

**THE EPIDEMIOLOGY OF *NEISSERIA GONORRHOEA* AND
CHLAMYDIA TRACHOMATIS GENITAL INFECTION
AND THEIR SEQUELAE**

by ANN JOLLY

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ABSTRACT

This historical prospective cohort study describes the epidemiology of *Neisseria gonorrhoea* and *Chlamydia trachomatis* genital infection, specifically with regard to incidence of recidivism, and the development of sequelae such as pelvic inflammatory disease, ectopic pregnancy, and tubal infertility.

While much is already known about the role of *C. trachomatis* as an aetiologic agent in pelvic inflammatory disease (PID) and other sequelae, no studies have yet been published on the incidence of PID in women who have been tested for chlamydia in the context of a control program, where treatment is readily available. The mechanism by which *C. trachomatis* causes PID and changes in the fallopian tubes is not well understood. *C. trachomatis* infection seems to be distributed widely through populations with differing demographic and socioeconomic characteristics. Therefore further research on chlamydial infection, while controlling for the effects of infection with gonorrhoea is valuable in developing appropriate control programs.

This document contains the background, methods, results and discussion of the pilot study which served to; 1) resolve the practical details of

computerised record linkage through individual identifiers, 2) validate diagnostic codes used in administrative records for Manitoba Health Services Commission, (MHSC), 3) provide a basic description of demographic and socioeconomic status among women with chlamydia, gonorrhoea and sequelae, and 4) provide accurate information on incidence of sequelae of infection. Although the study sample is small, incidence rates were compared with a control group of women who tested negative for *C. trachomatis*. Possible risk factors for progression to chlamydia sequelae are explored.

The completion of this project demonstrated that records from Cadham Provincial Laboratory, (CPL), could be matched successfully with those from MHSC; in addition, there was no evidence of significant threats to internal validity. When the sociodemographic characteristics of women with STDs were compared with controls, young age, being aboriginal, living in an urban area and low mean household income were associated with gonorrhoea and chlamydia coinfection. Women with gonorrhoea were more likely to be younger, live in an urban area, and be North American Indian, than were controls. Only age, and ethnic status were associated with having a positive diagnosis of genital chlamydia.

Having a subsequent diagnosis of an STD from a physician in an ambulatory care clinic was associated with having a positive lab test for chlamydia, gonorrhoea, or coinfection with both organisms. A second diagnosis of STD was associated only with having a previous positive test for chlamydia. Women who had experienced coinfection with *N. gonorrhoea* and *C. trachomatis* were at higher risk than were controls of being diagnosed with PID in an ambulatory setting. However, within this group of coinfecting women, aboriginal women were at much higher risk, and this risk was similar irrespective of whether they had been coinfecting or not.

The results of this study will be immediately relevant to the design of future chlamydia control programs, research on estimates of the cost benefits of screening programs and on the role of *C. trachomatis* as an aetiological agent in PID disease, involuntary infertility, and ectopic pregnancy.

CHAPTER 1

BACKGROUND

1.1 Introduction

Sequelae of *C. trachomatis* represent a substantial personal cost to individuals and a monetary cost to the health care system. In Canada, costs of sexually transmitted disease (STD) sequelae were estimated at \$140 million in 1984/85¹. The rise in incidence of chlamydia, now the most frequently occurring STD^{2,3,4,5}, 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. In most recent North American and European studies, *C. trachomatis* was isolated more often from women with symptomatic PID than was *N. gonorrhoea*, although the percentage of women with PID in whom *C. trachomatis* was isolated from the cervix varied from 5 to 51%, with by far the majority of researchers reporting above 20%.⁴

Although many studies have defined *C. trachomatis* as a causal factor in the development of PID and changes in pelvic anatomy, methods used in the research to date have not allowed for the estimation of the incidence of sequelae among women who have access to medical care. Screening

programs for *C. trachomatis* have been established on the basis of retrospective studies in the hope of reducing the rate of transmission, hence the incidence of new infections and sequelae. It is therefore important to describe the incidence of *C. trachomatis* sequelae where there is easy access to screening tests for chlamydia, so that a co-ordinated control program may be better tailored to decrease the rate of *C. trachomatis* infections and their sequelae. An historical prospective study of four groups of women was conducted in order to describe the epidemiology of *C. trachomatis* and sequelae, with the endpoints being the diagnosis of PID, tubal infertility, and ectopic pregnancy. In order to control for the effects of gonococcal infection on sequelae, a group of women with laboratory proven gonorrhoea were included in this study. A group of women coinfecting with both organisms were also included in the study in order to control for possible synergistic effects of infection with *N. gonorrhoea* and *C. trachomatis*.

1.2 Burden of illness

Both epidemiologic studies and recent clinical research have brought into question the premise that screening will lead to reduced incidence of sequelae. In order to explore this and in order to understand the impact of *C. trachomatis* infection on the incidence of PID, ectopic pregnancy and

tubal infertility, it is important to review the epidemiology of both etiologic agents of STD sequelae, *C. trachomatis* and *N. gonorrhoea*.

In this document, many references are made to the "incidence" of gonorrhoea and chlamydia. It is recognised that many cases will be prevalent, as they reflect asymptomatic infection at an unknown, previous point in time. These infections, particularly chlamydia, may persist for some months and perhaps years at a time before detection. However, as researchers and public health officials have not differentiated between the prevalent and incident cases in their data collection, cases of STD will be referred to as incident cases in the following review of the literature.

Chlamydia trachomatis is now the most common sexually transmitted disease in North America. Chlamydia was only recently made reportable nationally in Canada, although only 9 provinces including Manitoba require reporting of chlamydial infections; therefore the true incidence of *C. trachomatis* in Canada is not known.⁸ The cost of testing for the organism in Manitoba is now over \$1.2 million per year. 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 usage of the tests rather than the true incidence of disease) Rates of incidence of chlamydia

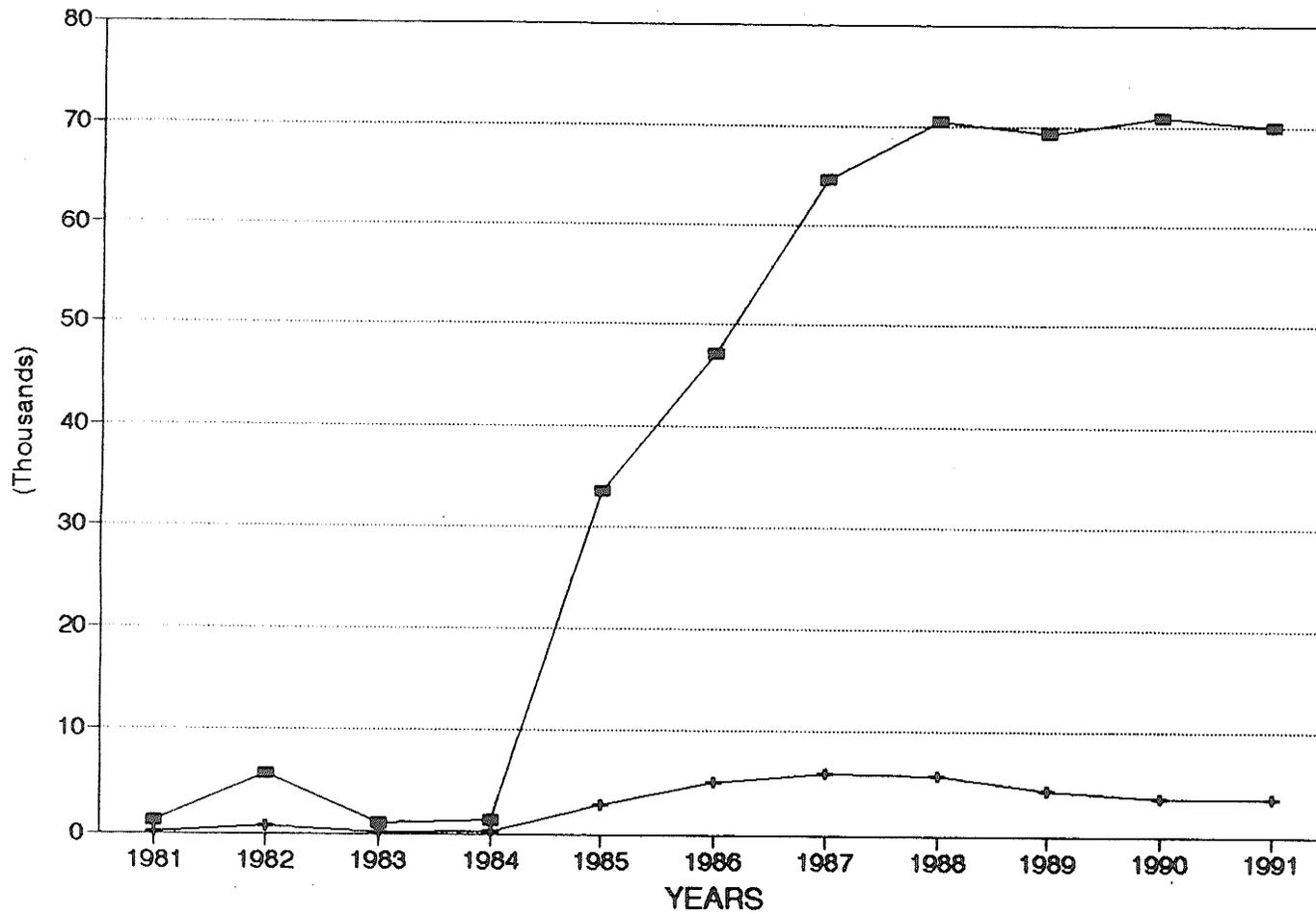
genital infection in Manitoba for males and females respectively were: 73/100,000 in 1988⁷ (both sexes), 27/100,000 and 72/100,000 in 1989⁸; 21/100,000 and 58/100,000 in 1990⁹, with females representing approximately two thirds of reported cases. An early study on the incidence of *C. trachomatis* in a population of female university students in British Columbia showed an initial incidence of 7,000/100,000 of those women tested in 1984/85, dropping to 4,400/100,000 in 1987/88. This decrease may have been due to a local health education campaign, but the number of women testing positive is substantial.¹⁰

The incidence of *C. trachomatis* infection is defined, in some respects, by the availability and use of tests for the bacteria. In the late 1970's and early 1980's the method for identification of the organism was culture¹¹; later, the direct immunofluorescent assay and the enzyme immunoassay became available. With advent of the less expensive assays, an increase in *C. trachomatis* screening became apparent, and with this, an increase in number of cases. In the early 1980's the reported incidence of chlamydial genital infections was influenced by detection bias; selection bias was also evident as a substantial proportion of tests were done only on women presenting with symptoms of STD, while those without symptoms may never have been tested.

TOTAL AND POSITIVE TESTS FOR CHLAMYDIA CPL, 1981 - 1991

FIGURE 1

OF TESTS
(Thousands)



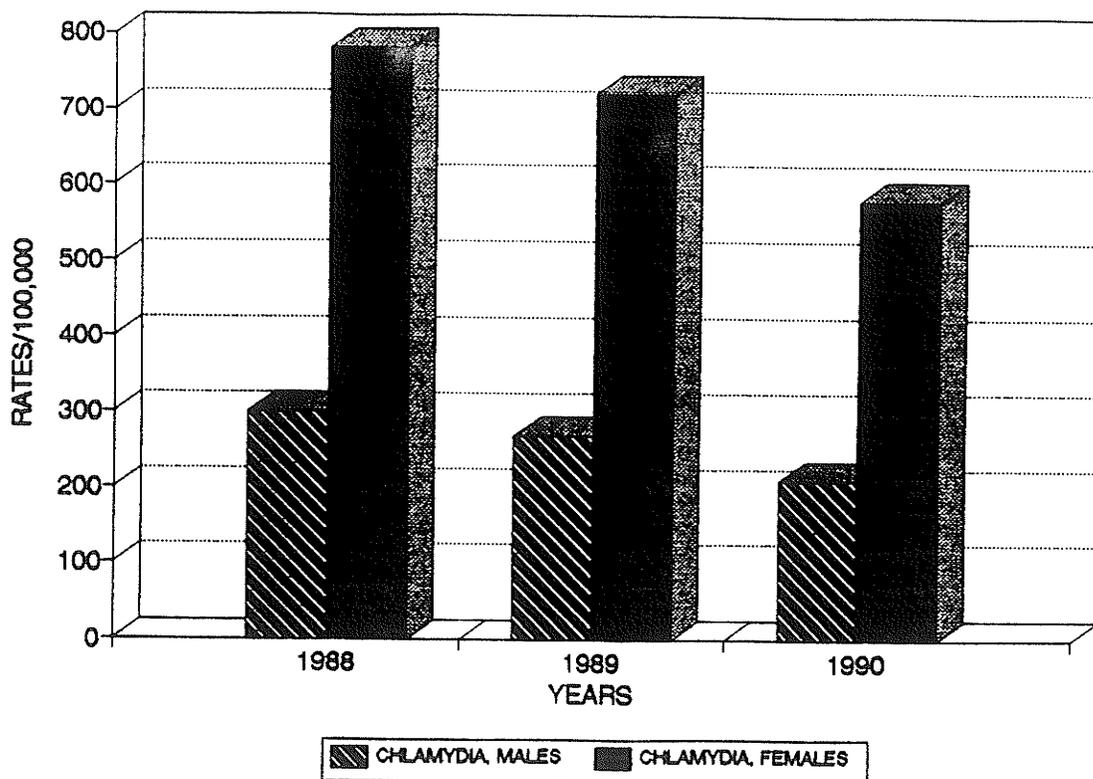
■ TOTAL TESTS ◆ POSITIVE TESTS

A second problem related to the logistics of testing for *C. trachomatis* is revealed in the incidence of the infection in women compared with that in men. In Manitoba, (and in other places¹²), the number of cases of chlamydia in women was 2.66 times that of the number of men in 1988 (Figure 1); this ratio may be as great as 3 in some areas. Gender-specific incidence rates reveal the detection of the organism in women who are screened routinely for the infection as opposed to men, who are not screened. Asymptomatic infected men may who are not routinely screened for *C. trachomatis* may have a substantial role in maintaining the epidemic. Although known partners of contacts are treated on a regular basis, routine screening and treatment of women may not be as effective as routine screening of both sexes, since women are continually exposed to a large pool of infected, undiagnosed and untreated men. However, it is recognised that there are technical difficulties involved in diagnosing infection in men.

The screening, treatment, and follow-up of sex partners in Manitoba is probably the major reason for the decrease in chlamydia rates shown in Figure 2. The decrease in positive test results is not due to decreased testing, which has remained constant for the last three years, (Figure 1).

FIGURE 2

CHLAMYDIA INCIDENCE MANITOBA 1988-1990
RATES/100,000, BY GENDER



Trends of *N. gonorrhoea* have varied over time, though general trends are similar in different places. Incidence of gonorrhoea decreased after World War II, and then rose in the 1960's to reach a peak in the 1970's. Rates of gonorrhoea have decreased since then in Manitoba (Figure 3), Canada, and in the United States especially after 1987, possibly due to changing behaviours in recognition of the importance of HIV infection.¹³

1.3 Etiology and Risk Factors

Much research has been done on describing the populations affected by *N. gonorrhoea*. Although *N. gonorrhoea* and *C. trachomatis* are both sexually transmitted, and the risk behaviour involved is identical, there are preliminary indications that the two diseases do not follow the same demographic or socioeconomic patterns.¹⁴ Making the distinction between populations at risk is important in defining risk of disease and in developing appropriate control programs.

