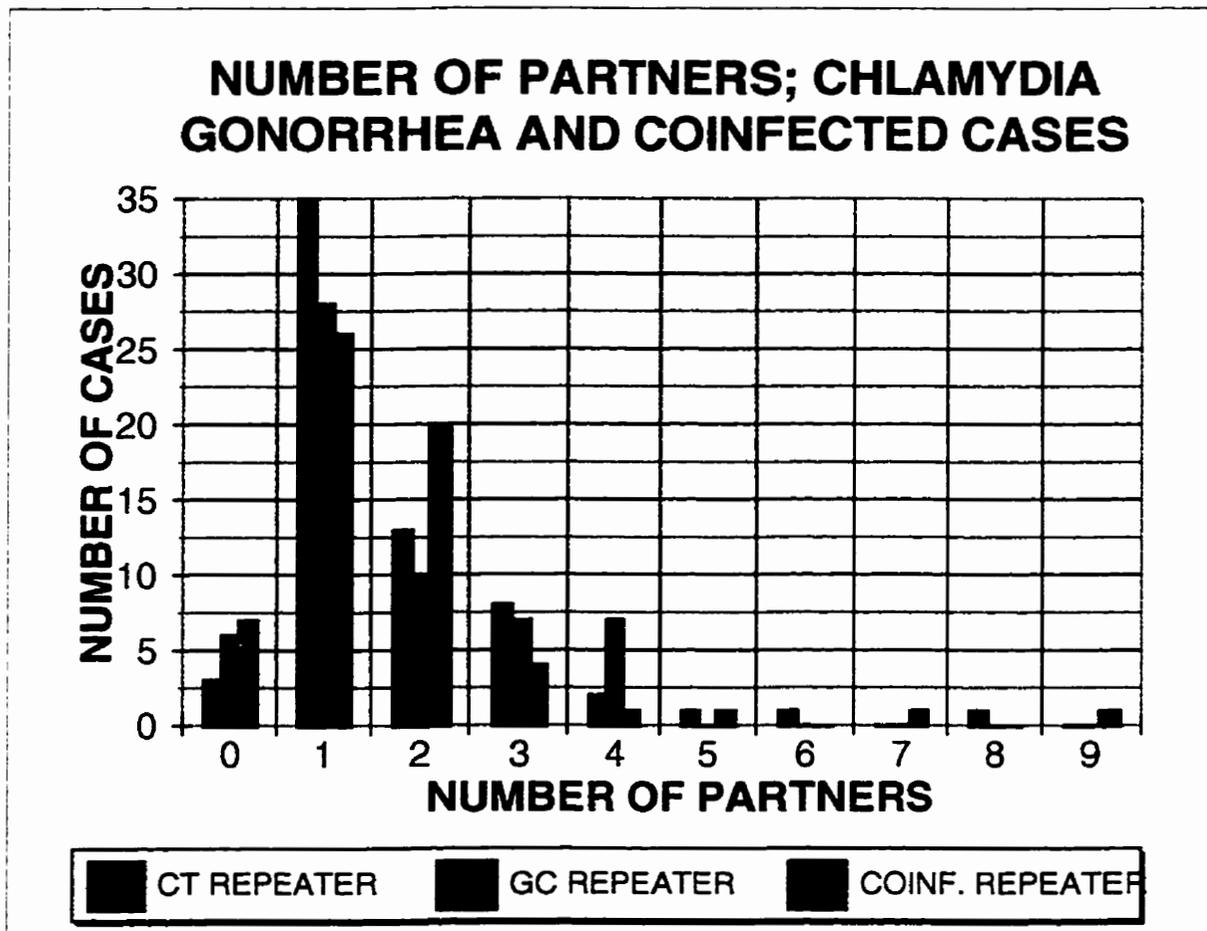


Figure 8.1 Histogram of number of partners of chlamydia, gonorrhea and coinfectd repeaters, Manitoba, 1990 - 1992.

The lack of significant differences in numbers of partners between repeater groups is interesting. Hook et al in a study on the behavioral differences between clients with chlamydia and gonorrhea also did not find significant differences in the median numbers of sex partners over the last 30 days; the median number of partners in that study was also one.⁸⁸ One might postulate that as chlamydia is more likely to be a chronic, asymptomatic

and less easily diagnosed infection, there is less likelihood that the patient will stop having sex, and/or to be treated. Hence the number of partners for chlamydia cases is more likely to have been gathered for the whole prior three month period as advised in the sexually transmitted disease guidelines for Manitoba.³² However, the clients with gonorrhea and coinfection are more likely to have symptoms, and the period of time for which partner data is collected is likely to be shorter. Differences in infections and duration times affect this analysis. As a result, the numbers of partners of gonorrhea and coinfecting clients over time are probably underestimated.

8.4 Results of comparison between contact repeaters and the comparison groups.

Analysis of difference in number of partners of repeatedly named contact and those contacts named only once was conducted in a similar fashion to that of case repeaters as outlined above. However, fewer data were available for contacts, as very few of them were ever proven cases. Because very few of them were cases, information only on how many people named them as contacts was available, and very little was available on whom they named. Information on whom they named would be available only after confirmation of infection and an interview by a health professional had taken place.

Multiply named contacts were also hypothesised to have greater risks of infection and transmission of sexually transmitted pathogens, and were also proposed core group

members. More complete information on multiply named contacts who may have had one confirmed infection was available from the case registry database, and this information, which was more accurate and complete than contact information was used in the following analyses.

The calculation of number of partners was made by adding the number of individuals who named the contact, and all those who were named by the contact, if the contact also was an established case. The total number of partners was averaged over all exposure events, and rounded to the nearest whole number. Those contacts who had been named only once had only one exposure event and therefore their total number of partners was analysed as it was.

Because fewer of the contacts were ever established cases, fewer were interviewed in order to collect sex partner information. This resulted in less sex partner data for many contacts, because the only information available was from who named them, and not who they named. The reverse was true of the cases, as many more of those had been named as contacts, and therefore, information which they gave on their sex partners was available for analysis, as well that given by the people who named them. The result was that for contacts, the lack of sex partner data rendered differences in number of partners more difficult to detect.

Distributions of numbers of sex partners of contact repeaters are shown in Fig 8.2. Compared with that of the cases, the upper ends of the tails are truncated.

NUMBER OF PARTNERS; CHLAMYDIA GONORRHEA AND COINFCETED CONTACTS

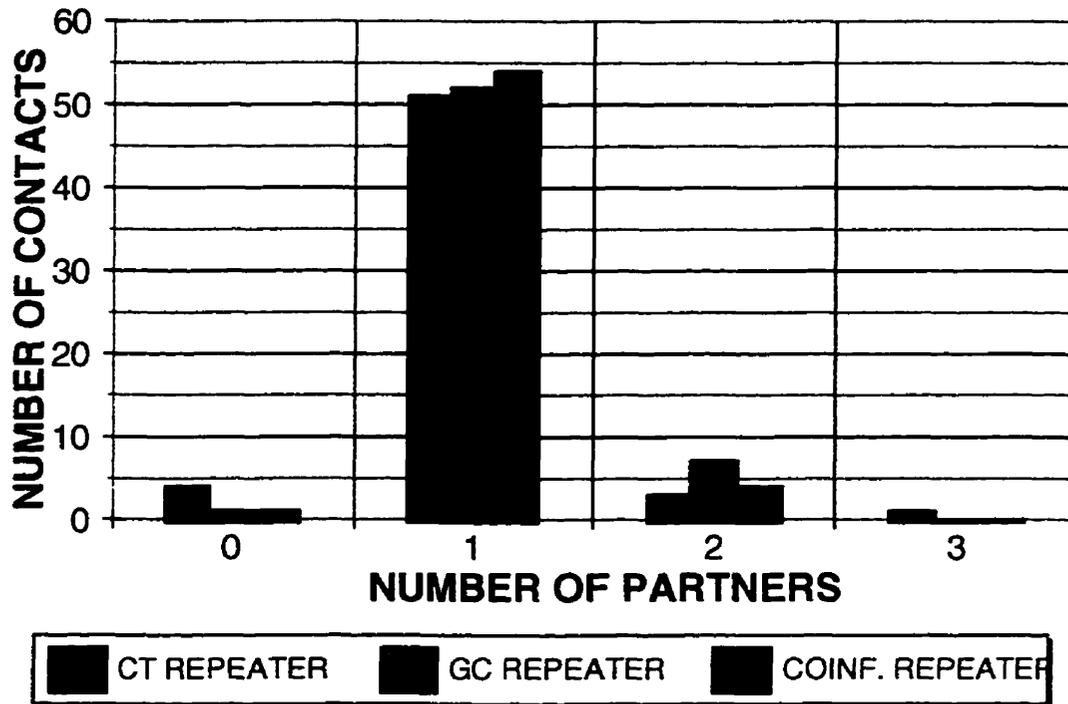


Figure 8.2 Numbers of partners of multiply named contacts of chlamydia, gonorrhea and coinfecting contacts, Manitoba 1990-1992.

8.5 Comparison of chlamydia, gonorrhea, and coinfecting contact repeaters.

In order to distinguish possible differences in chlamydia, gonorrhea and coinfecting core groups, the three groups of multiply named contacts were compared using Kruskal-Wallis tests for more than two samples. No statistical differences were found in the average number of partners per event. The mean number of partners per event for all three disease categories was similar; the number for multiply named chlamydia contacts was 1.02, for

gonorrhoea, 1.1, and for multiply named coinfecting contacts was 1.05. The medians of all three groups were one, and the variances were 0.18, 0.13, and 0.08, respectively.

This finding corresponds to that of the comparison of case repeaters where no differences in number of partners were found. These results are explained by the lack of information of the time periods over which these partners were recruited.

8.6 Conclusions; analysis of numbers of partners

The fact that neither coinfecting cases nor contacts were shown to have higher numbers of partners is interesting. It may be due to the fact that the sample size was not large enough to detect the differences in numbers of partners, although that in itself is an indication that the variation in numbers of sex partners may not be as great as one would expect for a key determinant of transmission and maintenance of endemicity. A significant problem in analysing these data is the relative clumsiness of multivariate methods which require normalisation or categorisation of non-normal data.

There are two interpretations to which these data lend themselves, and both have theoretical support in the literature on sexually transmitted disease epidemiology.

The lack of differences between repeaters of the three disease categories, even by Kruskal-Wallis tests, may indicate that no differences exist. That in turn may mean that all

repeaters may be members of a core group, hence their numbers of partners would be sufficient to maintain viable sexually transmitted infections in a population. One factor which supports this theory, is that the variances in numbers of partners of the non-repeater groups were always smaller than those of the repeater groups. In four of the six analyses between case and contact repeaters and non-repeaters, these differences in variances were statistically significant. High variances in numbers of sex partners have been noted as having a definite impact on the viability of infection in a population.¹⁹⁶ On the other hand, the fact that no differences were found may mean that the sample sizes were not large enough to detect them.

These results may also suggest that the number of partners alone does not determine the infection which is acquired. Number of partners is a very crude measure which does not take into account qualitative or quantitative measures of how, why and with whom sexual relationships are formed.^{137,138} In order to describe the relationship between sex partner recruitment and dissemination of disease, more sophisticated methods are required. These methods need to take into account not only the numbers of partners, but their likelihood of infection and other qualitative characteristics by which they may select, and be selected as suitable sex partners.

In order to explore the first possible interpretation of the sex partner data which is embodied in mathematical epidemiology, the following section will review the parameters of the mathematical equation for viability of infection using of the data afforded by this

research. The second interpretation supported by social network analysis will be examined in the section following that.

8.7 Use of sex partner data in mathematical formulae for the reproductive rate of infection

The data available from the studies above not only lent itself to comparing the numbers of partners of repeater groups, but also provided data on average rates of change of sex partners, and the variances in the populations. The data on number of sex partners is essential in solving the equation

$$R_0 = \beta c D$$

which defines the reproductive rate of a disease, i.e., the number of secondary infections generated by an index case per unit of time, which indicates whether the infection is viable in a population.¹⁹⁶ The contribution which this research brings to the formula is that of c , which is the mean rate of sex partner change, weighted by the variance in partner change. The reason for including the variance is that the people with higher rates of partner change affect the maintenance of the infection disproportionately.

The calculation of c is represented in the formula

$$c = m + \frac{\sigma^2}{m}$$

which assumes that sexual partnerships take place proportionately, i.e., that the equation allows for the fact that people in higher sexual activity classes "offer" more sexual liaisons than do those at lower classes, hence they have a higher likelihood of being selected.¹⁹⁶

This formula describes sexual partnerships which are basically initiated at random, with the only constraint being that individuals who tend to have higher numbers of partners will also be selected by others more often than individuals who have lower numbers of partners, (see Chapter 1, section 1.6.) The assumption that individuals form sexual relationships according to their own preferences for numbers of partners and those liaisons available to them may not be valid.¹⁹⁷ However, it is a first step in attempting to describe the reproductive rate of an infection in a population.

8.7.1 Calculations of formulae for the reproductive rates of chlamydia

The following tables show the calculations for c in the populations of chlamydia repeaters and non-repeaters from the samples described above in section 8.2.1.

Table 8.2 Values for c given by data from contacts and cases of chlamydia on numbers of sex partners by gender and repeater status over an estimated three month period.

	Three	month	period	
	c	m	σ^2	σ^2/m
Ct male repeaters	3.660	1.643	1.940	3.017
Ct male non-repeaters	2.681	0.308	0.731	2.373
Ct female repeaters	2.947	0.840	1.770	2.107
Ct female non-repeaters	1.541	0.397	0.454	1.144

The above table shows the number of sex partners of the sample repeater and non-repeater groups which the index case had named and also those who had named the index case.

Because we are interested in the change in partners and not the actual number, the mean number of partner change contained in the column labelled " m ", is calculated from the total number of partners less one showed the change rate of partners in this study group.

The variance of the numbers of changes is in the column " σ^2 ". The time of three months is estimated from the time for which health professionals are encouraged to ask for contacts in the event that the time of infection cannot be established.³² Because most chlamydial infections are asymptomatic, and because symptoms were not always noted accurately on the notification forms to Manitoba Health, (see Chapter 4), three months seemed a reasonable time frame. The variances are derived from the products. The multiplication of number of partners over three months to derive 12 month estimates may not be legitimate if people with one episode of chlamydia hesitate before initiating a new partnership, although at least one study has shown this not to be the case.¹⁹⁸

Table 8.2 shows the differences in the variances between the repeaters and non-repeaters clearly, and it is reassuring that the variances for the repeaters are consistently larger than those of the non-repeaters. The fact that there are a few people within the repeater groups who have large numbers of partners has a definite effect on the parameter c , which is consistently higher for the repeater groups.