American black men aged 25 - 44, were primarily responsible for the decrease in gonorrhoea in the United States. However, rates in American black males remained 10 times higher than those of white males. In 1987 an increase in rates occurred in white females aged 15-19. Age-specific rates showed that women aged 15-24 had rates 3 times those of the age

GONORRHOEA INCIDENCE MANITOBA 1982-1990 RATES/100,000, BY GENDER

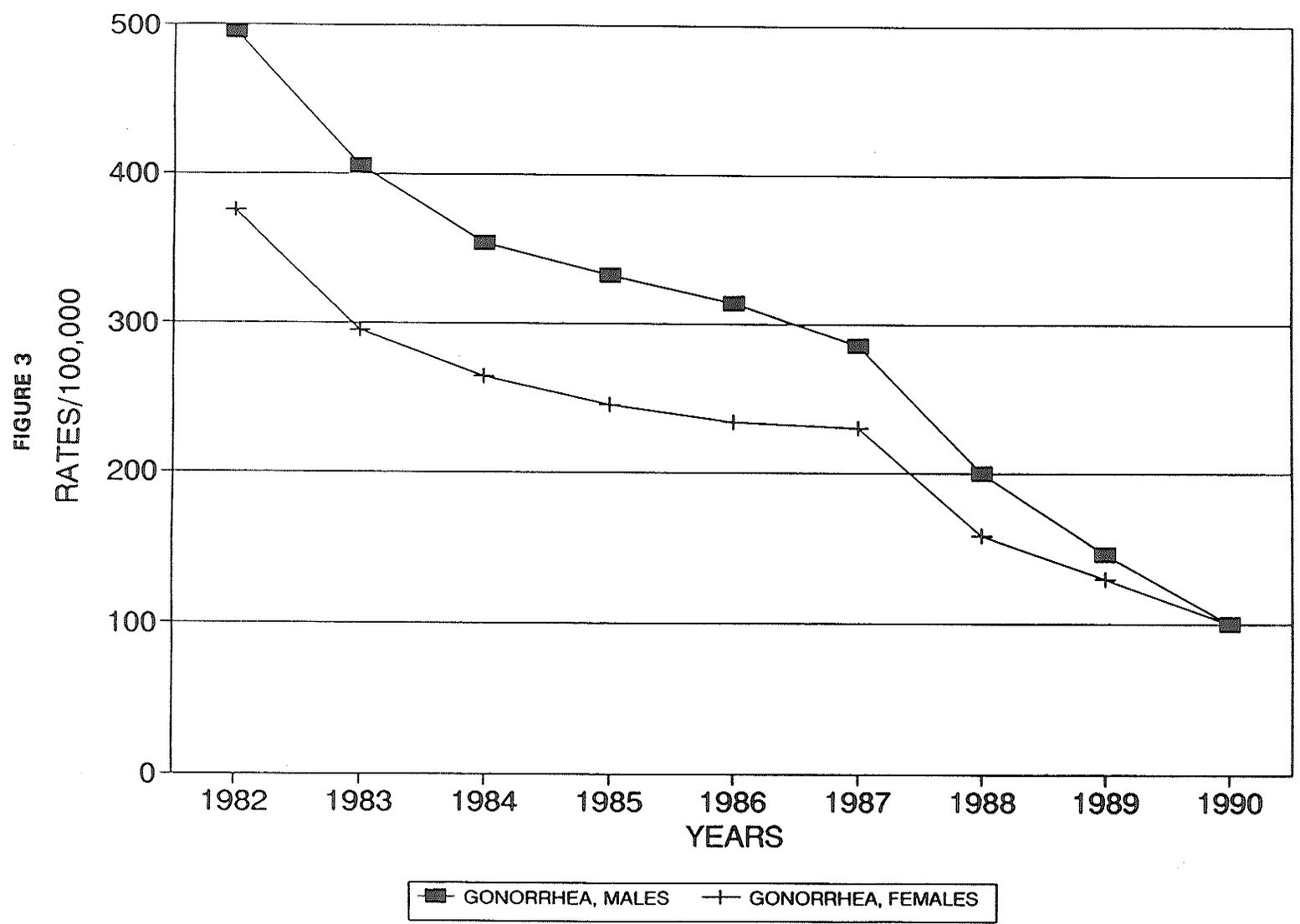


FIGURE 3

group with the second highest frequency, women aged 25- 29 years old. Males aged 20 - 24 had the highest incidence of *N. gonorrhoea*. The male:female ratio of infection with *N. gonorrhoea* has remained constant at 1.5:1 since 1973.¹³

Incidence of gonorrhoea in Canada has decreased since 1980.¹⁵ Rates in women aged 15 - 19 have not fallen as much as they have in other age groups, and this group experienced the highest incidence of infection among females. Men aged 20 - 24 had the highest rates of *N. gonorrhoea* compared with men in other age groups. Overall, men aged 20 - 24 had the highest rates of infection with women in the same age group having the second highest, but since 1985 teenage women had rates surpassing those of older women.¹⁶

In Manitoba, in 1989, women aged 20 - 29 had the highest incidence of gonorrhoea, although this may be due to the fact that the ages have been broken down into 10 year age groups, instead of 5 year age groups. Women aged 10 - 19 have the next highest incidence.⁷ Generally, teenage females seem to experience the highest rates of gonococcal infection when compared with women in other age groups. The age distribution of *C. trachomatis* infection is not as widely published, as some jurisdictions do not yet collect data on this infection.¹⁷ However, the number of infections

with *C. trachomatis* is estimated to be three times that of gonococcal infections.^{15,18} Statistics on age-specific infections are not available for the United States, although some clinic-based studies have been published, indicating that *C. trachomatis* infection is more common in younger, teenage women.^{19,20,21,22,23,24,25}

In Canada, results of chlamydia laboratory surveillance were reported for 1987.²⁶ Laboratories participating in the program recorded 163 949 specimens, of which 11 584 were positive. The incidence rate in women aged 15 - 19 years was the highest, surpassing any other age group of males or females. Approximately three quarters of the specimens found to be positive were from females.²⁷ Other research in Canadian clinics reveal chlamydial infection in females to be associated with young age, as is gonococcal infection.^{24,25}

In Manitoba, similar trends are seen; laboratory confirmed infections with *C. trachomatis* in females make up 73.1% of all positive reports⁸, and women aged 15 - 19 have the highest rates of infection, with women aged 20 - 24 having the second highest rates.

Research on gonococcal infections and socioeconomic group has indicated an association between the infection and low socioeconomic status.^{28,29}

Measures of socioeconomic status are not uniform and are often confounded with those for ethnic group;^{30,31,32,33} therefore conclusions drawn from other studies to date have some limitations. For the purposes of this study, the socioeconomic status of an individual is distinguished from his/her ethnic group. Another issue that complicates interpretations of socioeconomic status as a risk factor is that of selection bias. Many of the studies defining socioeconomic and demographic characteristics were done in STD clinics in the United States, which, in the absence of adequate health insurance, are used more by disadvantaged members of that society. In addition, reporting of notifiable STD's are more complete from those institutions than from private medical clinics.⁵

In a study conducted in King County,²⁹ Washington, case reports from public health clinics and private clinics were correlated with laboratory reports and socioeconomic data from the census tracts. Case reporting from the public health clinics was far more complete than that from the private medical clinics. This study reports that the highest incidence of gonorrhoea occurred in census tracts with the lowest socioeconomic status, independent of ethnic group. Census tracts were divided into 4 groups based on median family income, percentage of high school completion, percent employed in professional, managerial, or technical occupations, housing cost index, and percentage of home owners. These characteristics were compiled and

summarised into a single score for low, lower-middle, upper-middle, and high socioeconomic groups.

In general, researchers have traditionally associated high incidence of *N. gonorrhoea* with low socioeconomic status, although the variables used to measure it may have been questionable.^{2,5}

Characteristics of women with chlamydial infection have not been well described. Two review articles state that *C. trachomatis* infection occurs at all socioeconomic levels.^{2,5} This assumption seems to be borne out by research done in the United States. Two studies done in a clinic which serves lower socioeconomic groups and working class families, cite prevalence rates of 15.3%²³ and 25.4%¹⁸; another in a middle class neighbourhood shows a rate of 12%²⁰, and yet a fourth in a middle class and upper middle class neighbourhood reveals a rate of 14.5%²¹. A Canadian study done in a low to middle income area of Montreal revealed a prevalence rate of 7.1%, in 1985/86,²⁵ and in 1984/85, female university students were shown to have an prevalence rate of 8.1% dropping to 3.2% after a "safer sex" education campaign.¹⁰ Yet another Canadian study on middle class patients revealed rates of 11% in women seeking care from general practitioners.³⁴ It is assumed that university students may not be easily classified as belonging to a "low" socioeconomic group. One study in

Sweden found, contrary to the above, that women with a higher rate of chlamydia tended also to use social assistance more, although this group of women was recruited from a traditional STD clinic, whereas the comparison group comprised asymptomatic women participating in a screening program.³⁵ Another, in the United States suggests that level of education, independent of race, though not of age, is predictive of chlamydial infection.³⁶

There are a number of limitations to this research. Much of it may not be generalisable to areas outside of the area in which the study was done. In many of the studies, ethnic composition of the study groups differ, with minority groups belonging mainly to the lower socioeconomic groups, thereby confounding the effects of low socioeconomic status, cultural practices, and the social dynamics of living in an inner-city. The average income level of the residents of the area served by a clinic was mentioned in only one study; none of the others contained a definition of what exactly constitutes a low, middle or upper class neighbourhood.

The incidence of gonorrhoea has been higher in racial minorities in the United States than in white Americans.^{22,23,29,30,31,32,33,37,38} Rates in white Americans declined less between 1975 and 1984 than those of black Americans, which declined greatly in Black men aged 25 - 44 years old.

Nonetheless, their incidence rates remained 10 times higher than that of their white counterparts.¹³ In 1989, 25 black patients were reported to have gonorrhoea for every one white patient.² These surveillance statistics may not be a true reflection of comparative incidence, as white Americans, who tend to be more affluent, usually attend private medical clinics where reporting of notifiable diseases is not as complete as that in public health clinics. In addition, rates may differ considerably between different ethnic groups; so that rates for non-white Americans vary considerably from 3033 cases per 100,000 in Blacks, to 617/100,000 in Hispanics, to 190/100,000 in Asians.²⁹ These differences in gonorrhoea incidence between ethnic groups remain after controlling for socioeconomic status. Native North Americans are also at increased risk for STD, and one study shows that rates for chlamydial infection are very high for American Indians, 24% in women seeking pre-natal care at Indian Health Service Clinics.³⁷

Data on ethnic status and gonococcal infection are not commonly available in Canada. However, in some areas, incidence of gonorrhoea in aboriginal peoples has been noted as being higher than that of their non-aboriginal counterparts. In the Northwest Territories, where the vast majority of the population is aboriginal, the incidence of reported gonorrhoea was 10.52 times that of Canada as a whole. This ratio could not be attributed to differences in population age structure, as age-specific rates were calculated

and compare.³⁹ Aboriginals living in Manitoba in 1987 had a rate of reported gonorrhoea of 478/100,000.³⁹ The Canadian rate for that year was 109/100,000, 4.4 times lower than that of aboriginal Manitobans.⁴⁰

Chlamydia trachomatis infection in the United States has been described as occurring more frequently in Black women than in White women,^{22,38,41} although this may be a function of socioeconomic status. One American study showed that incidence of chlamydia did not differ between races when socioeconomic status, indexed by paternal occupation and maternal education, was the same.²³

As with gonococcal infections, there is little information on how Chlamydia affects different ethnic groups in Canada. Aboriginal people have higher reported rates of infection, at least as reported in the province of Manitoba, where provincial rates were 50/100,000,⁸ and the rate for Aboriginal males was 379/100,000 and for Aboriginal females was 1,026/100,000, (8 and 20 times higher respectively).³⁹

Much of the research into STDs is clinic-based in urban areas. Therefore type of area of residence, (urban, suburban or rural), has not been studied in any detail in the United States or in Canada. Association between inner city dwelling and high rates of gonorrhoea have been noted.^{2,5,23} However, one study in South Carolina reports an increased risk of gonococcal infection in

rural non-white individuals.²⁹ It is difficult to differentiate the effects of socioeconomic status, ethnic group and type of area of residence in these studies, as many do not measure all these characteristics simultaneously.

Area of residence and risk of Chlamydia infection has not been well described; one study in Canada suggests that rural populations have comparable risk of infection (11%)³⁴ as an adjacent urban population (7%).²⁵ Prevalence rates are available for populations served by certain clinics, usually in urban areas.^{18,20,21,22,23,24} However, there are no data comparing those rates with those of less populated areas, and certainly none where access to chlamydia testing is comparable in both urban and rural areas.

1.4 Complications and sequelae

The incidence of hospitalised PID in Canada showed a rise over the period, 1971 to 1983, expressed as number of cases of PID per hospital separations, Figure 2.⁴² The highest rates were in the 20 - 24 age group. Subsequently, the rate of PID started to decline, from 299.2/100,00 to a rate of 253.3/100,000 hospital separations in 1987/1988; the rate of PID in women aged 20 - 24 still remains the highest of any age group.⁴³ An estimated 10 - 15% of all patients with PID are treated in hospital; the remainder are treated on an ambulatory basis.⁴⁴ In Manitoba, the rates of

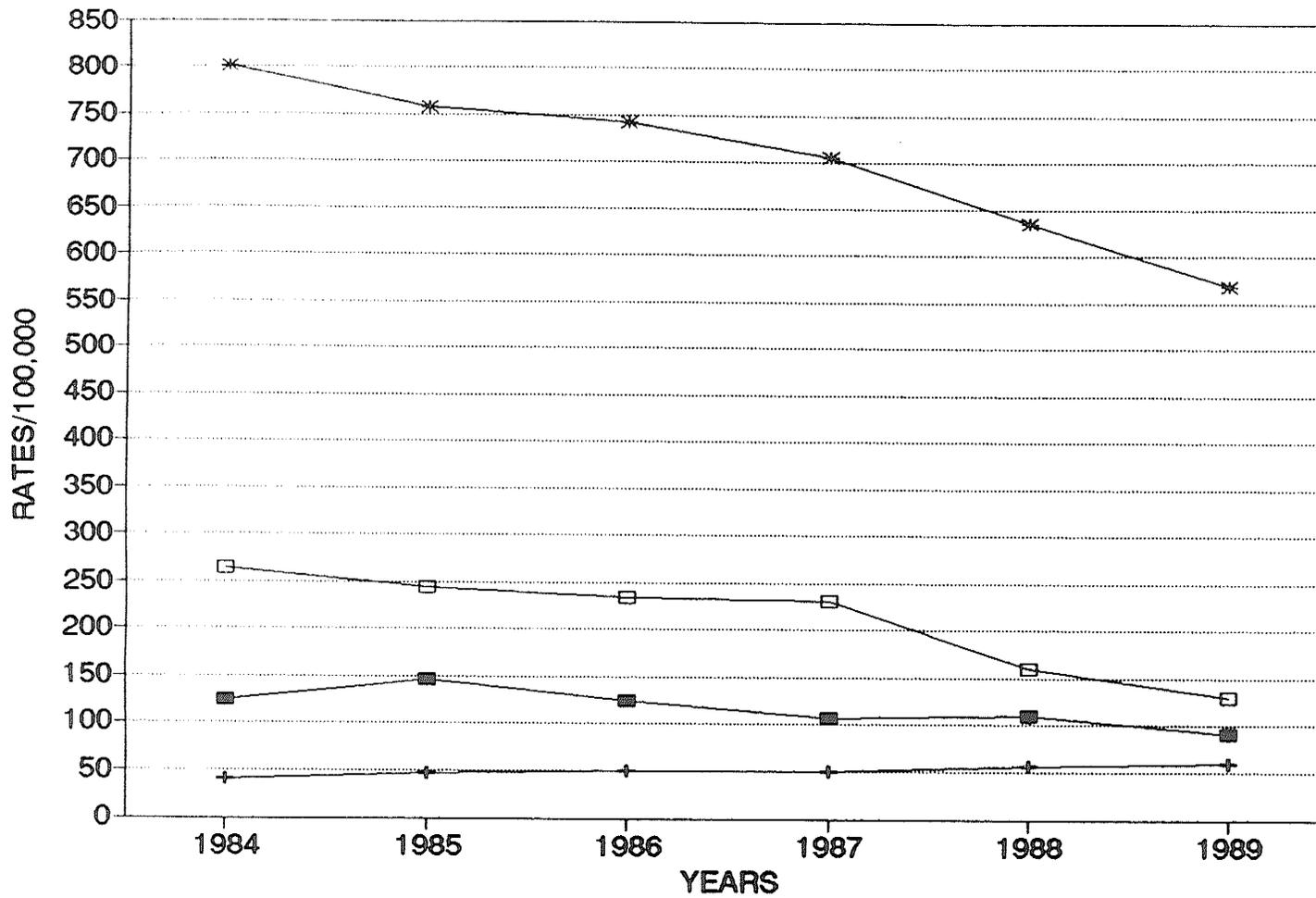
hospitalised PID have decreased gradually over time (1982 - 1988), with the exception of 1986, (Figure 4).

The rate of ectopic pregnancy in Canada has steadily increased from 5.7/1000 pregnancies in 1971 to 12.9 per 1,000 in 1984/1985.⁴² Although ectopic pregnancy has been associated strongly with previous PID, no increase in rates of PID parallel to that of ectopic pregnancy was evident. In Manitoba, the rate of ectopic pregnancy increased slowly in the period from 1982 to 1984 inclusive, and then increased more steeply in the period 1985 to 1988.⁴⁵ Again, this trend does not parallel that of hospitalised PID in Manitoba.

The contrasting trends of Chlamydia, PID and ectopic pregnancy point to some of the important questions of the role of *C. trachomatis* in PID, ectopic pregnancy and tubal infertility. The continued rise in incidence of ectopic pregnancy, despite a decline in hospitalised PID, may suggest changing criteria for admission of patients with PID; but most likely, a change in the nature of PID to a less symptomatic, but clinically more severe form.^{46,47,48,49,50,51,52} This last factor may be due to the decrease in gonorrhoea incidence in recent years and the fact that chlamydial PID, which is often asymptomatic, may be an important contributor to tubal changes, resulting in ectopic pregnancy.^{53,54,55,56}

INCIDENCE OF GONORRHEA AND STD SEQUAE
 MANITOBA, RATES/100,000, 1984 - 1989

FIGURE 4



HOSPITALISED PID
 ECTOPIC PREGNANCY
 AMBULATORY PID
 GONORRHEOA, FEMALES

C. trachomatis was first described as an aetiologic agent for PID and tubal infertility in Sweden in the 1960s. The methods used to confirm PID were invasive surgery, initially, and later, laparoscopy.⁴ In many case-control studies since then, the organisms associated with PID and tubal factor infertility have been investigated^{57,58,59,60,61} and in the majority of more recent studies, *C. trachomatis* has been found in women with PID more often than has *N. gonorrhoea*.^{4,62} Although a Canadian study of women with symptomatic PID did not show *C. trachomatis* as being the most frequent organism isolated, it did show significantly higher tubal infertility in those women who had chlamydial PID.⁴⁹ Other retrospective studies showed a significant association between past infection with *C. trachomatis* and tubal factor infertility, (see above).^{63,64} These studies are well supported by data from other areas. Also noted in one study was the high risk of tubal infertility associated with repeated experiences of PID.⁶⁵

Investigations have shown several problems associated with the diagnosis and aetiology of PID. First, isolation of the organism has been problematic. In some studies, cervical cultures and/or serology for antibodies to *C. trachomatis* were done. In others, cultures of *C. trachomatis* were taken from the endometrium and fallopian tubes. Difficulty in isolating *C. trachomatis* from certain sites may be partly due to the fact that the

mechanism by which sexually transmitted infections cause PID and changes in the pelvic anatomy is not well known. Cervical cultures may not show infection with *C. trachomatis* if the infection has ascended into the uterus and fallopian tubes; cultures of the organism from the fallopian tubes may not be successful due to small numbers of the bacteria and presence of local antibodies.⁴

Second, laparoscopy, once the "gold standard" in defining the state of pelvic inflammation, was shown not to be particularly sensitive to, or predictive of, chlamydial PID or tubal infertility.^{4,66,67} Third, the "silent", non-symptomatic PID in which *C. trachomatis* has been primarily implicated, may lead to loss of fertility presaged by no clinical signs and symptoms at all.⁶⁸ Finally, new hypotheses about the process by which *C. trachomatis* causes PID and anatomical changes in the female anatomy have been developed. These postulate that *C. trachomatis* is an initiating agent of other autoimmune and microbiological processes, and it is these processes, and not *C. trachomatis*, which may prove to be the direct cause of PID.^{69,70,71,72}

This last theory has broad implications for the control and treatment of STD and may act as an explanatory factor in analysing the trends of PID in Canada and in Manitoba. Essentially, it may mean that although screening

programs are in place, reduction of risk of sequelae in women with chlamydia infection may not take place to the extent expected, as tubal changes which occur are unaffected by treatment for chlamydia. Research on animal models suggest that early treatment for *C. trachomatis* is effective in partially preventing tubal inflammation, but given later than 10 days after infection, was not as effective.⁷³

In spite of these unknowns, screening, laboratory diagnosis, treatment, and in some provinces, surveillance of *C. trachomatis* are well-established in Canada. Cost benefit analyses have been conducted in the United States^{74,75,76,77} and in Canada⁷⁸, all recognising the benefits of screening for *C. trachomatis*, at least in populations at elevated risk. All of these analyses lack data showing the burden of chlamydia sequelae despite the existence of a laboratory testing program. Evaluations of screening programs, describing impact on sequelae, have not been published to my knowledge.

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CHAPTER 2

DESIGN AND METHODS

2.1 Objectives

1. To demonstrate the feasibility of linking CPL records, which provide test results for sexually transmitted disease, with MHSC billing records which provide information on sequelae of STD, through patient contacts with the health care system.
2. To determine the extent to which ICD-9 coding of medical and hospital billing records, is consistent with the laboratory tests ordered and the results obtained. (Validity check.)
3. To determine the differences in incidence of repeat STD, pelvic inflammatory disease (PID), infertility and ectopic pregnancy between four groups of women with laboratory proven chlamydia, gonorrhoea, both and neither.
4. To describe and compare the socioeconomic and demographic characteristics of the same four groups of women.

5. To describe and compare the sociodemographic characteristics of women who develop sequelae of STDs with those who do not.

2.2 Hypotheses

In order to describe the sociodemographic characteristics of each of the groups of women with STD compared to those of the control group, the following hypothesis was developed:

H_0 : Infection with gonorrhoea or chlamydia, or both, occurs independently of socioeconomic status, area of residence, (rural/urban), age and ethnic group.

H_1 : Infection with STD is associated with socioeconomic status, area of residence, age and ethnic group.

If socioeconomic status, age, area of residence, ethnic group are not associated with STD, then characteristics of women with STD should not differ from those of women in the control group.

In order to analyse data on sequelae in the four groups of women the following hypotheses were developed;

- H₀ Women who have experienced either gonorrhoea or chlamydia or both will be at the same risk of a subsequent episode of STD and development of sequelae as those women who have not experienced an episode of STD.
- H₁ Women who have experienced either gonorrhoea or chlamydia will be at different risks of a subsequent episode of STD and development of sequelae when compared with those women in the control group.
- H₀ Women with sequelae of STD do not differ significantly with respect to age, income, education, and area of residence from women with no sequelae.
- H₁ The sociodemographic characteristics of women with sequelae of STD differ significantly from women without sequelae.

The first set of hypotheses served to describe differences in rates of sequelae and recidivism of STD. The second set of hypotheses was developed in order to fulfill the last objective of this study.

2.3 Study design

Several issues were considered in selecting a study design. Many studies have been done on the associations between infection with gonorrhoea or

chlamydia and sequelae, as shown in Chapter 1. However, the incidence of sequelae in women with previous proven infection was not available, due to the nature of the case-control designs. In order to quantify the risks to women with STD, a prospective design is essential. The quantification of risks of sequelae is needed for an important reason: to define the burden of illness in a population of women with a history of STD compared with women who have no such history. The incidence of sequelae in women who have tested positive for an STD and have presumably been treated, will give an estimate of the risk of illness in this group, despite the existence of a chlamydia screening program. The evaluation of such costly programs is necessary in order to better direct prevention programs and justify funding.

Because of the necessity for a large sample size to study relatively rare events, and the existence of a database at CPL with a substantial number of positive STD records from 1986 to the present, an historic prospective study was initiated.

Four cohorts were defined for the purposes of this study. A group of women who had a negative test result for both *N. gonorrhoea* and *C. trachomatis* at some point in 1988, served as a control group in this study. A group who tested positive for gonorrhoea, a group who had tested positive for chlamydial infection and a group who had tested positive for

both infections concurrently, at some point in 1988, were chosen as cases. Incidence of sequelae was estimated for the four groups of women by counting the number diagnostic codes for PID, ectopic pregnancy, and infertility in their hospital or medical billing records from their laboratory specimen dates in 1988 to March 31, 1991, (the last edition of the administrative databases).

The risks of sequelae in women with gonorrhoea have been documented to be different in nature and in quantity from those in women with chlamydia. In order to control for the effects of gonococcal infection on sequelae, a group of women with laboratory proven gonorrhoea were included in this study. Women coinfecting with both organisms were included in the study in order to control for possible synergistic effects of infection with *N. gonorrhoea* and *C. trachomatis*. In addition, as control programs should be tailored for the specific groups of individuals for which they are intended, it is expeditious to include analyses of social and demographic characteristics of women with chlamydia, gonorrhoea and coinfection.

As MHSC data were available initially for small numbers of women only, three samples each consisting of 100 women each with positive lab tests for chlamydia, gonorrhoea, both organisms and 100 with negative test results in 1988 were selected for entry into the study. The sample

population of controls was women who had a negative test for gonorrhoea and chlamydial infections at any point during 1988. This method of selecting a control group was not ideal, for while they tested negative at a defined point in 1988, they may have subsequently tested positive for either STD previously later, or subsequently. Likewise, individuals of the sample categories of women with chlamydia, gonorrhoea and coinfection may have tested positive or negative later on in 1988 for *N. gonorrhoea* or *C. trachomatis*, contrary to their original results from which the study groups were constructed. However, the selection of controls and other groups was made this way in recognition of time and resource constraints. The effects of the impurity of the present control group is to underestimate differences in risks of sequelae experienced by the three STD infected groups, i.e. to make the analysis less sensitive. It is also recognised that more women in the control group are likely to belong to a subset of a large number of women who are routinely screened for chlamydia at an annual physical. As the rate of infection is low in this group, a low rate of sequelae may also be experienced in this group, so that although some may test positive for an STD, and be counted as cases, they may not resemble the three groups of women with STD exactly.

2.4 Sources of data

2.4.1 Health billing records

Manitoba Health Services Commission (MHSC), the provincial health insurance plan, maintains a computer database of all health services required by Manitoba residents. These services include both in- and out- patient hospital visits, laboratory services performed on an out-patient basis, physician visits, and use of home care services. Manitoba residents who have moved into and out of the province can be identified, as well as those who have changed their names. This computer database is divided into four computer files.

The Registry File contains non-nominal identifying information on residents of Manitoba who are registered with the MHSC. As the provincial health plan requires no payment of premiums, and as registering with the MHSC would allow a patient to receive all basic health services insured against by the provincial plan, nearly all residents of Manitoba are registered with MHSC. This computer file consists of the dates of commencement, interruption, and termination of insurance coverage for members of a family; the sex of the patient, date of birth and MHSC registration number. Because the identifying information is non-nominal, use of these data preserves

patient confidentiality, but allows for differentiation between users of health services over time.

The Hospital File contains; identifying information on the patient, the dates of admission and discharge of the patient, the name of the attending physician, the discharge diagnoses and the surgical procedures performed on the patient and the institution where the patient was hospitalised. If the patient is a resident of Manitoba, and is registered under the provincial health plan, hospitalisation in facilities outside of Manitoba is recorded in the database. (Treatment of registered Manitoba women occurring in institutions outside of Manitoba is billed by the institution concerned back to the MHSC.) This file, together with the patient registration file which was used to define episodes of hospitalised PID, ectopic pregnancy and infertility.

The Physician Claims File comprises records of services performed for patients by physicians. In order to be paid by the provincial health insurance plan which operates on a fee for service basis, physicians must submit a claim card to MHSC, for each patient visit or procedure performed. The claim card shows the patient's identifying information, the physician's identifying code, the code (tariff) for the type of service rendered, the diagnosis, and the fee charged to the Plan. If a diagnostic or treatment procedure was performed, the fee for this is added to the claim card. The

Physician Claims File therefore is a comprehensive record of insured services provided by physicians to patients. This file was used in combination with the Registry File to identify diagnoses of non-hospitalised PID.

Patient records in these files can be linked by use of the MHSC registration number, birth year, month and sex. The MHSC research database is located at the University of Manitoba, and contains data from insurance claims dating from 1973 through 1991. The files are updated regularly, on application to MHSC.

2.4.2 Laboratory records

Cadham Provincial Laboratory (CPL) performs approximately 90% of the testing for *C. trachomatis* in Manitoba. The Health Sciences Centre and Westman Region together process the remaining 10% of samples. The method for identifying *C. trachomatis* used initially at Cadham was culture, although since 1984, the direct fluorescent antibody test has been used. Even more recently, from 1986 on, the predominant technique was the enzyme immunoassay. Cadham Provincial Laboratory has maintained computerised records of all laboratory reports dating from the early 1980's; however, testing for Chlamydia began to be performed in significant numbers only in 1984.

Each requisition for a laboratory test for *C. trachomatis* at CPL may contain the patient's last name, give name or initial, MHSC registration numbers, date of birth, sex, current address, the physician's name and/or billing number, the code and/or name of the physician's facility, specimen source, date of specimen collection, the examination required, and a form on which the sender may include any other relevant information. Requisitions for chlamydia testing are filled out in the physician's office, and many contain incomplete or inaccurate patient information.¹

Once received at Cadham, the specimen was sent to the appropriate testing area, and a copy of the requisition was sent to data entry. Once there, the CPL database was searched using the first six letters of the patient's surname, initial and sex. A listing of all records on the CPL database which matched the patient's surname, initial and sex was displayed along with other demographic information such as MHSC number and address. A record would have been selected from this listing as a match, provided that the three fields had the same entries. The patient record would have been updated at this time, particularly the address. The requisition information was then added to that patient's record.

If the requisition information could not be matched to an existing patient record on the CPL database, i.e. 3 fields being identical, a new patient record was created using the information provided on the requisition.

In cases where the requisition demographic information was illegible, doubtful or insufficient for a match to be made, the MHSC registration file was consulted in order to attempt to identify the patient. When referencing the MHSC registration file, the MHSC registration number was used for the initial search. If the number was incorrect or not present another search was done using the first six letters of the patient's surname, the initial and sex.

If the MHSC number on the CPL requisition did not match that of the record on the registry file, but the surname, initial, and sex of the patient matches, the records were considered successfully matched. If discrepancies between the patient information on the requisition and the MHSC record on the MHSC patient registry file were found, the requisition information was entered exactly as the sender exactly as they had recorded it. This process was followed in 1988; it has since changed in order to update the requisition information to match that of the MHSC registry file, with a note to the sender that the information on the patient updated.

In 1988, all positive STD test results were handled differently from negative STD test results. As soon as a positive STD result was received by data entry, the patient information was verified against the MHSC registry file and then verified again with the CPL database. Patient information was updated as much as possible to ensure that information on STD's was as complete as possible.

During the study period, the data entry error checks were primarily confined to the positive results or those required for other critical purposes, such as the courts. Valid, but incorrect physician numbers did occur, resulting in the a few incidents of reports being sent to the wrong facility. These errors were either corrected before being sent out or were returned to CPL and re-issued.

The procedure of including registry information in the CPL database where the patient had a laboratory proven STD, and not including the same information where the patient did not have proven infection would lead to a different quality of information being available for different individuals. This may have implications for the potential to link CPL records with the MHSC registry file. Those women who tested negative for an STD are less likely to have accurate information to obtain a successful match, because information was not required for follow-up and contact tracing. Therefore all other

medical and hospital billing records may not be available for these women. Those women who tested positive for an STD had their personal information verified with the MHSC database and included in the CPL database, would be easy to match with hospital and medical records for visits in the future. The ultimate effect of the difference in quality of patient information available would be to minimise matches and subsequent records. Incidence of future STD and sequelae for women who did not have positive test results may be artificially low. When comparing future STD rates and sequelae of women with and without proven STD, differences may be exaggerated due to an underestimation of future sequelae in women without laboratory proven STD.

2.4.3 Statistics Canada data

An additional source of information used in this study was that gathered by Statistics Canada for the Census of 1986. There are 100 census tracts in Manitoba, which are divided into smaller enumeration units, each of which has about 200 households for a sum of about 600 people in each. For the purposes of attaching socioeconomic indicators to individual case records, census data are aggregated by these enumeration units.