Table 8.3 shows estimates of R_0 for chlamydia using the above values for c .

Table 8.3 Reproductive rates for chlamydia repeaters and non-repeaters with various assumptions of transmission probabilities, (β) and durations of infectiousness, (D).

	R_0	β	c	$D=10$ months
Ct male repeaters	9.058	0.75	3.660	3.3
Ct male non-repeaters	6.636	0.75	2.681	3.3
Ct female repeaters	7.294	0.75	2.947	3.3
Ct female non-repeaters	3.813	0.75	1.541	3.3
				$D=15$ months
Ct male repeaters	13.725	0.75	3.660	5
Ct male non-repeaters	10.055	0.75	2.681	5
Ct female repeaters	11.052	0.75	2.947	5
Ct female non-repeaters	5.777	0.75	1.541	5
		$\beta=0.10$		$D=10$ months
Ct male repeaters	1.208	0.1	3.660	3.3
Ct male non-repeaters	0.884	0.1	2.681	3.3
Ct female repeaters	0.973	0.1	2.947	3.3
Ct female non-repeaters	0.508	0.1	1.541	3.3

The values for D and β are from the literature. The value of 0.75 for the transmission of *C. trachomatis* between couples is from Viscidi et al, and Mares et al,^{34,199} respectively, and represents the highest published estimates of β . However, these values may not be the most appropriate as they reflect multiple episodes of intercourse which may have taken place over a lengthy period. They are cited here as a matter of completeness. The probability required by Anderson, who developed the formula, is that of transmission of chlamydia during one episode of sexual intercourse.¹⁹⁶ In the third set of calculations, I have used the transmission probability value estimated by Brunham et al,¹⁰¹ and adjusted by Stigum et al.²⁰⁰ Although the transmission probability is a mere estimate, it is probably impossible to actually measure transmission definitively for both ethical and practical reasons. There is some supporting evidence for the use of 0.10. First, studies done in the 1970's on naval recruits exposed to commercial sex workers with a known prevalence of gonorrhea infection, showed the transmission probability after one episode to be 0.19,²⁰¹ and 0.22.²⁰² Secondly, a study by Lycke et al shows that even after repeated exposures the transmission of chlamydia is less than that of gonorrhea.²⁰³ Therefore, allowing for more than one episode of intercourse with a new partner,⁹⁷ an estimate of between 0.10 and 0.20 seems reasonable.

The duration time of 15 months was adapted by Brunham et al¹⁰¹ from a study done by McCormick et al in 1979.¹⁰⁶ McCormick et al found that after 16 to 17 months of follow-up 28% of women followed still harbored *C. trachomatis*. However, the remaining 72% either cleared infection spontaneously before the 15 months, or were treated incidentally

with antibiotics which would have cured their infections. Therefore, I believe that the estimate of 1.25 years is too high for the duration of chlamydial infection, particularly in estimating durations in Manitoba, where there are active screening and contact tracing programs. I therefore calculated infectious days of the women from McCormick's study, with 28% infected for 16.5 months; 72% infected for half of 15 months or 229 days, and averaged them at 303 days or 83% of a full year for each woman. This is probably still an overestimate as it does not take into account the effect of control programs, although the fact that some women in the current study were treated inappropriately and consequently had a long infectious period may compensate for that. The lack of accurate transmission probabilities and duration times for chlamydia is largely due to the asymptomatic nature of the disease, making the time of initial infection difficult, if not impossible, to estimate.

In all cases, with all assumptions, the repeaters have higher values than the non-repeaters, which suggests that repeater populations are more effective in maintaining endemic infections than non-repeater populations. The actual values of R_0 vary greatly, as do the estimates of probability of transmission, β . If one accepts the transmission probabilities and the duration estimates in the third set of calculations as realistic, then the results show clearly that both repeater males and females are members of the mathematically defined core group where the reproductive rate is larger than one,⁹⁷ and in which chlamydia is a viable infection. This is the first attempt to calibrate the mathematical equations by comparing two populations and the first mathematical attempt to prove that core group for *Chlamydia trachomatis* genital infection alone, exists. Therefore, while the values

themselves may be estimates, the relative differences lend credence to the mathematical theorem.

8.7.2 Calculations of formulae for the reproductive rates of gonorrhoea

Table 8.4 shows the calculations for the genders of c , the weighted mean of the change in sex partners over a given period.

Table 8.4 Values for c given by data from contacts and cases of gonorrhoea on numbers of sex partners by gender and repeater status over an estimated three month period.

	Fifty-five	day	period	
	c	m	σ^2	σ^2/m
Gc male repeaters	2.371	0.973	1.360	1.398
Gc male non-repeaters	1.960	0.429	0.657	1.531
Gc female repeaters	2.334	0.34	0.678	1.994
Gc female non-repeaters	1.640	0.368	0.468	1.272

The above table shows the rate of partner change by gender for individuals with repeated episodes of gonorrhoea and those with only one episode. Partner change rates were calculated as for chlamydia above. The average number of partners for each episode was calculated, rounded to the nearest whole number, and diminished by one. In order to calculate the number of partners over the 12 month period, the above partner change rate for the 55 days was multiplied by 6.67 for each individual to reflect the whole year, and the frequencies and variances taken from that.

The time of 55 days was taken from early estimates of duration time of gonorrhoea in the presence of a control program. The time period may seem long, as people in the current study for whom symptom duration data were recorded, had symptoms for only five to seven days before seeking medical attention. Although gonorrhoea is often symptomatic, and most individuals concerned with the symptoms present promptly for care, proportions of up to 38% of men and 46% of women may continue to be sexually active,⁶ and not seek medical attention despite frank disease.¹⁹⁰⁻¹⁹² In addition, of course, there is a substantial proportion of individuals who are asymptomatic,⁶ and whose period of infectiousness would be halted only by contact tracing, a positive screening test or spontaneous clearance. For these reasons, the use of the estimated duration time of 55 days was justified.

Table 8.5 Reproductive rates for gonorrhoea repeaters and non-repeaters with various assumptions of transmission probabilities, (β) and durations of infectiousness, (D).

	R_0	$\beta=20$	c	$D=55$ days
Gc male repeaters	0.474	0.2	2.371	1
Gc male non-repeaters	0.392	0.2	1.960	1
Gc female repeaters	0.467	0.2	2.334	1
Gc female non-repeaters	0.328	0.2	1.640	1
Twelve month period				
		$\beta=0.35$		
Gc male repeaters	0.824	0.35	15.699	0.15
Gc male non-repeaters	0.684	0.35	13.022	0.15
Gc female repeaters	0.805	0.35	15.329	0.15

	R_0	$\beta=0.20$	c	$D=55$ days
Gc female non-repeaters	0.565	0.35	10.754	0.15
Fifty-five day period				
		$\beta=0.50$		
Gc male repeaters	1.185	0.5	2.371	1
Gc male non-repeaters	0.980	0.5	1.960	1
Gc female repeaters	1.167	0.5	2.334	1
Gc female non-repeaters	0.820	0.5	1.640	1

Above are the results for R_0 , using different estimates of β . The estimate of a 0.20 chance of infection after one episode of sexual intercourse comes from studies of exposure of naval personnel to infected sex workers.^{201,202} The risk of infection when women are exposed to infected men is higher; 0.50 to 0.70. The average of the two is 0.35 and I have substituted this into the equation. In the third set of calculations I have used the transmission probability estimated by Brunham and Plummer,¹⁰¹ which takes into account the fact that intercourse with a new partner usually takes place more than once in a session, therefore raising the probability of infection.⁹⁷

The fact that the reproductive rates for non-repeaters are close to those of repeaters indicates that, in general, individuals with gonorrhoea are at high risk of becoming core group members. This is supported by the epidemiology of gonorrhoea in Manitoba, which has decreased fivefold in 10 years to only 658 cases in 1995, with males and females almost equally represented.²¹ The consistent decrease in number of infections and application of control programs suggests that we are close to controlling infections in the

core, and that infection in non-core individuals has been eliminated to a large extent. This results in a lack of strong differentiation between core and non-core members.

8.7.3 Calculations of formulae for the reproductive rates of chlamydia and gonorrhoea coinfection

Table 8.6 contains the estimates of c , the weighted mean of the average change in numbers of partners of coinfecting individuals.

Table 8.6 Values for c given by data from contacts and cases on numbers of sex partners by gender and repeater status over an estimated three month period.

	Fifty- five c	day m	period σ	σ/m
Coinf. male repeaters	1.872	0.526	0.708	1.346
Coinf. male non-repeaters	1.233	0.4	0.333	0.833
Coinf. female repeaters	3.733	0.929	2.605	2.804
Coinf. female non-repeaters	2.635	0.412	0.916	2.223

The data shown above are for a period of 55 days. The fifty-five day period was taken from estimates of duration of gonorrhoea infectiousness. Because gonorrhoea is more often symptomatic than is chlamydia, and because people are more motivated to present for medical care, the 55 day estimate is reasonable for the estimation of the infectious period of gonorrhoea and chlamydia coinfection. In fact, infection with two organisms may cause more intense symptoms, and in this research, people with coinfection had symptoms

reported 1.79 times more often than people with gonorrhoea alone. This may mean that the duration time for coinfection should be shorter than that for gonococcal infection, but in the absence of any data in the literature, the conservative estimate of 55 days will be used. A more conservative estimate had the effect of reducing the parameter c , and hence also reduced the reproductive rate.

Table 8.7 Reproductive rates for coinfecting repeaters and non-repeaters with various assumptions of transmission probabilities, (β) and durations of infectiousness, (D).

	Fifty-five	day	period	
	R_0	$\beta=0.20$	c	$D=55$ days
Coinf. male repeaters	0.374	0.2	1.872	1
Coinf. male non-repeaters	0.247	0.2	1.233	1
Coinf. female repeaters	0.747	0.2	3.733	1
Coinf. female non-repeaters	0.527	0.2	2.635	1
		$\beta=0.10$		
Coinf. male repeaters	0.187	0.1	1.872	1
Coinf. male non-repeaters	0.123	0.1	1.233	1
Coinf. female repeaters	0.373	0.1	3.733	1
Coinf. female non-repeaters	0.264	0.1	2.635	1
		$\beta=0.50$		
Coinf. male repeaters	0.936	0.5	1.872	1
Coinf. male non-repeaters	0.616	0.5	1.233	1
Coinf. female repeaters	1.867	0.5	3.733	1
Coinf. female non-repeaters	1.318	0.5	2.635	1

There has been one study specifically addressing the transmission of gonorrhea along with chlamydia, but there was no account taken of the number of episodes or the length of time of infection and transmission between couples. Thirty-six percent of female partners of coinfecting males were themselves coinfecting, and 26% of males of coinfecting females were infected.²⁰³ Estimates close to these were used in the above analysis.

The above calculations show that the reproductive rate of the repeatedly coinfecting individuals is higher than that of the individuals who have been coinfecting only once in the three years study period. This suggests that individuals who are dually infected repeatedly with gonorrhea and chlamydia are more able to sustain viable infections in their population than those who have been coinfecting only once in a three year period. The mathematical definition of a core group of coinfecting individuals has to my knowledge, never been addressed,¹³⁹ although intuitively, the ability to contract two infections and to do so repeatedly would suggest high numbers of high risk sex partnerships.

The relative values of R_0 suggest also that females are more effective potential core group members than are men. This is probably due to participation in the commercial sex trade. It also must be noted that if many of these coinfections are associated with the commercial sex trade, that the parameter c is probably an underestimate, as many women may not be able to name their clients, and perhaps vice versa. The value of c for men seems to be lower than would be expected. It is possible that social norms prevent men from naming other steady partners, and it is also possible that many have no other regular partner.

Nonetheless, a single unprotected exposure to a sex worker carries a high risk of infection which is magnified on exposure to any other sex worker. Therefore, males may not require a large number of partners to maintain infection in the population.

The lower probabilities of 0.10 and 0.20 used earlier for the transmission of chlamydia do not produce a reproductive rate which is anywhere near to the rate needed to maintain a viable infection. This is due to the fact that chlamydia requires a longer duration time to be viable. The programs for gonorrhea control recommend epidemiologic dual therapy for gonorrhea and chlamydia and testing for chlamydia in anyone with gonorrhea.³² Therefore, in the population with frequent, symptomatic sexually transmitted disease, and frequent antibiotic therapy, it is logical that in a population with a high incidence of gonorrhea, chlamydia cannot be viable. This apparent contradiction has been found previously,³⁶ and this research provides the mathematics to support the hypothesis.

8.8 Conclusions; calculations of R_0

Partner change rates were calculated and were substituted into the mathematical equations which indicate whether or not a disease can be effectively maintained, i.e., whether it reproduces itself in sufficient numbers of hosts, (more than one), in order for it to be viable.¹⁹⁶ While exact estimates of the transmission probabilities β and D are not available for chlamydia, those for gonorrhea are more accurate, due to the fact that the disease

often produces symptoms, the start of which serve to define the duration as well as the successful transmission of the disease.

If one is very sceptical of the attempts to estimate the durations and transmission probabilities of chlamydia and gonorrhoea, then at the very least, the above formulae illustrate the relative difference in reproductive rates in repeater and non-repeater populations. This is very important in the development of mathematical epidemiology in general, as it serves to calibrate the equations. It is clear from the work in this section that regardless of the differing estimates of β and D , the repeater population has the potential to effectively maintain a viable sexually transmitted pathogen. The values for R_0 are higher, while the non-repeater population is not nearly as effective, indicated by a lower value for R_0 . The remaining task for future research is to try new methods to obtain more accurate estimates of β and D .

If the reader believes the “best” estimates of gonorrhoea and chlamydia transmission and duration quoted in the above tables; 0.10 - 0.20 for chlamydia with a 10 month duration, 0.36 - 0.50 for a gonorrhoea with a 55 day duration, and 0.26 - 0.36 for coinfection with a 55 day duration, then the absolute values of the equations are valid. The values for the proposed core groups comprising the repeaters are close to, or above 1, while those of the non-repeaters are much lower.

The other valuable information gained from this exercise is that it clearly demonstrates the mechanisms which result in the peculiar epidemiology of chlamydia and gonorrhea. Namely, that chlamydia cannot flourish in a repeater population with sufficient partner change rates and variance to maintain gonorrhea, where dual therapy occurs. The calculations also show that the gonorrhea repeaters and gonorrhea non-repeaters are not as different in their abilities to maintain gonorrhea as those for chlamydia. This is supported by the epidemiology of gonorrhea in Manitoba, which has decreased in the last 10 years due to active control programs which have reduced the gonorrhea infection rate in the peripheral groups to a great extent, and where the core or potential core group members form a large proportion of those now infected with gonorrhea.