The socioeconomic data are gathered on the Census form 2B commonly known as the "long form." These data are summed and averaged for each enumeration unit in Manitoba. The enumeration unit with the lowest reported average income is taken as a starting point for calculating an ordinal scale of income. Other enumeration units are sorted in ascending order of average reported income together with the cumulative total of number of individuals in Manitoba. At each decile of population totals in Manitoba, a new ordinal rank is assigned to the enumeration units falling within that decile. This method of designating income levels therefore assigns 10 income levels to 100% of the population living in Manitoba.²

The enumeration unit of each individual is not quoted on the MHSC registry file. However, the postal code from the MHSC patient registry record dated closest to the date of the laboratory test is available. The postal code can be linked to an enumeration unit through a program made available by Statistics Canada. There is a 0.5% linkage failure, where there were no people living in a postal code area, or where Statistics Canada may have omitted or was unaware of a postal code for an enumeration unit. However, more errors are generally encountered due to an out of date postal code recorded in the MHSC registration file.³

Income levels were available for the enumeration unit of each woman in a number of different formats. Mean household income was available as a continuous variable in dollars per annum; it was also available as an ordinal variable (1 - 10) of population deciles, with unequal dollar intervals, but equal population intervals; it could be divided into quintiles and treated as a categorical variable with the highest quintile as the base variable, or as deciles in a categorical rather than ordinal format. Complicating the decision about which format to use, was the fact that urban enumeration areas and postal code areas are more homogenous than rural areas with respect to income. Part of this is attributable to well defined areas in a city where houses may cost more, requiring, by necessity, that purchasers of property in that area have a certain level of income. Socioeconomic areas in the country are not as well defined or as homogenous as those in cities, and farm income may vary greatly within an enumeration or postal code unit. All statistical modelling was done on initially on women from urban areas only, as the income of urban postal code areas is more accurate than those applied to women in rural areas.

Bar charts of income deciles of the four groups of women were used, in order to clarify the problem of choice of variables for income. Women with chlamydia only and those with gonorrhoea only were compared to the control group as were women with gonorrhoea, with or without chlamydial

coinfection. Logistic regression analyses were completed using all formats of income described above.

The odds ratio of mean household income in single dollars to 2 decimal places was impossibly small, so mean income was divided by 1,000 with no decimal places and rounded off to the nearest whole number. Using income in 10 categories was not feasible, as the degrees of freedom were high, and the sample size would not support adequately sensitive analysis in that form. Analysis of income in quintiles was feasible, although any gradient within the quintiles would be undetectable. Ordinal values of income by population decile was another possible format, although the treatment of this variable in the model implied that it was a continuous variable. In assessing the models, the fit of the model, the corresponding degrees of freedom, and an examination of the frequency distributions were taken into account. An additional consideration was that of maintaining income in the form in which it most closely represented an income measure for each woman, would detect unexpected differences in income and infection with STD. Mean household income divided by 1,000 and rounded off, analysed as a continuous variable was finally selected.

2.5 Database management

Four hundred CPL records were selected using SAS Randomiser, and then converted to an ASCII file for use. Identifying information contained in the CPL file was stripped and imported into SAS, (mainframe edition), and was matched with corresponding identifying information in the MHSC patient registry file, also in SAS format. Individual MHSC patient registration numbers were changed in order to preserve confidentiality. Where adequate identifying information from the CPL files was available, it was merged with the patient registry files to produce a record which contained only patient identifying information, and demographic and administrative particulars. Three hundred and forty-nine records were produced by Ms. Carmen Steinbach at the Manitoba Centre for Health Policy and Evaluation. Data concerning the results of laboratory tests performed were not included in this original file.

The newly created file contained 69 variables, many of which were not relevant to the present study, such as years of health care plan coverage, and death date of spouse. These extraneous variables were deleted from the file using SAS, and only 6 variables remained for 349 records. This file was then exported out of SAS and imported into Epi Info. All numeric and date variables were recoded as they had been previously defined in SAS as

text fields; therefore no numeric or date operations could be carried out with them while in that form. The file was then merged in Epi Info with the original CPL file which had the laboratory information in it, to form as base file. Twelve records were missing a specimen date; the date on which the specimen was received was later requested from CPL staff. The specimen date for these 12 records was estimated as being two days before the specimen received date. This is the average lag time between specimen retrieval and its arrival at CPL.⁴ An age variable was defined as the birth date from the registry file subtracted from the specimen date. A variable indicating ethnic group was derived from the patient's municipal code, which began with an "A" if the person was a Registered North American Indian with a designated reserve, even though he/she may not be resident there. (Aboriginals who are not formally registered as status Indians or Metis are not therefore included in the "native" category in this study). This file, containing the relevant registry file data and the CPL test data formed the base file to which the medical, hospital and census data were added.

The hospital records of the matched were drawn from the MHSC hospital file in SAS format. Records were drawn using a scrambled MHSC Personal Health Insurance Number (PHIN) which is unique to each individual registered with MHSC, unlike the registration number, which is common to the nuclear family. The PHIN number, available in the registration file, was

the identifier used to select only those hospital records dating from April 1987, (the start of the financial year ending March 1988), through March 1991 of individuals in the study. The hospital file was constructed by staff at the Manitoba Centre for Health Policy and Evaluation; it contained 1088 records and 46 variables. Many of the variables were not relevant and were deleted from the file. In addition to patient identifying information, up to 16 ICD-9 diagnostic codes with 2 decimals, and 12 procedure codes were available for each record which denoted one hospital stay. Records containing only relevant diagnostic codes were selected from all 16 diagnostic codes of the 1088 records in the file; they included the following ranges of codes; (see page 11), 090.00 - 099.99, syphilis and other sexually transmitted diseases, 614.00 - 616.99, pelvic inflammatory disease, 054.1, 054.19, genital herpes, 078.18, chlamydia genital infection, 628.90 - 628.99, infertility and 633.00 - 633.99, ectopic pregnancy. Thirty-five records remained with 25 variables in each record.

Six hospital records were deleted because the date of admission was prior to the specimen date obtained from CPL. Twenty-six women had records of hospital stays during the study, and two hospital stays were recorded for three women in the study group of 305, for a final total of 29 records of hospital stays. The information in the hospital file was summarised in six new variables created in the base file formed with the registry file data and

the lab test data. The new variables indicated whether one or more hospital diagnoses of sexually transmitted disease, pelvic inflammatory disease, or ectopic pregnancy were present in the woman's hospital record or not. Another variable was created which indicated whether the individual had been hospitalised for any of the above conditions or not. None of the women were diagnosed with infertility in a hospital.

The Medical file of all medical clinic visits for all women in the study was prepared by staff at the Manitoba Centre for Health Policy and Evaluation, using the PHIN number as the unique identifier. The medical file consisted of 12,980 records, each denoting a single contact with the health system, with 10 variables in each record. Records which did not contain ICD-9 diagnostic codes of interest were deleted from the file, leaving 1,393 records. Only one diagnostic code comprising the first three digits of ICD-9 code categories is available for each record. Records containing the following ICD-9 codes were selected: 090 - 099, sexually transmitted disease, 614 - 615, pelvic inflammatory disease, 616, infection of the lower genital tract, 054, genital infection, 078, chlamydial infection, 628, infertility, and 633, ectopic pregnancy. This file was exported from SAS into Epi Info.

The base file, which now contained registry file data, laboratory data and hospital data was merged with the medical file, so that even though there was more than one medical visit for some women, each record contained all information presently available for each individual. In this format it was possible to erase 405 records of visits taking place before the specimen date.

New episodes of chlamydial infection were defined as those occurring more than 31 days after a previous infection, and episodes of gonorrhoea as those occurring more than 21 days after a previously diagnosed infection. These time periods were calculated by adding one incubation period (10 days in the case of gonorrhoea; 20 in the case of chlamydia⁵), to the treatment time, (10 days,) as specified in Canadian guidelines for the treatment of STDs in effect at the time. The rationale for selecting these periods of time was that they represent the shortest period wherein an individual could possibly contract and show symptoms of a new, separate STD episode.

Records with repeat infections occurring within the specified time limits were deleted, as they were deemed to be results of continuations of a previous episode of STD. This was done in Epi Info by selecting women in category 2, (the chlamydia group) and deleting all records with a diagnostic code of 078 (chlamydial infection) occurring within 31 days of the CPL

chlamydia positive specimen date. A similar procedure was executed for women in category 3 (gonorrhoea infection) with the diagnostic code there being 098, (gonorrhoea infection). Both procedures outlined above were executed on women in category 1, (coinfected group). For categories 1, 2 and 3 all records bearing the diagnostic code of 099 (other specified sexually transmitted disease) or 616 (inflammation of the cervix, vagina or vulva), were erased if the date of the medical visit occurred within 31 days of the CPL specimen date. The number of records of medical clinic visits was now down to 824 records from 1,393.

The remaining records were sorted by PHIN number and date of medical visit. The resulting printout simplified deletion of the remainder of repeat visits, as there is no method of selecting these records for deletion in Epi Info. Deleted records consisted primarily of multiple records bearing the same dates with the same diagnostic code assigned, but different tariff codes. Records containing the diagnosis of PID were deleted if they occurred within 90 days of a previous diagnosis of PID. This period of 90 days was determined from a review of literature and expert advice on length of care for chlamydial and gonococcal PID, treatment, and convalescence.^{6,7,8,9,10} Records containing repeat diagnoses of infertility were deleted. After this last group of medical records had been deleted, 398 records remained.

In order to develop single records of medical clinic visit history for each woman, a crosstab of number of visits by diagnostic code and PHIN number was constructed, and the results entered into the base file along with the single registry file, laboratory data and hospital record for each woman. Diagnostic codes of 054, 078, 098 and 099 were defined as ambulatory diagnoses of STD and the code 616 was defined as a diagnosis of probable STD. Diagnoses of ectopic pregnancy were billed for in conjunction with the physician attending a hospitalised patient, so this diagnosis was relevant only in the hospital record. Second visits for STD, probable STD and PID were noted in addition to total numbers of these diagnoses for each woman.

The last database, which contained information gathered from the 1986 census for each enumeration unit in Manitoba, was prepared by Dr. Cam Mustard of the Manitoba Centre for Health Policy and Evaluation in SAS format. Each woman in the original registry file who was successfully matched with CPL data had a PHIN number and postal code. Census Canada data could then be linked to each woman by means of postal code and PHIN number. Of the variables present, income mean and income deciles for rural and urban areas were retained. Education information because was not used because the study group included women who could not have completed Grade 12, due to young age; therefore any education

information available was applicable only to the parents of the women involved, and would be historical only.

The file of socioeconomic data was exported from SAS in ASCII file format, imported into Epi Info, then merged with the base file, using PHIN number as the unique identifier. Twelve of the records had PHIN numbers present, but lacked a postal code which is necessary to link socioeconomic data from each enumeration unit. Another 5 records had out-of-province postal codes, which could not be linked to income data, as those data are available only for the Province of Manitoba. One record had a Manitoba postal code, but it was not a postal code listed by Statistics Canada as having an enumeration unit linked to it. This unmatched case corresponds to previous experience in linking these data to apparently valid Manitoba postal codes, which yields a 0.5% failure rate.¹¹

Once all 5 files were merged to form one file, smaller files were created from the large one for each endpoint of interest, with the dates of medical clinic visit or hospital admission denoting the occurrence of the endpoint. The time between specimen date and date of the endpoint event was calculated in days for the purposes of performing proportional hazards analysis.

The following lists the endpoints defined for investigation:

1. An episode of STD subsequent to the CPL specimen date: a contact with the medical system to which the following ICD-9 codes have been assigned, and which occurs 10 days (period of treatment), and 1 incubation period (21 days, chlamydia; 10 days, gonorrhoea) from the last visit, if any.

054.1, 054.18 Genital herpes

078.18 Other diseases due to viruses and *Chlamydiae*

090.00-099.99 Syphilis and other venereal diseases

2. A second episode of STD subsequent to the CPL specimen date was defined as shown above.

3. An episode of lower genital tract infection subsequent to the CPL specimen date: a contact with the medical system to which the following ICD-9 codes have been assigned, and which occurs 10 days (period of treatment), and 1 incubation period (21 days, chlamydia; 10 days, gonorrhoea) from the last visit, if any.

616.00-616.99 Inflammatory disease of the cervix, vagina and
vulva

4. A second episode of lower genital tract infection subsequent to the CPL specimen date was defined as shown above.

5. Pelvic inflammatory disease diagnosed subsequent to the CPL specimen date: any contact with the health care system which is assigned the following ICD-9 codes and which occurs more than 90 days from a previous contact for the same purpose, if any. This period of 90 days was determined from a review of literature and expert advice on length of care for chlamydial and gonococcal PID, treatment, and convalescence.

614.00-614.99 Inflammatory disease of the ovary, fallopian tube, pelvic cellular tissue, and peritoneum.

615.00-615.99 Inflammatory disease of the uterus, except cervix

6. A second episode of PID was defined as above.

7. Infertility: any contact with the health care system which is assigned the following code. The diagnosis of infertility was validated by scanning the individual's subsequent hospitalisation diagnostic codes for pregnancy, including ectopic pregnancy. In addition, procedure codes indicating tuboplasties were examined.

628.2 Infertility, female

8. Ectopic pregnancy: any contact with a hospital which is assigned the following diagnoses in the hospital file of occurring more than 90 days after the specimen data supplied by CPL and from a previous contact with the same diagnostic code, if any.¹⁰

633.0-633.9 Ectopic pregnancy

9. Second ectopic pregnancy was defined as above.

The above endpoints were differentiated by mode of care; those diagnoses made in a medical clinic are analysed separately from those made in a hospital. It is of note that the medical file diagnostic codes are only the first 3 digits of the ICD-9 coding system.

2.6 Statistical Methods

All statistical analyses were done with Number Cruncher Statistical System. Databases were exported from Epi Info in Lotus file format and imported into NCSS from that format. (This method of file transfer proved to be simpler than exporting and importing in ACSII file format.)

Possible associations between the explanatory variables were explored. Age, ethnic group, urban/rural residence, and income, of all four categories of women were compared using Chi-square tests for categorical variables, (such as urban/rural residence and ethnic group), Student's t-tests or the Mann-Whitney *U* test for categorical variables and continuous variables, (such as ethnic group and age), and correlation for comparing two continuous variables, (such as age and income). In all cases significance was assessed at the 0.05 level.

Multivariate modelling using logistic regression and survival analysis was performed to investigate the association between these explanatory variables and diagnosis with gonorrhoea, chlamydia, or both, with the controls as a reference group. Multivariate modelling was also used to assess the association between the explanatory variables and repeat STD diagnoses and sequelae.

Forward stepwise logistic regression models were completed for each of the four groups. As the original hypotheses compared the gonorrhoea, chlamydia, and coinfecting groups with the control group, three separate analyses were necessary. After each forward regression model was completed, additional models were calculated, omitting each of the variables contained in the final model in succession; the beta values of each of the

models were compared in order to determine the existence of interactions. Two of the models had beta values which changed at the addition of another variable. New explanatory variables, (interaction terms) were created by multiplying the variables together, and they were tested for significance in a logistic regression model using all variables available. If they were not significant, i.e. the interaction was not detectable, the original stepwise model was selected as the final model. The use of logistic regression analysis was particularly useful in this analysis as it allows the unique impact of each explanatory variable to be measured. Therefore the effects of aboriginal and socioeconomic status on infection with chlamydia, gonorrhoea or both, are untangled, and odds ratios represent the unique impact of each variable on the outcome.

In order to detect differences in the incidence of sequelae and repeat STD diagnoses over time, survival analysis techniques were used as followup times were different for each woman. Survival curves of the four categories of women were compared using the Logrank test for two group comparisons, so that the survival curve of each category of women could be compared with that of the control group. If differences in incidence of sequelae or repeat STD were detected, Cox Proportional Hazards models were used in order to describe the unique relationships of explanatory variables to the outcomes.

The three variables which denoted the groups in which differences in outcome curves were found, formed the basic proportional hazards model. Age, ethnic group, income and urban/rural residence were tested with the basic model one at a time, in order to determine if they added significantly to the model. If one variable did, it was selected and placed in the model, and then the remaining variables were included individually in the model, depending on whether their addition improved the fit of the model significantly.

The estimates parameters were checked at each addition of a new variable. If changes were found, the confounded variables were multiplied and these terms were tested in the model for significance of an interactive effect. Analysis of subgroups was performed and appropriate parametric or non-parametric tests were done to confirm associations of explanatory variables and outcomes in subgroups of the total study population.