Lastly, the R_0 for the coinfecting group corroborates the findings on multivariate analysis, in that it appears that females who ever experienced coinfection (once or multiple times), and who may be involved in the sex trade, are effective core transmitters. Their clients who have lower identified numbers of partners, nevertheless, play an essential role in maintaining infection. If the client is infected and transmits infection to the sex worker, the effect of the one sexual intercourse episode is magnified by the numbers of partners she has subsequently, possibly before the onset of symptoms.

The above attempts to calculate the reproductive rate are not intended to be the final answers to chlamydia and gonorrhea epidemiology; they are intended to provide a starting point for investigating new methodologies and measurements to explain the epidemiology

of the two diseases, and evaluate control programs. To this end, the following section explores social network analysis and its possible uses in describing STD epidemiology.

8.9 Social network analysis

The feasibility of constructing sexual networks (contact tracing trees) for all case repeaters and contacts who have been named multiple times was also assessed. This method is adapted from network studies in sociology, although constructing “contact tracing trees” was a common practice in the 1960's and 1970's.¹⁴⁰ It was useful in defining the origin of HIV infection leading to AIDS, and proved a common link (sexual intercourse), between individuals from Los Angeles and New York. It has the advantage of showing clear connections between people with STD as well as potentially defining those individuals who are most successful in propagating the infections.¹⁴²

Originally, the objective of this phase of the research was to clarify the numbers of partners of individuals, their partners and their partners' partners. It would also allow the calculation of the number of infections caused directly or indirectly by individuals.⁶⁴ The calculation of lowest number of individuals who contribute to the largest number of infections would have been another possible method by which to identify and then describe core group members. A basic measure of the number of people involved in a sexual network would also have been useful in order to estimate the size of core groups, and

define the proportion of individuals, particularly the repeaters within them, who could be considered peripheral and not core.

Because the network sizes had never before been explored using contact tracing data at the time of research, estimations of sample sizes were made using a small convenience sample of the first 48 repeaters and 41 non-repeaters. The feasibility study yielded dyads and triads and one small network. In addition, a network of over 900 individuals was discovered, despite the fact that staff at Manitoba Health estimated that the largest network would comprise about 20 individuals. Because the process of construction of the networks could not be computerized due to inadequate unique identifiers of contacts, and therefore had to be completed manually, it took three weeks to construct the network. It became too large to continue because of transcription errors and other errors which would decrease the accuracy of the network, therefore, work was halted after the network reached 900 individuals.

However, a short summary of social network analysis, social network measures and their possible uses is presented along with the networks which were discovered.

8.9.1 A brief introduction to social network analysis

Social network analysis has developed since the 1930's and is now considered a subdiscipline of sociology, although mathematicians have also made substantial contributions to its evolution.¹⁴³ A social network is a set of objects, people or events

which are connected by relationships.¹⁴² The analysis of the relationships is known as social network analysis. The persons, objects or events are referred to as actors, nodes, or vertices. The links between the people are called ties, or arcs or edges.²⁰⁴ Social network analysis has a basis in graph theory, where nodes are placed in a graph and are connected by lines in space.¹⁴¹ These lines are usually defined by the type of relationship between the actors. They can denote roles, eg., professor, student, boss; cognitive or affective relationships, eg., hate, love, is friends with, action or interaction, e.g., lends money to, has sex with, reports to, spatial or geographic relationships, e.g., travel and lastly, they can denote derived networks; individuals belonging to the same organization or event, but who may not themselves be linked. As one may imagine from the variety of relationships, there are many applications of social network analysis.

The display of social network analysis is actually closely connected to the analysis of them; the depiction of points in a set of relationships is mathematically defined as graph theory. The meaning and intuitive grasp of a set of people joined by relationships has long been recognised, particularly by public health personnel involved in contact tracing.¹⁴⁰ However, the analysis of them was facilitated only recently by the introduction of powerful computers in the 1970's.

Figures 8.3 and 8.4. illustrate an important danger in drawing conclusions about networks based only on their depiction. Figure 8.3 shows a loosely connected group of friends in which nodes 1,3,2, and 4 are closer friends and meet more often than 5, 6, 7, 8, 9, and 10.

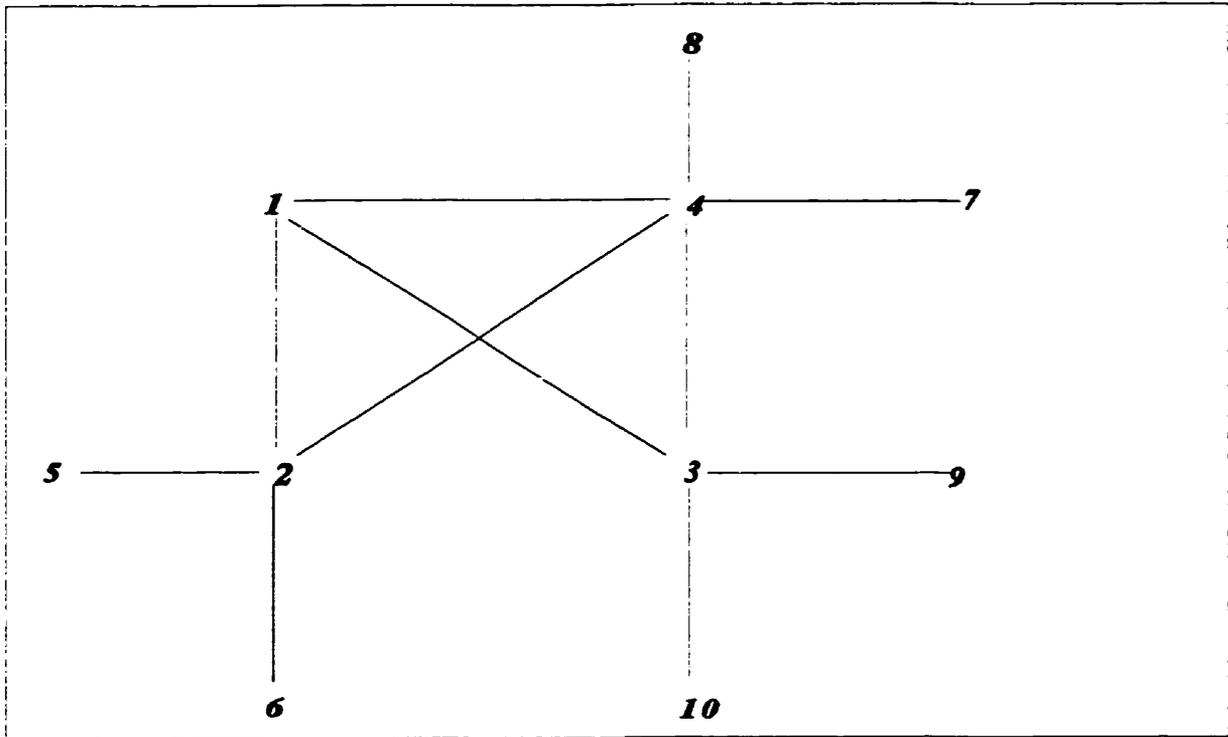


Figure 8.3 Network of 10 friends in which the edges show whether they had met over the past week.

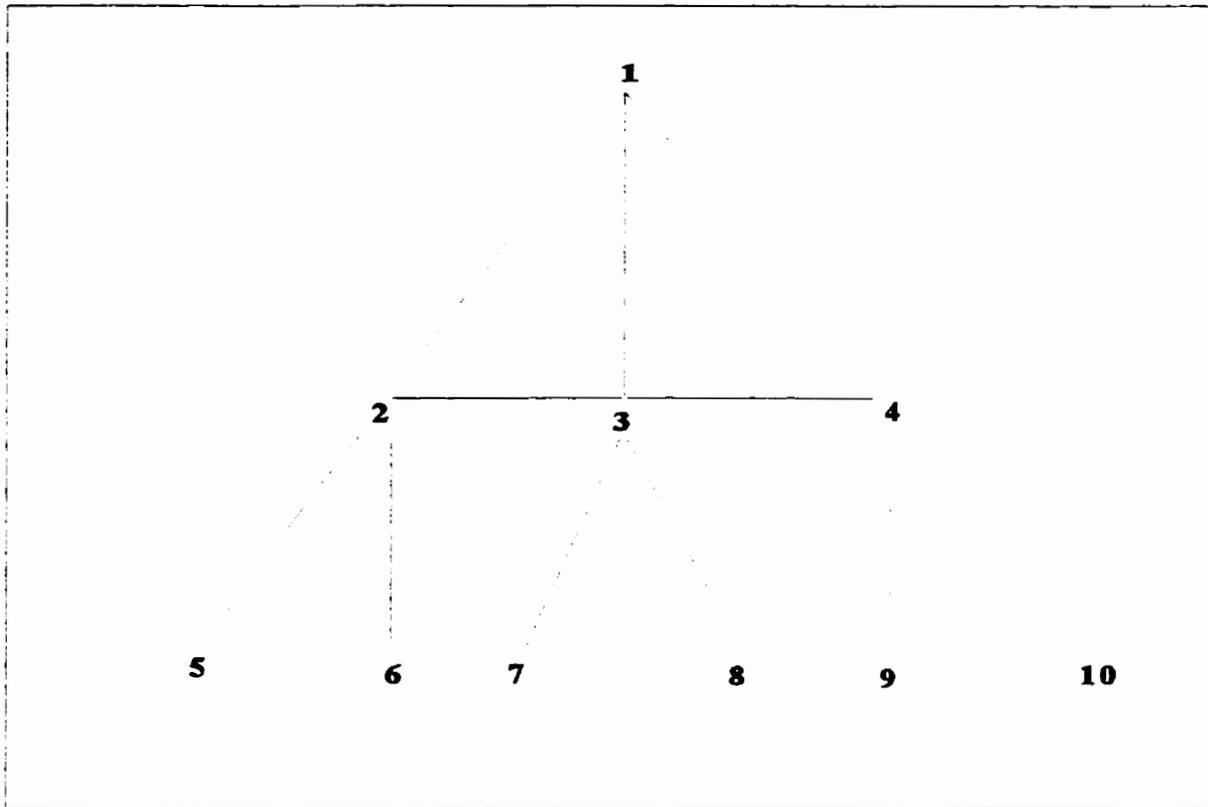


Figure 8.4 Network of interaction between executive officers and workers in a company. This network has exactly the same number of people and structure as Figure 8.3, but with a different display and interpretation.

In order to generate a drawing and perform analysis, an adjacency matrix is necessary. The following is an adjacency matrix for the network in Figure 8.5.

	1	2	3	4	5	6
1	0	1	1	0	0	0
2	1	0	1	0	0	0
3	1	1	0	1	1	0
4	0	0	1	0	0	0
5	0	0	1	0	0	0
6	0	0	0	0	0	0

Positive numbers indicate the existence of a relationship and zeros denote no relationship. Relationships can be weighted; so an actor loves (3), or is friends with (2), or acquainted with (1), another. One can incorporate the amount of money which has been lent, or the amount of times a reference has been cited. Relationships can also be directional. It is possible that 3 lends money to 1 but not the other way around.

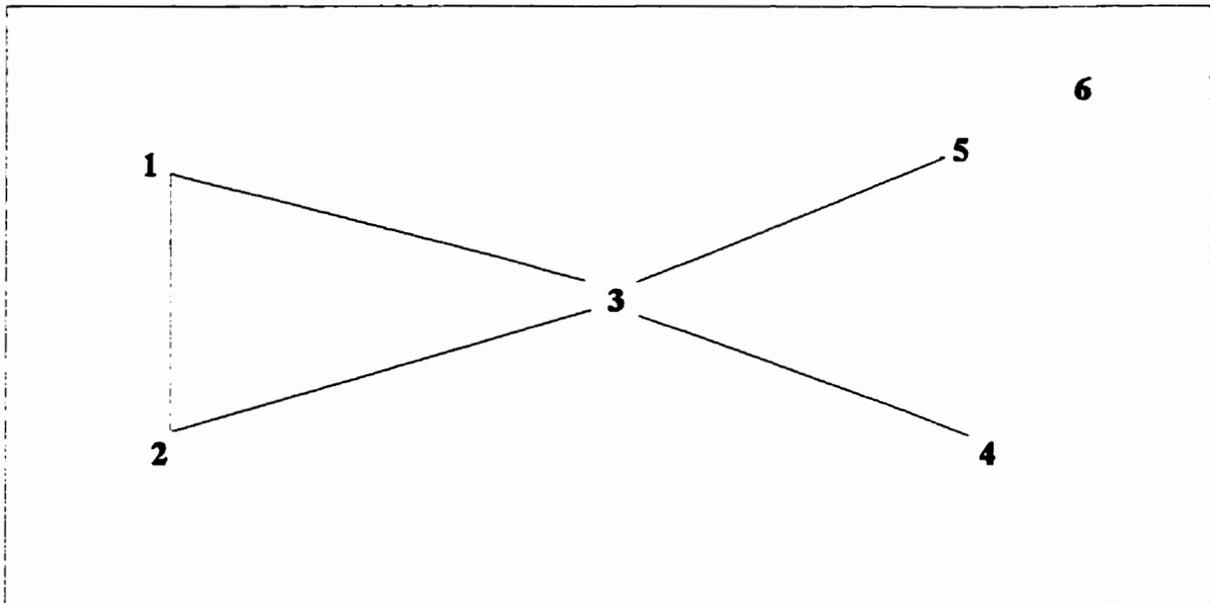


Figure 8.5 Network illustration of adjacency matrix, above.

Note that node six is disconnected from the rest of the graph, and in the adjacency matrix there are all 0's in that line.

Using the network in Figure 8.5, we can define some important network measures, used to discuss the sexual networks derived from this research. If there is a tie joining two actors, then they are “adjacent”; so one and two are adjacent, joined by an edge. The

number of actors adjacent to an actor is called the degree of the actor. For example, three has four degrees, one has two degrees, and five has one degree. Density is a measure of the amount of activity in a network, ranging from 0 to 1 and is the percentage of ties existing of all those that could possibly exist. It is calculated by summing the total number of edges divided by the maximum possible number of edges. The network in Figure 8.5 has a density of 0.33 which is not very dense.

A path is a chain of ties which connect any actor to any other actor without retracing steps. There may be more than one path from actor x to actor y. For example, one can go directly to two or can go from one to three to two. The length of a path is the number of edges in a path. The shortest path from actor one to five is through three, and is called a geodesic. If paths connect all actors in a network, all actors are “reachable” from one another. Six is not connected to anyone, therefore not reachable. All others are reachable by however many edges it takes; only one or two in this network. Reachability is also an important concept in disease transmission.

Degree is one measure of centrality as it measures how many other actors an actor has relations with. Betweenness centrality allows us to measure the centrality of an actor in relation to all others in the network. An actor who is located on a lot of communication paths has great influence in dissemination of disease or information. This measure counts all geodesics between all pairs of actors and assigns scores to actors located on the geodesics. The actor with the highest score who is located on the most geodesics is the

most central. There are other more complex measures of centrality,¹⁵⁰ but this is merely an introduction to social network analysis and sexually transmitted diseases.

One last important concept is that of an edge connecting two actors which, if one actor breaks the relationship, the bridge is lost and the network disconnects, see Figure 8.6.

This is important for understanding infectious disease transmission, as it shows how infections can diffuse from one population (core) to another, (periphery). In infectious disease control, the actors on either side of a bridge may be ideal participants in intervention/ vaccination.

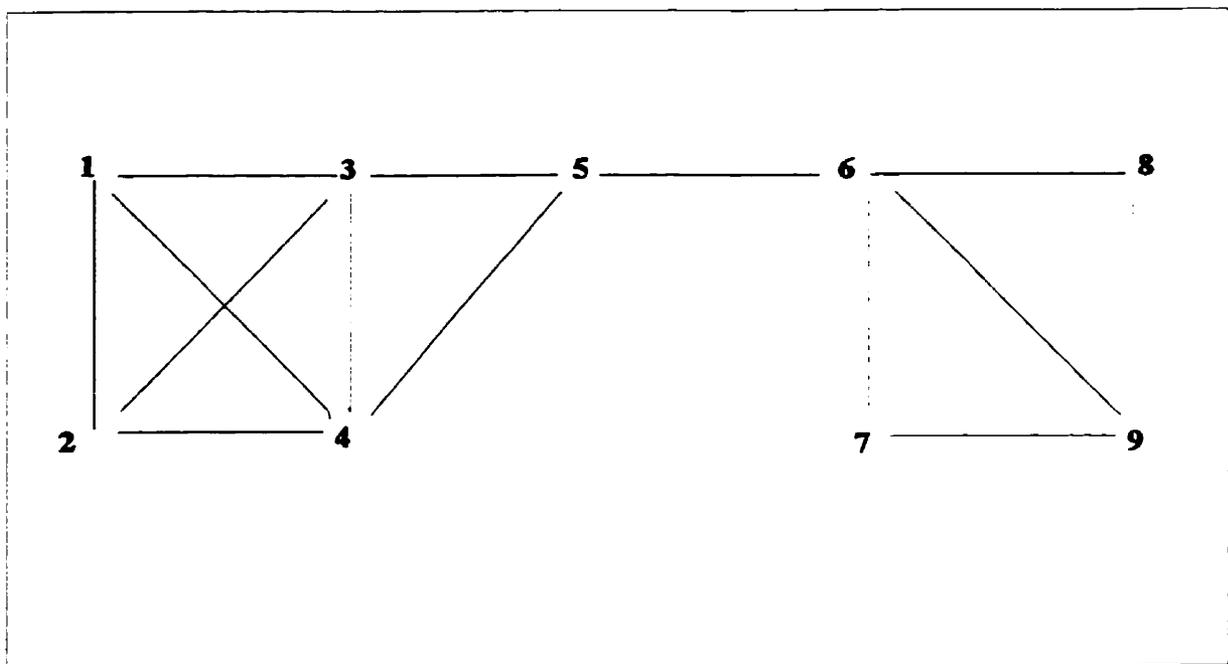


Figure 8.6 Network depicting a bridge, which if either actor five or six breaks the tie, the network will disconnect.

Different statistical methods are required for social network analysis, because network measurements violate basic assumptions of statistics. Firstly, we are measuring dyadic or

shared attributes such as sexual relationships, or lending money each to other.

Conventional statistics measure attributes of single items or people (monadic), such as size or weight. Therefore statistical techniques which are used must account for the fact that no attribute we are measuring can be independent of every other attribute, because they are all connected in a network. Complex matrix algebra has been developed to create network measures.

8.10 Results of network construction

Most of the eleven contact and case networks completed for the feasibility study were small, as shown in Figure 8.7, below. The six digit numbers depict case individuals and those less than six digits were named contacts without laboratory-confirmed infection in three years. The capital "M" designates a male and an "F", a female.

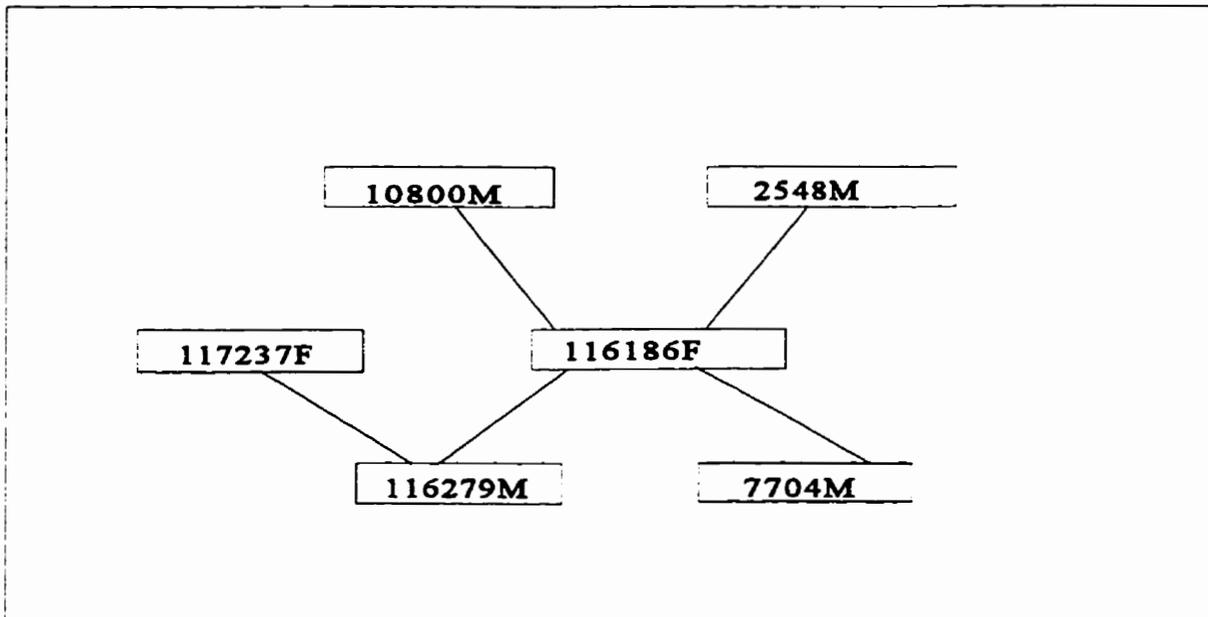


Figure 8.7 Typical small network from the feasibility study.

Figure 8.8 illustrates some of the epidemiologic findings in the differences between cases and contacts. This was one of the two medium sized networks of a repeater individual who was selected as part of the feasibility sample. It shows chlamydia infection in a network of individuals who named each other as sexual contacts over a space of 3 years. Of ten males in the network, only four, (40%) were tested for chlamydia, while of eight women, all were tested for chlamydia, and all but one tested positive. The untested males, if infected could have very long infectious periods and could potentially infect many more women. It is important to note that this may be a partial representation of all of the real participants in the network, as some may not have been named. It is not difficult to imagine one or more of the untested males being the source case for another similar network.

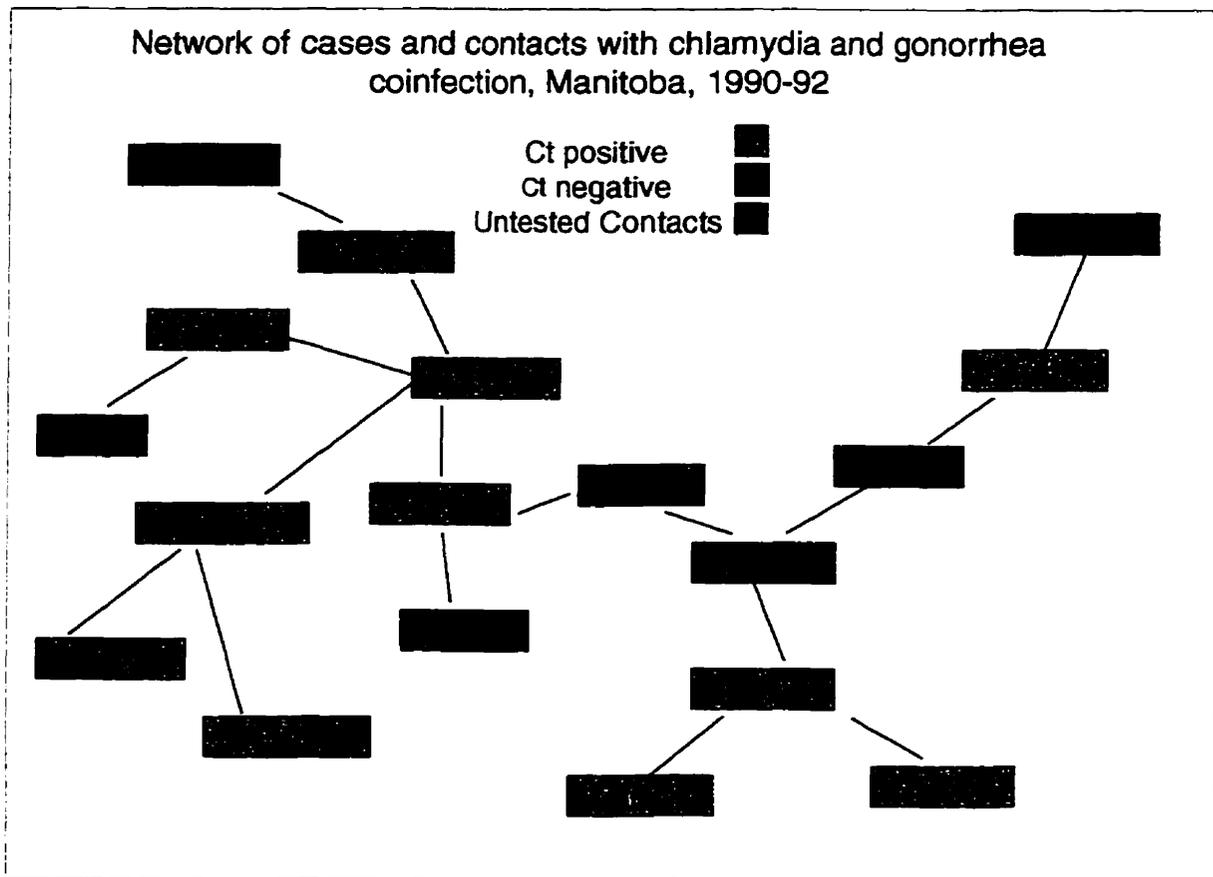


Figure 8.8 Chlamydia network showing those who tested positive; those who tested negative and those who were not tested.

Figure 8.9 below shows the same network, and also shows the diffusion of chlamydia infection through time. The colours fading from light pink through dark red show the relative dates of diagnoses beginning in June of 1990 to December of 1992. Note that the two female cases 127435F and 125698F who have earlier dates of diagnosis than their sex partners do not exclude the male case 127681M, from being the “source” case, as physicians are more reluctant to swab men than they are women. Inconsistencies in dates may also indicate incomplete information on sex partners.

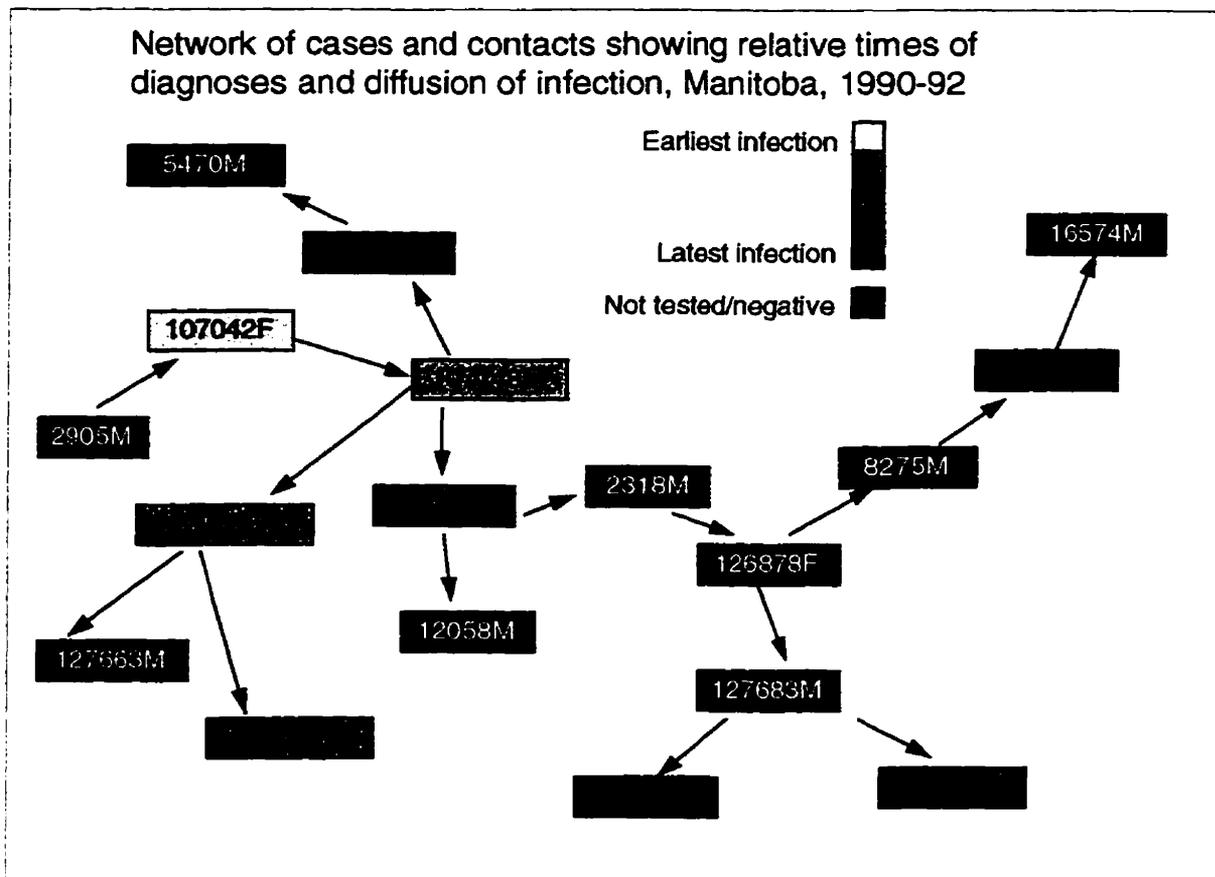


Figure 8.9 Network of cases and contacts showing relative times of diagnosis and diffusion of infection, Manitoba 1990 - 1992.