Incidence rates were calculated for all outcome variables. As women had differing lengths of follow-up time, rates were calculated per 100 woman-years. The number of days of followup were calculated for each category, and were divided by the 365.25 to give years. The number of cases was divided by the number of years of followup for the appropriate category and

multiplied by 100. Odds ratios and relative hazards were calculated from the beta estimates given by logistic regression or proportional hazards analysis.

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CHAPTER 3

RESULTS

3.1 The record linkage process

Four hundred records were selected using SAS Randomiser for the year 1988 from the CPL database. One hundred were women who had positive tests for both gonorrhoea and chlamydia concurrently (Category 1), another 100 were women with positive results for chlamydia tests only (Category 2), 100 were women with positive tests for gonorrhoea only (Category 3), and the last 100 were women who had tested negative for both organisms.

Of the 400 original records, only 349 files from Cadham contained MHSC registration numbers. CPL records without registration numbers could not be matched with MHSC records due to lack of adequate identifying information in the Cadham file. Forty-four of the 349 CPL records with registration numbers were matched manually as there was more than one record in the MHSC registration file with the same registration number as the record in the CPL file. Sixteen of the "tied" records were broken manually. Decisions about matches were then made on the basis of two additional attributes; either birth month, birth year, or gender of the individual. For

example, if the registration number of the individual was matched, but the gender and birth year were incorrect, that individual's record was deleted from the study. On the other hand, if the registration number was matched, and the birth month and gender were matched, but not the birth year, the record would be retained and the birth year amended according to the registration file. Many of the 16 ties that were matched, had birth months that were different by only one month; others contained an incorrect third digit of the birth year, so that the birth year was inaccurate by 10 years.

Of those 349 records with registration numbers 29 were not able to be matched with any individual registration records in the MHSC registry file. In these cases, missing data such as an accurate birth month and birth year or MHSC registration number made direct linkage with the MHSC data impossible.

The number of records available for study was further reduced by one, as one woman had duplicate records in the original random sample of records from Cadham. This may have been due to the fact that this woman had more than one test at CPL in 1988, was drawn from all records for all women tested in 1988. Second tests during that year for *C. trachomatis* or for *N. gonorrhoea* were not excluded from the sampling frame. This individual for whom records were duplicated was categorised in the CPL file

as belonging to both category 4 (the controls) and category 2 (chlamydia positive only). In order to preserve the integrity of the control group she was added to category 2. The final number of records matched were therefore 319 (79.75%) of the 400 CPL records.

Although records of tests for women aged 15 - 44 only were requested from MHSC, 10 records of children under age 15 and of four women over age 44 were present in the original sample of 400 records. Again, this was due to fact that the sample frame included all females tested for chlamydia and/or gonorrhoea, and women under or over the specified ages were not deleted from the sampling frame prior to sampling. These records were deleted from the study only after the birthdates had been verified with the registry file. The final study group consisted of 305 women, evenly distributed across all four categories of women, (see Table 1).

The sample population was drawn randomly from all women tested in 1988 for *C. trachomatis* and *N. gonorrhoea*. The request for this sample had specified that those women who were infected with both organisms should have had positive tests for both organisms within a week of each other. This was an arbitrary date set to define women with positive tests seven days apart or less as being coinfectcd. The seven day period was set to ensure that if samples were taken within two or three days of each other

and/or arrived at the laboratory separately, and if they were positive for both organisms the woman they were taken from could still justifiably be defined as having coinfection. Only one specimen date was available for both tests, and it is likely that both specimens were taken at the same time.

The women for whom there was no MHSC registration number were distributed evenly throughout the 4 categories of women. Ten women were missing registration numbers from categories 1 and 3, while 16 were missing from category 2 and 15 from category 4. Birthdates were missing from 2 records in category 1 and 1 from category 4. One of the objectives of this study was to describe the demographic and social characteristics of the four groups of women, and it was recognised that these characteristics may affect sequelae of STD, which were also of interest. Any maldistribution of information available for selected women would result in biased descriptions of characteristics common to women in each category. Information available on women coinfecting with *N. gonorrhoea* and *C. trachomatis* who may belong to inner city, mobile, higher risk groups who are less accessible by government systems was comparable to those women who tested negative for these STDs, therefore maintaining the credibility of the study results.

The number of CPL records which did not have information consistent with the MHSC registry file may indicate that the information on the laboratory requisitions completed at the medical clinic where the patient was seen was inaccurate. Transpositions of digits for birth years were common, and one record with a registration number showed no matching records in the whole patient registry file. The reason for the differences between the CPL records and the MHSC registry file is that CPL uses its own database of 450,000 records as an initial reference database. The contents of the database are largely unverified data available from the laboratory requisitions submitted by medical clinics and hospitals. Only if a requisition with a name that is not already in the CPL database is encountered, will the MHSC database be used to create a new patient record with all the appropriate information.

While CPL primarily serves patients from Manitoba, it also serves patients who are from outside of the province; obviously these patients would not have records in the MHSC database. However, if the data verification process were reversed, i.e. if names on laboratory requisitions were first matched with MHSC data, a database much more consistent with that of MHSC would result. However, it is worth noting that the medical clinic staff who submit the requisitions initially, need to be able to match the laboratory result report with the patient's file. Amending the CPL database with current data therefore may alter the record to make identification of the

patient impossible for clinic staff. A large portion of duplicate patient records in the CPL database consist of women who have married and changed their names; thereby creating two records for one individual. Records may be able to be concatenated every so often by reviewing previous years' records in the MHSC registry file.

3.2 Validity checks

A validity check was then done on the 398 medical records remaining after records of repeat visits for the same ongoing STD episode were deleted. A crosstab of tariff codes by diagnostic code was done. This served to show procedures completed during a visit to which a diagnostic code of STD, PID or infertility was assigned. Tariff codes used for billing purposes varied extensively with diagnoses, ranging from the expected codes for cervical sample and regional history and examinations to thyroid function tests and tests for total cholesterol. The most common tariff codes were those for regional history and internal examination, and taking of cytological smears for cancer screening. In order to delete records containing gross errors or inconsistencies, an internal medicine specialist with experience in sexually transmitted diseases, (Dr. Orr), screened records for inappropriate diagnostic or tariff codes. Most diagnoses of STD were accompanied by one of the most common tariff codes, and the remainder by an equally plausible tariff

code. Only one record was deleted; which had been assigned a code of 099, (gonorrhoea) but the accompanying tariff code was 7111, for mammography. Mammography in Manitoba is done by a radiologist or radiology technician and a diagnosis of "other specified sexually transmitted disease" could not possibly be made from a mammography procedure alone.

In addition, the diagnosis of infertility was checked as far as was possible by checking the full file of hospital records in SAS for diagnostic codes of childbirth. Seven women had records of medical visits with the diagnosis of infertility (628, see section 2.5) assigned to them; only three of the women were found not to have had a baby in the years between their infertility diagnosis and March 1991, when the period of followup ended. One of the women had had a sterilisation and following that a tuboplasty in 1990. As this was voluntary infertility, this medical record was excluded from our analysis.

A similar validity check for the hospital file was done. All diagnostic codes and procedure codes were inspected for any inconsistencies, but none were found.

Diagnostic coding for medical bills is not as accurate as that recorded by hospitals. Coding is done by a variety of people, some of whom have no

formal training in this procedure. Coding may also be done by the attending physician. The example of the woman who was given a diagnosis of ICD-9 099 for a mammography consult, may be an indication that if a woman went in for an initial visit concerning an STD, subsequent visits would tend to be coded the same way. This suspicion was not able to be verified, and the general principle in evaluating validity in this study, was not to delete a record unless definite evidence for inconsistency existed, such as in the case of the mammography consult. Although the continuous "labelling" of patients with STD diagnosis may overestimated the number of second visits for STD, the use by physicians of the ICD-9 code 616 for "inflammatory disease of the cervix, vagina and vulva" (see section 2.5), probably underestimates the number of women with confirmed STD. The practice of using the 616 code may be an attempt by physicians to maintain confidentiality.¹

4.3 Sociodemographic characteristics of the four categories of women

Summaries of the study results are presented before a more detailed discussion and analysis of findings.

Descriptive statistics for the four categories of women in this study are presented below, (see Table 1). Although 13% of records were deleted

because they did not meet the study criteria, the distribution of number of women in each category remained fairly even. Mean ages of the various groups were calculated. Women in the control group were older than women in all other groups, who were significantly younger in multivariate analysis. Mean household incomes differed between groups, with the control group earning the highest amount, and women with chlamydia earning a comparable amount. Women with gonorrhoea and chlamydia or gonorrhoea alone had lower household incomes than either of the other two groups. The control group contained a much lower proportion of aboriginal women than did any of the other groups. Proportions of women in the various categories living in urban areas was comparable.

TABLE 1

Descriptive statistics of four categories of women

Character-istics	Category 1 Coinfected	Category 2 Chlamydia	Category 3 Gonorrhoea	Category 4 Controls
Sample size	78	74	74	79
Mean age	21	22	23	26
Mean Income	\$21,900	\$25,670	\$21,900	\$25,650
Percent Aboriginal	47.4	45.9	41.9	21.5
Percent Urban	57.5	58.9	65.2	61.1

The first category of women, (with positive test results for both *N. gonorrhoea* and *C. trachomatis*) was compared with the control group, (Table 2). Young age, being aboriginal, urban residence and mean annual household income were found to be significant explanatory variables for coinfection. Aboriginal women are at 7 times the risk of non-aboriginal counterparts for laboratory confirmed coinfection, and women living in an urban area are at three times the risk of women living in a rural area. Table

3 contains odds ratios for risk of disease for women of selected ages.

Variations of this model, adding each variable sequentially were calculated, and changes in the parameter estimates were assessed by creating interaction terms; ethnic group x urban/rural residence, ethnic group x income, and urban x income. None of these were found to add a significant amount of explanatory power to the model, therefore evidence of confounding was not detected.

TABLE 2

Women coinfectd with gonorrhoea and chlamydia compared with controls

Variables	Beta Estimate	Odds Ratio	95% C. I.	Prob.
Age	-.21	0.81	0.73,0.89	0.00
Aboriginal Status	1.92	6.84	2.61,18.02	0.00
Urban residence	1.13	3.10	1.23,7.81	0.02
Mean Income	-0.04	0.96	0.92,1.00	0.05
Intercept	4.49			

TABLE 3

Odds ratios of three ages, using the mean study age
as a reference

Women with coinfection

Age	Odds ratio
15	2.73
23	1.00
39	0.02

When women with laboratory proven gonorrhoea were compared with the control group, (Table 4); age, ethnic group and urban residence were associated significantly with infection. Younger women were more likely to be infected with *N. gonorrhoea* (Table 5), and aboriginal women were 4 times as likely to be diagnosed with gonorrhoea as non-aboriginal women. Residing in an urban area carries a risk of gonococcal infection two and a half times that of residing in a rural area. Again, this model was checked at the addition of each variable, and the beta estimates were examined. New variables were created; ethnic group x urban and urban x income. Neither of these terms were significant, hence confounding was found not to be present.

TABLE 4

Women with gonorrhoea compared with controls

Variables	Beta Estimate	Odds Ratio	95% C. I.	Prob.
Age	-0.10	0.90	0.85,0.97	0.00
Aboriginal status	1.34	3.82	1.49,9.78	0.01
Urban residence	0.91	2.49	1.04,5.97	0.04
Intercept	2.41			

TABLE 5

Odds ratios of three ages, using the mean as a reference

Women with gonorrhoea

Age	Odds ratio
15	2.21
23	1.00
39	0.21

Women with a positive test for chlamydia were compared with the control group, (Table 6). Only age and ethnic group were associated significantly with this infection. Table 7 shows that women who are young are at increased risk of infection compared to older counterparts. Aboriginal women were three times as likely as non-aboriginal women to have laboratory proven chlamydia infection. On addition of each variable to the model the estimated parameters did not change, and no interaction terms were created to assess the possibilities for confounding.

TABLE 6

Women with chlamydia compared with controls

Variables	Beta Estimate	Odds Ratio	95% C. I.	Prob.
Age	-0.12	0.91	0.84,0.95	0.00
Aboriginal Status	1.14	3.11	1.45,6.68	0.00
Intercept	2.42			

TABLE 7

Odds ratios of three ages, using the mean as a reference

Women with chlamydia

Age	Odds ratio
15	2.31
23	1.00
39	0.14

As has been found in other studies, younger women had a higher risk of coinfection with chlamydia and gonorrhoea than did older women.^{2,3} The average age in this group of women is 21 compared with the control group which has an average age of 26 years. A one year decrease in age, therefore, carries an increased risk of 1.23, (Beta estimate -.21, Table 2), of being diagnosed with coinfection with gonorrhoea and chlamydia. Ignoring all other explanatory variables for the moment, and using a woman of average age, (21) in this category as a reference, (i.e. have an odds ratio of 1), a woman aged 16 has 2.89 times the probability of having laboratory diagnosed infection with chlamydia and gonorrhoea, when compared to a woman aged 21.

Aboriginal women had a much higher chance of having coinfections with chlamydia and gonorrhoea than did non-aboriginal women. Because multivariate modelling techniques were used, the risk of coinfection associated with being aboriginal is independent of and distinct from the risk of infection associated with income. Rates for sexually transmitted disease in this population have been reported to be higher than those of non-aboriginals, although differences in health care systems have sometimes confounded the issue. This study suggests elevated rates of STD in aboriginal women. It is important to recognise that high rates of STDs in aboriginal people may have many causes some of which may be rapid change or loss of traditional culture, and the adoption of unhealthy sexual practices of a dominant culture. High STD rates in any group are not determined by the racial characteristics of that group; racial characteristics are merely a risk marker and not a risk factor.

Urban residence was significantly associated with coinfection with chlamydia and gonorrhoea. "Urban" is defined by Statistics Canada as areas having a population density of more than 400 people per square kilometre⁴. Rates of STD in urban populations have been reported to be high⁵, (see section 1.3), although this study is among the first to present random sample data from a defined geographic area (the province of Manitoba), which contains patients from both rural and urban areas. Hence results of

the comparison of the two groups are more legitimate and credible than those comparing selected clinic population subgroups. Reasons for the association of higher rates in urban areas may include different age structures of the population, so that people living in urban areas may include more people in those age groups associated with higher rates of STD. In addition, the locations of a "core" transmitter population has been described as being an urban phenomenon.^{2,6} "Core" group theory allows for the mathematical modelling of STD incidence, based on the premise that a relatively small proportion of the population is responsible for maintaining the STD epidemic. Through high rates of partner change, high prevalence of asymptomatic infection and mixing to some extent with non-core group members, the core group influences the incidence of STD in a population to a degree not suggested by their numbers.⁷ Higher rates in this population comprise infections resulting from "core" group activity between members, and mixing of core group members with non-members; adjacent non-core members being more numerous in urban than in rural areas. In addition, people with highly risky behaviours such as commercial sex workers and drug users, congregate in urban areas, making the rates there higher than those experienced in rural areas.

Low mean household income was associated with coinfection with gonorrhoea and chlamydia. Table demonstrates the practical implications of the logistic regression analysis:

TABLE 8

Women coinfectd with gonorrhoea and chlamydia
Odds ratios of selected income groups

Income in dollars	Odds ratio
10,000	4.95
30,000	2.23
50,000	1.00

Ignoring all other variables, and assuming that a reference individual has a household income of \$50,000, i.e, an odds ratio of 1, means that a person earning \$10,000 has five times the risk of having a laboratory confirmed diagnosis of gonorrhoea and chlamydia coinfection as a person earning \$50,000 a year.

Although studies on income and infection with STD have been published,^{2,8,9} data have been scarce on this subject, and the linking of mean household income for each enumeration area of Manitoba to

individuals affords a more precise description of the risk associated with income. The tendency of homogenous groups to recruit similar sexual partners is supported by the relationship between income and coinfection, as core transmitters are often located in urban, poor, ethnically diverse areas.⁴ While income is an important indicator of socioeconomic group, it may also be a marker of level of education, so that the causative factor in the elevated risk of STD may actually be lack of education and not lack of income itself.

When women with gonorrhoea were compared with controls, young age, ethnic group and urban residence were significant risk factors. Mean household income was not important in describing women with gonococcal infection alone, possibly due to small numbers. It is also possible that women in this group may have been less homogenous in terms of core group membership, so that they represent core group members as well as a significant number of non-core group members. Being aboriginal carries an odds ratio of 4 for infection with gonorrhoea. This is supported by other reports of higher gonorrhoea rates in aboriginal North Americans.^{4,10,11,12,13} This risk factor, if taken on its own, may be confounded with low socioeconomic status. Higher rates of sexually transmitted disease should not be attributed only to membership in any

ethnic group; education levels, culture, and breakdown of traditional social structures must all be taken into account in this analysis.