The last diagram shows part of the largest network discovered in this research Figure 8.9. Because of the lack of adequate identifiers for contacts, the network was drawn manually on pieces of paper. This method is far from ideal, as the chance of error is high. However, it remained the only practicable option. The work was halted when the network reached over 900 cases and contacts linked over the space of three years, and the task became unmanageable. Figure 8.9 shows a section of the network comprising 126 individuals; only a fraction of the network. Contacts who were never confirmed cases are shown in violet, and have identification numbers of less than six digits, while confirmed

cases of either gonorrhea or chlamydia or both, are shown in light pink, and have identification numbers of six digits. Males have a suffix “M” after the identification number, and females have the suffix “F”.

It is noteworthy that the construction of networks from routinely collected notifiable disease data had not been attempted at the time of this research, after which only one research study has been published.¹⁵¹ While the network discovered there comprised 1,272 people, it was divided into 402 smaller components in which individuals were actually connected. The largest component of the network had only 35 people, despite the fact that data were collected over two years, and the period for which contact data was requested was similar to that used by Manitoba Health; three months prior to presentation. Larger networks have been discovered in Colorado Springs, where a connected component of 3,600 people was discovered (personal communication, Dr R. Rothenberg, April 13, 1998).^{141,143,149} However, these networks were not exclusively sexual, and data were collected by questionnaire and not from routinely gathered public health data.

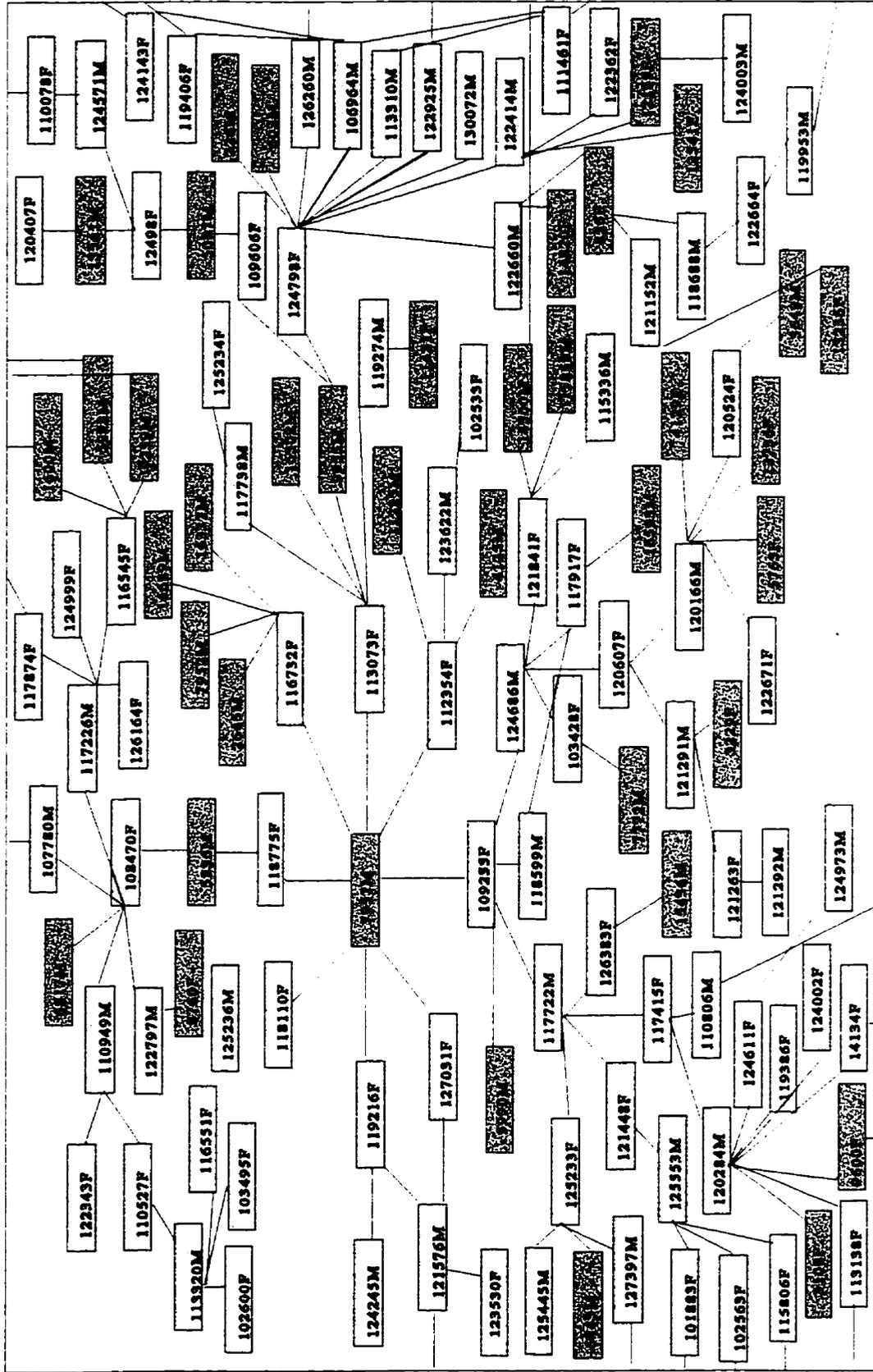


Figure 8.10 A section of the large network showing the most central contact "7957M", surrounded by 126 individuals.

The portion of the network displayed shows the most central contact in the network.

Degree centrality is a measure of the number of people adjacent to the individual, and the individual off centre left, "7957M" is the contact in the database who was named most often, and who never became a case. "7957M" was named thirteen times on different occasions by eight people starting in January of 1990 and ending in December of 1992.

Women who named him were confirmed as having gonorrhoea, chlamydia, and three had both infections. Although he was reported as having been located four times, he was noted in the contact database as not being infected three times, and once was noted as having infection and being treated, but no record of him is present in the confirmed case database. By the network measure of degree centrality, this individual has the most important role in connecting this network.

The case at the far right centre, "124798F", named 10 known sexual partners 14 times, and had four confirmed STD episodes. No additional partners whom she had not named, named her. She was treated appropriately all four times for chlamydia and gonorrhoea.

Another person with a high number of partners was the individual, "120284M", at the bottom left. He named four partners during two episodes of infection, and the other four partners named him. He was treated appropriately for both gonorrhoea and chlamydia, and the four partners who named him reported dates of exposure ranging from 1990 through 1992.

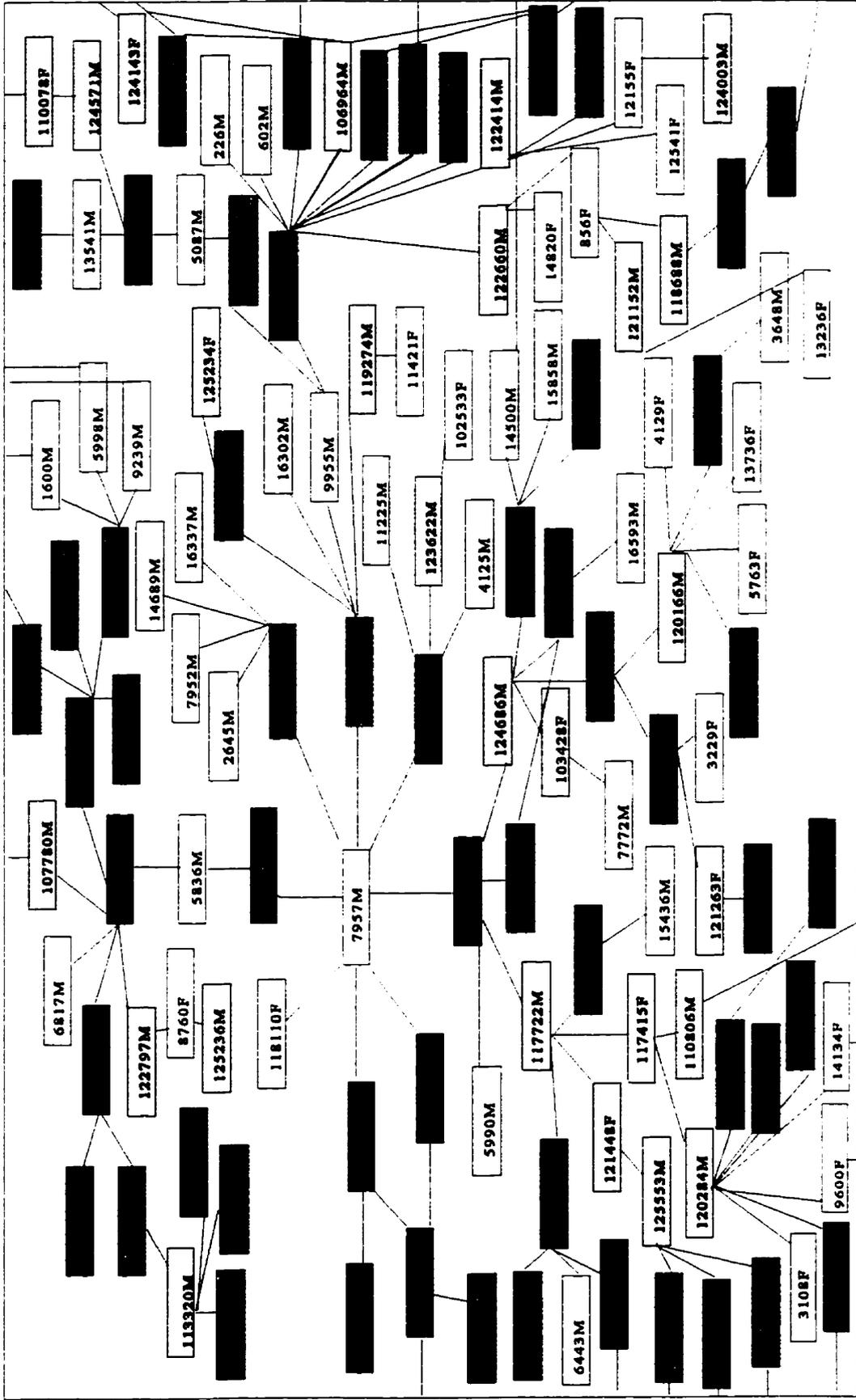


Figure 8.11 The same section of the network shown above, (Fig. 8.10) with the gonorrhea cases in yellow, the chlamydia cases in blue and those with both in green. Contacts and those with unknown diagnoses are in white.

8.11 Conclusions

The networks which have been constructed using notifiable disease data gathered routinely by public health staff in the administration of the Public Health Act are an important advance in the use of these data and social network analysis. In addition to the theoretical and analytical techniques offered by social network analysis which serve to enhance our knowledge of STD epidemiology,^{27.141} they offer new strategies for disease control.^{152.205.206}

The analytic methods used in social network analysis provide the mathematics for the analysis of shared attributes, i.e. exactly the nature of sexual relationships. The mathematics of core group theory have proved difficult to verify, and possibly even more laborious to apply directly to disease control strategies.^{27.141} In addition, as decreases in the reproductive rate of a disease are achieved, this in turn causes changes in disease control and education programs which determine duration times of infectiousness, numbers of partners, and transmission probabilities. Therefore, because of the constantly changing parameters of the reproductive rate, we may be in the position of trying to examine an ice cube, which melts at room temperature as we examine it.

Social network analysis may provide us with the methods to attain the elusive core group, and to ultimately define which group of people are able to transmit infection to more than one host over a specified time. It may provide us with the parameters for the

mathematical formulae where population estimates fail us, thus we may be able to compare the results of two methods which yield information on core group members.

Because such research is in its infancy, and the computer programs for large networks are still in development,^{151,207} this research is an initial step in the process of furthering our knowledge of sexual networks in sexually transmitted diseases and their possible uses. In order to make full use of these valuable data, future research will include the computerisation of all sexual links from the databases in this study comprising approximately 17,000 contacts, and 10,000 cases. Only once that is complete, can the identification of cliques within the network, and the calculations of centrality measures be accomplished. These measures will establish the importance of individuals' interactions in maintaining the endemicity of chlamydia and gonorrhoea.

Chapter 9

Conclusions

9.1 Summary

The ultimate goal of this research was to describe characteristics, and define risk markers for chlamydia and gonorrhoea core groups in Manitoba. Individuals with repeated infections with chlamydia and/or gonorrhoea and those who were multiply named contacts of cases were proposed as comprising either the whole core groups for those infections or at least a substantial part of them. The essence here was to describe the risk potential of an individual to be a core group member, not the absolute proof of infection. The first set of hypotheses proved that the case repeaters differ from those with only one infection. If no differences were found, there would have been little point in going further, because even if a core group existed, it would not be detectable.

Because multiply named contacts of cases of STD may remain asymptomatic and infectious for a long period of time during which they have substantial numbers of sex partners, they form an ideal core group. The second set of hypotheses (see Chapter 2, Figure 2.1) established that multiply named chlamydia contacts and multiply named coinfecting contacts are significantly different in their demographic characteristics from

chlamydia and coinfecting contacts named only once. However, multiply named contacts of gonorrhoea cases are similar to those who have been named only once.

The results of the first two sets of hypotheses are summarised in Table 9.1, below. The odds ratios and corresponding p values are the results of comparing the chlamydia, gonorrhoea and coinfecting case repeaters with the comparison group of each disease category with only one disease episode. Likewise, the odds ratios show the differences between the multiply named contacts of chlamydia, gonorrhoea or coinfecting cases and those contacts of each disease category named only once. The dashes indicate that the information was not available for contacts, and therefore was not analysed. For example, the table shows that contacts named more than once by people with laboratory confirmed chlamydia were 1.8 times more likely to be aboriginal, likely to be younger than those named only once, and were 1.96 times more likely to live in an area where the average household income is less than <\$29,572 - the lowest income quintile in Manitoba.

Table 9.1 Odds ratios of chlamydia, gonorrhea and coinfecting repeat cases compared with non-repeaters, and multiply named contacts of chlamydia, gonorrhea and coinfecting cases compared with those contacts named only once.

Variables	Chlamydia		Gonorrhea		Coinfecting	
	Cases	Contacts	Cases	Contacts	Cases	Contacts
Treaty status	2.42†	1.80†	1.96†	-	1.92†	2.11†
Used alias	1.66†	-	1.59**	-	1.69**	-
Treated	1.44†	-	-	-	2.16**	-
inappropriately Symptoms noted	1.25†	-	-	-	2.71†	-
Log age	0.39†	0.43†	0.44†	-	0.38*	-
Female	-	-	-	-	1.50*	0.53†
Quintile 1 <\$29,572	1.60†	1.96†	1.57**	-	-	-
Quintile 2	1.14	1.16	1.41	-	-	-
Quintile 3	1.14	1.61*	-	-	-	-

- variable not available for contacts

* p=0.05 - 0.01

** p=0.002 - 0.009

† p<0.001

Chlamydia repeat cases and multiply named contacts differed in many respects from cases with only one disease episode, and those contacts named only once. However, there were fewer differences between those with repeated laboratory confirmed gonorrhea and those

with one episode, and no differences at all between multiply named contacts of gonorrhea cases and those named only once. This indicates that as gonorrhea has decreased in Manitoba, and the reservoir of infection has shrunk, the group which had gonorrhea is becoming more and more homogenous, as the epidemic shrinks toward the core. Last, there were many differences between those repeatedly coinfecting and those with only one episode of coinfection, and some between multiply named contacts of coinfection, and those named only once. The table clearly shows that with the exception of gonorrhea contacts, all repeaters and multiply named contacts are distinguishable from non-repeaters, and are viable candidates for core group membership.

The third set of analyses showed that the chlamydia, gonorrhea and coinfection repeater cases were different from each other (Table 9.2.) Chlamydia repeat cases and multiply named contacts differed greatly from coinfecting repeat cases and multiply named contacts of coinfection. For example, the first column shows the comparison between chlamydia repeater cases and coinfecting repeater cases. Coinfecting repeater cases were 1.73 times more likely to be aboriginal, 1.53 times more likely to use a street name or alias 2.58 times more likely to report symptoms and were 0.43 (approximately half) as likely to be treated inappropriately than were individuals with repeated diagnoses of chlamydia.

Table 9.2 Odds ratios of chlamydia repeat cases and multiply named contacts compared with coinfecting repeater cases and multiply named contacts; chlamydia repeat cases and multiply named contacts and compared with those for gonorrhoea, and coinfecting repeater cases and contacts compared with those for gonorrhoea.

Variables	Chlamydi/Coinfected		Chlamydi/Gonorrhoea		Gonorrhoe/Coinfected	
	a	a	a	a	a	a
	Cases	Contacts	Cases	Contacts	Cases	Contacts
Treaty status	1.73†	1.43*	1.55†	1.38*		
Used alias	1.53†	-		-	1.42*	-
Treated	0.43†	-		-		-
inappropriately Symptoms	2.58†	-	1.64†	-	1.79†	-
noted						
Log age	0.13†		3.37†	2.80**	0.07†	0.20†
Female	0.59†	1.63*	0.17†	0.04	3.13†	0.28†
Quintile 1	1.46*	3.02†	2.50†	2.61†		
<\$29,572						
Quintile 2,3,4,5	0.94	1.24	1.74*	1.58*		
Quintile 3,4,5	0.87		1.09			
Two or more	1.61†	-	1.28*	-		-
partners						
Female * age				5.46*		
interaction						

- variable not available for contacts

* p=0.05 - 0.01

** p=0.002 - 0.009

† p<0.001

The populations which differed the least were those of the gonorrhoea and coinfecting repeaters. The many differences between repeaters with chlamydia, and those with gonorrhoea and coinfection prove that people with chlamydia infection alone are substantially different from both the gonorrhoea and coinfecting case repeaters. The results of the comparison of the multiply named contacts were very similar to those of the repeat cases. Multiply named contacts of gonorrhoea were more similar to the multiply named coinfecting contacts than they were to the multiply named chlamydia contacts.

The most striking results are those of the comparisons between the case repeaters and multiply named contacts (Table 9.3.) The odds ratios shown are the results of comparing the repeat cases of each disease category with contacts named repeatedly by index cases of the same disease category. For example, the first column shows that chlamydia cases are 35 times more likely to be women, and older, than contacts who are named multiple times by individuals with chlamydia. Likewise, people with laboratory confirmed gonorrhoea are 1.28 times more likely to be First Nations than multiply named contacts of a gonorrhoea case. Not only did this analysis help in defining whether multiply named contacts were similar to cases and could be considered part of a core group, but it also identified and quantified barriers which prevent contacts of proven cases from becoming laboratory confirmed cases themselves.

Table 9.3 Odds ratios of chlamydia repeat cases compared with chlamydia multiply named contacts, gonorrhoea repeat cases compared with gonorrhoea contacts and coinfecting repeat cases compared with coinfecting multiply named contacts

Variables	Chlamydia	Gonorrhoea	Coinfecting
Female	35.64†		4.63†
Log age	2.74†		
Urban			1.16
Treaty status		1.28**	2.16†
Quintile 1			0.46**
<\$29,572			
Quintile 2,3,4,5			0.40†
Urban*female			3.4†
interaction			

* p=0.05 - 0.01

** p=0.002 - 0.009

† p<0.001

These results proved that the case and contact repeaters were actually very similar demographically, and that in the case of gonorrhoea and chlamydia could be seen as two unified core groups, despite the fact that some did not have laboratory-confirmed infections. Differences between multiply named contacts of coinfection and repeated laboratory-confirmed cases of coinfection are not as easily explained. There are differences in gender, which may be accounted for by testing practices for chlamydia. However, there are also differences in proportions of those who live in urban areas, are

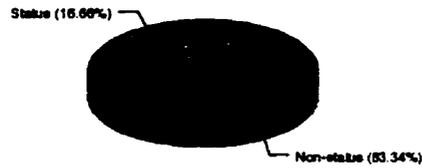
registered as treaty Indians and those who live in areas where household income levels are low. These differences may be explained by the differences between commercial sex workers and their clients, which account for the differences in gender, areas of residence, income levels and ethnic groups. Likewise it may also be fallacious to assume all of these differences are attributable to commercial sex, but they may be markers for other risk factors of which we are unaware. To summarize, the proposed core groups of case and contact repeaters have distinctive characteristics which are different from those of the non-repeaters. Not only that, but the proposed core groups for gonorrhoea and chlamydia comprising those individuals who have repeated infection and those who are multiply named contacts, are very similar.

9.2 The nature of the core groups

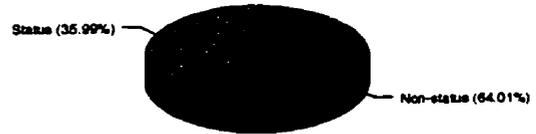
Despite the complex study design, hypothesis testing cannot adequately describe all groups simultaneously. Insight into the differences between repeaters with chlamydia, gonorrhoea and coinfection is revealed in the simplest statistics from the six groups of cases. The proportion of aboriginal people rises gradually from chlamydia non-repeaters (16.6%), chlamydia repeaters (35.9%), gonorrhoea non-repeaters (27.6%), gonorrhoea repeaters (46.9%), coinfecting non-repeaters (35.1%) and coinfecting repeaters (51.6%), (Figure 9.1.)

REPEATER AND COMPARISON CASES BY ETHNIC GROUP, MANITOBA, 1990-1992

Chlamydia non-repeaters



Chlamydia repeaters



Gonorrhoea non-repeaters



Gonorrhoea repeaters



Coinfected non-repeaters



Coinfected repeaters



Figure 9.1 Proportions of First Nations people in the chlamydia, gonorrhoea, and coinfecting repeater and comparison groups.

These graphs show an increase in the proportion of aboriginal people from those infected with chlamydia to those infected with gonorrhoea, and finally the highest proportion of aboriginal people in the coinfecting groups, despite the fact that they form only 7% of the Manitoba population.

Income levels also show proportions of people with very low incomes becoming progressively higher through chlamydia groups, gonorrhoea, and finally coinfecting groups, which had the highest proportions of people in the lowest income quintile (Figure 9.2.)

INCOME QUINTILES, REPEATER CASES & COMPARISON GROUPS, MANITOBA 1990-1992

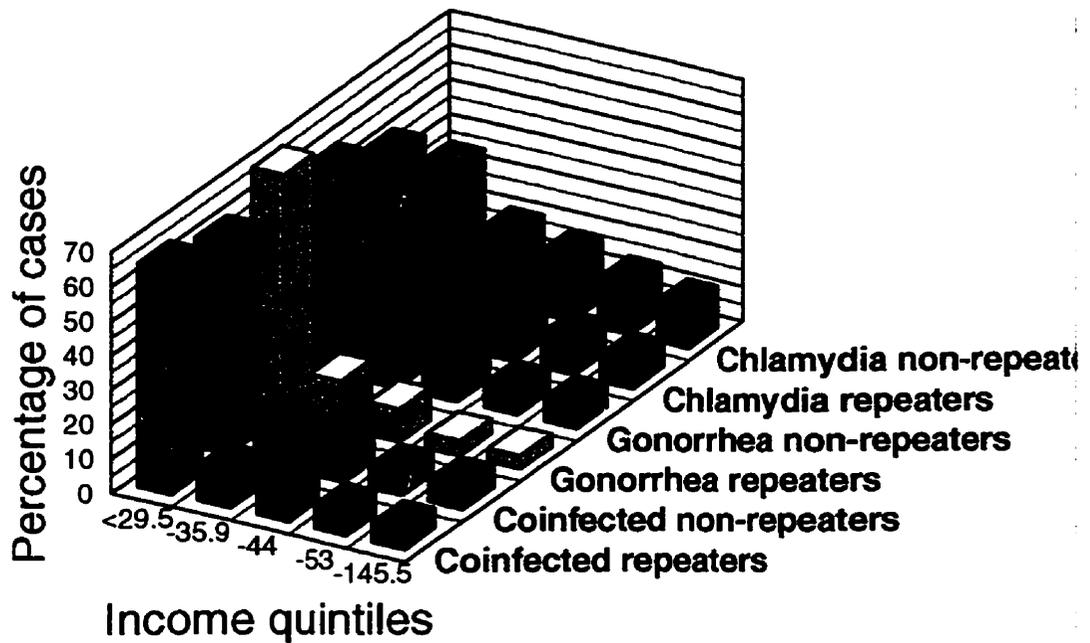


Figure 9.2 The proportions of chlamydia, gonorrhea and coinfecting repeaters and comparison groups by income quintile.

The proportion of people using aliases also show a progression from chlamydia groups to gonorrhea (Figure 9.3), and finally the coinfecting repeater group with the highest proportion of individuals using aliases, (33.9%).

REPEATER AND COMPARISON CASES BY USE OF ALIAS, MANITOBA, 1990-1992

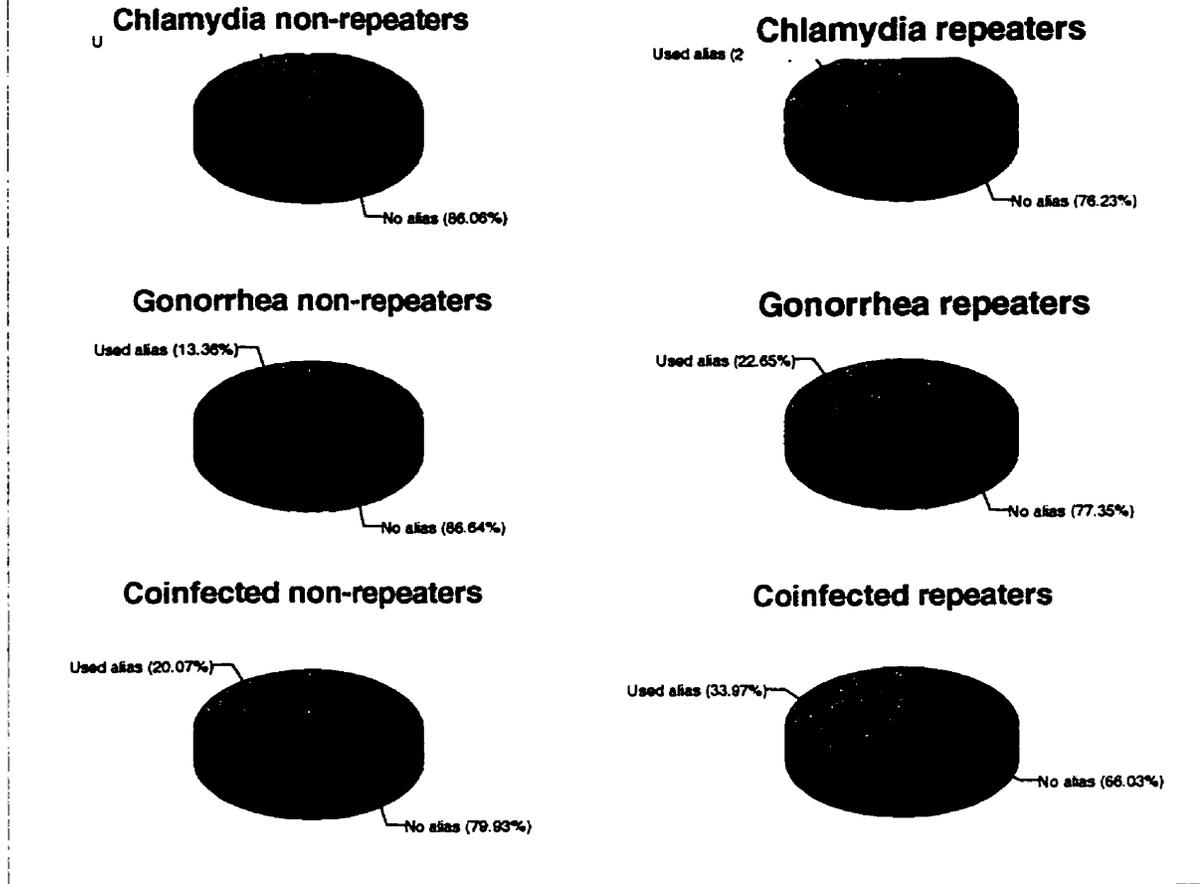


Figure 9.3 The proportions of people using aliases in chlamydia, gonorrhea, and coinfecting repeater and comparison groups.

Symptoms are also graded, so that people with chlamydia have the lowest proportion reporting symptoms, with coinfecting repeaters with the highest (Figure 9.4.)