Urban residence was associated significantly with gonococcal infection. As above,^{2,3} this is again supported by previous studies and the theory of a core group of transmitters which resides in urban areas. It is interesting to note that the odds are lower here than in the analysis of urban residence in the coinfecting group. This may indicate that the gonorrhoea category contains more women who do not belong to the core group, and therefore are less likely than coinfecting women to live in an urban area.

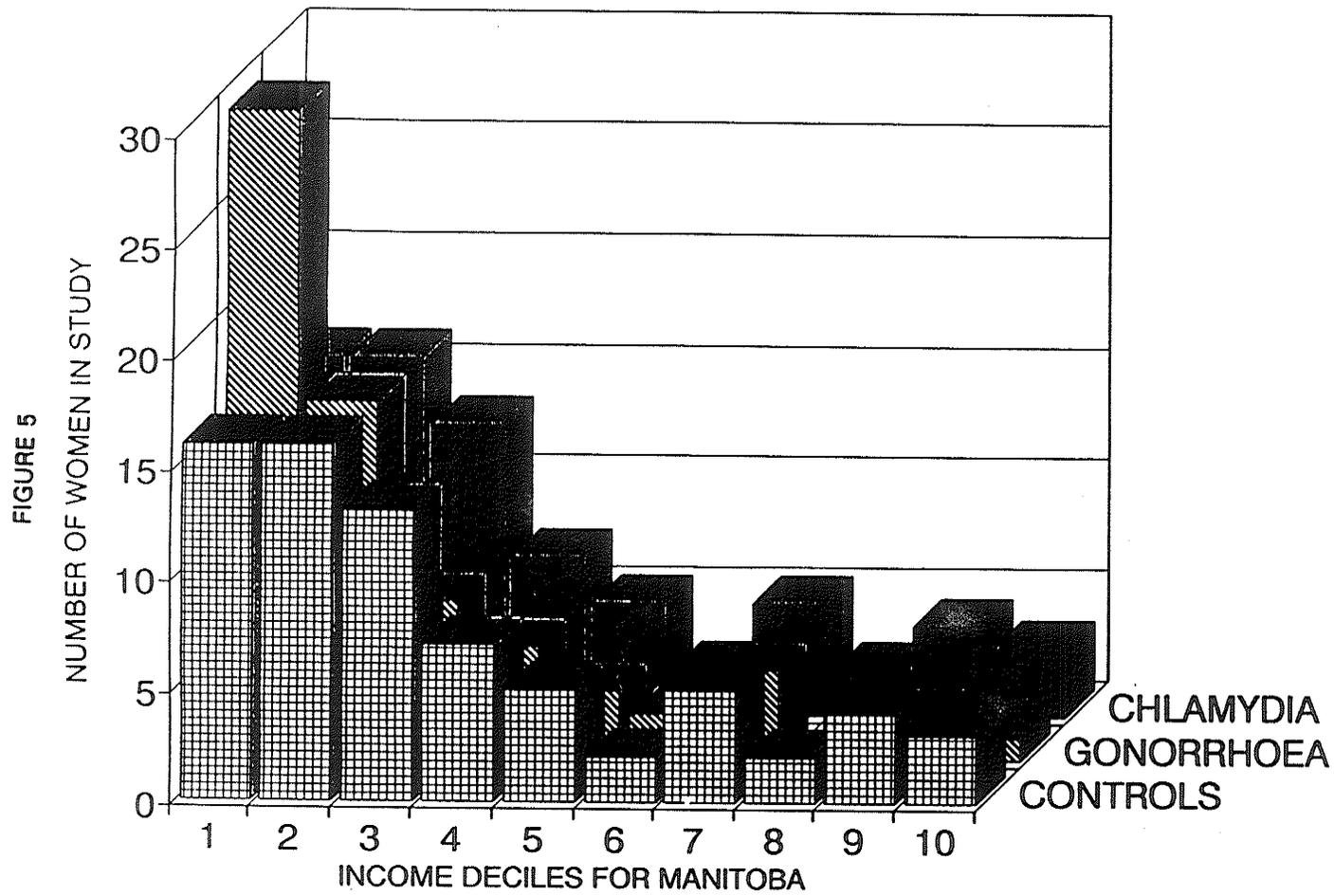
C. trachomatis infection was associated negatively with age, and positively with being aboriginal. Aboriginal women were 3 times as likely as their non-aboriginal counterparts to have chlamydia. This confirms the few reports in the literature on chlamydia in North American aboriginal populations.^{7,9,10} The effect of age on risk of chlamydial infection is well-documented and is demonstrated below.

Neither income nor urban residence were associated with chlamydial infection. This may indicate that the sample size was not adequate to detect differences, or that no differences exist. Another possibility is that the core group responsible for transmitting the majority of chlamydial

infections is not the same as that of gonorrhoea, i.e. the descriptors used in this 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 gonorrhoea, and individuals may in fact often be coinfecting with both organisms. The second core group may not be characterised by urban residence or low income level. 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 neighbourhoods, (above Table 1, Figure 5),¹⁴ but low rates of gonorrhoea.^{15,16} This is not consistent with rates of chlamydia gathered in lower socioeconomic or inner city groups.^{7,9,10,17}

In conclusion, these results reinforce the findings of other research, which has found that risk of STDs is highest in urban, poor, minority populations. However, differences in characteristics of women with chlamydial infection when compared with controls require more research, as the risk factors for this infection do not appear to be the same as those for gonorrhoea.

INCOME DECILES FOR WOMEN WITH CHLAMYDIA, GONORRHOEA AND CONTROLS



4.4 Incidence of repeat STD and sequelae

The objective of this part of the study was to define the incidence of subsequent diagnoses of STD and sequelae for women who had laboratory confirmed test(s) for chlamydia, gonorrhoea, coinfection with both, and a group of controls. Numbers of STDs and sequelae were counted for each woman for the period between each specimen date at CPL in 1988 and March 31, 1991, the latest point of coverage defined for the administrative databases. Periods of follow-up in days differed for each woman, as they depend on the date of her specimen at any point in 1988.

Diagnoses of subsequent STD for the individuals in the study groups were drawn from hospital and medical billing records. Some diagnostic codes used to indicate STD were very specific, however, a larger number of patients were assigned an ICD-9 code of 616; a non-specific code used to denote "cervical or vaginal infection." Assigning a non-specific code to a billing record may be a mechanism for preserving patient confidentiality. In addition, the physician may be unwilling to "label" the infection as an STD in the absence of laboratory tests which confirm the organism involved.

As the non-specific code of 616 was estimated to yield more women who may not have a sexually transmitted infection, these records were analysed

as an outcome distinct from the more specific diagnostic codes 098.0 - 099.9. The more specific codes suggested that the attending physician was more confident of his/her diagnosis of STD.

In order to describe the incidence of diagnosis with STD, (ICD-9 code 098.0 - 099.9), subsequent to the first test in 1988 by CPL, two-group log-rank tests comparing the control group of women, (Category 4), with all the other groups were performed. All comparisons were significant; categories 1 and 4, $p = 0.0005$, categories 2 and 4, $p = 0.03$, categories 3 and 4, $p = 0.002$.

Cox's Proportional Hazards Model was developed, defining explanatory variables for the outcome of diagnosis with an STD, which would have occurred subsequent to the initial specimen processed at CPL. For women with gonorrhoea, or chlamydia, or both, this diagnosis of an STD would represent a second STD within the study period. For control women, it would represent their first diagnosis of an STD in the study period. Table 8 shows the incidence rates in 100 woman/years of and STD diagnosed subsequent to the CPL specimen date. Table 9 shows risk factors which are significantly associated with diagnosis of STD made in an ambulatory setting. Figure 6 shows survival curves for this endpoint for all four categories of women

TABLE 9

**Incidence in 100 woman years of subsequent diagnosis
of STD in a medical clinic**

Category 1 Coinfected	Category 2 Chlamydia	Category 3 Gonorrhoea	Category 4 Controls
17.72	11.88	15.68	5.04

SURVIVAL CURVES FOR WOMEN WITH SUBSEQUENT DIAGNOSIS OF STD

FIGURE 6

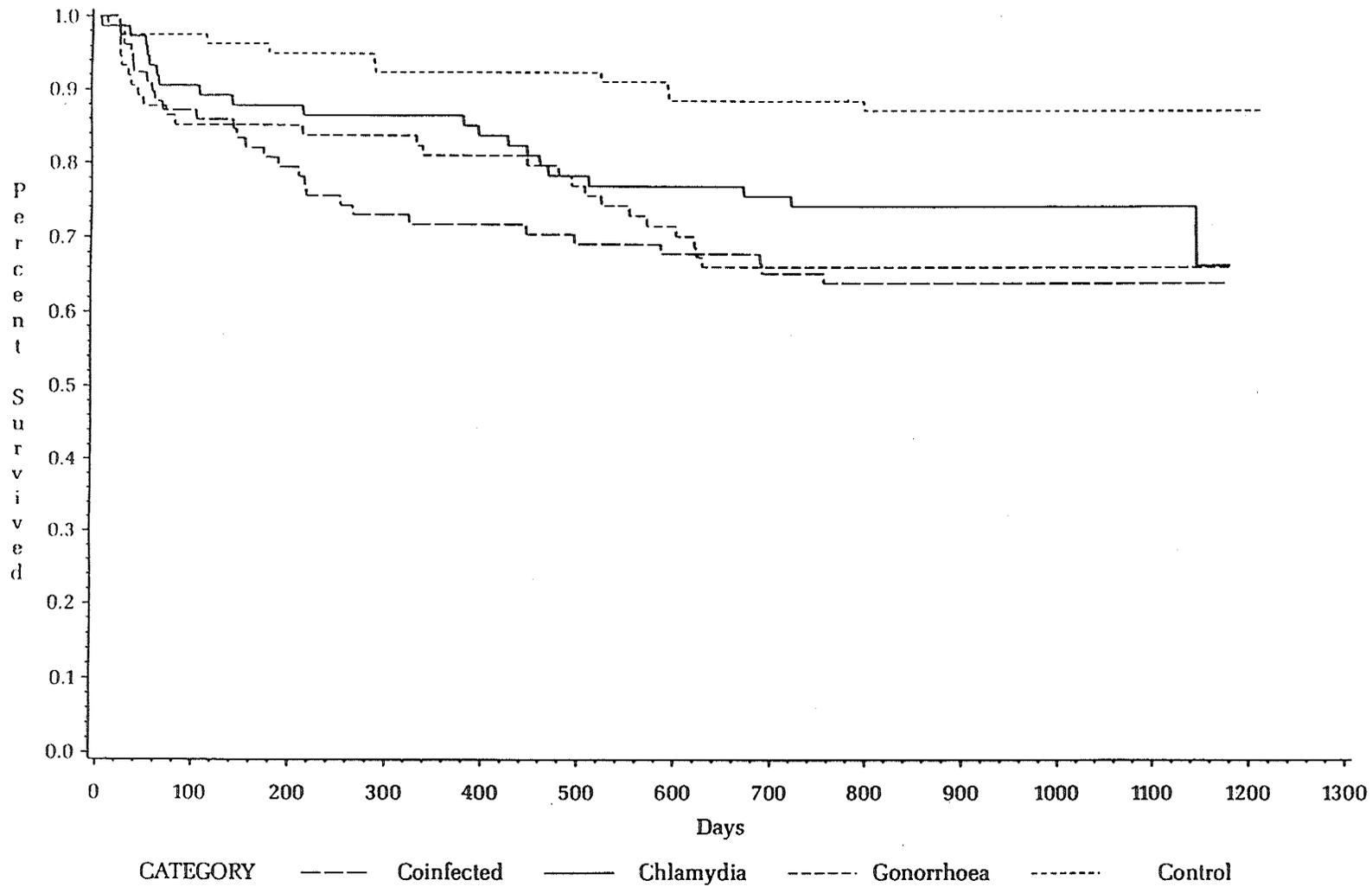


TABLE 10

Risk factors for subsequent medical clinic diagnosis of STD

Variables	Beta Estimate	Relative Hazard	95% C. I.	Prob.
Chlamydia	0.84	2.32	1.08,4.90	0.03
Gonorrhoea	1.11	3.03	1.45,6.30	0.00
Chlamydia	1.22	3.39	1.65,6.96	0.00

The relative hazard of having a diagnosis of STD from a physician in a medical clinic is highest for those women who had laboratory diagnosed coinfection with *N. gonorrhoea* and *C. trachomatis*; those with gonorrhoea had slightly less risk, and those with chlamydia were least likely to be diagnosed with a subsequent STD, (Table 9). Even so, women with laboratory diagnosed chlamydial infection were twice as likely to have a subsequent diagnoses of an STD, and those who were coinfectd were over three times as likely.

In addition to describing the incidence of a first diagnosis of STD after the initial tests in 1988 at CPL, records of a second diagnosis were also analysed, (Table 11). Table 10 shows the incidence in 100 woman years of second diagnosis of STD for all categories of women. For all women except

those in the control group, the second diagnosis of STD subsequent to the CPL specimen date would constitute the third diagnosis of STD before the study cutoff date, March 31, 1991.

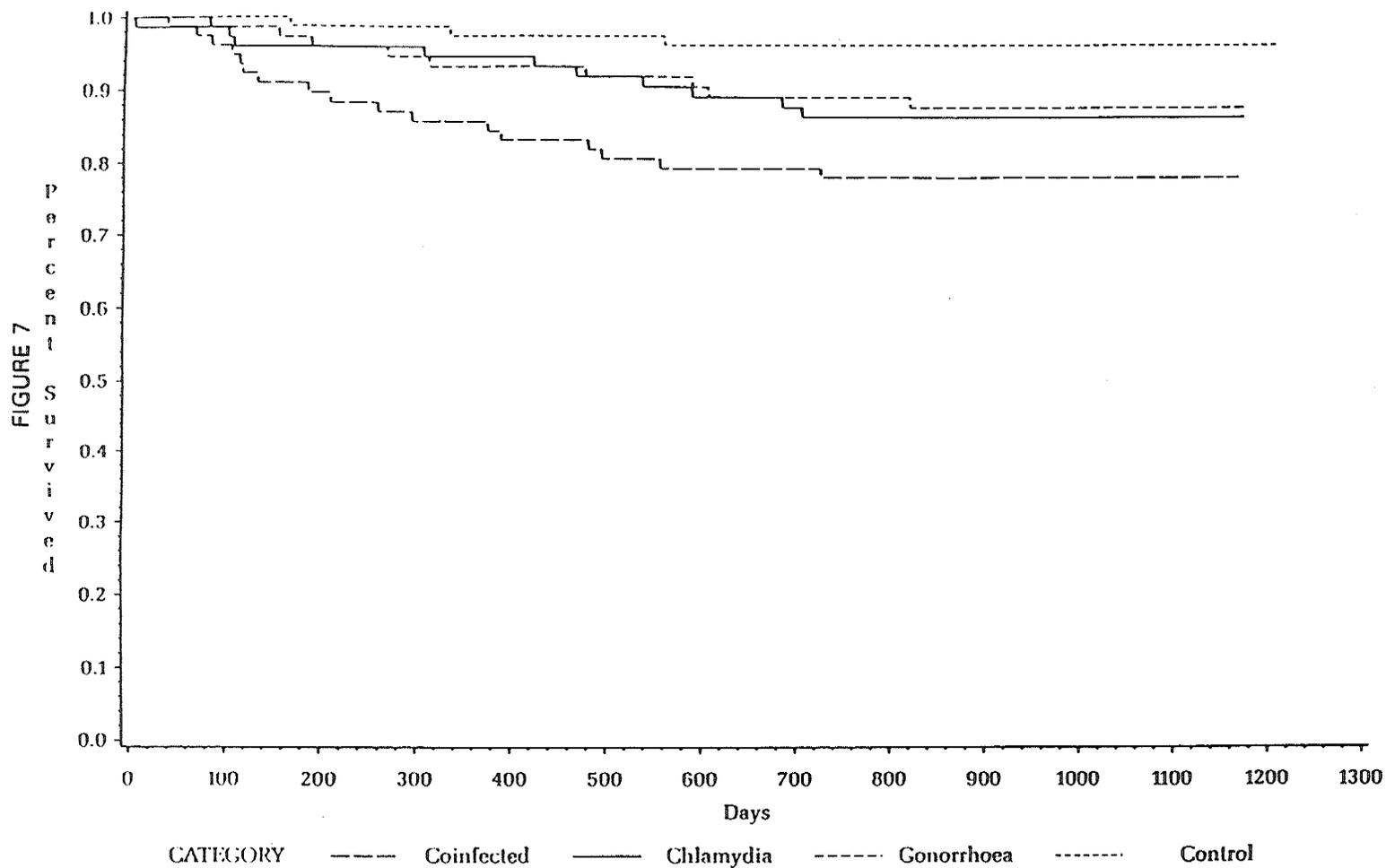
When the survival curves for this endpoint, (Figure 7), were compared with that of the control group, women in the category 2, the chlamydia group differed substantially, ($p = 0.03$) from controls, as well as women who were coinfectd, (category 1, $p = 0.0007$).

TABLE 11

**Incidence in 100 woman years of second subsequent diagnosis
of STD in a medical clinic**

Category 1 Coinfected	Category 2 Chlamydia	Category 3 Gonorrhoea	Category 4 Controls
10.89	5.29	4.61	1.41

SURVIVAL CURVES FOR WOMEN WITH A SECOND SUBSEQUENT DIAGNOSIS OF STD



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TABLE 12

Risk factor for a second subsequent medical clinic

diagnosis of STD

Variables	Beta Estimate	Relative Hazard	95% C. I.	Prob.
Chlamydia	1.31	3.71	1.02,13.46	0.03

The only factor associated significantly with a second diagnosis of STD, when the chlamydia group were compared with controls, was that of having a positive test for chlamydia, (Table 11). Age, ethnic group, income, or residence in an urban or rural area were not found to be important in explaining a second diagnosis with STD made in an ambulatory care setting.

Both age and coinfection are important factors in comparing the second subsequent medical clinic diagnosis of STD in the control group and the coinfecting group. A proportional hazards model could not be accurately constructed, due to low numbers of the endpoint. However, Table 12 will serve to clarify the relationship between age, coinfection and diagnosis with a second STD in a medical clinic.

TABLE 13

Coinfected women and a second subsequent medical clinic
diagnosis of STD

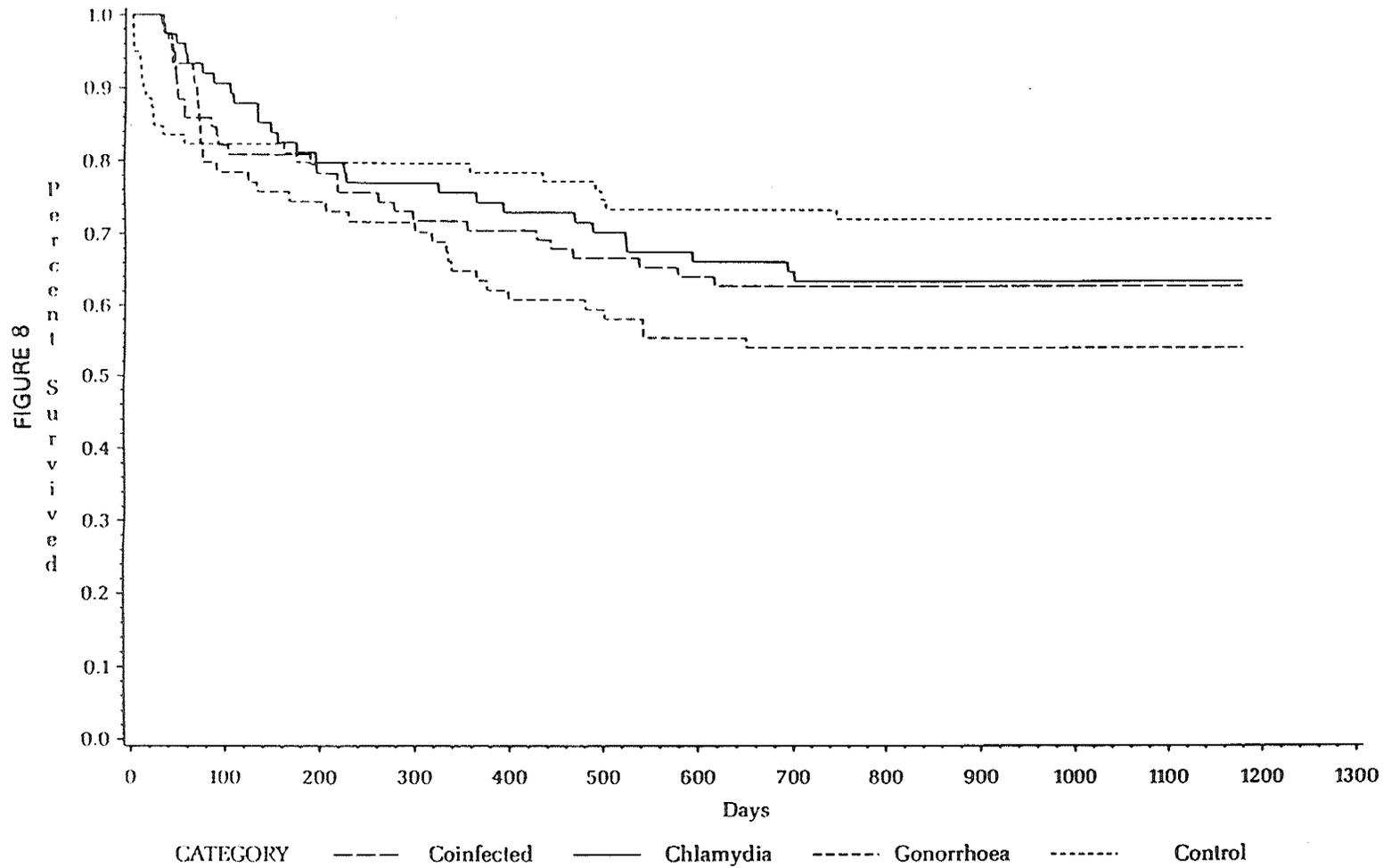
Age	Category 1 Incidence	Category 4 Incidence	Relative Hazard
< 20	18%	13%	1.4
21 - 25	14%	4%	3.5
26 +	62%	0%	-

Overall, the incidence of a second diagnosis of STD in an ambulatory care clinic was higher in the coinfecting group than in the control group.

However, as women in the coinfecting group become older, the risk of having a diagnosis of a second STD becomes very much more than that of women in the control group.

Diagnoses which indicated infection of the cervix and vagina, (ICD-9 code 616), were analysed separately. Women with chlamydia and gonorrhoea (category 1), women with chlamydia only, (category 2), and those with gonorrhoea only, (category 3) were compared with women in the control group using the Log-rank test. Differences in the curves, (Figure 8), were

SURVIVAL CURVES FOR WOMEN WITH A SUBSEQUENT DIAGNOSIS OF LOWER GENITAL TRACT INFECTION



found between women with gonorrhoea and those in the control group, ($p = 0.05$).

A proportional hazards model was fitted with gonorrhoea and ethnic group as explanatory variables, (Table 14). Table 13 shows incidence in 100 woman/years of a diagnosis of lower genital tract infection subsequent to the CPL specimen date in 1988.

TABLE 14
Incidence in 100 woman years of subsequent diagnosis
of lower genital tract infection in a medical clinic

Category 1 Coinfected	Category 2 Chlamydia	Category 3 Gonorrhoea	Category 4 Controls
17.98	17.64	24.34	13.17

TABLE 15

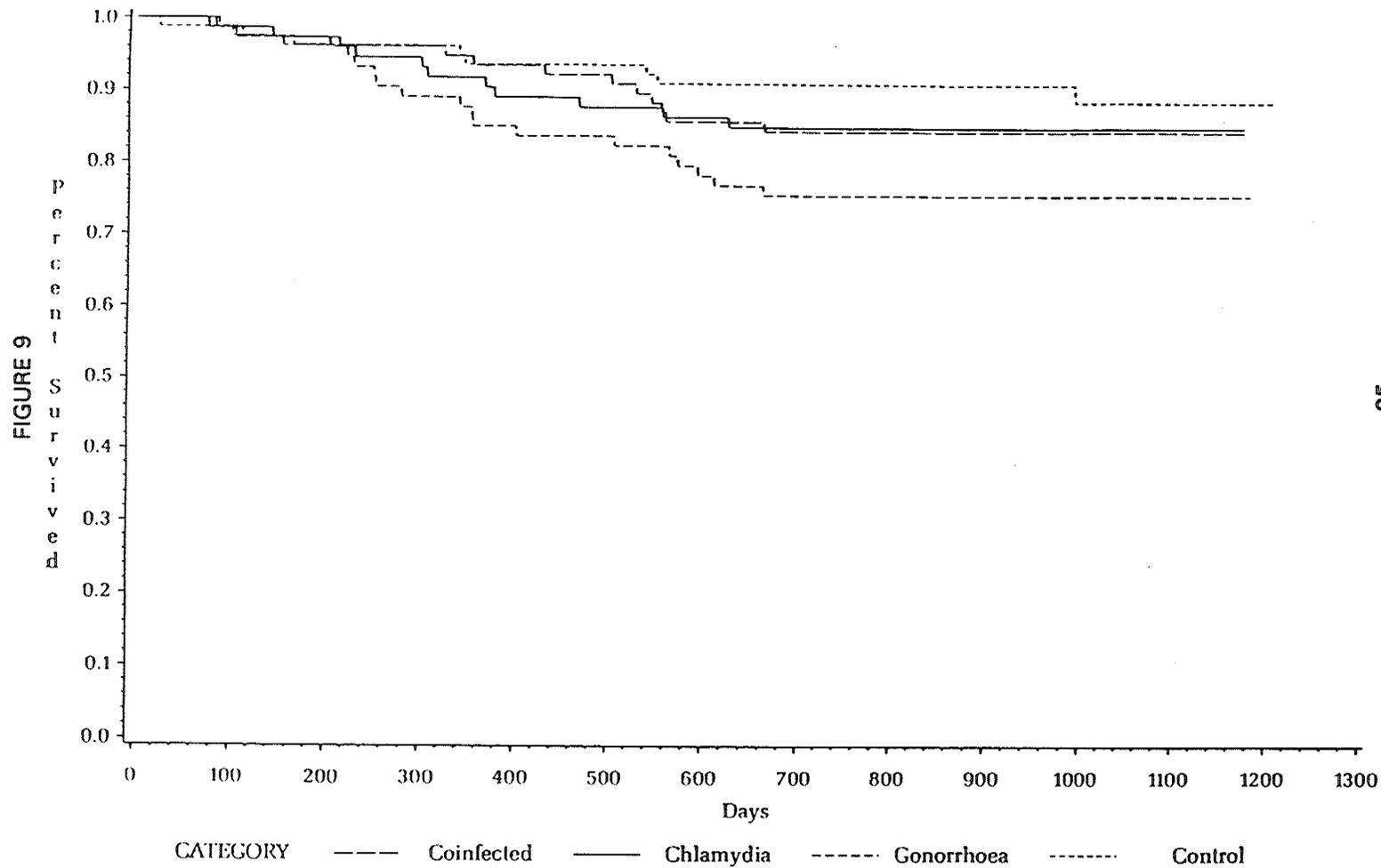
Risk factors for subsequent medical clinic
diagnosis of lower genital tract infection

Variables	Beta Estimate	Relative Hazard	95% C. I.	Prob.
Gonorrhoea	0.67	1.96	1.13,3.40	0.02
Aboriginal Status	-0.67	0.51	0.27,0.96	0.04

Laboratory confirmed gonorrhoea was positively associated with a diagnosis of genital infection subsequent to the CPL test; women in the gonorrhoea category were almost twice as likely as women who tested negative for gonorrhoea at CPL to be diagnosed with a genital infection. Diagnosis with genital infection, rather than the more specific diagnosis of STD was negatively associated with aboriginal women; that is, aboriginal women were less likely to receive this non-specific diagnosis than their non-aboriginal counterparts, (Table 14).

In addition to analysing the endpoint of probable diagnosis for an STD subsequent to the CPL tests, survival curves, (Figure 9), of a second diagnosis of genital infection were analysed. Category 3 (women with

SURVIVAL CURVES FOR WOMEN WITH A SECOND SUBSEQUENT
DIAGNOSIS OF LOWER GENITAL TRACT INFECTION



gonorrhoea) and 4 (control women) differed significantly, ($p = 0.02$).

TABLE 16

Incidence in 10 woman years of second subsequent diagnosis
of lower genital tract infection in a medical clinic

Category 1 Coinfected	Category 2 Chlamydia	Category 3 Gonorrhoea	Category 4 Controls
5.96	5.89	10.14	3.90

TABLE 17

Women with gonorrhoea and a second subsequent medical clinic
diagnosis of lower genital tract infection

Variables	Beta Estimate	Relative Hazard	95% C. I.	Prob.
Gonorrhoea	0.94	2.55	1.11, 5.87	0.03

Women who were in category 3, i.e. had a positive test for gonorrhoea in 1988 had two and a half times the risk as gonorrhoea-negative women of being diagnosed for a second time in an ambulatory clinic with a genital

infection, (Table 15). Ethnic group was not associated with a second diagnosis of genital infection.

Survival curves, for PID and infertility, (Figure 10), diagnosed in a medical clinic were compared between the three categories of women with STD and those in the control group, using the Log-rank test. Women in category 1, (those with coinfection), had a significantly different curve from those women in the control group, ($p = 0.035$). A proportional hazards model was developed with an interaction term in order to describe other factors in the progression these sequelae of STD. It was significant, but due to small numbers, it could not be accurately interpreted. Stratified univariate analysis was completed as shown in Table 17. Table 16 shows incidence of STD sequelae diagnosed in an ambulatory care facility.

TABLE 18

Incidence in 100 woman years of subsequent diagnosis
of STD sequelae in a medical clinic

Category 1 Coinfected	Category 2 Chlamydia	Category 3 Gonorrhoea	Category 4 Controls
6.05	5.34	4.14	1.90

SURVIVAL CURVES FOR WOMEN WITH SEQUELAE DIAGNOSED IN A MEDICAL CLINIC

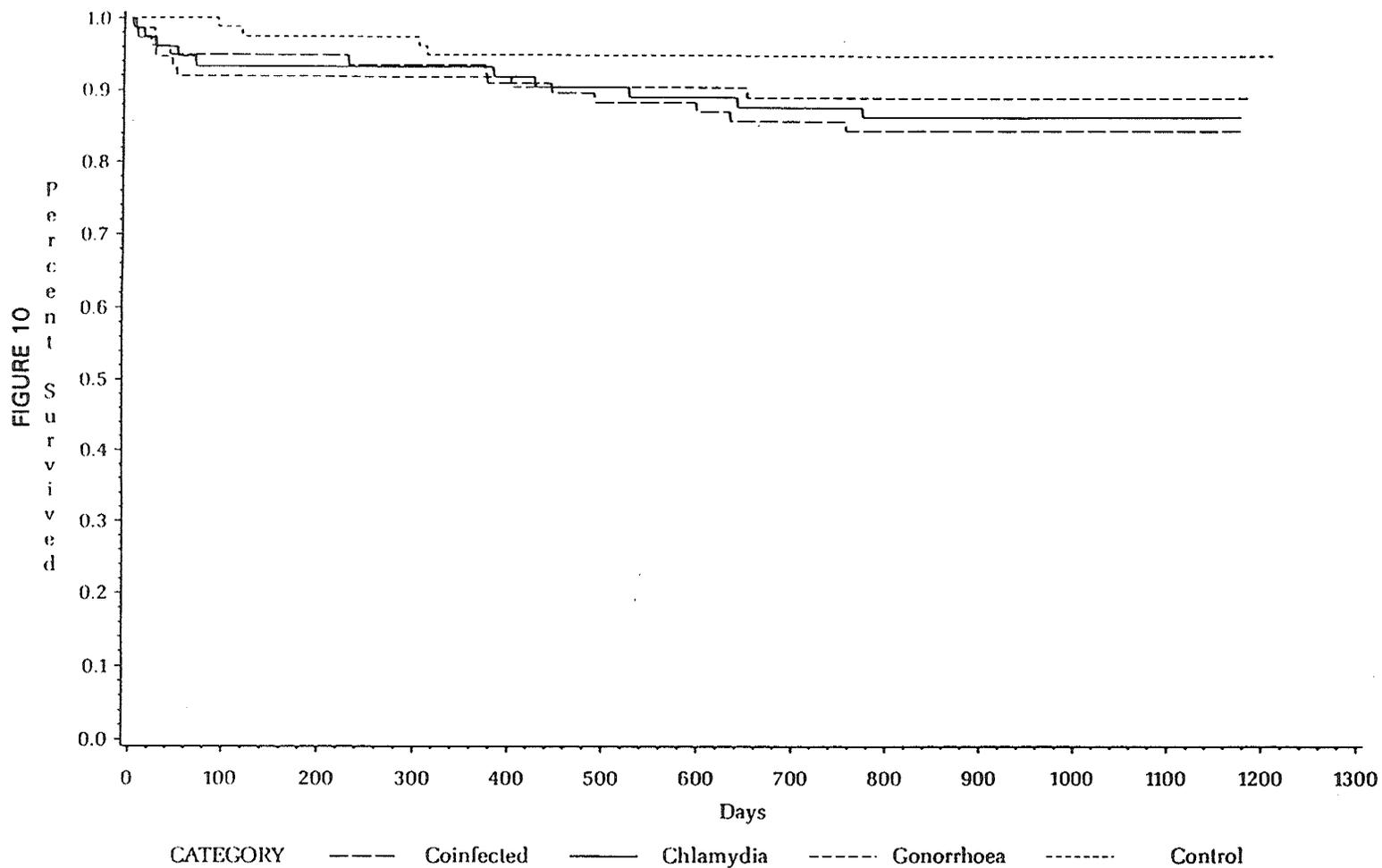


TABLE 19

Relative hazards of coinfecting women and aboriginal women for sequelae of STD diagnosed in a medical clinic