REPEATER AND COMPARISON CASES BY SYMPTOMS, MANITOBA, 1990-1992

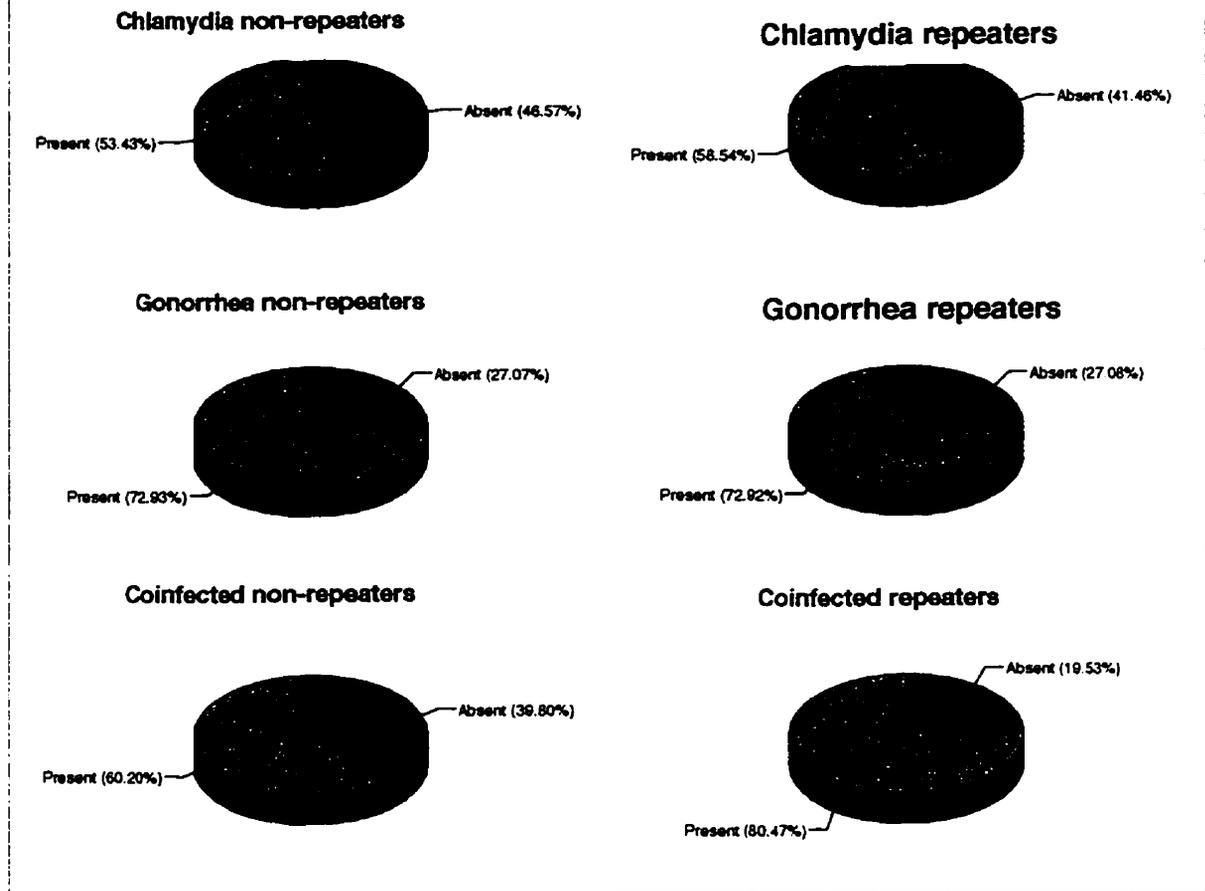


Figure 9.4 The proportions of people with symptoms in the chlamydia, gonorrhoea, and coinfecting repeater and comparison groups.

The graphs of income levels and proportions of First Nations people in the contacts are very similar to those of the cases, shown above. The similarity of the income quintile distributions of cases and contacts is shown in these analyses and in the work of Ramstedt et al, who found similar income levels in cases of chlamydia and their contacts in Sweden.¹⁸

The concept of core groups reflected in the graphs is that of a continuous variable, not a categorical one. It may be impossible to describe in absolute terms which group is or is not a core group. Rather, it seems that there is a progression of risk behavior and risk environment from chlamydia non-repeaters who seem the least at risk of being core group members, chlamydia repeaters who may be more so, through gonorrhea non-repeaters, gonorrhea repeaters, coinfecting non-repeaters and finally coinfecting repeaters, who may be at the centre of the core (see Fig 9.5.) This concept is not in itself unknown in STD research, as many studies have classified chlamydia and gonorrhea prevalences according to geographic areas; “core,” “adjacent” and “periphery.”^{36,64-66,100,128} These categories were not intrinsic to the data or the individuals under study; they were imposed measures based on prevalence rates. The unique contribution of this analysis is that it has clearly defined the inherent risk factors for confirmed repeaters of chlamydia, gonorrhea, and coinfection. These risk markers indicate points of a continuum from low risk groups to higher risk groups who may form the core group. The differing proportions and means of risk markers and their progression toward the core are shown in Figure 9.5 (as suggested by Dr. Brunham and other readers). As one progressed toward the core, the proportion of First Nations people increased, as did the proportion of people who experienced symptoms, and the proportion who used aliases. The oldest people were those with one episode of gonorrhea alone; the mean ages are lower in people with one episode and those with repeated chlamydia, and lowest of all in chlamydia and gonorrhea coinfecting individuals. Last, the proportion of people treated inappropriately for their infections was

lowest at the centre of the core; higher for individuals for with gonorrhoea alone, and highest for those with one or multiple episodes of chlamydia.

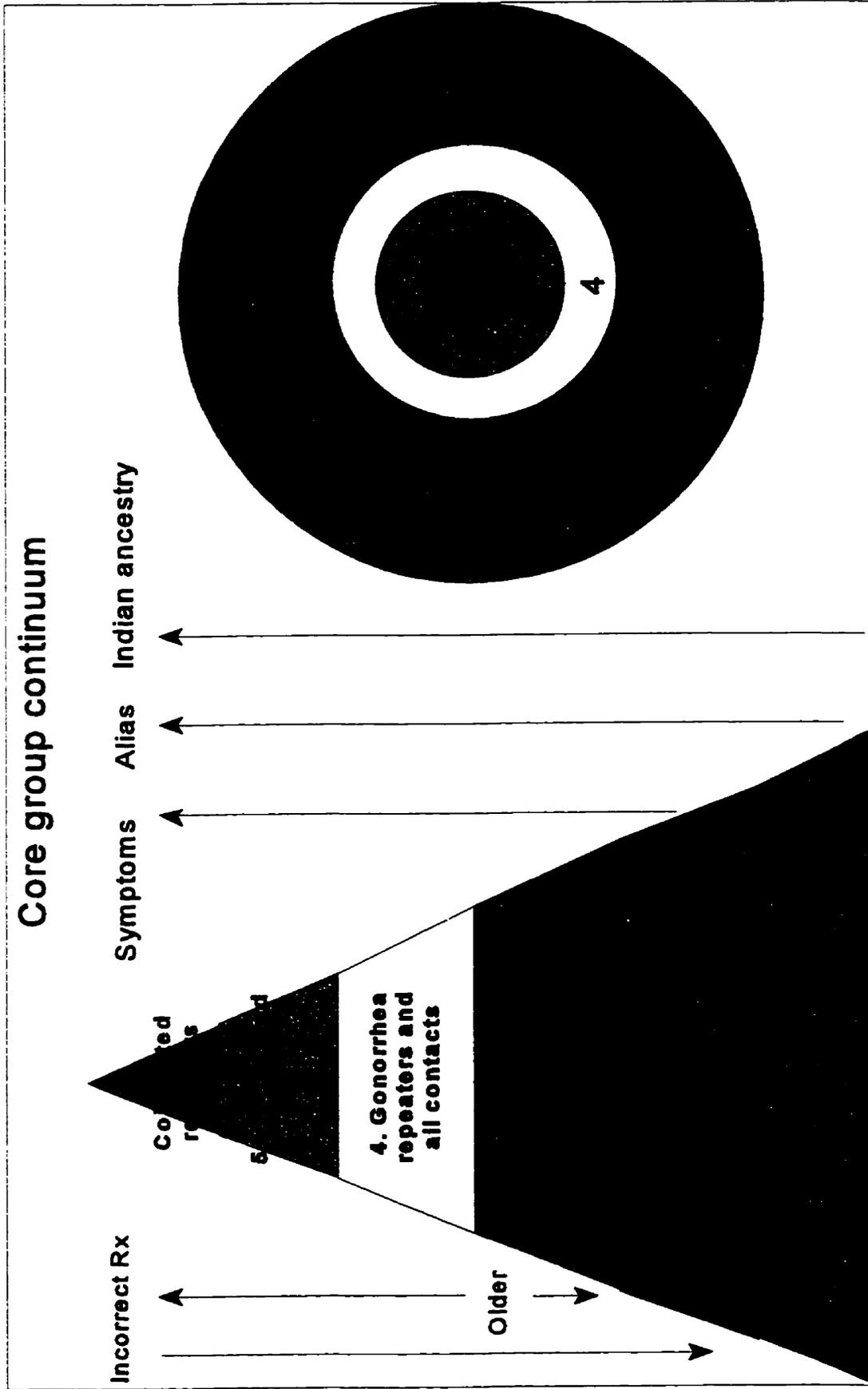


Figure 9.5 Diagram showing continuum of risk markers towards the core.

9.3 The reproductive values of the core groups

The mathematical equations formulated by Anderson and May were calculated using sex partner change rates and variances from a sample of the repeater and comparison populations. While statistical tests could not detect differences in the number of partners, the variances were significantly greater, and the calculations of R_0 with a variety of estimates of duration D and transmission β , consistently showed repeater populations with higher reproductive rates (Table 9.4.)

Table 9.4 Mean rates of partner change ($m-1$), variance (σ) of the number partners and R_0 for the study populations, (chlamydia=ct, gonorrhoea=gc, and coinfectd=coinf.), showing higher partner change rates, variances, and reproductive values for all repeater populations compared with non-repeaters.

	$m-1$	σ	R_0
<i>Duration = 10 months, $\beta=0.10$</i>			
Ct female non-repeaters	0.40	0.45	0.51
Ct male non-repeaters	0.31	0.73	0.88
Ct female repeaters	0.84	1.77	0.97
Ct male repeaters	0.64	1.94	1.21
<i>Duration =55 days, $\beta=0.50$</i>			
Gc female non-repeaters	0.37	0.47	0.82
Gc male non-repeaters	0.43	0.66	0.98
Gc female repeaters	0.34	0.68	1.17
Gc male repeaters	0.97	1.36	1.19
<i>Duration =55 days, $\beta=0.50$</i>			
Coinf. female non-repeaters	0.41	0.92	1.32
Coinf. male non-repeaters	0.40	0.33	0.62

	$m-l$	σ	R_0
Coinf. female repeaters	0.93	2.61	1.87
Coinf. male repeaters	0.53	0.71	0.94

This is the first study which has attempted to calibrate the study population by using a comparison, non-core group population. The higher values of R_0 indicate that infection is certainly more likely to thrive in the repeater groups, than in non-repeater groups.

Although estimates of D and β from the literature vary, when some of those based on sound research were used, the repeater populations showed values of R_0 which were just greater than one, while the non-repeater populations were just below one. This is the ideal proof that the repeater populations described are indeed core groups.

Another interesting phenomena which arose from the calculations is that of the non-viability of chlamydia in a population where there is a high incidence of gonorrhea. When substituting a lower transmission rate for chlamydia in the mathematical equation, and the time duration for gonococcal infection from the literature, the R_0 values dropped considerably below zero. It is likely that due to constant infection with gonorrhea, which is usually symptomatic, and where individuals are treated automatically for chlamydia if gonorrhea is suspected, that chlamydia infection cannot be endemic. This is due to the lower transmission rates of chlamydia (0.10); durations of infectiousness curtailed by dual therapy on diagnosis of incident gonorrhea, and possible partial immunity of clients - an environment in which chlamydia may not be able to survive, and in which it is effectively controlled. This phenomenon has direct implications for control of the chlamydia, as a

program should be designed for populations where the gonorrhea incidence is relatively high and another for a population in which it is low.

9.4 Sexual networks

An alternative to the difficult and uncertain exercise of calculating R_0 , is that of social network analysis. Groups with repeated infections over a three year period or those who have been multiply named is a rough approximation of those individuals who in fact are core group members, transmitting infection to more than one individual. A person could have repeated reinfections all of which may be from the same source contact, and may not have transmitted infection to anyone. Nonetheless, that individual would have been included in this proposed core group which contaminates the sample of core group members. The construction of sexual networks clearly depicts all named sex partners of each individual, and the lack thereof. A variety of social network measures may be useful in defining and describing core group members, and further research into which these may be, is essential. Computer programs for large networks are being developed, and although it requires expert computer programming to convert the data from its registry format into a matrix, it is certainly feasible. Once the social network measures which indicate core group membership have been defined and the members described, changes in core group membership over time should be investigated. If we knew which factors caused individuals to enter or pass out of core groups, we may be able to intervene and prevent disease more effectively.

9.5 Practical applications

The primary research finding which has the most impact on control programs is that it proves the existence of core groups within Manitoba. Not only is their existence established, but a thorough description of them is provided. In the context of shrinking resources and diminished number of cases, an efficient strategy for control and eradication is the concentration of efforts on those who have most impact on incidence rates.

Diminishing infection within core groups will lead to a disproportionately greater decrease in disease, than intervening in non-core groups.

In addition to describing core groups, the second major goal of this research was to develop predictive models, so that public health staff and physicians would be able to classify clients into possible core group members, and non-core group members. This was successful to the extent that the models captured approximately 75% of core group members. In order to improve the specificity, adding further measures such as a question on number of partners is necessary. Originally, this research was to include some testing of these models on a sample of individuals from the core and non-core groups who would consent to answer a questionnaire. This was not possible, as the questionnaire research was conducted five years after some of these individuals would have been reported to Manitoba Health, hence their behavior could not be regarded as representative. However, the questionnaire research on sexual practices being conducted presently at Manitoba Health could yield a further tool to add to the models.

Most important, these models can be used with only the most basic information on a sex partner of an infected person. Control of gonorrhea and chlamydia would be improved if the models were used to prioritize which contacts public health staff should spend large amounts of time trying to locate and those for which it may not be cost-effective to do so. This research has shown the importance of contacts with no confirmed infection in maintaining chlamydia and gonorrhea endemicity. Once individuals at high risk of being core group members are identified, it is recommended that enhanced STD intervention be offered to them. This may include; immunization against hepatitis B, pap smears for women, HIV testing, ensuring syphilis testing, single dose therapy for gonorrhea and chlamydia, polymerase chain reaction (PCR) testing for chlamydia in males, and enhanced safe sex education.