Category	Aboriginal	Non-aboriginal
Coinfected	12.68	7.85
Controls	12.06	1.00

The above table demonstrates that the risk of being diagnosed with pelvic inflammatory disease and/or infertility was comparable in aboriginal women, regardless of whether they had laboratory diagnosed coinfection with chlamydia and gonorrhoea or not. Non-aboriginal women who were coinfecting had risk almost 8 times that of controls of contracting sequelae of STD. These relative hazards were confirmed by running Fisher's Exact tests of association of sequelae between aboriginal coinfecting and non-coinfecting women, ($p < 0.05$, n.s.). A Fisher's Exact test of association of sequelae between non-aboriginal coinfecting women and controls was, however, significant, ($p = 0.03$). Being coinfecting was a risk factor for a diagnosis of sequelae only in non-aboriginal women; aboriginal women were at equal risk of having STD sequelae whether they were coinfecting or not.

Other sequelae of STD, such as ectopic pregnancy and PID diagnosed in a hospital were also defined for the study groups; however, numbers were too small to allow for proportional hazards analysis, or no difference in survival curves could be shown. Tables 20 and 21 show the incidence in 100 woman-years of the endpoints defined in the study.

TABLE 20

Incidence in 100 woman-years of STD sequelae

Incidence (Cases) Total followup days	Category 1 Coinfected	Category 2 Chlamydia	Category 3 Gonorrhoea	Category 4 Controls
Infertility	0.91 (2) 80,333	0 75,481	0.47 (1) 77,758	0 79,758
Ectopic Pregnancy	0.81 (1) 45,077	1.67 (2) 43,782	0.77 (1) 46,851	2.50 (3) 43,863
Hospitalised PID	1.40 (3) 78,384	0.98 (2) 74,572	0.96 (2) 76,084	0.46 (1) 79,455
Ambulatory PID	4.97 (10) 73,476	5.34 (10) 68,395	4.14 (8) 70,539	1.9 (4) 76,721
2nd Dx Ambulatory PID	0 81,481	0.99 (2) 73,913	1.44 (3) 75,858	0.46 (1) 78,921

TABLE 21

Incidence in 100 woman-years of subsequent STD

Incidence (Cases) Total fol- lowup days	Category 1 Coinfected	Category 2 Chlamydia	Category 3 Gonorrhoea	Category 4 Controls
1st Dx of STD	17.72 (28) 57,718	11.88 (20) 61,453	15.68 (25) 58,253	5.04 (10) 72,527
2nd Dx of STD	10.89 (17) 67,585	5.29 (10) 69,035	4.61 (9) 71,323	1.41 (3) 77,643
1st Dx Genital Infection	17.98 (28) 56,883	17.64 (27) 55,895	24.34 (33) 49,524	13.17 (22) 61,012
2nd Dx Genital Infection	5.96 (12) 73,520	5.89 (11) 68,262	10.14 (18) 64,850	3.90 (8) 74,855

Infection with chlamydia or gonorrhoea or coinfection with both these organisms are important factors in the diagnosis in a medical clinic for an STD defined by the ICD-9 codes 098 - 099 subsequent to the initial laboratory results from Cadham. A subsequent diagnosis of STD may be due to a number of causes: 1), that the individual actually has another disease episode, secondly, 2) that despite the attempt to separate disease

episodes by allowing an incubation period and a treatment time of 10 days to elapse before another diagnosis of STD was recorded as being valid, the episode is a continuation of the initial disease episode, tested for at CPL. Another possibility involves inadequate treatment of the sexual partner of the woman, so that reinfection takes place; a "ping-pong" infection. Yet a fourth possibility is that the woman was returning for a followup visit or test of cure, and the diagnosis for the original episode was applied to this visit. It is likely that the reasons for the subsequent diagnosis of STD would include a mixture of all of the above possibilities. Theoretically, preventable new episodes of STD would include the "ping-pong" reinfections and new infections acquired as a result of "risky" behaviour and the dynamics of partner mixing.

Characterisation of recidivist populations has been completed most commonly for gonorrhoea patients using the notifiable diseases registries, where information on chlamydia is not usually available. Recidivism and chlamydia has not been well described; characteristics and incidence of gonorrhoea recidivists may not apply to chlamydia recidivists. In view of proven differences in characteristics between the gonorrhoea group and the chlamydia group described in Section 4.3, the possibility of differences between the chlamydia and gonorrhoea recidivist populations is real. Another factor which should be taken into account when assessing the

importance of a subsequent diagnosis of an STD in the chlamydia group, is that in 1988 a return for test of cure was not recommended for chlamydia as it was for gonorrhoea, so a second diagnosis may be more indicative of risky sexual practices and inadequate treatment than a subsequent diagnosis for STD following a lab test positive for gonorrhoea, for which a return visit for test of cure was recommended. This reason may account for a lower incidence rate of subsequent diagnosis for STD in women with chlamydial infection.

The incidence rates and the relative hazards of subsequent diagnosis with STD provide a mechanism for assessing the medical costs associated with STD management. Lab costs and notifiable disease registries may not represent the total amount of physician visits and therefore costs to the health care system. This methodology allows for a more accurate accounting of costs of STD.

Interestingly enough, a positive lab test for chlamydia was the only significant explanation for a second subsequent diagnosis of an STD at medical clinics. For women in this group, this diagnosis may represent a third infection with a sexually transmitted organism over the study period, January 1988 - March 1991. A number of reasons may exist for the above association: chlamydia is asymptomatic in a large number of cases and

treatment compliance may be more difficult to attain than for gonorrhoea, which is more likely to produce symptoms. Women may be named again as infectious contacts, hence the return visits to obtain treatment. Initial inadequate treatment for chlamydia may also be a factor in the need for another visit; penicillin was effective only for gonorrhoea, and chlamydia requires treatment with erythromycin or tetracycline. A third possibility may involve the incidence of chronic PID following diagnosis with *C. trachomatis*. Women may be returning with PID, which is assumed to be due to initial infection with chlamydia, hence the diagnosis of 098 - 099.

Women coinfecting with gonorrhoea and chlamydia also had survival curves for the endpoint of second diagnoses of STD which differed significantly from those of controls. Age was also found to be an important factor in a second diagnosis with an STD. The relationship with age was complex; for young women with coinfection the relative hazard of 1.4, was almost identical to that of their non-infected colleagues. However, as women in the coinfecting group became older, the odds of a second diagnosis increased. Therefore, the older a woman is when diagnosed with coinfection, the more likely she is to have a repeated diagnosis of STD. The reasons for this may include habitually risky behaviour on the part of the individual; a tendency for medical clinic staff to "label" patients with that diagnosis; complications of treating coinfection effectively, or the need to ensure cure in a high risk

individual. However, as treatment complications and "labelling" would be consistent over all age groups, the most likely explanations remain habitually risky behaviour and ascertainment of cure.

The diagnosis of infection of the lower genital tract, (ICD-9 616) was positively associated with a previous positive lab result for gonorrhoea and non-aboriginal ethnic group. Women with a positive test for gonorrhoea are twice as likely to receive this diagnosis than are controls, and white women are twice as likely to receive the diagnosis than are aboriginal women. While the necessity for a test of cure and a second visit is clearly recognised, some of these visits may be due to a new infection or the continuance of the original infection. New infections may be due to risky behaviour, and/or inadequate follow-up and treatment of sexual partners.

The association of between being non-aboriginal and non-specific diagnosis with "lower genital tract infection" is disturbing. It may imply that physicians identify more with white women and so diagnose them using a non-specific term in order to avoid "labelling" them with the more blatant coding for STD, or in order to maintain confidentiality within the medical billing system. Such consideration does not appear to be present for aboriginal women. Another possible explanation for the racial association is that aboriginal women may not return for follow-up visits, and hence no

diagnosis is necessary. A third explanation may be that aboriginal women are either less likely to exhibit symptoms of infection, or less likely to seek medical care for them, hence appearing to have a lower rate of diagnosis of lower genital tract infection. It is likely that the truth is a mixture of all the above factors.

A second diagnosis of lower genital tract infection is associated only with previous lab diagnosis of gonorrhoea. Return visits for tests of cure, treatment and follow-up of contacts may be the major cause of these second visits. Other causes include a new infections, "ping-pong" infections, and continuation of a previous episode of STD. This last cause is unlikely, as second visits would have taken place longer than 21 days from the first visit, which in turn would have been longer than 21 days from the specimen date recorded by CPL.

Sequelae of STD in an ambulatory care setting comprise a diagnosis of infertility (ICD-9 code 628), (verified by a lack of a subsequent birth during the study period), and PID (ICD-9 code 614). Differences in survival curves for this outcome were significant only in coinfecting women and controls. Coinfection and ethnic group are significant risk factors for development of sequelae diagnosed in a medical clinic. Aboriginal women are at higher risk than non-aboriginal women of STD sequelae diagnosed in an ambulatory

facility, (PID and infertility). In a sub-analysis of the aboriginal group, being coinfectd does not put aboriginal women at higher risk of sequelae.

Reasons for this may not be attributed to the somewhat arbitrary selection of the control group. As women may have had a test result subsequent to the date of the initial specimen result on which they were classified, women in the control group could have had laboratory proven coinfection later on in 1988. However, study bias associated with this phenomenon would not logically be confined to aboriginal women only, but would include non-aboriginal women also.

A legitimate reason for the high risk of PID in aboriginal women may be that aboriginal women may not experience symptoms as often as non-aboriginals and may not present early on in the disease process; they may be less likely to seek care for the symptoms that they do have, and hence be at higher risk of progression to sequelae. Aboriginal women may be more susceptible to PID than non-aboriginal women, due to differences in immune system composition and responses. Other possibilities may include inadequate treatment of sexually transmitted infections, or lack of patient compliance with a drug regimen.

It is possible, given the traditionally high rates of STD in aboriginal people, that the "background" level of undetected infection in the population is so

high, that sequelae are not found to be associated with STD. This last explanation is also consistent with the higher rate of sequelae in coinfecting aboriginals than in their non-aboriginal coinfecting counterparts, (relative hazard 1.6). Such a question can only be solved in future research.

Incidence rates for other sequelae were calculated. Analysis could not be performed on these endpoints because of small numbers, therefore no tests of significance or confidence limits are present. It is interesting to note that ectopic pregnancies were highest in Category 3, the control group, although rates of PID treated in a medical clinic or hospital were not as high. It is possible that previous asymptomatic episodes of chlamydia may be responsible for the relatively high rate of ectopic pregnancy in the control group. Rates of ectopic pregnancy in some countries¹⁸, including Canada, have recently increased, although rates of gonorrhoea, another important cause of ectopic pregnancy have decreased. It has been suggested that chlamydial infections are the major cause of the increase¹⁹, although in this study, the numbers are too small to be reliable. Hospitalised PID and infertility were highest in the coinfecting groups. This is not unexpected, as complications of sequelae would be due to both *N. gonorrhoea* and *C. trachomatis*. PID rates diagnosed in an ambulatory care facility are highest for the chlamydia group. This is consistent with other research which

suggests that chlamydial PID is less acute and tends to be more chronic than gonococcal PID²⁰.

Incidence of subsequent diagnoses of STD is interesting in that the first diagnoses are highest in the gonorrhoea group. This is consistent with the need for a return visit for a test of cure. A second subsequent visit is higher in women with chlamydia, perhaps indicating a more complex disease process or care process, recognising that care is dependent on the disease to some extent. An example of the above would be lack of compliance in treatment because the infection is more likely to be asymptomatic than gonorrhoea, or more likely to cause PID. High rates of "lower genital tract" infection in the gonorrhoea group is likely due to the need for return visits for tests of cure.

Although this study was fairly small, valuable information has been gathered from it. Higher rates of subsequent diagnoses of STD in the women infected with STD indicate the nature of the disease burden and the financial costs of STD. Racial differences may be due, in part, to different preventive and curative health care systems servicing aboriginal people and their needs; lastly, elevated risks of STD sequelae is an indication of serious personal, financial and health costs which are preventable to some extent.

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CHAPTER 4

CONCLUSION

4.0 Conclusion

This study was conducted to define the methodology for record linkage study of laboratory records and health billing data. The addition of socioeconomic data from Statistics Canada files makes it a powerful tool for the analysis of populations accessing medical care for specific health problems. Although there are many inaccuracies in the coding of medical data, the entry of personal details of patients, and the application of general socioeconomic data to small areas, this method has demonstrated that large populations can be analysed successfully, with meaningful results. Although data are not as accurate as those gathered primarily for research purposes, the sheer numbers which can be analysed give at least an idea of incidence of rare events such as STD sequelae. This kind of information is critical in the planning, justification and evaluation of STD control efforts.

Validity of data of this kind is a problem, if only because of the large numbers of records to be validated. It is essential for the future credibility of research into medical diagnostic coding that a random number of records be verified with charts in a hospital and medical clinic setting. However,

internal inconsistencies can be easily identified by comparing procedure or tariff codes with diagnostic codes. If accuracy of CPL data for individuals were to be improved, the substantial challenge involved in research using the CPL database and in matching records with those of MHSC would be greatly simplified.

The description of patients with STD yielded an understanding of important socioeconomic characteristics. The quantification of risk by age in years is more specific than that by age group, and the risks of ethnic status, urban residence and income confirm, and add to, knowledge of STD epidemiology in Canada. The consistent high levels of risk in youth and in aboriginal peoples indicate that the medical structure, both preventive and curative, may not be adequate or appropriate to support their needs.

Repeated STD visits may be somewhat confounded by STD management strategies, and the need to return for tests of cure. However, repeat visits may indicate the need for more effective patient education regarding therapy and behaviour change. The higher risks of PID among aboriginal women are serious in their implications for other sequelae such as ectopic pregnancy. While the methodology was successful in demonstrating that the risk of sequelae can be quantified, it could not clarify the care seeking or care giving behaviours which influence the risk of sequelae in aboriginal women.

4.1 Future Studies

After the completion of the analysis of data, several research priorities are immediately obvious: The first of these is to continue the analysis of incidence of endpoints into the future with the larger study sample. This will be of value as women who are infected may have an episode of PID months later, and years after that may be diagnosed as having tubal infertility. Women who were identified with chlamydial infection in 1984 will be followed in this study for five years, those who were identified in 1989 will have been followed only for one year; it is important in calculating trends in chlamydial infection, PID, infertility and ectopic pregnancy over time, to have current annual data.

Continuing study of the relationship between infection with *N. gonorrhoea* and *C. trachomatis* and sequelae will provide a valuable component in the evaluation of Manitoba's STD control program, and efficacy of treatment in preserving fertility, and prevention of condition such as PID and ectopic pregnancy.