Two other issues of immediate importance were discovered tangentially in this research. The first is that of the proportion of inappropriate therapy prescribed to clients with gonorrhea and chlamydia. A research study evaluating this aspect of the control program has recently been funded. However, the obligations under the Public Health Act to treat clients, and the necessity of controlling disease require that correct treatment be given in the interim. This can be done by adapting the computerized algorithm in this research to flag those records of clients with incorrect therapy. As the physician's billing number is already on the computerised records, this can be linked with the physician address file, and a computerised letter generated to alert him or her of the error. If the written record was

incorrect, and the client did receive the correct medication, this letter may encourage physicians to note the correct medication on the notification form.

The other major issue demonstrated by the networks and in the analyses is that 46% of all multiply named contacts were never confirmed as cases in the three year study period.

There are a number of sociological and diagnostic reasons for this, but the fact that they are undiagnosed allows the cycle of transmission to continue. Research into amplification tests for gonorrhoea and chlamydia in men is continuing at Cadham Provincial Laboratory, but education of physicians and public health professionals on the necessity of diagnosis may improve contact management. The practice of sending medication home with a woman for her to pass on to her partner places undue responsibility on her, and may leave her vulnerable to harm. Likewise, failing to test men does not induce compliance with medication.

Related to the above, is the importance of constructing network diagrams. As the number of cases of gonorrhoea has dropped to about 600 in 1996 in the whole of Manitoba,²¹ further reductions in cases will require different control strategies.²⁷ With computerized data, it is feasible to construct sexual networks for clients with gonorrhoea and provide them to field staff. The diagrams will help focus investigations on those individuals with the highest number of partners who seem to have eluded diagnosis. With computerized data, it is feasible to construct sexual networks for clients with gonorrhoea and provide them to field staff. The diagrams will help focus investigations on those individuals who

seem to have eluded diagnosis. This is not a new idea, as the original “epidemiologists” trained at the Centers for Disease Control advocated the same technique, and stored data on different patients together if they were part of the same sexual network.¹⁵⁰ However, this method may be even more useful than it was then, as core individuals move between communities and jurisdictions, forming continuous conduits for STD. Sexual networks constructed with centralized data may be invaluable in breaking chains of transmission despite modern, rapid methods of transport, and in decreasing incidence rates in communities.

9.6 Limitations of the research

Although all attempts were made to use every available piece of information on cases and contacts in this research, there remain some limitations. These were due to the nature and practice of public health follow-up of STD cases and contacts; the collection and computerisation of data, and lastly, due to the theoretical and practical constraints of mathematical epidemiology and social network analysis.

First, the public health practice patterns of locating, notifying, testing and treating clients is more thorough for the follow-up of gonorrhoea than for chlamydia.¹⁸⁰ This, added to the fact that clients are more motivated to seek care for gonorrhoea than for chlamydia because more of them experience symptoms, results in more complete follow-up of clients with gonorrhoea; hence data on these clients are also more complete.

The databases used in this research include named contacts and laboratory-confirmed cases, which is sufficient for case management. However, data on contacts who were anonymous, or were known only by a nickname or first name, are absent from all the analyses, despite the fact that those are probably the sexual encounters of the highest risk.

Another source of error related to the above was the matching of the contacts to cases, in order to obtain complete partner information. However, the criteria used were fairly strict, so that the matching process would have underestimated the numbers of sex partners, rather than overestimating them.

No data were recorded on the use of condoms during sex for either cases or clients. Therefore, it is possible that the analysis of core groups and display of sexual networks may be misleading, and that some of the individuals named as source cases may not have transmitted disease, or have been exposed to it.

The use of the census data on socioeconomic status supplements the rest of the data with an ecological approach. Individuals were assigned an average household income of the enumeration area in which they lived; their actual income may have been above or below that level. Converting the data to income quintiles obviated concerns over variances in average household income within enumeration areas; while the separation of the effects of ethnic group and income level on core group status is invaluable.

A limitation of the study design itself resulted in the inclusion of individual repeaters within the proposed core groups, who may not have transmitted infection to anyone. This would occur when a person may be repeatedly reinfected by an untreated, infected contact. In the absence of any other known contacts for the reinfected case, this person cannot justifiably be classified as a core group member. However, in order to apply the mathematical formulae for use by public health professionals, likely members of core groups had to be selected *a priori*. This selection may also help account for the fact that some of the reproductive rates may be just below one, instead of above one.

While the predictive models developed in this research had adequate sensitivity, ideal screening models would have had higher specificity in order to differentiate core group members from non-core group members. However, given the need to apply mathematical epidemiology to practical public health questions, and the constraints of the computerised data, higher specificities were not possible. Further research is needed to determine which additional screening tools may be used to raise the specificity of the models, so that a smaller number of people can be offered enhanced interventions.

Lastly, the lack of knowledge of precise disease transmission probabilities, and duration times hindered the calculation of reproductive rates. However, the knowledge is unlikely to improve, as studies to define transmission rates and duration times, in the context of known therapies and severe sequelae from infection, may not be practically or ethically

possible. Another problem with the use of Anderson and May's formulae, is that the calculation of c using the formula:

$$c = m + \frac{\sigma^2}{m}$$

The formula assumes that partner mixing patterns are proportionate, determined only by the number of sexual partnerships "offered" and "accepted" by those with higher and lower numbers of sex partners. This may not be the case in reality, as sexual partnerships may be more assortative, or depend on other characteristics of individuals, such as age, or ethnic group.

9.7 Conclusions

This research has successfully described three groups of people who, by the mathematical definition of having a high reproductive rate, are able to maintain chlamydia and gonorrhoea as endemic diseases within Manitoba. While people with repeated infections have been proposed as core group members before, this research also identified multiply named contacts as active core group members. Not only was this evident in sexual network diagrams, but was also proved conclusively, as multiply named contacts of individuals with gonorrhoea and chlamydia were similar to the case repeaters on multivariate analysis.

The exercise of calculating reproductive rates for all core groups not only confirmed their existence, but also contrasted their values with those of non-core members, which were consistently lower. The calculations also show that the population coinfecting with gonorrhoea and chlamydia may not be able to maintain chlamydia as a viable infection, unless substantial partner mixing occurs outside of the core.

Finally, the feasibility of constructing sexual networks has been established with great success. With the decreasing numbers of gonorrhoea and chlamydia cases in Manitoba, this method may prove to be not only an analytical technique, but also a road map for public health staff which may direct their efforts.

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Appendix I

MANITOBA FORWARD SORTATION AREAS

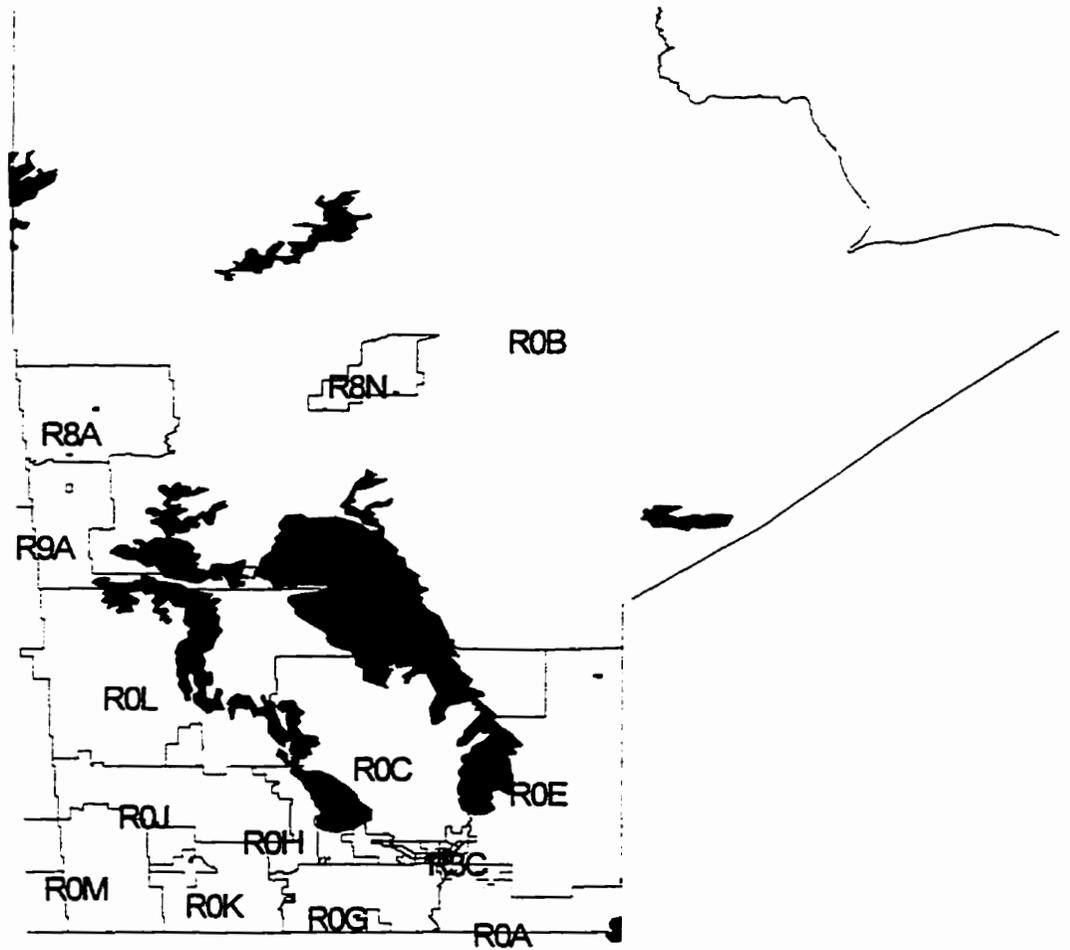
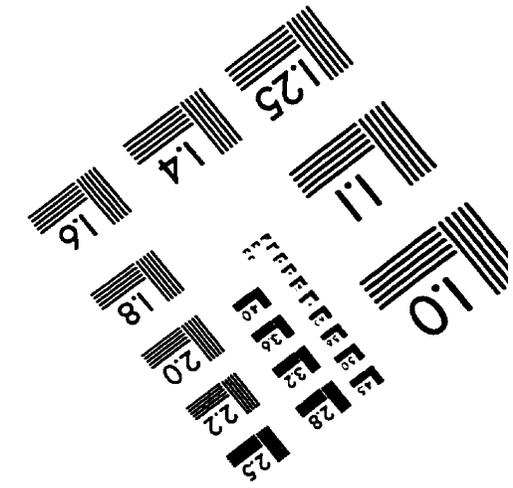
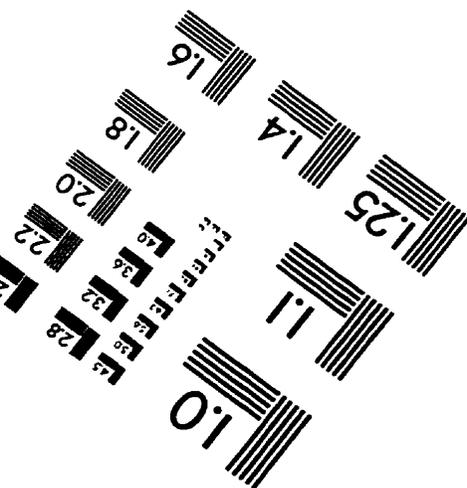
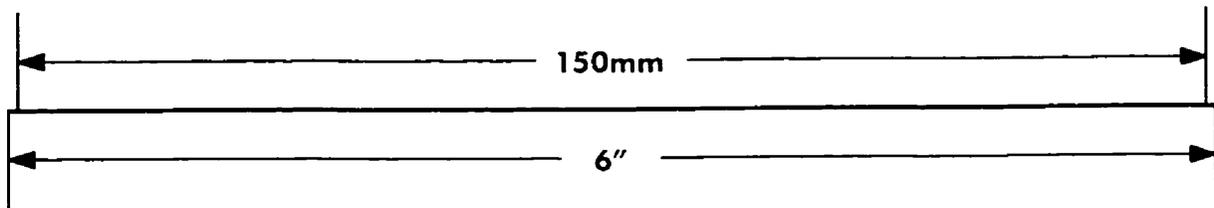
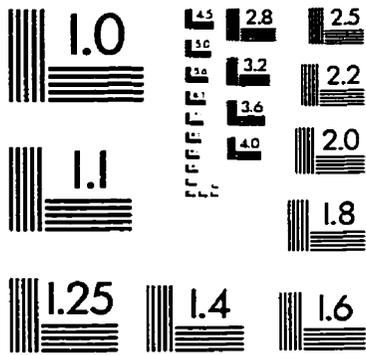
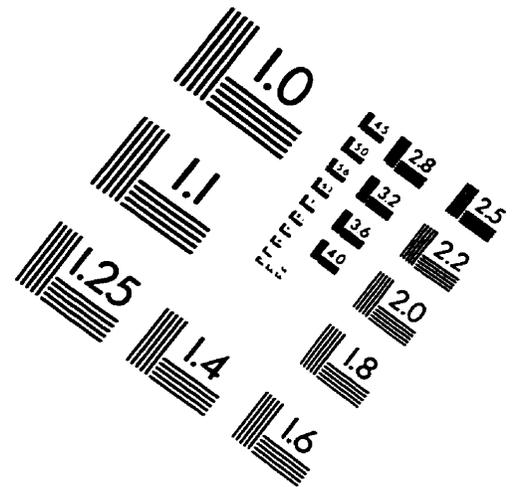
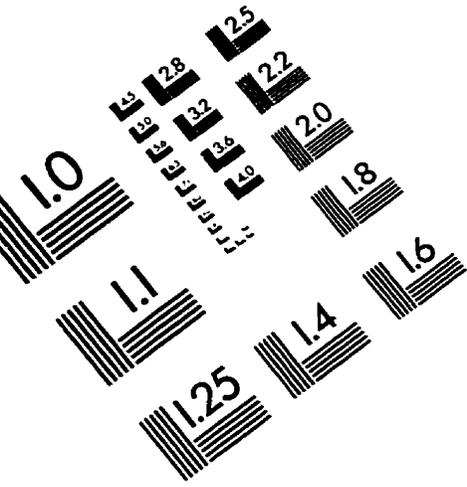


IMAGE EVALUATION TEST TARGET (QA-3)



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